Clinical Manual
for Management of the HIV-Infected Adult

2006 Edition

Providing Healthcare Professionals with
Quality Education to Improve HIV Care

AETC
AIDS EDUCATION &
TRAINING CENTERS
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The AETC National Resource Center (NRC) provides education and training resources for the regional AETCs to support their mission to offer timely, high quality, state-of-the-art information to healthcare professionals working with existing and emerging populations affected by HIV. In partnership with the Center for HIV Information (CHI), the AETC NRC works to identify and develop information on HIV care, prevention, and policy through electronic media, including Internet and CD-ROM. The AETC NRC is administered by the François-Xavier Bagnoud (FXB) Center at the University of Medicine and Dentistry of New Jersey. The FXB Center provides clinical care, education and technical assistance in the United States and globally to support capacity development for addressing the HIV/AIDS epidemic.

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Clinical Manual for Management of the HIV-Infected Adult

About This Manual

This guide is the collaborative effort of clinical faculty associated with the AIDS Education and Training Centers. *(See the list of contributors below.)* The 2006 edition comes 13 years after the first edition, which was produced by the Midwest AETC (MATEC) and the Southeast AETC (SEATEC). The original manual was conceived to address the needs of the "midlevel" clinician—advanced practice nurses, physician assistants, etc—who comprise a significant proportion of the HIV primary care providers in the United States (and elsewhere). Experience has shown us that the whole range of providers—physicians, pharmacists, nurse practitioners and advanced practice nurses, physician assistants, dentists, and others, appreciate the nuts-and-bolts format of the guide. This edition maintains the practical approach of prior editions, but its content has been broadened somewhat, in recognition of its wide audience.

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This manual is intended for use in collaborative practice models, for example, those involving medical, nursing, physician assistant, and pharmacy staff. Geographic variations in health care practice conventions and frequent changes in HIV care require that clinicians maintain familiarity with current HIV practice standards. The treatment guidelines should be carefully reviewed by the clinical care team in your facility to make sure they conform to acceptable local and contemporary approaches. Medical treatment updates are posted frequently to several Web sites, including the http://www.aidsinfo.nih.gov site, and it is recommended that every provider be familiar with all relevant guidelines.

This manual may be reproduced in whole or in part for noncommercial use, with appropriate attribution. However, reproduction for commercial purposes is prohibited. Please note that these treatment recommendations are not intended to replace clinical research literature or current U.S. Department of Health and Human Services (DHHS) guidelines, and may not include the full range of treatment options for all HIV-infected patients. Independent verification of all information is necessary before undertaking care of HIV-infected clients, particularly in the face of rapidly changing HIV treatment standards. Some recommendations are not in accord with U.S. Food and Drug Administration (FDA)-approved usage for certain drugs, but are based on findings from clinical trials and recommendations from expert providers. For more information or to offer comments, please contact us at editor@aidsetc.org.

About the AIDS Education and Training Centers

Based in leading academic centers, the AETCs serve all 50 states, the District of Columbia, Puerto Rico, the US Virgin Islands, and the six US-affiliated Pacific Jurisdictions. Sixty-six universities participate in the program. The AETCs aim to increase the number of healthcare providers who are effectively educated to counsel, diagnose, treat, and medically manage individuals with HIV infection, and prevent high-risk behaviors that lead to HIV transmission.

Training targets providers who serve minority populations, the homeless, rural communities, persons in correctional facilities and migrant health centers, and Ryan White CARE Act-funded sites. AETCs focus on training a diverse group of clinicians including physicians, nurses and advanced practice nurses, physician assistants, oral health professionals, and pharmacists.

Since the first AIDS cases were identified, knowledge about the disease and its treatment has increased exponentially. The AETC program was designed to improve the dissemination of new information to interdisciplinary healthcare providers through expert clinical consultation, intensive clinical rotations and preceptorships, workshops and seminars, hands-on supervised clinical experience, and technical assistance.

The AETC program is administered by the Health Resources and Services Administration (HRSA), HIV/AIDS Bureau (HAB).

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Initial History

Background

This chapter includes essential points to cover during an initial clinic intake visit.

Conducting a thorough initial history and physical examination is important even if previous medical records are available. This is the best opportunity to get a complete picture of the patient's HIV disease status and his or her physical and emotional condition, as well as to establish the basis for an ongoing relationship with the patient. Many of the conditions that put immunocompromised patients at risk for disease can be detected early, by means of a thorough assessment.

The information gathered through the initial history and physical examination will provide a comprehensive standardized database for the assessment and treatment of HIV-related problems, including acute intervention and ongoing supportive care. For essential aspects of the physical examination to cover in an initial clinic intake visit, see chapter *Initial Physical Examination.*

O: Objective

Document the patient's full name, date of birth, date of assessment, and any other information standard to your practice (Tables 1 and 2). Perform a review of systems (Table 3).

Table 1. Patient Information

First Name:	Last Name:
Date of Birth: _____ / _____ / _____	Date of Assessment: _____ / _____ / _____

Table 2. Initial History Checklist

Category / Subject Matter	Questions
History of Present Illness	
HIV Testing	What was the date of your positive HIV test?
	Did you have a previous test? If so, when was the last negative HIV test?
	When do you think you were infected?
Treatment Status	Where do you usually receive your health care?
	Have you ever received care for HIV?
	What was the date of your last HIV care visit?
	Do you know what your first CD4 (T-cell) count was?
	What was your lowest CD4 count?
	What was your highest CD4 count?
	What is your current CD4 count?
	Do you know what your first viral load count was?
	What was your highest viral load count?
	What was your lowest viral load count?
	What is your current viral load count?
	Have you participated in any research protocols?
	Would you be interested in participating?

Risk for HIV and Other Sexually Transmitted Diseases	How do you think you were exposed to HIV?
Sexual	Please tell me about any experience you've had with unprotected anal, vaginal, or oral sex.
	Have you had sex with men? With women?
	Have any of your sex partners:
	Told you they were HIV infected or had AIDS?
	Told you they used injection drugs?
	Ever been in jail or prison?
	Had a sexually transmitted disease?
	Had hemophilia?
	Received a blood transfusion?
	Have you ever received donated sperm during artificial insemination?
Substance Use	Please tell me about your experience with injected substances.
	Have you shared your needles or injection equipment (works) with another individual?
Transfusion	Did you receive any blood or blood products between 1977 and 1985?
Occupational	Have you had an on-the-job injury that involved contact with a body fluid?
	What was the injury, and was HIV evaluation a part of the work injury follow-up?
Tattoos	Do you have any tattoos?
	Were sterile needles and ink-wells used to place your tattoo?
HIV-Related Illnesses	What opportunistic infection(s) have you had, if any? (PCP, MAC, cryptococcal meningitis, TB, etc)
	What year(s) were you diagnosed with the above?
	Have you had cancer(s)?
	What other HIV-related illnesses have you had?
Active Tuberculosis (TB) and TB Testing History	When was your last TB skin test (PPD)?
	What were the results of this test?
	Have you ever had a positive TB skin test?
	What year and what health care setting?
	What medications did you take and for how long?
	Have you ever had active tuberculosis?
Medications	Are you taking HIV medications now?
	If so, can you name them or describe them, and give their dosing frequency?
	How many doses have you missed in the last 3 days? The last week? The last month?
	What HIV medicines have you taken in the past (names or descriptions)? [If possible, have patient list all ARVs and ARV combinations, with dates and corresponding CD4 counts and viral loads.]
	When did you start and stop them (dates)?
	Do you know why you stopped these medications?
	Do you know what your HIV viral load or your CD4 counts were while you were taking your medications?
	Have you ever had a resistance test done?
	What other medications are you taking now?
	What herbs, over-the-counter (OTC) products, or vitamins are you taking now?

Past Medical and Surgical History		
Chronic Diseases	Do you have any chronic conditions, such as diabetes, high blood pressure, heart disease, cholesterol problems, asthma, emphysema, sickle cell disease, ulcers, acid reflux, irritable bowel syndrome, thyroid disorders, kidney or liver problems, or mental health disorders?	
	If so, do you receive medical care for these conditions?	
Previous Illnesses	Have you had any hospitalizations? Where, when, and for what reason?	
	Have you had any surgeries? When and where?	
	Have you had any major illnesses, including mental health conditions?	
Hepatitis	Have you ever had hepatitis? What type (A, B, C)?	
	Do you have chronic hepatitis?	
	Do you know your immunity status to hepatitis A or hepatitis B? Have you been vaccinated?	
Gynecologic	When was your last Papanicolaou (Pap) smear?	
	What were the results?	
	Have you ever had an abnormal Papanicolaou (Pap) smear?	
	When was your last menstrual period?	
	What is the usual length of your cycle?	
	Have you noticed changes in your menstrual cycle?	
	Have you had any lower abdominal pain?	
	Do you get yeast infections? How often?	
	Do you get urinary infections?	
	Have you ever had kidney stones?	
Obstetric	How many pregnancies have you had?	
	How many miscarriages or therapeutic abortions?	
	How many live births? Ages of children now?	
	Was HIV tested during any pregnancy?	
	Did you deliver an infant while you were HIV infected?	
	Was HIV medication given during pregnancy and delivery?	
	Do you have children who are HIV infected?	
	Do you intend to become pregnant?	
Anorectal History	Have you ever had an anal Papanicolaou (Pap) smear?	
	What were the results?	
Sexually Transmitted Infections (STIs)	Have you ever been treated for:	
	Syphilis?	Vaginitis?
	Genital herpes?	NGU (nongonococcal urethritis)?
	Gonorrhea?	Genital warts (HPV)?
	Chlamydia?	Proctitis?
	Pelvic inflammatory disease (PID)?	

Health-Related Behaviors	Do you smoke? How long have you smoked? How many cigarettes per day?
	Do you smoke anything besides tobacco?
	Do you chew tobacco?
	How much alcohol do you drink?
	Any experience with blackouts due to alcohol?
	Do you use any street drugs we haven't covered in earlier questions?
	If so, what drugs and how do you use them (inject, smoke, inhale, etc)?
	When did you last inject a substance?
	How about inhaled or snorted substances?
	Have you shared your equipment with another person?
	When did you last inhale a substance?
	Or smoked substances?
	Have you shared your equipment?
	When did you last smoke a substance?
	Are you interested in treatment for alcohol or drug use?
	What pain relievers do you use on a regular basis?
Immunizations	When was your last vaccination for:
	Tetanus?
	Streptococcal pneumonia (Pneumovax)?
	Influenza?
	Hepatitis A?
	Hepatitis B?
	Did you have chickenpox as a child, or were you vaccinated against chickenpox?
	What about measles, mumps, and rubella?
Allergies	What allergies do you have to medications?
	What was the reaction?
	What allergies to foods or environmental substances?
Family History	
	Do you have a family history of:
	Heart disease? Heart attacks or strokes?
	Cholesterol problems? Diabetes?
	Cancer?
	Mental health conditions (such as depression, anxieties, phobias)?
	Addictions?
	Which family member(s) and what is their health status currently?

Social History	
Relationship Situation	What is your relationship status (single, married, partnered, divorced, widowed)?
	Do you have children?
Living Situation	Do you live alone or with others? With whom?
Support System	Who knows about your HIV status?
	Which individual is the most supportive of your HIV diagnosis?
	Who is the least supportive of your status?
	Have you used any community support services such as support groups?
Employment	Are you currently employed?
	Where do you work?
	Describe your job task(s).
	What setting do you work in on a daily basis?
	Does your employer provide health insurance?
	If on disability: How long have you been on disability?
	What medical condition has made you disabled?
Travel	Where have you traveled outside the United States?
	When did travel take place?
Diet	Tell me what you eat during a typical day.
	Do you consume raw (unpasteurized) milk, raw eggs, raw or rare meat, deli meats, soft cheeses, or raw fish?
	How much water do you drink during the day?
	What is your source of water?
	How much caffeine do you drink during a typical day?
Pets	Do you have or have you had any pets?
	What kind of pets, and who cleans up after them?
Exercise	What kind of physical exercise and recreational activity do you participate in?
	How often?

Sensitive Sexual History Questions	
General Sexual	Do you have sex with men, women, or both?
	In the past, have you had sex with men, women, or both?
Sexual Identity	Do you consider yourself male or female?
	Have you had or considered treatment for sex change?
	Have you had hormone therapy?
	Have you had any sex-change surgery?
Sexual Practices	Do you have anal, vaginal, and/or oral sex?
	Do you protect yourself from sexually transmitted infections, or HIV reinfection? How?
	For men who have sex with men: Are you the receptive or insertive partner, or both?
	How often do you use alcohol or drugs before or during sex?
Prevention	Do you know the HIV status of your partner(s)?
	Do you protect your partners from HIV? How?
	In what situations do you or your partner use condoms or some other barrier?
Sex Trading	Have you ever exchanged sex for food, shelter, drugs, or money?
Contraception	What birth control measures do you use, if any?
	Do you use condoms or other latex barriers?
	Do you have plans for you or your partner to become pregnant?
Mental Health	
Coping	How do you handle your problems/stresses?
	What do you do to relax?
Therapy	Have you thought about seeing a mental health provider?
	Have ever been diagnosed with depression, anxiety, panic, bipolar disorder, etc?
	Have you taken or are you taking any medications for these conditions?
	Are you seeing a therapist or mental health professional?
	Have you had any previous counseling or mental health problems?
	Have you ever been hospitalized for a psychiatric condition?
	Have you ever thought about hurting yourself? If yes, probe for previous suicide attempts: Are you feeling that way now? (*See chapter* Suicidal Ideation *and prepare for immediate referral if necessary.*)
Violence	Have you ever been sexually abused, assaulted, or raped?
	In your adult life, have you lived in any situation with physical violence or intimidation?
	When has this occurred?
	Are you afraid for your safety now?
Childhood Trauma	Who reared you (one or both parents, other relatives, foster care)?
	Was there any alcoholism or drug abuse in your household when you were a child?
	Did you experience or observe violence; physical, sexual, or emotional abuse; or neglect?

Key to abbreviations: ARV = antiretroviral; HPV = human papillomavirus; MAC = *Mycobacterium avium* complex; PCP = *Pneumocystis jiroveci* pneumonia; PPD = purified protein derivative; TB = tuberculosis.

Table 3. Review of Systems

For each positive answer, document location, characteristics, duration of symptoms, and exacerbating and alleviating factors.

General	
General	Do you ever wake up feeling tired?
Fever	Do you have fevers? How high, and for how long?
Night Sweats	Do you ever sweat so much at night that it soaks your sheets and nightclothes?
Chills	Do you experience shaking or teeth-chattering when you feel cold?
Anorexia	How is your appetite?
Weight	What was your weight 1 year ago?
	What is a normal weight for you?
	Have you lost or gained weight unintentionally?
Body Changes	Have you noticed any changes in the shape of your body (describe)? For example, has there been an increase in your waist, collar, or breast size or a decrease in your arm, leg, or buttocks size?
	Have you noticed increased visibility of veins in your arms and legs?
	Have you noticed thinning of your face?
Head, Ears, Eyes, Nose, and Throat	
Vision	Have you noticed any changes in your vision, especially blurred vision or vision loss, double vision, new "floaters" or flashes of light?
	Have you noticed this problem in one or both eyes?
	When did you first notice these changes?
Mouth, Ears, Nose, Throat	Have you noticed any white spots in your mouth or a white coating on your tongue (thrush, oral hairy leukoplakia)?
	Do you ever get sores in your mouth or the back of your throat? Gum problems?
	Any nosebleeds?
	Hearing loss, ringing in your ears, ear pain?
Cardiovascular	
Cardiac	Any palpitations or chest pain?
	Any shortness of breath during activities or while you are lying down?
	How far can you walk or run before you get short of breath?
	Any swelling in feet or hands?

Pulmonary	
Cough	Do you have a cough?
	Can you describe it? Dry or productive, amount, color, odor, presence of blood in sputum? When is it the worst?
Dyspnea	Do you ever feel short of breath?
	Does that happen when you are sitting still, lying down, or moving around?
	How severe is your shortness of breath?
	Does it prevent you from doing anything?
	Do you ever wheeze?
Gastrointestinal	
Dysphagia	Do you have any problems with food sticking in your throat or being difficult to swallow?
	Do you notice it's easier to swallow liquids or solids?
	Do you gag or get nauseated when trying to eat?
Odynophagia	Do you have pain in your throat, esophagus, or behind your breastbone when you swallow?
Nausea/Vomiting	Do you have nausea or vomiting?
	When? Are there specific things that cause this?
Dyspepsia/Reflux	Do you ever have heartburn?
	When does it happen—after eating, lying down, on an empty stomach?
	Do you get the taste of stomach acid in your mouth?
Diarrhea	Do you have diarrhea, or more than 3-5 unformed stools a day?
	Stool characteristics: bloody, pus, mucus?
	Pain or cramping with diarrhea? Tenesmus?
Bowel Habits	How frequently do you have bowel movements?
	Do you have problems with constipation, blood in the stools, or other?
	Do you have problems with flatulence or belching after eating?

Genitourinary	
Genital	Do you have any lesions or sores on your genital area now, or have you in the past?
	Have you ever had genital herpes? If yes, how often do you have outbreaks?
	When was the most recent outbreak?
Women	Have you had any lower abdominal pain?
	Have you noticed a vaginal discharge or odor?
	Do you have any burning or pain on urination?
	Frequent urination?
	Do you lose control of your urine or have problems getting to the bathroom before you start to urinate?
Men	Have you noticed any swelling or testicular pain?
	Do you have difficulty starting your stream of urine?
	Are you getting up at night to urinate?
	Have you had burning or pain on urination?
	Do you lose control of your urine or have problems getting to the bathroom before you start to urinate?
	Have you ever had kidney stones?
	Do you have any difficulty developing an erection or maintaining one?
	Any discharge from your penis?
Musculoskeletal	
	Do you have any muscle aches or pains?
	Back pain, joint pain, and/or swelling?
	Have you ever broken any bones?
	Do you have chronic pain?
	Describe the pain—location, duration, rating (scale of 1-10), alleviation factors.
Skin	
Herpes Zoster	Have you ever had chickenpox (varicella)?
	Have you ever had "shingles" (zoster)?
	Where were the lesions?
Tinea	Do you have fungal infections on your skin, especially groin, fingernails, toenails, or feet?
Folliculitis	Do you have any itchy bumps on your face, back, or chest?
Seborrhea	Do you have flaking or itching on your skin or scalp?

Skin Lesions	Have you noticed any rash or skin problems? If so, where?
	Have you noticed any new moles, bruises, or bumps on your skin?
	Do you have any moles that changed shape, size, or color?
Neurologic	
Headache	How often do you get headaches?
	Describe the headaches—location, timing, duration, alleviating or aggravating factors.
	Do they cause nausea or vomiting?
	Does sensitivity to light lead to headaches?
Memory	Do you have difficulty with your memory or ability to concentrate? If so, describe.
Gait	Have you noticed any changes in the way you walk?
Neuropathy	Do you have any numbness, tingling, burning, or pain in your hands or feet?
Seizures	Have you ever had a seizure or "fit"?
	If so, describe the seizure—When? How long did it last? Loss of consciousness? Was medical care sought?
Weakness	Do you have or have you had any weakness in your arms or legs?
Endocrine	
Diabetes	Have you had any increase in thirst, hunger, or urination?
Thyroid	Have you noticed changes in your energy level?
	Do you have intolerance to heat or cold?
	Have you noticed changes in your hair (thinning, coarse texture)?
Sex Steroids	Have you noticed any changes in your libido?
Hematologic/Lymphatic	
Adenopathy	Do you have swollen glands?
	If so, describe—location, painful, size if measurable.
Bruising or Bleeding	Have you noticed easy bruising or prolonged bleeding after injury?
	Nosebleeds or bleeding gums?

Psychiatric	
Mood	Depression screening: Have you experienced a decrease in your interest or pleasure in your activities? Have you felt depressed, down, or hopeless?
	Do you feel more angry, sad, depressed, numb, irritable, or anxious than usual?
	Have any major life events have occurred to cause you to feel sad or depressed?
	When did these events occur?
Sleep	How is your sleep?
	How many hours do you sleep each night?
	What is your sleeping schedule—time to bed and time to rise?
	Do you take naps?

A: Assessment and Plan

- Conduct a physical examination, focusing on subjective findings elicited in the history. (See chapter *Initial Physical Examination*.) Note: If significant time has elapsed between the ROS and physical exam, perform another ROS.
- Compose a problem list. Initiate a medication list (if appropriate).
- Order baseline/intake laboratory work. (See chapter *Initial and Interim Laboratory and Other Tests.*)
- Refer the patient to social services, mental health, community and other resources, or other clinic services as needed.

During today's visit or a future visit:

- Perform PPD testing if not done in the last year, or if the patient was previously PPD negative. The patient can return to have the PPD read.
- Perform immunizations for pneumonia (Pneumovax), influenza (as appropriate), and other immunizations as indicated. (See chapter *Immunizations for HIV-Infected Adults and Adolescents.*)
- Provide counseling on prevention of HIV transmission (eg, safer sex and injection practices), as appropriate.

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Initial Physical Examination

Background

Many of the conditions that put immunocompromised patients at risk for disease can be detected early, by means of a thorough history and physical evaluation. This chapter presents essential aspects of the initial physical examination of the HIV-infected individual. (For essential aspects of the history to cover in an initial clinic intake visit, see chapter *Initial History*.)

S: Subjective

- When an HIV-infected patient presents for an initial examination, document the patient's full name, date of birth, date of assessment, and any other information standard to your practice (Table 1).

Table 1. Patient Information

First Name:	Last Name:
Date of Birth: _____ / _____ / _____	Date of Assessment: _____ / _____ / _____

O: Objective

Assess the patient's general appearance, affect, demeanor in answering questions, body language, and other relevant characteristics such as vital signs (Table 2). Perform a physical examination (Table 3).

Table 2. Vital Signs

Vital Sign	Recommendation	
Weight	Record at each visit.	
Height	Should be measured once.	
Temperature	Document at each visit.	
Blood Pressure	Use BP cuff size appropriate for the patient's arm circumference.	
Heart Rate	Provide a baseline rate for later evaluation of anemia, dehydration, and other physical conditions.	
Waist, Hip	Waist and hip circumference should be measured for comparison in case the patient later develops metabolic complications of ART.	
	Abdominal circumference: >102 cm (39") in men = abdominal obesity >88 cm (35") in women = abdominal obesity	Waist-hip ratios: >0.95 in men = increased risk of CHD >0.85 in women = increased risk of CHD
Body Mass Index (BMI)	BMI can be helpful in determining obesity, wasting, and ART-related weight gain. Perform at baseline and upon changes in weight.	**BMI calculation:** $\frac{\text{(weight in pounds)}}{\text{(height in inches) x (height in inches)}}$ X 703 **or** $\frac{\text{(weight in kilograms)}}{\text{(height in meters) x (height in meters)}}$ BMI <18.5 = underweight 18.5–24.9 = normal range 25–29.9 = overweight ≥30 = obese

Key to abbreviations: ART = antiretroviral therapy; BMI = body mass index; CHD = coronary heart disease.

Table 3. Physical Examination

Eyes
• Visual acuity and visual fields by confrontation. • Tests of extraocular movements and pupillary size and reaction. • Funduscopic examination—with or without mydriatics; especially important if CD4 count is <100 cells/µL. • Note any retinal lesions, white or yellow retinal discoloration, infiltrates, or hemorrhages (could indicate cytomegalovirus retinitis, retinal necrosis, or ocular toxoplasmosis). • Referral to ophthalmologist for retinal examination every 6 months if the CD4 count is <100 cells/µL. • Refer immediately if the patient has retinal lesions or new visual disturbances.
Ears/Nose
• Examine ear canals and tympanic membranes. • Visualize nasal turbinates. • Palpate frontal and maxillary facial sinuses.
Oral Cavity
• Good lighting is essential. • Assess gingiva and teeth. • Assess mucosal surfaces (remove dentures, if present); note any lesions, discolorations, or skin abnormalities. • Have patient lift tongue to assess the posterior side. • Note whether tonsils are absent or present and any abnormality in tonsil size. • Pharynx—lesions, exudate?
Endocrine
• Check thyroid for enlargement, tenderness, nodules, and asymmetry.
Lymph Nodes
• Document site, size, and characteristic of each palpable node.

Node Sites	Characteristics
• Posterior cervical chain • Anterior cervical chain • Submandibular • Submental • Supraclavicular • Axillary • Epitrochlear • Inguinal • Femoral	• Size (2 dimensions, in millimeters) • Consistency (hard, fluctuant, soft) • Tenderness • Mobility • Definition (discrete, matted) • Symmetry

Skin
• Examine the entire body, including scalp, axillae, palms, pubic and perianal areas, soles of feet. • Describe all lesions: size, borders, color, symmetry/asymmetry, distribution, raised/flat, induration, encrustation. • Note evidence of folliculitis, seborrheic dermatitis, psoriasis, Kaposi sarcoma, fungal infections, prurigo nodularis, etc.
Lungs
• Auscultate and percuss. • Note any abnormal sounds including crackles or wheezes (signs of infections, asthma, congestive heart failure, etc). • Note any absence of air movement (pneumothorax, pleural effusion, etc).
Heart
• Note rate and rhythm, heart sounds, murmurs, extra heart sounds. • Palpate for PMI (point of maximal impulse). • Examine for JVD (jugular venous distension).
Breasts
• Palpate for breast masses in both men and women. • Check for symmetry, discharge, dimpling, and masses.
Abdomen
• View—note distension, obesity, undernutrition, vascular prominence, petechiae. • Auscultate—note bowel sounds. • Percuss—record liver size. • Palpate—note hepatomegaly or splenomegaly; note any tenderness or rebound.

Genitals/Rectum

- Inspect the genitalia and perirectal area; note lesions, warts, etc.
- Culture discharges, ulcerative lesions, vesicles, and crusted lesions for herpes simplex virus, chancroid, chlamydia, and/or gonorrhea (GC), as appropriate, and send an RPR (rapid plasma reagin) or VDRL (Venereal Disease Research Laboratory) test.

Female Patients

- Speculum examination–note any lesions on vaginal walls or cervix.
- Obtain a Papanicolaou smear. (Note: Abnormal or inconclusive Papanicolaou smears require colposcopic follow-up, because invasive cervical cancer may progress rapidly in women with HIV. See chapter *Cervical Dysplasia*.)
- Obtain endocervical swab for GC and chlamydia, and a posterior pool swab for wet mount evaluation for trichomoniasis, *Candida*, and bacterial vaginosis.
- Bimanual exam–note size of uterus and ovaries, shape, and any tenderness or pelvic pain.
- Rectal examination for anorectal lesions, warts, etc, and evaluation of uterine abnormalities.
- Anal Papanicolaou smear.*

Male Patients

- External genitalia–note whether male is circumcised; note any lesions, discharge, other abnormalities, as above.
- Testicular examination for masses, tenderness.
- Rectal exam—digital examination to evaluate rectal tone, discharge or tenderness, masses, lesions; prostate exam if appropriate.
- Anal Papanicolaou smear.*

* Anal Papanicolaou smear: Consider this test if follow-up evaluation of abnormal Papanicolaou test results is available. The suggested approach in HIV-infected women and men for anal dysplasia screening is similar to the cervical Papanicolaou screening guidelines for women: perform anal Papanicolaou test at initial diagnosis and, if normal, repeat at 6 months. If the first 2 anal Papanicolaou smears are normal, repeat annually. If a Papanicolaou test shows ASCUS (atypical squamous cells of undetermined significance) or SIL (squamous intraepithelial lesion), refer for anal colposcopy and biopsy. (See chapter *Anal Dysplasia*.)

Extremities/ Musculoskeletal

- Joints—note any enlargement, swelling, or tenderness.
- Muscles—for the major muscle groups, pay close attention to muscle bulk (normal or decreased), tenderness, or weakness.
- Look for evidence of peripheral fat atrophy.
- Consider measuring baseline arm, thigh, and chest circumferences for later comparison.
- Note nail changes (clubbing, cyanosis, fungal infections).
- Assess for pedal or leg edema.

Habitus

- Subcutaneous fat loss (face, extremities, buttocks).
- Central fat accumulation (neck, dorsocervical, breasts, abdomen).

Neurologic

- Mental status—including orientation, registration, recent and remote memory, and ability to calculate (serial subtraction)
- Cranial nerves
- Peripheral sensory examination should include pinprick, temperature, and vibratory stimuli.
- Extremity strength and gait to discern myopathy, neuropathy, and cerebellar disease
- Fine motor skills such as rapid alternating movements (often abnormal in dementia)
- Deep tendon and plantar reflexes

Psychiatric

- Patient's general mood (depressed, anxious, hypertalkative, etc)
- Verbal content–answers questions appropriately; discussion of suicide
- Inappropriate or unusual behavior, such as extremes of denial, hostility, or compulsiveness
- See *Neuropsychiatric Disorders* section for more complete information on common pathologies.
- Emergency situations, such as potential suicide or violence—refer to crisis mental health services for immediate evaluation

A: Assessment and Plan

After completing the initial history and physical examination:

- Complete the patient's database with the information garnered through the history and physical examination.
- Document a problem list, assessment, and plan for patient care.
- Complete follow-up or laboratory studies suggested by the history and physical exam. (See chapter *Initial and Interim Laboratory and Other Tests.*)
- Prescribe opportunistic infection (OI) prophylaxis as appropriate. (See chapter *Opportunistic Infection Prophylaxis*.)
- Refer for dental, nutrition, social services, and mental health care as appropriate.
- Refer for any additional specialty care identified in the history or physical exam.
- Order any appropriate vaccinations. (See chapter *Immunizations for HIV-Infected Adults and Adolescents*.)
- Make follow-up appointment with health care provider.
- Answer the patient's questions.

Patient Education

A very important aspect of caring for HIV-infected individuals is educating patients about HIV infection, including goals of care and ways of achieving those goals.

Review the following with each patient:

HIV disease

- Transmission and progression
- Significance of CD4 count and HIV viral load
- Possible treatment approaches
- Disclosure—whom the patient may need to tell about HIV status; approaches to disclosure

HIV transmission prevention and risk reduction for HIV-positive individuals

- Safer-sex approaches, including the use of condoms/latex barriers during all sexual contacts
- Safer use of recreational drugs

Nutrition

- Maintaining a healthy weight
- Nutritional support resources, if appropriate
- Importance of including a nutritionist in medical care

Mental health

- Stress reduction
- Rest and exercise to enhance a healthy mental state

Adherence

- Importance of keeping medical appointments
- Need for adhering to any medication regimen and the consequences of missed HIV medication doses
- Return appointment

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Initial and Interim Laboratory and Other Tests

Background

This chapter provides guidelines for monitoring patients with HIV infection.

Note that documentation of a confirmed HIV serologic test should be included in the chart.

O: Objective

Monitor patients with laboratory testing for HIV, hepatitis, sexually transmitted diseases, and other opportunistic infections (Table 1).

Table 1. Initial Laboratory Evaluations for HIV-Infected Patients

Test	Rationale	Result	Frequency and Comments
HIV Staging and Antiretroviral Therapy (ART) Monitoring			
CD4 Count	• For HIV staging and prognosis • Guides initiation of ART • Indicates risk of opportunistic illnesses and guides initiation of prophylaxis against opportunistic infections • Used to monitor immune reconstitution during ART	• Reported in cells/µL	• Repeat every 3-4 months for patients not taking ART. • Repeat every 2-4 months for patients taking ART. • Repeat if results are inconsistent with the clinical picture or with previous trends. • See chapter *CD4 Monitoring and Viral Load Testing.*
CD4 Count Percentage	• Used in addition to the absolute CD4 count for monitoring trends; may be discrepant from absolute CD4 • PCP prophylaxis is indicated for CD4% <14 regardless of absolute count (see below).	**CD4 count** / **Expected CD4%** >500 / >29% 200-500 / 14-28% <200 / <14%	• Usually obtained with absolute CD4 count
Quantitative Plasma HIV RNA (HIV Viral Load)	• Estimates level of HIV replication • Monitors effect of ART • Diagnoses acute HIV infection (Not FDA approved for diagnosis of HIV, but has high sensitivity in setting of acute infection. Must be confirmed by positive HIV antibody test.)	• Reported in copies/mL. • In untreated patients, detectable (with rare exceptions) and measured to the upper limit of detection (usually >500,000 copies/mL). • In patients taking ART, ideally suppressed to undetectable levels (usually <50 or ≤75 copies/mL).	• Baseline. values (2 tests) • For patients on new or modified ART regimen: perform 2-8 weeks after initiation or change in ART. • For patients on stable ART: perform every 3-4 months. • For patients not taking ART: perform every 3-4 months; more frequently if CD4 count is low. *Factors that may temporarily alter viral load:* • Immunizations • Active infections
Drug Resistance Testing (Genotype, Phenotype)	• To assess antiretroviral medications to which the patient's HIV virus is likely to be resistant	• Genotype: detects specific mutations to ARV medications • Phenotype: measures HIV viral replication in the presence of ARVs	• Genotype (one time) is recommended in all ARV-naive patients. For greatest accuracy, should be done as early as possible in the course of HIV infection. • Acute or primary infection: recommended • Chronic infection and treatment naive: recommended before initiation of ART. • Pregnancy: recommended before initiation of ART or in those with detectable HIV RNA during ART. • Virologic failure: recommended (See chapter *Resistance Testing* for additional information.)

Complete Blood Count (CBC) **with Differential and Platelets**	• Detects anemia, thrombocytopenia, leukopenia	• Normal	• Repeat every 3-6 months.
		• Abnormal	• Requires follow-up evaluation as indicated; may influence choice of ARVs. • Repeat more frequently if the patient's results are abnormal or he/she is taking bone marrow suppressive drugs.
Chemistry Profile (Electrolytes, Creatinine, Blood Urea Nitrogen, Liver Transaminases)	• Detects electrolyte abnormalities, renal insufficiency, hepatic enzyme elevations	• Normal/abnormal	• Repeat every 3-6 months, and as needed to monitor ART. • May influence ARV selection. • May be useful to monitor drug toxicities. • Abnormalities should prompt evaluation of cause.
Lipid Profile (Total Cholesterol, LDL, HDL, Triglycerides) **Glucose** (preferably fasting)	• Baseline before starting ART • Monitoring during ART	• Normal	• Repeat annually or more frequently (every 3-6 months) based on initial results, ARV use, or risk of cardiovascular disease.
		• Abnormal	• For interventions, see chapter *Dyslipidemia*.
Hepatitis Screening			
Hepatitis A Serology (HAV IgG)	• Screen for immunity to hepatitis A; vaccinate those not immune	• Negative	• Offer hepatitis A vaccine if indicated. (See chapter *Immunizations for HIV-Infected Adults and Adolescents.*)
		• Positive	• Immune; no vaccine necessary
Hepatitis B Serology	• Assess hepatitis B status		
Hepatitis B Surface Antigen (HBsAg)	• Indicates active hepatitis B	• sAg negative	• Consider vaccination if HBsAb negative (not immune).
		• sAg positive	• Indicates chronic or acute hepatitis B infection; requires further evaluation (check HBV DNA)
Hepatitis B Core Antibody (Anti-HBc, IgG)	• Indicates past exposure or ongoing infection	• Anti-HBc negative	• The patient most likely has not been infected with hepatitis B; consider vaccination if HBsAb negative and HBsAg negative.
		• Anti-HBc positive	• The patient most likely has been infected with hepatitis B; this test alone does not distinguish past exposure from active infection. • In rare cases, may be falsely negative in some with chronic infection. • If sAb negative and sAg negative, check HBV DNA to rule out active infection. • If sAb is positive, patient is immune.
Hepatitis B Surface Antibody (Anti-HBs)	• Indicates immunity status	• Anti-HBs negative	• The patient is not immune to hepatitis B; consider vaccination, unless patient has active hepatitis (sAg positive or HCV DNA positive).
		• Anti-HBs positive	• The patient is immune to hepatitis B either by previous infection or by immunization; may be negative in acute hepatitis B infection.

Hepatitis C Serology			
Anti-HCV Antibody (HCV Ab)	• Hepatitis C status	• HCV negative	• Patient is not infected with hepatitis C. • Consider annual screening in high-risk patients.
		• HCV positive	• Patient has chronic hepatitis C infection or past infection with immunity; confirm positive results with HCV RNA.
Other Opportunistic Infection Screening Tests			
***Toxoplasma gondii* IgG**	• Detects exposure; if positive, increased risk of developing CNS toxoplasmosis if CD4 count <100 cells/µL	• Normal/negative	• Repeat if patient becomes symptomatic or when CD4 count drops to ≤100 cells/µL.
		• Abnormal/positive	• Note as baseline information. • Start toxoplasmosis prophylaxis when CD4 count drops to ≤100 cells/µL.
PPD (tuberculin skin test) (if no history of TB or positive PPD)	• Detects latent TB infection	• Normal	• Repeat every 6-12 months. • Repeat if CD4 count was <200 cells/µL on initial test but increases to >200 cells/µL.
		• Abnormal (induration ≥5 mm)	• Evaluate for active TB. (See chapter *Latent Tuberculosis.*)
Chest X-Ray (if pulmonary symptoms are present or positive PPD)	• Detects latent or active diseases	• Normal	• Repeat as indicated for pulmonary symptoms or positive PPD.
		• Abnormal	• Evaluate for TB, PCP, or other pathology.
Papanicolaou Smear (cervical for women; anal for women and men)	• Detects abnormal cell changes, dysplasia	• Normal	• Repeat in 6 months; then annually if negative on 2 smears and no ongoing risk factors.
		• Abnormal	• Perform workup, treat (see chapters *Cervical Dysplasia* and *Anal Dysplasia*) and follow up more frequently as indicated by condition.
STD Testing: Identify sexually transmitted infections in any patient at risk.			
Venereal Disease Research Laboratory (VDRL); **or Rapid Plasma Reagin** (RPR)	• Syphilis screening	• Negative titer	• Repeat every 3-12 months, depending on risk factors.
		• Positive titer: confirm with treponemal test	• Treat patient; refer partner(s) of previous 60 days for evaluation and treatment; counsel about safer sex. • Perform serial testing if monitoring active disease. (See chapter *Syphilis*.)

Women			
Gonorrhea, Chlamydia, and Trichomoniasis Testing	• STD screening in sexually active women at risk	• Negative	• Counsel about safer sex and avoiding STDs. • Repeat every 6-12 months; more frequently if at high risk.
		• Positive	• Treat patient; refer partner(s) of previous 60 days for evaluation and treatment; counsel about safer sex.
Gonorrhea and Chlamydia Testing, Rectal	• STD screening in sexually active women at risk • STD screening in sexually active women who have receptive anal sex	• Negative	• Counsel about safer sex and avoiding STDs. • Repeat every 6-12 months; more frequently if at high risk.
		• Positive	• Treat patient; refer partner(s) of previous 60 days for evaluation and treatment; counsel about safer sex.
Men			
Gonorrhea and Chlamydia Testing, Urethral	• STD screening in sexually active men who are at risk, especially men who have sex with men (MSM)	• Negative	• Retest every 3-6 months in patients with risk factors.
		• Positive	• Treat; refer partner(s) of previous 60 days for evaluation and treatment; counsel about safer sex.
Gonorrhea and Chlamydia Testing, Pharyngeal	• STD screening in sexually active men who are at risk, especially MSM who have oral-genital contact	• Negative	• Retest every 3-6 months in patients with risk factors.
		• Positive	• Treat; refer partner(s) of previous 60 days for evaluation and treatment; counsel about safer sex.
Gonorrhea and Chlamydia Testing, Rectal	• STD screening in sexually active men who are at risk, especially MSM who have receptive anal sex	• Negative	• Retest every 3-6 months in patients with risk factors.
		• Positive	• Treat; refer partner(s) of previous 60 days for evaluation and treatment; counsel about safer sex.
Consider/Optional			
G6PD Level	• Prevent hemolytic reactions by screening susceptible men of African, Mediterranean, Asian, Sephardic Jewish descent • Some would recommend screening all patients	• Normal range	• No intervention is necessary beyond documentation.
		• Abnormal range	• Avoid oxidant drugs such as dapsone, primaquine, and sulfonamides, if possible.
Cytomegalovirus (CMV) **Antibody** (anti-CMV IgG) for those at low risk of CMV, especially those who are not MSM or injection drug users	• Detects exposure; may reveal future disease risk	• Negative	• Avoid exposure by practicing safer sex. • If blood transfusion is required, use CMV-negative or leukocyte-reduced blood.
		• Positive	• Be aware of disease risk in advanced HIV infection, when CD4 count <50 cells/µL.
Prostate Specific Antigen (PSA)	• Prostate cancer screen (African American men over 45; other men over 50 with >10-year life expectancy)	• Normal	• Repeat annually.
		• Abnormal	• Refer to urology specialist for evaluation.
Urinanalysis (UA)	• Detects proteinuria or pyuria	• Normal	• Repeat annually.
		• Abnormal	• Rule out HIV-associated nephropathy and other causes of nephropathy.
Dilated Retinal Examination	• Detects CMV, ophthalmic toxoplasmosis, or HIV retinopathy	• Normal	• CD4 count >100 cells/µL: repeat annually. • CD4 count <50 cells/µL or symptoms of retinal changes: repeat every 6 months.
		• Abnormal	• Follow up immediately with ophthalmologist.

Patient Education

- Discuss safer sex (review specifics appropriate to the patient's sexual practices and infections) to prevent the patient's exposure to herpes, hepatitis B, hepatitis C, and other sexually transmitted diseases, and to prevent the patient from exposing others to HIV or other pathogens. (See chapters *Preventing Transmission/Prevention with Positives* and *Preventing Exposure to Opportunistic and Other Infections.*)
- If toxoplasma IgG test result is negative, see chapter *Preventing Exposure to Opportunistic and Other Infections*.
- If cytomegalovirus (CMV) test result is negative, counsel the patient that CMV is shed in semen, vaginal and cervical secretions, saliva, and urine of infected people. Latex condoms will help reduce risk. For women considering childbearing, CMV should be avoided assiduously to prevent severe disease and even death of the neonate. (See chapter *Preventing Exposure to Opportunistic and Other Infections.*)
- For people who are hepatitis C negative and still use injection drugs, offer referral to a drug treatment program. (See chapters *Preventing Transmission/Prevention with Positives* and *Preventing Exposure to Opportunistic and Other Infections.*)

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Interim History and Physical Examination

Background

This chapter suggests information to gather and document for a standard written record of clinically important data over many visits. With this information, the clinician can track disease progression and formulate and maintain an appropriate care plan.

It is important to document new or ongoing symptoms and functional limitations at each visit. This information is particularly useful when outside agencies must determine the patient's disability status. (See chapter *Karnofsky Performance Scale*.)

Table 1 lists the suggested frequency and follow-up intervals of the history and physical examination for monitoring HIV-infected patients. Note that specific medications and abnormalities may call for additional directed examinations.

Table 1. History and Physical Examination: Frequency and Follow-Up Intervals

History				Physical Examination	
Every visit (at least every 3 months)					

• New symptoms
• Medications
  • HIV-related medications
  • Medications for other conditions
  • Over-the-counter medications
  • Herbs or vitamins
	• Adherence to medications and clinical care visits
	• Risk reduction; prevention with positives
		• Mood
		• Alcohol and recreational drug use
		• Tobacco use
		• Allergies
		• Pain
			• Social supports
			• Housing
			• Insurance
			• Domestic violence
				• Vital signs (temperature, blood pressure, heart rate, respiratory rate)
				• Weight
				• General appearance, body habitus (including evaluation for lipodystrophy)
				• Skin
					• Oropharynx
					• Lymph nodes
					• Heart and lungs
					• Abdomen
					• Psychiatric–mood, affect
					• Neurologic

Every 6 months					
As above	**As above plus:** • Visual and funduscopic exam	• Ears/nose	• Screening for chlamydia, gonorrhea, and syphilis in all patients at risk for these infections		
Every 6 months (twice) , and, if both are normal, annually thereafter (See chapters *Cervical Dysplasia* and *Anal Dysplasia*.)					
As above	• Women: cervical and anal Papanicolaou smear, pelvic exam			• Men: anal Papanicolaou smear	
Annually					
Update initial history: HIV-related symptoms, hospitalizations, major illnesses, family history				Complete physical to include: • Genitorectal exam • Prostate exam	• Breast exam • Testicular exam

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HIV Classification: CDC and WHO Staging Systems

Background

HIV disease staging and classification systems are critical tools for tracking and monitoring the HIV epidemic and for providing clinicians and patients with important information about HIV disease stage and clinical management. Two major classification systems currently are in use: the U.S. Centers for Disease Control and Prevention (CDC) classification system and the World Health Organization (WHO) Clinical Staging and Disease Classification System.

The CDC disease staging system (last revised in 1993) assesses the severity of HIV disease by CD4 cell counts and by the presence of specific HIV-related conditions. The definition of AIDS includes all HIV-infected individuals with CD4 counts of <200 cells/μL (or CD4 percentage <14%) as well as those with certain HIV-related conditions and symptoms. Although the fine points of the classification system rarely are used in the routine clinical management of HIV-infected patients, a working knowledge of the staging criteria (in particular the definition of AIDS) is useful in patient care. In addition, the CDC system is used in clinical and epidemiologic research.

In contrast to the CDC system, the WHO Clinical Staging and Disease Classification System (revised in 2005) can be used readily in resource-constrained settings without access to CD4 cell count measurements or other diagnostic and laboratory testing methods. The WHO system classifies HIV disease on the basis of clinical manifestations that can be recognized and treated by clinicians in diverse settings, including resource-constrained settings, and by clinicians with varying levels of HIV expertise and training.

S: Subjective

When a patient presents with a diagnosis of HIV infection, review the patient's history to elicit and document any HIV-related illnesses or symptoms (see chapter *Initial History*).

O: Objective

Perform a complete physical examination and appropriate laboratory studies (see chapters *Initial Physical Examination* and *Initial and Interim Laboratory and Other Tests*).

A: Assessment

Confirm HIV infection and perform staging.

P: Plan

Evaluate symptoms, history, physical examination results, and laboratory results, and make a staging classification according to the CDC or WHO criteria (see below).

CDC Classification System for HIV Infection

The CDC categorization of HIV/AIDS is based on the lowest documented CD4 cell count (Table 1) and on previously diagnosed HIV-related conditions (Tables 2 and 3). For example, if a patient had a condition that once met the criteria for Category B but now is asymptomatic, the patient would remain in Category B. Additionally, categorization is based on specific conditions, as indicated below. Patients in categories A3, B3, and C1-C3 are considered to have AIDS.

Table 1. CDC Classification System for HIV-Infected Adults and Adolescents

CD4 Cell Categories	Clinical Categories		
	A Asymptomatic, Acute HIV, or PGL	B Symptomatic Conditions,#* not A or C	C AIDS-Indicator Conditions*
(1) ≥500 cells/µL	A1	B1	C1
(2) 200-499 cells/µL	A2	B2	C2
(3) <200 cells/µL	A3	B3	C3

Key to abbreviations: CDC = U.S. Centers for Disease Control and Prevention; PGL = persistent generalized lymphadenopathy.

For symptomatic conditions, see Table 2.

* For AIDS-indicator conditions, see Table 3.

Table 2. CDC Classification System: Category B Symptomatic Conditions

Category B symptomatic conditions are defined as symptomatic conditions occurring in an HIV-infected adolescent or adult that meet at least 1 of the following criteria:

a) They are attributed to HIV infection or indicate a defect in cell-mediated immunity.

b) They are considered to have a clinical course or management that is complicated by HIV infection.

Examples include, but are not limited to, the following:

- Bacillary angiomatosis
- Oropharyngeal candidiasis (thrush)
- Vulvovaginal candidiasis, persistent or resistant
- Pelvic inflammatory disease (PID)
- Cervical dysplasia (moderate or severe)/cervical carcinoma in situ
- Hairy leukoplakia, oral
- Idiopathic thrombocytopenic purpura
- Constitutional symptoms, such as fever (>38.5° C) or diarrhea lasting >1 month
- Peripheral neuropathy
- Herpes zoster (shingles), involving ≥2 episodes or ≥1 dermatome

Table 3. CDC Classification System: Category C AIDS-Indicator Conditions

- Bacterial pneumonia, recurrent (≥2 episodes in 12 months)
- Candidiasis of the bronchi, trachea, or lungs
- Candidiasis, esophageal
- Cervical carcinoma, invasive, confirmed by biopsy
- Coccidioidomycosis, disseminated or extrapulmonary
- Cryptococcosis, extrapulmonary
- Cryptosporidiosis, chronic intestinal (>1-month duration)
- Cytomegalovirus disease (other than liver, spleen, or nodes)
- Encephalopathy, HIV-related
- Herpes simplex: chronic ulcers (>1-month duration), or bronchitis, pneumonitis, or esophagitis
- Histoplasmosis, disseminated or extrapulmonary
- Isosporiasis, chronic intestinal (>1-month duration)
- Kaposi sarcoma
- Lymphoma, Burkitt, immunoblastic, or primary central nervous system
- *Mycobacterium avium* complex (MAC) or *M kansasii*, disseminated or extrapulmonary
- *Mycobacterium tuberculosis*, pulmonary or extrapulmonary
- Mycobacterium, other species or unidentified species, disseminated or extrapulmonary
- *Pneumocystis jiroveci* (formerly *carinii*) pneumonia (PCP)
- Progressive multifocal leukoencephalopathy (PML)
- Salmonella septicemia, recurrent (nontyphoid)
- Toxoplasmosis of brain
- Wasting syndrome due to HIV (involuntary weight loss >10% of baseline body weight) associated with either chronic diarrhea (≥2 loose stools per day ≥1 month) or chronic weakness and documented fever ≥1 month

WHO Clinical Staging of HIV/AIDS and Case Definition

The clinical staging and case definition of HIV for resource-constrained settings were developed by the WHO in 1990 and revised in 2005. Staging is based on clinical findings that guide the diagnosis, evaluation, and management of HIV/AIDS, and does not require a CD4 cell count. This staging system is used in many countries to determine eligibility for antiretroviral therapy. Clinical stages are categorized as 1 through 4, progressing from primary HIV infection to advanced HIV/AIDS (Table 4). These stages are defined by specific clinical conditions or symptoms. For the purpose of the WHO staging system, adolescents and adults are defined as individuals aged ≥15 years.

Table 4. WHO Clinical Staging of HIV/AIDS for Adults and Adolescents (Interim Definitions)

Primary HIV Infection		
• Asymptomatic	• Acute retroviral syndrome	
Clinical Stage 1		
• Asymptomatic	• Persistent generalized lymphadenopathy	
Clinical Stage 2		
• Moderate unexplained weight loss (<10% of presumed or measured body weight) • Recurrent respiratory infections (respiratory tract infections, upper respiratory infections, sinusitis, bronchitis, otitis media, pharyngitis) • Herpes zoster		• Minor mucocutaneous manifestations (angular cheilitis, recurrent oral ulcerations, seborrheic dermatitis, prurigo, papular pruritic eruptions, fungal fingernail infections)
Clinical Stage 3		
Conditions for which a presumptive diagnosis can be made on the basis of clinical signs or simple investigations		
• Severe weight loss (>10% of presumed or measured body weight) • Unexplained chronic diarrhea for >1 month • Unexplained persistent fever for >1 month (intermittent or constant) • Oral candidiasis (thrush) • Oral hairy leukoplakia • Pulmonary tuberculosis within the last 2 years		• Severe presumed bacterial infections (eg, pneumonia, empyema, pyomyositis, bone or joint infection, meningitis, bacteremia) • Acute necrotizing ulcerative stomatitis, gingivitis or periodontitis
Conditions for which confirmatory diagnostic testing is necessary		
• Unexplained anemia (hemoglobin <8 g/dL) • Neutropenia (neutrophils <500 cells/µL)		• Thrombocytopenia (platelets <50,000 cells/µL)
Clinical Stage 4		
Conditions for which a presumptive diagnosis can be made on the basis of clinical signs or simple investigations		
• HIV wasting syndrome, as defined by the CDC (see Table 3, above) • *Pneumocystis jiroveci* (formerly *carinii*) pneumonia • Recurrent severe or radiologic bacterial pneumonia • Chronic herpes simplex infection (oral or genital, or anorectal site) for >1 month		• Esophageal candidiasis • Extrapulmonary tuberculosis • Kaposi sarcoma • Central nervous system toxoplasmosis • HIV encephalopathy
Conditions for which a confirmatory diagnostic testing is necessary		
• Cryptococcosis, extrapulmonary • Disseminated nontuberculosis Mycobacteria infection • Progressive multifocal leukoencephalopathy • Candida of the trachea, bronchi, or lungs	• Cryptosporidiosis • Isosporiasis • Visceral herpes simplex infection, cytomegalovirus infection (retinitis or organ other than liver, spleen, or lymph node)	• Any disseminated mycosis (eg, histoplasmosis, coccidioidomycosis, penicilliosis) • Recurrent nontyphoidal salmonella septicemia • Lymphoma (cerebral or B-cell non-Hodgkin) • Invasive cervical carcinoma • Visceral leishmaniasis

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Determining Risk of HIV Progression

Background

The absolute CD4 cell count and CD4 percentage are used for disease staging, and to determine when to start antiretroviral therapy (ART) and prophylaxis against opportunistic infections. The HIV RNA level (viral load), when used in conjunction with the CD4 count, also provides prognostic information in patients who are naive to ART.

Data from various cohort studies have demonstrated the strong relationship between lower CD4 count or higher viral load and the risk of progression to AIDS. Tables 1 and 2 and Figure 1 below show the risk of disease progression and death in patients who have not been treated with ART and in patients starting ART in several North American, European, and Australian cohorts. The data consistently indicate the importance of initiating ART before the CD4 count declines to <200 cells/µL, if possible.

Table 1. Relationship between CD4 Count or Viral Load and AIDS Progression

CD4 Count (cells/µL)	Viral Load (copies/mL)	AIDS Progression in Men (%)	
		Over 3 Years	Over 9 Years
<200	<10,000	14%	64%
	10,000-30,000	50%	90%
	>30,000	86%	100%
200-350	<10,000	7%	66%
	10,000-30,000	36%	85%
	>30,000	64%	93%
>350	<10,000	7%	54%
	10,000-30,000	15%	74%
	>30,000	40%	85%

Adapted from: Mellors JW, Rinaldo CR Jr, Gupta P, et al. Prognosis in HIV-1 infection predicted by the quantity of virus in plasma. Science. 1996 May 24;272(5265):1167-70.

Figure 1. Prognosis according to CD4 Cell Count and Viral Load in the Pre-HAART and HAART Eras

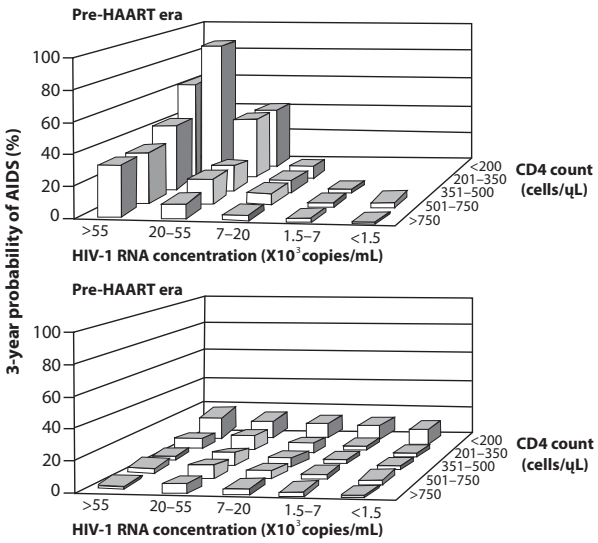

Figure shows Kaplan-Meier estimates of the probability of AIDS at 3 years.
HAART = highly active antiretroviral therapy

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Table 2. Predicted 6-Month Risk of AIDS according to Age and Current CD4 Cell Count and Viral Load, Based on a Poisson Regression Model

	Predicted Risk (%) at Current CD4 Cell Count (x 10^6 cells/L)*									
Viral Load (copies/ml)	50	100	150	200	250	300	350	400	450	500
Age 25 years										
3,000	6.8	3.7	2.3	1.6	1.1	0.8	0.6	0.5	0.4	0.3
10,000	9.6	5.3	3.4	2.3	1.6	1.2	0.9	0.7	0.5	0.4
30,000	13.3	7.4	4.7	3.2	2.2	1.6	1.2	0.9	0.7	0.6
100,000	18.6	10.6	6.7	4.6	3.2	2.4	1.8	1.4	1.1	0.8
300,000	25.1	14.5	9.3	6.3	4.5	3.3	2.5	1.9	1.5	1.2
Age 35 years										
3,000	8.5	4.7	3.0	2.0	1.4	1.0	0.8	0.6	0.5	0.4
10,000	12.1	6.7	4.3	2.9	2.0	1.5	1.1	0.9	0.7	0.5
30,000	16.6	9.3	5.9	4.0	2.8	2.1	1.6	1.2	0.9	0.7
100,000	23.1	13.2	8.5	5.8	4.1	3.0	2.3	1.7	1.3	1.1
300,000	30.8	18	11.7	8.0	5.7	4.2	3.1	2.4	1.9	1.5
Age 45 years										
3,000	10.7	5.9	3.7	2.5	1.8	1.3	1.0	0.7	0.6	0.5
10,000	15.1	8.5	5.4	3.6	2.6	1.9	1.4	1.1	0.8	0.7
30,000	20.6	11.7	7.5	5.1	3.6	2.6	2.0	1.5	1.2	0.9
100,000	28.4	16.5	10.6	7.3	5.2	3.8	2.9	2.2	1.7	1.3
300,000	37.4	22.4	14.6	10.1	7.2	5.3	4.0	3.1	2.4	1.9
Age 55 years										
3,000	13.4	7.5	4.7	3.2	2.3	1.7	1.2	0.9	0.7	0.6
10,000	18.8	10.7	6.8	4.6	3.3	2.4	1.8	1.4	1.1	0.8
30,000	25.4	14.6	9.4	6.4	4.6	3.3	2.5	1.9	1.5	1.2
100,000	34.6	20.5	13.3	9.2	6.5	4.8	3.6	2.8	2.2	1.7
300,000	44.8	27.5	18.2	12.6	9.1	6.7	5.0	3.9	3.0	2.4

* Shading distinguishes risk: <2%, no shading; 2-9.9%, light gray; 10-19.9%, mid-gray; >20%, darkest gray.

Reprinted with permission from Lippincott, Williams & Wilkins [Phillips A; CASCADE Collaboration. Short-term risk of AIDS according to current CD4 cell count and viral load in antiretroviral drug-naive individuals and those treated in the monotherapy era. AIDS 2004; 18 (1):51-8]. Lippincott, Williams & Wilkins online: http://lww.com

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CD4 Monitoring and Viral Load Testing

Background

CD4 Monitoring

CD4 cells (also called T cells or T-helper cells) are the primary targets of the HIV virus. The CD4 count is the number of CD4 cells per microliter (μL) of blood. It is the standard test for assessing HIV stage and prognosis, and for monitoring progression to AIDS and risk of opportunistic illnesses. It also guides the provider in formulating differential diagnoses in symptomatic patients (see Table 1, below), deciding about initiating antiretroviral treatment (ART), and beginning prophylaxis for opportunistic infections.

Most laboratories report the CD4 count as part of a list of several types of lymphocytes, as both an absolute count and a relative percentage. The important numbers are the absolute number of CD4 cells per microliter and the CD4 cell percentage, which is the proportion of CD4 cells as a subset of all lymphocytes.

The CD4 count typically declines over time as HIV infection progresses. Many other factors may affect CD4 counts more transiently, including illness, vaccination, diurnal variation, laboratory error, and inter-laboratory differences (see "Patient Education" below). Because fluctuations in the absolute CD4 count are likely, definitive conclusions should rarely be drawn from a single CD4 value. When results are inconsistent with previous trends, tests should be repeated, and treatment decisions usually should be based on 2 or more similar values. The CD4 percentage sometimes is used in coordination with the absolute value to assess the significance of changes in the absolute CD4 count. The absolute CD4 count can fluctuate as overall lymphocyte counts vary, but the CD4 percentage often remains stable during insignificant CD4 fluctuations. CD8 cell (or cytotoxic T cell) counts do not appear to predict clinical outcomes.

As untreated HIV infection progresses, the CD4 count declines by approximately 4% per year. In response to successful ART, the CD4 count typically increases by >50 cells/μL within weeks after viral suppression, and then increases by 50-100 cells/μL per year thereafter until a threshold is reached. In some patients, CD4 counts may not increase this quickly or steadily, even with durable viral load suppression.

The CD4 count is one of many factors (including clinical status, viral load status, and medication adherence) that should be assessed before starting or changing ART. The U.S. Department of Health and Human Services has provided recommendations for starting therapy based on symptoms, CD4 count, and viral load (Table 2). (See chapters *Antiretroviral Therapy* and *Adherence*.) Prophylaxis against opportunistic infections also is based on CD4 count, and sometimes on CD4 percentage. For example, a CD4 count of <200 cells/μL or a CD4 percentage of <14% is an indication for prophylaxis against *Pneumocystis jiroveci* pneumonia; a CD4 count of <50 cells/μL is an indication for prophylaxis against *Mycobacterium avium* complex. (See chapter *Opportunistic Infection Prophylaxis*.)

For monitoring purposes, the CD4 count should be repeated approximately every 3-4 months both in stable untreated patients and in patients on stable ART. The CD4 count should be checked more frequently according to the clinical situation (Table 3).

Viral Load Testing

In untreated HIV infection, replication usually produces billions of new viral copies daily. Plasma HIV RNA (viral load) testing quantifies the HIV viral burden in the plasma. In areas of the world with access to viral load monitoring, the viral load is a standard tool used to monitor treatment response in patients taking ART and, in conjunction with the CD4 cell count, to assess HIV progression. In certain settings in which HIV antibody tests may be negative or misleading, such as in acute HIV infection or neonatal infection, the HIV viral load may be used to help diagnose HIV infection. In some situations, the viral load may factor into decisions to initiate or change ART.

Viral load assays include HIV RNA polymerase chain reaction (Amplicor HIV-1 Monitor; Roche Laboratories), the branched chain DNA (Versant HIV-1 RNA assay; Bayer), and nucleic acid sequence-based amplification (NucliSens HIV-1 QT test; bioMerieux). The lowest level of detection differs for each test. Ultrasensitive assays (which are preferred in most circumstances) measure viral loads to 50-80

copies/mL, depending on the specific test, whereas the older assays usually have a cut-off at <400 copies/mL. A viral load below the level of detection ("undetectable") indicates inability of the assay to detect HIV in the plasma, but does NOT indicate absence or clearance of the virus from the body. Suppressing HIV RNA to an undetectable level (<50-75 copies/mL as measured by the ultrasensitive assay) is an important goal of ART. These assays also have different values for the highest levels of detection, ranging between 500,000 copies/mL and 750,000 copies/mL. Viral loads higher than these levels are reported, for example, as >500,000 copies/mL.

Whereas the absolute CD4 cell count is more predictive of clinical disease progression than is the baseline viral load, studies have shown that patients who have high plasma viral loads have an increased risk of progression to symptomatic disease and AIDS compared with patients who have low or undetectable levels. Patients with acute HIV infection who are undergoing seroconversion, and those with advanced disease, may have viral loads >500,000 copies/mL, whereas asymptomatic persons with chronic infection usually have considerably lower viral loads. Viral loads, like CD4 counts, are affected by laboratory variation, assay fluctuations, and patient variables such as acute illness and recent vaccinations. Variations less than approximately 0.5 $\log_{10}$ copies/mL (3-fold) usually are not clinically significant. Viral load results that are inconsistent with previous trends should be repeated, and treatment decisions usually should be based on 2 or more similar values. If patients have had recent illnesses or vaccinations, viral load measurement should be deferred for 4 weeks, if possible.

Viral load should be checked at least twice at baseline, before starting an ART regimen. Follow-up viral load measurement should be performed at regular intervals, depending on the patient's clinical situation (Table 3). In the stable patient, viral load should be monitored every 3-4 months. With new therapy or changes in therapy, significant change in viral load or CD4 count, or declining clinical status, the viral load should be measured at closer intervals.

S: Subjective

A patient presents with HIV infection.

O: Objective

Complete the initial or interim physical examination according to the protocol. (See chapters *Initial Physical Examination* and *Interim History and Physical Examination*.)

A: Assessment

See chapters *Initial History, Initial Physical Examination*, and *Initial and Interim Laboratory and Other Tests*.

P: Plan

Laboratory

- Obtain a CD4 count and perform viral load testing. See chapter *Initial and Interim Laboratory and Other Tests* for other recommended laboratory work.
- Monitor the results and manage patients using the schematic in Table 2 as a guide. See chapter *Antiretroviral Therapy* for more specific information.

Table 1. Correlation between CD4 Cell Counts and Complications of HIV Infection

CD4 Count* (cells/µL)	Infectious Complications	Noninfectious Complications#
>500	• Acute retroviral syndrome • Candidal vaginitis	• Persistent generalized lymphadenopathy (PGL) • Guillain-Barré syndrome • Myopathy • Aseptic meningitis
200-500	• Pneumococcal and other bacterial pneumonias • Pulmonary tuberculosis • Herpes zoster • Oropharyngeal candidiasis (thrush) • Cryptosporidiosis (self-limited) • Kaposi sarcoma (cutaneous) • Oral hairy leukoplakia • Herpes simplex (oral/genital)	• Cervical intraepithelial neoplasia • Cervical cancer • B-cell lymphoma • Anemia • Mononeuronal multiplex • Idiopathic thrombocytopenic purpura • Hodgkin lymphoma • Lymphocytic interstitial pneumonitis • Fatigue
<200	• *Pneumocystis jiroveci* pneumonia (PCP) • Disseminated histoplasmosis and coccidioidomycosis • Miliary/extrapulmonary tuberculosis • Progressive multifocal leukoencephalopathy (PML)	• Wasting • Peripheral neuropathy • HIV-associated dementia • Cardiomyopathy • Vacuolar myelopathy • Progressive polyradiculopathy • Non-Hodgkin lymphoma
<100	• Disseminated herpes simplex virus • Toxoplasmosis • Cryptococcosis • Cryptosporidiosis, chronic • Microsporidiosis • Candidal esophagitis • Kaposi sarcoma (visceral/pulmonary)	
<50	• Disseminated cytomegalovirus (CMV) • Disseminated *Mycobacterium avium* complex (MAC)	• Central nervous system (CNS) lymphoma

* Most complications occur with increasing frequency at lower CD4 cell counts.

\# Some conditions listed as "noninfectious" are probably associated with transmissible microbes. Examples include lymphoma (Epstein-Barr virus) and cervical cancer (human papillomavirus).
Adapted from Bartlett JG, Gallant JE. Medical Management of HIV Infection. Baltimore: Johns Hopkins University School of Medicine; 2005-2006. Used with permission.

Table 2. DHHS Guidelines for Initiating Antiretroviral Therapy in Chronically Infected Adults

Clinical Category	CD4 Count (cells/µL)	Plasma HIV Viral Load (copies/mL)	Antiretroviral Therapy Recommendations	Repeat CD4 and HIV Viral Load Test
Asymptomatic	>350	<100,000	Defer therapy	Every 3-4 months if not on ART (see below if on ART)
Asymptomatic	>350	≥100,000	Most clinicians recommend deferring therapy, some may treat	Every 3-4 months until ART is started, then check for viral load response at 2-8 weeks; monitor CD4 and viral load every 3-4 months if satisfactory response
Asymptomatic	≥200 but ≤350	Any value	Treatment should be offered	As above
Asymptomatic, AIDS	<200	Any value	Treat	As above
AIDS-defining illness or severe symptoms	Any value	Any value	Treat	As above

Adapted from U.S. Department of Health and Human Services. Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents. May 4, 2006..

Table 3. Indications for CD4 Count and Plasma HIV RNA (Viral Load) Testing

Clinical Indication	Test and Information Provided	Use
Syndrome consistent with acute or primary HIV infection	HIV viral load: establishes diagnosis when HIV antibody test is negative or indeterminate	Diagnosis (should be confirmed by standard HIV antibody test 2-4 months after initial test)
Initial evaluation of newly diagnosed HIV infection	Baseline CD4 and viral load values; disease staging	Decision to start or defer ART*
Every 3-4 months in patients not on therapy	CD4 cell count and viral load; disease monitoring	Decision to start or defer ART*
2-8 weeks after initiation of or change in ART	CD4 count and viral load: Initial assessment of drug regimen efficacy	Decision to start or defer ART*
3-4 months after starting ART	CD4 count and viral load: Assess treatment efficacy; viral load should be undetectable by 16-24 weeks; CD4 cell count likely to continue to increase	Decision to start or defer ART*
Every 3-4 months in patients on ART	CD4 count and viral load: Assess durability of immunologic response (CD4 increase) and virologic suppression (undetectable viral load)	Decision to start or defer ART*
Clinical event, or significant decline in CD4 cells or increase in viral load	CD4 count and viral load: Check for association of clinical events with changing or stable CD4 cell count and/or plasma HIV viral load; confirm changes in CD4 and viral load	Decision to initiate, continue, or change therapy*

* Decisions to initiate or change antiretroviral therapy (ART) should be based on 2 or more similar CD4 and viral load values.
Adapted from U.S. Department of Health and Human Services. Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents. May 4, 2006.

Patient Education

- CD4 counts are the best indicator of how healthy the immune system is and whether a person is at risk of getting certain infections.
- CD4 counts are variable. Caution patients not to pin emotions and hopes to a single lab result.
- The HIV viral load is the best indicator of how active HIV is in the patient's body.
- Several ARVs may be used in combination to reduce the amount of virus in the body of someone with HIV. For each of these regimens, it is important to take each dose on time, every time. (See chapters on *Antiretroviral Therapy* and *Adherence* if the patient is getting ready to start ART.)
- ART directly affects the activity of HIV in the body and will lower the viral load. With less HIV present, the body is able to produce more CD4 cells and improve the immune system.
- An undetectable viral load does not mean HIV is cured or that the patient is not infectious to others. It means that virus cannot be detected in the blood, although it exists in other parts of the body.
- If the patient's CD4 count increases with successful ART, he or she may be protected from infections and other illnesses related to HIV.

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Primary HIV Infection

Background

Primary HIV infection refers to the very early stages of HIV infection, or the interval from initial infection to the time that antibody to HIV is detectable. During this stage of HIV infection, patients typically have symptoms of acute HIV seroconversion illness, very high HIV RNA levels of >100,000 copies/mL, and negative or indeterminate HIV antibody tests.

The diagnosis of patients with primary HIV infection is a clinical challenge. The symptoms of primary HIV are nonspecific, and although many patients seek medical care for symptoms of HIV seroconversion illness, the diagnosis commonly is missed at initial presentation. The difficulties involve recognizing the clinical presentation of acute HIV infection and testing patients appropriately. In HIV treatment clinics, clinicians generally do not see patients with primary HIV infection, unless they are referred with this diagnosis already established. In other health care settings, clinicians may not be familiar with the signs and symptoms of acute HIV infection and often do not consider this diagnosis.

After infection with HIV, it takes a median of 25 days before the HIV antibody test becomes positive; in some individuals, it may be several months before seroconversion. Individuals with known exposures to HIV, whether occupational or not, should be monitored closely beginning at about 3 weeks after exposure (routine monitoring at 6 weeks, 3 months, and 6 months after exposure to HIV is likely to result in delayed diagnosis of HIV infection). For information on postexposure prophylaxis, see chapters *Nonoccupational Postexposure Prophylaxis* and *Occupational Postexposure Prophylaxis*.

S: Subjective

More than three quarters of patients who become infected with HIV develop symptoms consistent with primary HIV infection. Symptoms typically appear a few days to a few weeks after exposure to HIV, and generally include several of the following:

- Fever
- Rash, often erythematous maculopapular
- Fatigue
- Pharyngitis
- Generalized lymphadenopathy
- Urticaria
- Myalgia/arthralgia
- Anorexia
- Mucocutaneous ulceration
- Headache, retroorbital pain
- Neurologic symptoms (eg, aseptic meningitis, radiculitis, myelitis)

This symptomatic phase usually persists for 2-4 weeks or less, although lymphadenopathy may last longer. These symptoms and signs are similar to those of many other illnesses, including other viral syndromes. To diagnose early HIV infection, clinicians must consider HIV in the differential diagnosis for at-risk patients with symptoms resembling flu or mononucleosis. A history of recent risk behaviors should be obtained from all patients who present with symptoms consistent with acute HIV infection.

O: Objective

During the symptomatic phase of HIV seroconversion, the HIV antibody test is likely to be negative or indeterminate. For patients who have symptoms consistent with seroconversion illness and a recent high-risk history for HIV exposure, an HIV RNA (viral load) test should be performed, in addition to the HIV antibody test, as part of the evaluation. Patients with negative antibody tests but high HIV viral loads (>100,000 copies/mL) can be considered to be infected with HIV, although the antibody test should be repeated later to confirm seroconversion. False-positive HIV viral loads have been reported in approximately 5% of patients who were tested after HIV exposures. A low viral load (<1,000 copies/mL) usually indicates a false-positive result at this stage, because viral loads typically run very high (ie, >100,000 copies/mL and often millions of copies/mL) in acute infection. Patients who have indeterminate HIV antibody test results, low HIV viral loads, and no clear HIV risk factors or symptoms of primary HIV infection should have repeat antibody testing in 4-6 weeks, without other interventions. For patients without significant risk factors, indeterminate results rarely indicate evolving seroconversion.

A: Assessment and Plan

Patients with primary HIV infection will need additional medical evaluation, baseline laboratory testing, and intensive support, counseling, and education about HIV infection. See chapters *Initial History, Initial Physical Examination,* and *Initial and Interim Laboratory and Other Tests* for detailed information on the initial evaluation of HIV-infected patients.

Laboratory

The initial laboratory work should include the following:

- The CD4 count and HIV viral load should be checked on 2 occasions within several weeks.
- A baseline HIV genotype test should be obtained for all patients with primary HIV infection, even those who do not choose to start antiretroviral treatment (ART). In some cities in the United States and Europe, up to 15-20% of individuals infected in recent years have acquired HIV virus strains with mutations that confer resistance to antiretroviral medications. These resistance mutations may be identified by early resistance testing, but later may not be detectable. (See chapter *Resistance Testing*.)
- The HIV antibody test should be repeated in 4-6 weeks to document the HIV status of patients who are presumed to have primary HIV infection.

Treatment

It is reasonable to consider starting combination ART in patients with acute HIV infection, because some limited evidence suggests that treatment initiated during primary HIV infection may preserve HIV-specific immune function that would otherwise be lost as the infection progresses. However, it is not yet clear whether initiating early treatment yields long-term immunologic, virologic, or clinical benefits. The potential advantages of ART for primary infection must be weighed against the possibility of short- and long-term toxicities, the possibility of developing drug resistance, and the adherence challenges associated with starting antiretrovirals quickly in newly diagnosed patients. These issues are complex, and consultation with an HIV expert or referral to a clinical trial is recommended.

For patients who choose to start therapy during primary HIV infection, the choice of agents and the monitoring of patients on treatment are similar to those in the treatment of chronic HIV infection (see chapter *Antiretroviral Therapy*). The initial goal of therapy in primary HIV infection is to suppress the HIV viral load to undetectable levels.

Clinical trials across the country currently are recruiting individuals to evaluate both the natural history of primary HIV infection and the possible benefits of treatment of acute HIV infection. Information on clinical studies of primary HIV may be obtained through the AIDS Clinical Trials Information Service (ACTIS) on its Web site at http://www.aidsinfo.nih.gov/clinicaltrials or by telephone at 800-HIV-0440. Issues concerning the possible treatment of primary HIV infection also are reviewed in the U.S. Department of Health and Human Services *Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents*.

Patient Education

Patients with primary HIV infection need support and counseling, as do all newly diagnosed patients. Intensive education about HIV infection, the course of disease, prognosis, and the risks and benefits of ART must be undertaken. Counseling about safer sex and drug injection techniques, as indicated, is especially important for these patients because they may have ongoing high-risk behaviors for HIV transmission and because they may be highly infectious during the primary infection period. (See chapter *Preventing HIV Transmission / Prevention with Positives* for more information about patient support and counseling in these areas.)

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Rapid HIV Testing

Background

It is estimated that as many as 300,000 individuals in the United States are unaware that they have HIV infection. It is also estimated that about 25% of these individuals account for approximately 55% of the 40,000 new infections occurring in the United States each year. Studies have shown that once individuals learn about their HIV infection, they substantially reduce their high-risk sexual behaviors. However, even when people are tested for HIV with standard HIV tests, many do not return to obtain the results. With rapid HIV testing, clients can receive their results during the same visit. A rapid test can allow referrals for urgent treatment, such as in pregnant women, as well as non urgent referrals to engage patients in medical care. Rapid testing also provides immediate information for making clinical decisions, such as whether to offer postexposure prophylaxis.

Clients and Settings for Rapid Testing

Rapid HIV testing is recommended for settings in which the availability of rapid HIV test results would influence medical care immediately, or HIV prevalence is high but clients are not likely to return for the results of HIV tests. These settings include labor and delivery settings (to allow intervention to reduce the risk of perinatal HIV transmission in women with undocumented or unknown HIV status) as well as hospital emergency departments, urgent care and acute care clinics, sexually transmitted disease clinics, drug treatment clinics, and clinical care or testing sites. Rapid HIV testing also is available or being implemented in employee health departments at many hospitals as part of evaluation for and provision of postexposure prophylaxis.

Rapid HIV Tests

The U.S. Food and Drug Administration has approved 4 rapid tests for use in the United States (Table 1). Federal regulations under the Clinical Laboratory Improvement Amendments (CLIA) program categorize tests as waived, moderate complexity, or high complexity. Two rapid tests are approved as CLIA-waived tests, meaning that they may be done at the point of care after appropriate staff training and with procedures in place to insure quality control. These tests use whole blood or oral fluid and require a few simple steps to perform. Other rapid tests are "non waived" tests and must be performed in laboratories. Results for rapid tests done at the point of care are available in less than 30 minutes; results for those done in a laboratory should be available within 1 hour.

Table 1. FDA-Approved Rapid HIV Antibody Screening Tests

Test	Specimen Type	CLIA Category	Sensitivity (95% CI*)	Specificity (95% CI)	Manufacturer	Approved for HIV-2 Detection
OraQuick Advance Rapid HIV-1/2 Antibody Test	Whole blood (finger stick or venipuncture)	Waived	99.6% (98.5-99.9)	100% (99.7-100)	OraSure Technologies www.orasure.com	Yes
	Oral fluid	Waived	99.3% (98.4-99.7)	99.8% (99.6-99.9)		
	Plasma	Moderate complexity	99.6% (98.9-99.8)	99.9% (99.6-99.9)		
Uni-Gold Recombigen HIV	Whole blood (finger stick or venipuncture)	Waived	100% (99.5-100)	99.7% (99.0-100)	Trinity Biotech www.unigoldhiv.com	No
	Serum/plasma	Moderate complexity	100% (99.5-100)	99.8% (99.3-100)		
Reveal G2	Serum	Moderate complexity	99.8% (99.2-100)	99.1% (98.8-99.4)	MedMira www.medmira.com	No
	Plasma		99.8% (99.0-100)	98.6% (98.4-98.8)		
MultiSpot HIV-1/HIV-2	Serum/plasma	Moderate complexity	100% (99.9-100)	99.9% (99.8-100)	BioRad Laboratories www.biorad.com	Yes, differentiates HIV-1 from HIV-2
	HIV-2		100% (99.7-100)			

Adapted from Health Research and Education Trust (HRET). FDA-Approved Rapid HIV Antibody Screening Tests, January 10, 2005. Prepared by Stanger K, Margolin F, Lampe M, et al. Available at: http://www.hret.org/hret/programs/hivtransmrpd.html. Accessed May 25, 2006.

Interpreting Rapid Test Results

All of the rapid tests are highly sensitive and specific. The negative predictive value of all rapid HIV tests is close to 100%. This means that a client who receives a negative rapid test result is almost assuredly not infected, barring recent exposures (sexual contact or needle sharing with an infected person within 3 months). A client with a history of recent HIV risk behaviors or possible exposures should repeat the HIV test in the near future because it may take up to 3 months for HIV antibodies to be detectable after infection with HIV.

The positive predictive value of a single positive rapid HIV test depends on the specificity of the test and the HIV prevalence in the community. Given the high specificity of the rapid tests (Table 1), this means that if the rapid test result is positive, the likelihood that a client is truly HIV infected depends on the local HIV prevalence. In a population with a high HIV prevalence, a positive rapid test result is likely to be a true positive, but in a population with a low HIV prevalence, that result may be a false positive. For this reason, every positive rapid HIV test is considered a preliminary result and must be confirmed by either Western blot or immunofluorescence assay (IFA).

Information for the Client

Counseling the Client before Testing

Many clients believe the following:

1) they must consent to HIV testing to receive any medical care; or
2) they have been tested while getting medical care, and, because no one informed them otherwise, they must be HIV negative.

Because these assumptions are false, it is important to offer rapid HIV testing as a health screening test, to educate clients about the test and to give them an opportunity to ask questions and to decline testing. The provider should reassure clients that the rapid HIV test is just as accurate as the standard HIV test. When possible, rapid testing should be made available during the current office visit so that clients do not face additional waiting time. The provider should emphasize that a second test is always done to confirm a positive rapid test.

Giving Reactive (Preliminary Positive) Rapid Test Results

Example of simple language to use outside labor and delivery settings

The following wording is suggested when the client's rapid test result is positive:

"Your preliminary test result was positive, but we won't know for sure if you are infected with HIV until we get the results from your confirmatory test. In the meantime, you should take precautions to avoid transmitting the virus. This means protecting sexual partners from possible exposure (using condoms, for example), not sharing injection drug needles or syringes, and so forth."

Emphasize the importance of a confirmatory test, arrange for the confirmatory test to be done as soon as possible, and schedule a return visit for the results.

Language to use in labor and delivery settings

The following wording is suggested when the client's rapid test result is positive:

"Your preliminary HIV screening result was positive. You may have HIV infection. It is important to start medication to reduce the risk of passing HIV to your baby while we wait for the second (or confirmatory) test result. It is important to delay breast feeding until we have the second test result."

Follow-Up for Results of Confirmatory Tests

Clinical sites that offer rapid HIV testing should have a protocol for conveying the results of confirmatory HIV tests to clients. Rapid testing sites should either provide this service in-house or have mechanisms in place for referring clients to community-based HIV services. For example, when women have preliminary positive results on tests done during labor and delivery, confirmatory test results may be sent to their obstetrician, but often may be sent to the local health department. These women should be given appointments specifically for receiving their confirmatory test results. Clinicians should be familiar with community resources for referring clients with positive rapid test results. All clients with confirmed positive HIV test results should be referred for HIV care; testing sites should establish reliable referral pathways to qualified HIV care providers.

Patient Education

In general settings and in situations not involving labor and delivery, patient education should include the following points:

- Rapid HIV testing is an important health screening. Learning that you have HIV infection early can improve your prognosis (can keep you well).
- Knowing that you have HIV infection can help you take precautions to keep from passing HIV to others.
- You can refuse an HIV test, and it will not affect the care you receive.
- The results from the rapid tests are available at the same visit, usually in less than 1 hour.
- If the rapid test is positive, a second, confirmatory test is always done to be sure the rapid test was accurate.
- The rapid test is very accurate—as accurate as the standard HIV test.
- It is important that you come back for the results of the confirmatory test.
- If the test is negative, you do not have HIV infection, but the test may not show recent infection.
- The test results are kept confidential. However, if the confirmatory test is positive, the law requires that the results be reported to the health department (although this may not be the case in certain states). There are places you can go for more information and for counseling, care, or treatment.

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Immunizations for HIV-Infected Adults and Adolescents

Background

Immunocompromised individuals are at higher risk for many types of infections compared with immunocompetent people. Although HIV-infected persons could benefit greatly from immunization against preventable infections, little specific research on the effectiveness of immunizations in this population has been completed. In general, vaccines have better efficacy in HIV-infected patients when immune function is relatively well preserved, notably when the CD4 count is >200 cells/μL. Persons with advanced immunodeficiency (see Table 1) may have an impaired humoral response, and may not respond to vaccines, or they may require supplemental doses to develop serologic evidence of protection. If possible, vaccines should be administered before the CD4 count decreases to <200 cells/μL.

Live vaccines generally should not be administered to those with HIV infection, particularly those with advanced immunodeficiency, unless the anticipated benefits of vaccination clearly outweigh possible risks.

Table 1 presents recommendations about vaccination for patients with HIV infection.

Table 1. Vaccine Recommendations

Vaccine Type	Recommendation
Pneumococcal (polysaccharide)	• Recommended for all; consider revaccination every 5 years. • If CD4 count is <200 cells/μL, may be less effective; revaccinate when CD4 count increases in response to ART.
Hepatitis A Virus (HAV)	• Recommended, for persons with chronic hepatitis C or hepatitis B, injection drug users, men who have sex with men, international travelers, and hemophiliacs. Consider for all, unless there is serologic evidence of previous disease. • 2 doses (0, 6-12 months)
Hepatitis B Virus (HBV)	• Recommended, unless there is evidence of immunity (HBV surface Ab+) or active hepatitis B infection (HBV surface Ag+, or HBV core Ab+ and evidence of HBV activity). • 3 doses (0, 1-2, 4-6 months)
Influenza (inactivated vaccine)	• Recommended (yearly) • Vaccination is most effective among persons with CD4 count >100 cells/μL and HIV RNA <30,000 copies/mL. • In patients with advanced disease and low CD4 count, inactivated vaccine may not produce protective antibodies. • Live, attenuated cold-adapted vaccine (LAIV, FluMist) is contraindicated in patients with HIV infection.
Tetanus-Diphtheria	• Recommended (booster is recommended every 10 years in adults; or, if injured, after 5 years)
Measles, Mumps, Rubella (MMR)	• Recommended if indicated (eg, if contact with measles is likely through travel or other exposures). For live vaccine, use caution in those with low CD4 counts. • Consider for all susceptible people who are not severely immunosuppressed.* • Contraindicated in severe immunosuppression.
Varicella Zoster (VZV)**	• Consider for asymptomatic patients with relatively high CD4 counts, if they have no history of chickenpox and no evidence of immunity or significant exposure. • Avoid in patients with advanced immunosuppression. • Avoid exposure to VZV, if possible. If someone without immunity to VZV is exposed to VZV, administer VZIG as soon as possible, at least within 96 hours.

Key to abbreviations: ART = antiretroviral therapy; Ab = antibody; Ag = antigen.

* HIV-infected persons with CD4 counts <200 cells/μL, history of an AIDS-defining illness, or clinical manifestations of symptomatic HIV are considered to have severe immunosuppression. Asymptomatic HIV-infected persons with CD4 counts of 200-500 cells/μL are considered to have limited immune deficits.

** HIV-negative susceptible household contacts (especially children) of HIV-infected susceptible patients should be vaccinated against VZV, so that they will not transmit VZV to the HIV-infected patient. HIV-infected susceptible patients should limit their contact with recently vaccinated children or adults for 12-14 days after vaccination.

Immunizations for HIV-Infected Patients Traveling to Developing Countries

Routine vaccinations should be reviewed and updated before travel. All patients traveling to other countries should be evaluated for both routine and destination-specific immunizations and prophylaxes. Killed and recombinant vaccines (eg, diphtheria-tetanus, rabies, hepatitis A, hepatitis B, Japanese encephalitis) should be used for HIV-infected persons just as they would be used for HIV-uninfected persons anticipating travel. For further information, see the Centers for Disease Control and Prevention (CDC) Web page at http://www.cdc.gov/travel/. Recommendations specific to HIV-infected travelers are located in "The Immunocompromised Traveler" under the section called "Special Needs Travelers." Select the "Traveler's Health" option for regional travel documents and information on outbreaks.

Decisions about immunization for the HIV-infected traveler should take into consideration the traveler's current CD4 count, history of an AIDS-defining illness, and clinical manifestations of symptomatic HIV. In the CDC recommendations, asymptomatic HIV-infected persons with CD4 counts of 200-500 cells/μL are considered to have limited immune deficits, whereas patients with CD4 counts >500 cells/μL are considered to have no immunologic compromise. For patients taking antiretroviral therapy, current CD4 counts rather than nadir counts should be used in deciding about immunizations.

The following should be noted about specific vaccinations:

- Inactivated (killed) enhanced potency-polio and typhoid vaccines should be given instead of the live, attenuated forms. In adults aged >18 years, vaccinate 8 weeks before travel to allow time for the initial 2 doses of polio vaccine.
- Measles or measles-mumps-rubella (MMR; omit if patient has evidence of immunity) should not be given to severely immunocompromised patients. Instead, immune globulin should be given to measles-susceptible, severely immunocompromised persons traveling to measles-endemic countries.
- Yellow fever vaccine is a live-virus vaccine with uncertain safety and efficacy for HIV-infected persons and should be avoided if possible. Travelers with asymptomatic HIV infection and relatively high CD4 counts who cannot avoid potential exposure to yellow fever should be offered the choice of vaccination. If travel to a zone with yellow fever is necessary and vaccination is not administered, patients should be advised about the risk of yellow fever, instructed about avoiding the bites of vector mosquitoes, and provided with a vaccination waiver letter.
- The influenza season in the southern hemisphere is April through September, but in the tropics influenza is a year-round infection. Immunocompromised patients should be protected according to influenza risk at the destination. HIV-infected patients should not be given live intranasal influenza vaccine.

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Nutrition

Background

Maintaining good nutritional status is important to support overall health and immune system function in people with HIV/AIDS. Many HIV-related conditions affect and are affected by the body's nutritional status. These include conditions related to HIV itself (eg, opportunistic infections and other illnesses), comorbid conditions, and adverse effects of therapies.

Inadequate nutrition in people with HIV infection may result from many factors-including conditions such as nausea, vomiting, or anorexia-that may prevent adequate intake of nutrients and medications; diarrheal infections that prevent absorption of nutrients and medications; systemic illnesses (including HIV itself) that create a catabolic state; and psychological conditions (such as depression) that impair patients' ability to nourish themselves. In addition, financial constraints may limit patients' access to nutritious food.

Evaluation and enhancement of patients' nutritional status may help correct or compensate for deficiencies (eg, in the case of weight loss or nutrient deficits), may be a key treatment modality for certain conditions (eg, dyslipidemia, hyperglycemia), and may help to maintain good health and immune function. This chapter focuses on the evaluation of patients with nutritional deficiencies, particularly weight loss, and simple strategies for maintaining good nutrition in individuals with barriers to maintaining adequate weight.

Ideally, HIV-infected individuals will receive the services of HIV-experienced nutrition specialists, who may contribute to the patient care team in the following ways:

- Conducting routine screening to identify and treat nutritional problems
- Preparing a tailored nutritional plan to optimize patients' nutritional status, immune status, and overall well-being
- Screening and developing interventions for growth problems in children
- Developing strategies to prevent loss of weight and lean body mass
- Adapting dietary recommendations to help reduce the risk of comorbid conditions such as diabetes and heart disease, or treating these complications
- Educating patients about how to modify their dietary habits to maximize the effectiveness of medical and pharmacologic treatments
- Tailoring nutritional recommendations to fit patients' lifestyles and financial resources
- Counseling patients to promote nutrition self-care using available resources
- Providing nutritional support to patients may help to do the following:
- Treat common problems associated with HIV disease and its treatment (eg, weight loss, wasting, fatigue, loss of appetite, adverse changes in taste, dental problems, gastrointestinal complaints)
- Treat chronic comorbid conditions (eg, cardiovascular disease, hypertension, diabetes, cirrhosis)
- Improve quality of life
- Enhance immune responses, slow disease progression, and prolong life

S: Subjective

History

Identify nutrition risk factors through interview, questionnaire, or both at the start of care. Update the history at least annually. The history should record nutrition-related signs, symptoms, and habits (Table 1); dietary habits (Table 2); and symptoms suggesting nutritional deficiencies (Table 3).

Table 1. Nutrition-Related Questions for Patient History

Signs, Symptoms, and Comorbid Conditions:

- Poor or sporadic appetite
- Early satiety
- Weight gain or loss
- Trouble chewing or swallowing
- Dental problems including poor dental hygiene
- Gastrointestinal complaints, including nausea, diarrhea, constipation, heartburn, gas
- Changes in body contours with fat gain in abdomen, back of neck, and breasts (lipodystrophy) and/or fat loss in extremities and face (lipoatrophy)
- Depression, stress
- Fatigue
- Chronic pain
- Other diseases affecting diet and nutrition

Medication-Related Factors:

- Medications, including over-the-counter and herbal products
- Medication side effects
- Difficulty coordinating meals with medicines
- Use of nutritional supplements

Social and Behavioral Factors:

- Frequent eating out
- Smoking
- Alcohol or substance abuse
- Erratic meal patterns
- Unbalanced diet (eg, high intake of low-nutrient foods; deficiency in key nutrients)
- Resources to ensure secure, continued food access
- Availability of food storage and preparation facilities
- Housing: stable, or homeless/marginally housed/in transition
- Nutrition literacy

To develop a specific dietary history, use the following questions.

Table 2. Questions for Dietary History

Usual Dietary Intake

- Frequency of intake of foods providing key nutrients (eg, dairy products, fortified or whole grains, fruits and vegetables, fluids, meat, eggs, beans) as well as those that perhaps should be limited (fast-food items, highly processed or salted products)
- Usual meal patterns (number of times per day, snacks) and whether meals are prepared and eaten at home or eaten at restaurants or fast-food establishments
- Specific information about nutritional supplements (eg, vitamins, minerals, herbs, protein), including contents, amounts, formulation (pills, powders, drinks), cost, and overlap among products

Factors That May Affect or Limit Intake

- Amount of money available for food, or participation in food assistance programs (eg, food stamps, food pantries)
- Appetite, general well-being (eg, fatigue, pain, depression)
- Food allergies, intolerances
- Problems with dentition, swallowing, heartburn, diarrhea, constipation
- Coordination of foods and supplements with medications (HIV or other)

Elicit symptoms that may be related to nutritional deficiencies.

Table 3. Symptoms with Possible Relationship to Nutritional Deficiencies

- General symptoms (eg, fatigue, decreased cognitive function, headache)
- Behaviorial changes (eg, irritability, apathy, decreased responsiveness, anxiety, attention deficit)
- Body habitus changes (eg, loss or gain of fat)
- Gastrointestinal symptoms (eg, diarrhea, constipation, bloating)
- Changes in skin, nails, hair (eg, dryness, breaking, thinning)
- Muscle loss
- Neurologic symptoms (eg, weakness, sensory changes, gait abnormalities)

O: Objective

Physical Examination

Perform a careful physical examination, if possible with anthropometric and body composition testing as described below (Table 4). Compare current findings with past assessments and review at least every 6 months.

The physical examination should include the following:

- Vital signs, with orthostatic vital signs if dehydration is suspected
- Weight (compare with previous values) and body mass index (BMI)
- General appearance and gross nutritional status (eg, obesity, cachexia, wasting)
- Body habitus: loss of subcutaneous fat in face, buttocks, arms and legs and/or increase fat in abdomen, breasts, back of neck, and upper back ("buffalo hump")
- Muscle mass
- Mouth: breakdown in oral mucosa, cheilosis, angular stomatitis, glossitis, papillar atrophy
- Abdomen: hepatomegaly (due to fatty infiltration)
- Skin: dryness, peeling, breakdown, pallor, hypopigmentation or hyperpigmentation
- Nails: pale nail beds, fissures or ridges
- Neurologic system, including strength, sensation, coordination, gait, deep tendon reflexes

Anthropometric and body composition tests are usually performed by registered dietitians. They can provide important information about patients' nutritional status.

Table 4. Anthropometric Measurements for Adults and Children

	Height	Weight	Assessment for Changes over Time
Adults	Measure at baseline (self-report is not accurate).	Measure at least quarterly and consider intervention when small changes are observed. Do not wait until major amounts of weight have been lost or gained. Record sequentially at the front of the patient's chart and monitor for trends.	Use healthy, premorbid weight to assess change, not the first clinic weight or the ideal weight. (Use the patient's weight at a time when she or he is healthy, feels well, and can easily maintain that weight.)#*
Children	Measure at least quarterly using length board (0-2 years) or wall-mounted stadiometer (≥2 years).	Measure at least quarterly and consider intervention when small changes are observed. Do not wait until the patient has dropped significantly on the growth chart. Calculate age and plot the measurements on growth charts specific for age, sex, and country.*	Assessment of optimal growth is based on the observed pattern over time. General goals include a weight relatively "matched" for length or height (about the same percentile) and relative stability of percentile tracking over time.

* BMI (body mass index) is useful as an evaluative index. BMI can be calculated using the following formula: weight in pounds/(height in inches x height in inches) x 703; normal BMI = 19-25. See also the Centers for Disease Control and Prevention's (CDC) Division of Nutrition and Physical Activity, National Center for Chronic Disease Prevention and Health Promotion online calculators for BMI in adults, children, and teens. Available at: http://www.cdc.gov/nccdphp/dnpa/bmi/index.htm.

Growth charts for children in the United States are available online from the CDC at http://www.cdc.gov/growthcharts. A variety of growth charts are also available for children from specific ethnic groups (eg, Chinese, Vietnamese, Thai), children with selected conditions affecting growth (eg, Down syndrome), or those who are born prematurely. Percentiles for both height and weight should be recorded sequentially.

Body Composition Testing

Body composition is commonly tested by bioelectrical impedance analysis (Table 5) or skinfold thickness and cirumference (Table 6).

Table 5. Bioelectrical Impedance Analysis

Bioelectrical impedance analysis (BIA) testing is the standard of care for adults but has not been well validated for children:
• BIA is useful for assessing disease progression or health maintenance, documenting response to treatment, and justifying the cost of nutritional supplements and AIDS-wasting medications.
• The test is simple, noninvasive, and quick (<5 minutes). However, staff training and specialized software are required to interpret the results.
• Perform BIA at baseline. Update every 6-12 months, or more frequently if the patient is ill, has a decline in immune status, or has a weight change of 5-10%.
• The BIA test reports the following:
  ◦ Body cell mass (BCM): the target component, reflecting cells in muscles, organs, and the circulation; losses may indicate AIDS wasting. BCM is recorded in pounds. Monitor for trends.
  ◦ Fat: an index of energy stores; recorded in pounds and percentage.
  ◦ Phase angle: a measure of cellular integrity, an independent indicator of morbidity and mortality in HIV-infected patients.

For a good BIA "primer", see also: AIDS Project Los Angeles. "Bioelectrical Impedance Analysis: Glossary of Terms". 2002. Available online at http://www.apla.org/programs/nutrition.html. Accessed June 1, 2006.

Table 6. Skinfold Thickness and Circumference Measures
Skinfold thickness and circumference measures can be used for adults and children in resource-limited settings, and when bioelectrical impedance analysis is not available. Circumference measures also can also be used to monitor changes over time associated with lipodystrophy in adults. • Skinfold thicknesses are measured with calipers. • Circumference measures are taken at specific anatomical landmarks with nonstretchable tape. • Tables of age- and sex-specific reference values (percentiles) are available at: http://www.cdc.gov/nchs/products/pubs/pubd/series/ser.htm (select Series 11, #238 and go to pages 41-50).

See also: AIDS Project Los Angeles. "Anthropometric Procedures". 2002. Available online at www.apla.org/programs/nutrition.html. Accessed June 1, 2006. The Web site includes an overview on how to take basic measurements, including skinfold thickness and circumference, and where to locate equipment and reference tables.

Laboratory Testing

Perform basic laboratory (blood) tests, including the following:

- Hemoglobin or hematocrit
- Total protein, albumin
- Fasting glucose
- Lipids (fasting triglycerides, total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol)
- CD4 cell count and HIV viral load, if no recent values are available
- Specific vitamin and nutrient tests as indicated by symptoms (eg, iron studies in case of anemia, vitamin B12 in case of peripheral neuropathy)
- Others tests, such as testosterone and thyroid hormone levels as appropriate, to rule out other causes of symptoms

A: Assessment

Assess subjective information and objective findings to evaluate nutritional status.

Identify Nutrition Concerns

Several factors may influence nutrition:

- Barriers to good nutrition (eg, lack of knowledge or motivation for self-care, poor appetite, lack of money for food, lack of facilities for food storage and preparation)
- Lifestyle factors (eg, smoking, substance abuse, frequent eating out, erratic eating patterns, hectic schedule, high stress)
- Physical problems affecting food and nutrient intake (eg, poor appetite, nausea, fatigue, pain, weakness, mouth or throat pain, acid reflux, missing or decayed teeth, poorly fitting dentures, poor eyesight, constipation)

- Nutrient losses (eg, due to diarrhea, vomiting)
- Potential confounding factors (eg, use of multiple overlapping or questionable supplements)

Evaluate Dietary Intake

Assess the following diet-related issues:

- Expected excesses or deficiencies from dietary history or interview
- Rating of food security, including access to cooking and refrigeration
- Food intolerances, aversions, or allergies likely to affect adequacy of intake
- Special needs related to other conditions (eg, documented cardiovascular disease, diabetes, hypertension)

Evaluate Weight, Body Composition, and Weight Distribution

Assess physical findings of malnutrition and confirm with nutrition history, laboratory tests, and anthropometric evidence. Table 7 describes normal and abnormal findings of anthropometric tests and recommendations for monitoring changes over time.

Table 7. Evaluating the Findings of Anthropometric Tests

	Monitoring Trends and Recommendations

Adults	• Chart trends over time relative to previous measurements and the following population norms:
	• BMI (healthy range: 19-25)
	• BIA:
	  ◦ BCM (% of weight): women 30-35%; men: 40-45%
	  ◦ Fat (% of weight): women 20-30%; men 15-25%
	  ◦ Phase angle: women >5; men >6
	• Skinfold thicknesses and circumferences: Chart changes in absolute measures and percentiles
	• Changes in body contours: Evaluate lipodystrophy (excess accumulation of fat in abdomen, breasts, dorsocervical area) and lipoatrophy (loss of subcutaneous fat in face, extremities, buttocks)

Children	• Plot measurements on growth charts and track percentiles over time (the consistency of percentiles rather than the absolute percentile is important) • Skinfold thicknesses and circumferences: Chart changes in absolute measures and percentiles

Key to abbreviations: BMI = body mass index; BIA = bioelectrical impedance analysis; BCM = body cell mass.

Evaluate Laboratory Findings

- Evidence of malnutrition (eg, low iron or protein stores)
- Evidence of disease or risk of disease for which dietary treatment is indicated (eg, high fasting glucose, hypertension, hyperlipidemia)

Develop a Problem List

Table 8 suggests a useful format for a nutrition-related problem list.

Table 8. Nutrition-Related Problem List Format

Problem #	Description of Problem (circle/describe)
	Nutrition barriers: insufficient knowledge, poor appetite, food insecurity, no food preparation or storage facilities, homelessness
	Lifestyle: substance abuse, smoking, erratic eating, frequent fast-food intake, high stress
	Weight or body composition: undesirable weight gain or loss (adult), changes in growth trajectory (children), loss of lean body mass (wasting), gain of excess fat (obesity), lipoatrophy or lipodystrophy
	Physical problems: fatigue, pain, early satiety, poor dentition, clinical signs of malnutrition
	Laboratory findings: low hematocrit or hemoglobin, low protein or albumin, low or high fasting glucose, high total cholesterol, high low-density lipoprotein, high triglycerides, low high-density lipoprotein, low testosterone
	Gastrointestinal: diarrhea, vomiting, reflux, constipation
	Poor diet: poor food choices, bingeing, skipping meals, high sugar intake, high alcohol consumption, high intake of refined foods, low fruit and vegetable intake, insufficient protein, insufficient calcium, food allergies or intolerances limiting intake
	Comorbid conditions: diabetes, hypertension, cardiovascular disease, cancer, gastroesophageal reflux disease (GERD)
	Medications: drug-drug or drug-nutrient interactions or difficulty coordinating medicines with meals
	Supplements: insufficient or excessive intakes, cost of supplements unaffordable, supplements with potential or unknown risks

P: Plan

Develop a nutritional plan and provide practical nutrition education for common problems. Some useful online sources for patient handouts include:

- AIDS Project Los Angeles Nutrition Fact Sheets Available at http://www.apla.org/programs/nutrition.html.
- Health Resources and Services Administration, HIV/AIDS Bureau. Health Care and HIV: Nutritional Guide for Providers and Clients; 2nd ed. Online manual, also in Spanish. 2002. Available at http://www.aids-etc.org/aidsetc?page=et-30-20-01.
- Association of Nutrition Services Agencies Available at http://www.aidsnutrition.org.

Evaluate and treat concurrent medical problems (eg, diarrhea, nausea, infections, malignancies, depression). For severe or persistent nutritional problems, or for specific needs, refer to a nutrition specialist for evaluation and treatment.

Table 9 lists of common nutrition-related problems and some simple suggestions that may help resolve them and help patients maintain adequate nutrition.

Table 9. Practical Interventions for Common Nutrition-Related Problems

Problem	Suggestions	

Weight Loss (decrease in both body cell mass and fat)	• Early identification and ongoing monitoring are key.
	• Identify and treat underlying risk factors.
	• Try to add calories without adding "bulk":
	  ◦ Fat (9 calories/gram): butter, margarine, avocado, cream, mayonnaise, salad dressing
	  ◦ Carbohydrate (4 calories/gram): jam, jelly, sugar, icing, gum drops
	  ◦ Protein (4 calories/gram): protein powders, cheese, nut butters, trail mix, powdered breakfast drinks, nonfat dry milk
		• Eat more frequently.
		• Maximize good days.
		• Use canned supplements (eg, Ensure, Boost).
		• For wasting or substantial weight loss, consider referral for therapies such as appetite stimulants or human growth hormone.

Diarrhea	• Increase soluble fiber; decrease insoluble fiber. • Replenish beneficial bacteria (eg, with lactobacilli preparations). • Avoid intestinal irritants and stimulants. • Decrease dietary fat.	• Decrease or eliminate lactose. • Increase fluids and provide electrolytes (sodium, potassium). • Treat with pancreatic enzymes.
Early Fullness	• Take small, frequent meals. • Concentrate on solid foods, with liquids between meals. • Eat lower-fat, lower-fiber foods.	• Wear loose-fitting clothing. • Sit up while eating. • Eat, walk, and eat again.
Nausea	• Take small, frequent meals. • Try dry snack foods. • Avoid fried foods, very sweet foods, spicy foods, and foods with strong odors.	• Try cool, clear beverages, popsicles. • Try ginger-containing foods and drinks. • Keep liquids to a minimum at meals.
Changes in Taste	• Eat a variety of foods, not only favorite foods. • Try protein sources other than red meat. • Marinate foods, use sauces. • Use more and stronger seasonings.	• Try tart foods. • Use sugar or salt to tone down the flavor of foods. • Try a mouth rinse of 1 teaspoon of baking soda in 1 cup of warm water before eating.
Loss of Appetite	• Rely on favorite foods. • Ask family members and friends to prepare meals. • Eat small, frequent meals. • Keep snacks handy for nibbling. • Eat before bedtime.	• Eat in a pleasant place, with other people. • Make the most of good days. • Try light exercise to stimulate appetite. • Add extra calories without adding bulk. • Consider appetite stimulants (megestrol, stimulants).

Difficulty Chewing or Swallowing or Sore Mouth and Throat	• Choose soft, nutritious foods. • Blend or puree foods (eg, soup or stew, smoothies). • Add cream sauces, butter, or gravy for lubrication. • Sip liquids with foods. • Use a straw or drink foods from a cup.	• Choose bland, low-acid foods. • If hot foods cause pain, serve foods cold or at room temperature. • Avoid alcohol and tobacco. • Soothing lozenges or sprays may help.
Food Insecurity	• Refer to social services for assistance with accessing resources such as food stamps, community meals, or a food pantry program.	• Refer to a dietitian for assistance with low-cost food ideas. • Use materials at http://www.cheapcooking.com/index.htm
Unbalanced Diet and/or Other Conditions Requiring Dietary Modification	• Refer to a dietitian for counseling and education.	• Use materials at http://www.mypyramid.gov to assist with general counseling about dietary adequacy, balance, and portion size.

Nutrition Specialists

Whenever possible, nutritional services should be provided by a registered dietitian (RD) who is a qualified HIV care provider. In the United States, holding this status requires a nutrition degree from an accredited college, graduation from an approved internship or master's degree program, and maintenance with 75 continuing-education units every 5 years, including specific and ongoing HIV training. An RD with HIV/AIDS expertise in the United States can be located by going to http://www.eatright.org, clicking on "Find a Nutrition Professional," entering the patient's zip code or city, and selecting "HIV/AIDS" under areas of specialty. Membership in the HIV/AIDS Dietetic Practice Group (http://www.hivaidsdpg.org) also may indicate HIV experience.

Resources

The following online resources were referenced in this chapter:

- 2000 CDC Growth Charts: United States. CDC, National Health and Nutrition Examination Survey. http://www.cdc.gov/growthcharts/.
- Anthropometric Reference Data and Prevalence of Overweight: United States, 1976-80. Najjar, M. F., Rowland, M. October 1987. 84 pp. PB91-213033. PC A05 MF A01. CDC, National Center for Health Statistics. National Health Survey, Series 11, No. 238. Tables 31-41. http://www.cdc.gov/nchs/products/pubs/pubd/series/sr11/240-221/240-221.htm.
- Body Mass Index Home. CDC, Division of Nutrition and Physical Activity, National Center for Chronic Disease Prevention and Health Promotion. Online calculators for calculating BMI in adults, children, and teens. http://www.cdc.gov/nccdphp/dnpa/bmi/index.htm.
- CheapCooking.com. Web site with recipes using low-cost ingredients and tips for frugal meal planning. http://www.cheapcooking.com.
- HIV/AIDS Dietetic Practice Group. Affiliate of the American Dietetic Association. Web site includes screening tool, Nutrition Screen and Referral Criteria for Adults (18+ Years) with HIV/AIDS. http://www.hivaidsdpg.org.
- MyPyramid.gov. U.S. Department of Agriculture Web site with dietary guidelines, tips, resources, and consumer-oriented information.http://www.mypyramid.gov.

References

- AIDS Project Los Angeles. *APLA Nutrition Fact Sheets.* Los Angeles: APLA; 2005. Available online at http://www.apla.org/programs/nutrition.html. Accessed June 1, 2006.
- Association of Nutrition Services Agencies. *ANSA Nutrition Guidelines and Fact Sheets.* (Select "Resources", then "ANSA Publications"). Accessed June 1, 2006.
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Nonoccupational Postexposure Prophylaxis

Background

Although avoiding exposure to HIV is the only reliable way of preventing HIV infection, postexposure prophylaxis (PEP) can decrease the risk of infection after exposure to HIV. Antiretroviral (ARV) therapy is an important prophylactic intervention in appropriate persons with nonoccupational exposures (eg, sexual contact; sharing of injection drug needles or other equipment), as well as those with occupational exposures (eg, needlesticks). The U.S. Department of Health and Human Services has established guidelines for nonoccupational PEP (nPEP) based on data from animal models, perinatal clinical trials, and observational studies.

Overall, the data suggest that nPEP is more likely to be effective when the exposure is a single episode and nPEP is initiated in a timely manner. It is not appropriate for cases of multiple sexual exposures or injection drug use (IDU) exposures over time or for exposures that occurred more than 72 hours before starting nPEP treatment (Figure 1).

The model for nPEP is derived in part from protocols for occupational PEP (eg, in terms of risk stratification, pretreatment testing, timing of treatment, treatment regimens, and duration of treatment). However, the recommendations for PEP and nPEP are distinct from each other and should not be confused. The nPEP guidelines exclude exposures to workers in health care, public safety, sanitation, and laboratory settings. Guidelines for the management of these occupational exposures to HIV, hepatitis B virus (HBV), and hepatitis C virus (HCV) are available at: http://www.aidsinfo.nih.gov.

S: Subjective

The patient reports potential exposure to HIV through a sexual encounter or the sharing of needles or other equipment for intravenous drug use.

Take a thorough history of the specific sexual or drug-use activities and the time the exposure occurred, the HIV status of the source person (if known), and HIV risk factors of the source person (if HIV status is not known). In cases of sexual assault, evidence collection and specific paperwork may be required as well.

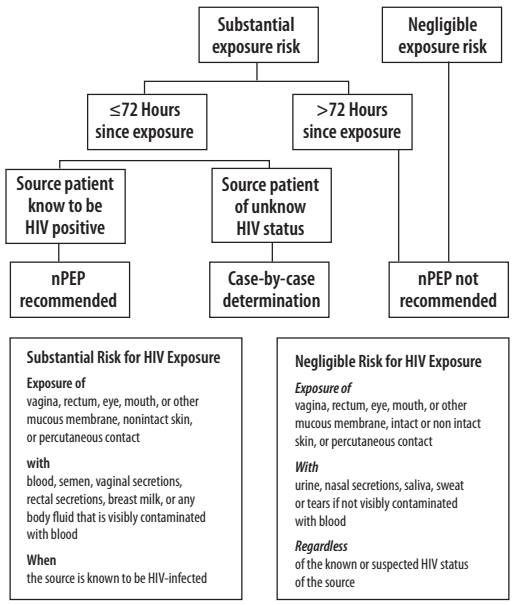
O: Objective

Examine for trauma and for signs or symptoms of sexually transmitted diseases (STDs), which may increase the risk of HIV transmission. In injection drug users, examine for abscesses and signs or symptoms of infection. For women who may be pregnant, perform a pregnancy test.

A: Assessment

Assess potential exposures to HIV, other STDs and bloodborne pathogens. The risk of HIV infection depends on the HIV status of the source and on the characteristics of the exposure. The estimated risk of HIV exposure will determine whether nPEP should be offered. Figure 1 presents an algorithm for risk evaluation and treatment decisions.

Figure 1. Algorithm for Evaluation and Treatment of Possible Nonoccupational HIV Exposures



Source: Antiretroviral Postexposure Prophylaxis After Sexual, Injection-Drug Use, or Other Nonoccupational Exposure to HIV in the United States, Recommendations from the U.S. Department of Health and Human Services. January 2005. See http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5402a1.htm#fig1 for original image.

P: Plan

Laboratory Testing

Provide pretest counseling and perform a baseline HIV antibody test. Evaluate and test for other infections transmitted through sexual or IDU exposures, including chlamydia, gonorrhea, syphilis, herpes simplex virus infection, hepatitis B (HBV surface antigen, surface antibody, core antibody), and hepatitis C (HCV antibody). Obtain complete blood count (CBC), liver function tests (LFTs), and chemistry panel at baseline before treatment with ARV medications.

Treatment

Follow the algorithm in Figure 1 to determine whether the patient should be offered nPEP medications. If the patient is a candidate for treatment, counsel him or her about the potential risks and benefits of nPEP. If the patient elects to start therapy, see Table 1 for potential regimens. Select a regimen that is likely to be effective but tolerable; consider the potential adverse effects of ARV agents. Note that certain ARV agents, including nevirapine, should not be used for PEP. Avoid efavirenz in pregnant women.

If the HIV status of the source person is unknown and the exposure is considered to be of relatively low risk, consider 2-drug nPEP (eg, zidovudine + lamivudine) to minimize toxicity. If the source person is known or suspected to have infection with HIV that is resistant to ARV medications, seek expert consultation in selecting an appropriate nPEP regimen.

Table 1. Antiretroviral Regimens for Nonoccupational Postexposure Prophylaxis of HIV Infection

Preferred Regimens	
NNRTI-based	Efavirenz*+ (lamivudine or emtricitabine) + (zidovudine or tenofovir)
PI-based	Lopinavir/ritonavir (co-formulated as Kaletra) + (lamivudine or emtricitabine) plus zidovudine
Alternative Regimens	
NNRTI-based	Efavirenz + (lamivudine or emtricitabine) + abacavir or didanosine or stavudine#
PI-based	Atazanavir + (lamivudine or emtricitabine) + (zidovudine or stavudine or abacavir or didanosine) or (tenofovir plus ritonavir [100 mg/day])
	Fosamprenavir + (lamivudine or emtricitabine) plus (zidovudine or stavudine) or (abacavir or tenofovir or didanosine)
	Fosamprenavir/ritonavir§ + (lamivudine or emtricitabine) + (zidovudine or stavudine or abacavir or tenofovir or didanosine)
	Indinavir/ritonavir§** + (lamivudine or emtricitabine) + (zidovudine or stavudine or abacavir or tenofovir or didanosine)
	Lopinavir/ritonavir (co-formulated as Kaletra) + (lamivudine or emtricitabine) + (stavudine or abacavir or tenofovir or didanosine)
	Nelfinavir plus (lamivudine or emtricitabine) + (zidovudine or stavudine or abacavir or tenofovir or didanosine)
	Saquinavir (hgc or sgc)/ritonavir§ + (lamivudine or emtricitabine) + (zidovudine or stavudine or abacavir or tenofovir or didanosine)
Triple NRTI	Abacavir plus lamivudine + zidovudine (only when an NNRTI- or PI-based regimen cannot or should not be used)

Key to abbreviations: NNRTI = non-nucleoside reverse transcriptase inhibitor; PI = protease inhibitor; hgc = saquinavir hard-gel capsule (Invirase); sgc = saquinavir soft-gel capsule (Fortovase); NRTI = nucleoside reverse transcriptase inhibitor.

† Efavirenz should be avoided in pregnant women and women of childbearing potential.

Stavudine may cause a higher incidence of lipoatrophy, hyperlipidemia, and mitochondrial toxicities than other NRTIs.

§ Low-dose (100-400 mg) ritonavir. See Table 4 from the Adult Antiretroviral Guidelines (cited below) for doses used with specific PIs.

** Use of ritonavir with indinavir might increase the risk of renal adverse events.

Source: U.S. Department of Health and Human Services. *Antiretroviral Postexposure Prophylaxis After Sexual, Injection-Drug Use, or Other Nonoccupational Exposure to HIV in the United States*. Table 2. MMWR Recomm Rep. 2005 Jan 21;54(RR02);1-20. Available online at http://aidsinfo.nih.gov/Guidelines/GuidelineDetail.aspx?GuidelineID=11.

Once the decision is made to institute nPEP, do the following:

- Begin ARV prophylaxis as soon as possible after the exposure, but always within 72 hours. Treatment should be continued for 28 days.
- Provide counseling about the efficacy of nPEP, including the importance of protection against future HIV exposures, timely initiation of nPEP medications, and adherence to these medications for 28 days. Continued counseling about HIV risk reduction may be appropriate. In cases of sexual assault, refer the patient to a rape counselor.

Follow-Up

Patients should be evaluated at 1 week for review of all test results and further risk reduction counseling. For patients taking nPEP, this follow-up should include adherence assessment and evaluation of any adverse effects. A 2-week blood screening (CBC, LFTs, and chemistry panel) should be done for patients on the 28-day nPEP regimen to monitor for nPEP toxicity. Follow-up testing for HIV antibody in patients with a negative baseline HIV antibody test should be done at 6 weeks, 3 months, and 6 months after the exposure. Some patients may also need health education counseling and emotional support during their follow-up visits. If patients develop acute HIV infection or are discovered to be HIV seropositive at follow-up testing, refer to an HIV specialist for evaluation and care (see chapter *Primary HIV Infection*).

Prophylaxis against HBV and HCV

Prophylaxis against HBV is recommended for patients with potential exposure to HBV who have not been vaccinated against HBV. Give HBV immune globulin (HBIG) as a 0.06 mL/kg intramuscular injection and initiate the vaccination series. For patients who received the vaccine series but did not develop protective antibody (HBV sAb+), give HBIG at the time of the postexposure workup and repeat in 1 month. For patients with immunity to HBV (HBV sAb+), no treatment is indicated.

For HCV, no recommended prophylactic treatments are available. After potential exposure, check a baseline HCV antibody test. If the source is known to have HCV infection, consider alanine aminotransferase (ALT) and HCV viral load testing at 4-6 weeks. HCV antibody testing should be repeated at 4-6 months. If HCV seroconversion occurs (indicated by ALT elevation, detectable HCV viral load, or confirmed positive HCV antibody test), refer the patient to a hepatologist because early treatment of acute HCV may be indicated.

Patient Education

- Patients should contact a medical provider or go to an emergency room as soon as possible after a potential HIV exposure has occurred. PEP may be effective if it is started within 72 hours of exposure, but the sooner medications are initiated, the better the chance for preventing HIV transmission.
- PEP medications should be taken as directed for the full 28 days. Adherence to PEP medications is essential for successful treatment.
- If patients are experiencing uncomfortable adverse effects, they should contact their providers. Providers may prescribe medications to alleviate the adverse effects or select other PEP medications.
- The most effective way to prevent HIV infection is to prevent exposure to HIV by practicing safer sex and safer IDU techniques. Using condoms and not sharing needles are successful preventive measures. It is crucial to the success of PEP treatment that patients not engage in risky sexual or needle-use behaviors. If patients have questions about access to condoms or clean needles, they should contact their health care providers for assistance.

References

- U.S. Department of Health and Human Services. *Antiretroviral Postexposure Prophylaxis After Sexual, Injection-Drug Use, or Other Nonoccupational Exposure to HIV in the United States.* MMWR Recomm Rep. 2005 Jan 21;54(RR02);1-20. Available online at http://aidsinfo.nih.gov/Guidelines/GuidelineDetail.aspx?GuidelineID=11. Accessed May 19, 2006
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Occupational Postexposure Prophylaxis

Background

Health care workers (HCWs) and other employees in medical, public safety, sanitation, and laboratory settings are at risk of occupational exposure to HIV. Although avoiding exposure to HIV is the only reliable way of preventing HIV infection, postexposure prophylaxis (PEP), defined as antiretroviral (ARV) therapy initiated soon after exposure to HIV, has been highly effective in preventing HIV infection in exposed HCWs.

This chapter examines the general issues involved with PEP in occupational settings. The information is based on the U.S. Public Health Service (USPHS) guidelines for PEP (see "References" below). For information on PEP for nonoccupational HIV exposures (such as sexual exposure), see chapter *Nonoccupational Postexposure Prophylaxis*. Note that other bloodborne pathogens, particularly hepatitis B virus (HBV) and hepatitis C virus (HCV), also may be transmitted through occupational exposure; it is important to consider these potential infections when assessing occupational exposures. For information on the management of occupational exposures to HBV and HCV, refer to the 2001 USPHS PEP guidelines on (see "References" below). In addition, the National Clinicians' Post-Exposure Prophylaxis Hotline (PEPline) is available 24 hours a day for telephone consultation at 888-HIV-4911 (888-448-4911).

The risk of HIV infection after exposure depends on several factors that are related to the exposure itself and to the source patient (see below). Before deciding whether to recommend PEP and what PEP regimen to recommend, the clinician must assess the risk of HIV infection from the particular exposure, as well as other factors such as the exposed worker's willingness and ability to take ARV medications. After this assessment, the clinician and the exposed worker must weigh the possible benefit of PEP (in relation to the risk of HIV transmission from the injury) against the potential toxicity of the regimen. HCWs who are pregnant at the time of their exposure also must weigh the risk of fetal exposure to HIV against the potential teratogenic and other risks of the ARV drugs. The efficacy of PEP is related to the specific PEP regimen, the timing of PEP, and the exposed worker's adherence to the PEP regimen. PEP should be initiated within 72 hours of the exposure, but is more likely to be effective when it is initiated within hours of the exposure. The optimal duration of PEP is not known; studies support treatment for 28 days.

In the work setting, HIV infection may occur through percutaneous injuries (eg, needlesticks) or mucocutaneous exposures (eg, mucous membrane or nonintact skin exposure to blood or other infectious body fluids). The risk of HIV seroconversion after occupational exposure is best described for needlestick injuries: 0.3%, on average after a needlestick with an HIV-contaminated hollow-bore needle. The risk varies depending on the specific incident. In general, exposures that involve prolonged contact with larger volumes of infectious body fluids, or higher HIV RNA levels in the blood or fluid, convey a higher risk of HIV transmission. In a retrospective case-control study of HCWs with percutaneous exposure to HIV, the following exposure and source patient factors were associated with an increased risk of HIV transmission:

- Large-gauge (<18-gauge) hollow-bore needle
- Deep injury
- Visible blood on the device
- Procedure with needle in a blood vessel
- Terminal AIDS in the source patient

Compared with percutaneous injury, mucocutaneous exposure of infectious body fluids to mucous membranes (eg, eye or mouth) or to skin with an obvious impairment of integrity (eg, abrasion or wound) typically involves a lower risk of HIV transmission. However, mucocutaneous exposures that involve large volumes of blood or other infectious fluid from an HIV-infected patient with a high HIV RNA level may be significant.

S: Subjective

The HCW reports possible exposure to HIV through a needlestick injury or mucocutaneous exposure.

Ideally, the HCW immediately decontaminated the injured or exposed skin with soap and water, or flushed

the exposed mucous membranes with copious amounts of water or saline. The HCW should report the exposure immediately to the appropriate authorities in his or her health care institution (eg, the institution's needlestick hotline).

Take a thorough history of the specific exposure, including the type of exposure, the type and amount of body fluid involved, the point of entry or exposure, the time it occurred, the HIV status of the source patient (if known), and HIV risk factors of the source patient (if HIV status is not known).

A: Assessment

Assess potential exposure to HIV (as well as HBV and HCV). The HIV status of the source and the characteristics of the exposure should be assessed to estimate the risk of HIV infection. The decision about whether to offer PEP should be based on the estimated risk of HIV exposure. See Table 1 (percutaneous exposures) and Table 2 (mucocutaneous exposures) for recommendations about PEP.

Table 1. Recommended HIV Postexposure Prophylaxis after Percutaneous Injuries

	Infection Status of Source*				
Exposure Type	**HIV Negative**	**HIV Positive (Class 1)**	**HIV Positive (Class 2)**	**Unknown HIV Status**	**Unknown Source**
Less Severe (eg, solid needle, superficial injury)	No PEP warranted	Recommend basic 2-drug PEP	Recommend expanded ≥3-drug PEP	Generally, no PEP warranted; however, consider basic 2-drug PEP for source with HIV risk factors*# §	Generally, no PEP warranted; however, consider basic 2-drug PEP if exposure to HIV-infected persons is likely
More Severe (eg, large-bore hollow needle, deep puncture, visible blood on device, needle used in patient's artery or vein)	No PEP warranted	Recommend expanded ≥3-drug PEP	Recommend expanded ≥3-drug PEP	Generally, no PEP warranted; however, consider basic 2-drug PEP for source with HIV risk factors	Generally, no PEP warranted; however, consider basic 2-drug PEP if exposure to HIV-infected persons is likely

* HIV positive (class 1): asymptomatic HIV infection or known low HIV RNA viral load (eg, <1,500 copies/mL); HIV positive (class 2): symptomatic HIV infection, AIDS, acute seroconversion, or known high viral load; unknown HIV status: for example, a deceased source person with no samples available for HIV testing; unknown source: for example, a needle from a sharps disposal container.

The recommendation "consider PEP" indicates that PEP is optional; a decision to initiate PEP should be based on a discussion between the exposed person and the clinician regarding the risks versus benefits of PEP.

§ If PEP is offered and administered, and the source is later determined to be HIV negative, PEP should be discontinued.

Adapted from: Centers for Disease Control and Prevention. *Updated U.S. Public Health Service Guidelines for the Management of Occupational Exposures to HIV and Recommendations for Postexposure Prophylaxis*. MMWR Recomm Rep. 2005 Sep 30; 54(RR09); 1-24. Available online at http://aidsinfo.nih.gov/Guidelines/GuidelineDetail.aspx?GuidelineID=10.

Table 2. Recommended HIV Postexposure Prophylaxis after Mucous Membrane Exposures and Nonintact Skin Exposures*

	Infection Status of Source#				
Exposure Type	**HIV Negative**	**HIV Positive (Class 1)**	**HIV Positive (Class 2)**	**Unknown HIV Status**	**Unknown Source**
Small Volume (eg, a few drops)	No PEP warranted	Consider basic 2-drug PEP §	Recommend basic 2-drug PEP	Generally, no PEP warranted	Generally, no PEP warranted
Large Volume (eg, a major blood splash)	No PEP warranted	Recommend basic 2-drug PEP	Recommend expanded ≥3-drug PEP	Generally, no PEP warranted; however, consider basic 2-drug PEP for source with HIV risk factors**	Generally, no PEP warranted; however, consider basic 2-drug PEP if exposure to HIV-infected persons is likely

* For skin exposures, follow-up is indicated only if evidence exists of compromised skin integrity (eg, dermatitis, abrasion, or open wound).

HIV positive (class 1): asymptomatic HIV infection or known low HIV RNA viral load (eg, <1,500 copies/mL); HIV positive (class 2): symptomatic HIV infection, AIDS, acute seroconversion, or known high viral load; unknown HIV status: for example, a deceased source person with no samples available for HIV testing; unknown source: for example, a needle from a sharps disposal container. .

§ The recommendation "consider PEP" indicates that PEP is optional; a decision to initiate PEP should be based on a discussion between the exposed person and the clinician regarding the risks versus benefits of PEP.

** If PEP is offered and administered, and the source is later determined to be HIV negative, PEP should be discontinued.

Adapted from: Centers for Disease Control and Prevention. *Updated U.S. Public Health Service Guidelines for the Management of Occupational Exposures to HIV and Recommendations for Postexposure Prophylaxis.* MMWR Recomm Rep. 2005 Sep 30; 54(RR09); 1-24. Available online at aidsinfo.nih.gov/Guidelines/GuidelineDetail.aspx?GuidelineID=10.

P: Plan

Laboratory Testing

Provide pretest counseling and perform a baseline HIV antibody test. Test for other infections transmitted through occupational exposure, particularly hepatitis B (HBV surface antigen, surface antibody, core antibody), and hepatitis C (HCV antibody). Obtain complete blood count (CBC), chemistry panel, and liver function tests (LFTs) at baseline, before treatment with ARV medications. For women who may be pregnant, perform a pregnancy test.

Treatment

Consult Table 1 or Table 2 to determine whether the worker should be offered PEP medications. For occupational exposures to infectious body fluids from an HIV-infected source patient, the USPHS guidelines state that PEP should be recommended or considered, depending on the assessed risk. The assessed risk also helps to determine whether a "basic" 2-drug regimen or "expanded" ≥3-drug regimen should be selected. Other considerations in choosing the medications for a PEP regimen include:

- The likelihood that the source patient's virus is resistant to ARV medication(s)
- Possible drug toxicities for the exposed HCW
- Drug-drug interactions with other medications the HCW may be taking

If the HCW is a candidate for PEP, counsel him or her about the potential risks and benefits of PEP. If the worker elects to start therapy, consider potential regimens (Table 3). Select a regimen that is likely to be effective but tolerable; consider the potential adverse effects of ARVs. Note that certain ARV agents, including nevirapine, should not be used for PEP. Efavirenz should be avoided in pregnant women.

Table 3. Antiretroviral Options for Occupational Postexposure Prophylaxis of HIV Infection

Basic 2-NRTI Regimens	
Preferred	
• Zidovudine 300 mg + lamivudine 150 mg twice daily (available as Combivir, 1 tablet twice daily) • Zidovudine 300 mg twice daily + emtricitabine 200 mg once daily	• Tenofovir 300 mg once daily + lamivudine 300 mg once daily • Tenofovir 300 mg once daily + emtricitabine 200 mg once daily (available as Truvada, 1 tablet once daily)
Expanded Regimens (one of the following may be added to a basic regimen)	
Protease Inhibitors	
Preferred	
• Lopinavir/ritonavir combination 400/100 mg twice daily	
Alternative	
• Atazanavir 300 mg once daily + ritonavir 100 mg once daily • Atazanavir 400 mg once daily*	• Fosamprenavir 1,400 mg twice daily • Fosamprenavir 700 mg twice daily + ritonavir 100 mg twice daily
NNRTI Regimen	
• Efavirenz 600 mg once daily (not recommended in pregnant women)	

Key to abbreviations: NRTI = nucleoside analogue reverse transcriptase inhibitor; NNRTI = nonnucleoside reverse transcriptase inhibitor.

* Atazanavir cannot be used as a sole protease inhibitor if it is coadministered with tenofovir (use atazanavir + ritonavir).

Adapted from: Centers for Disease Control and Prevention. *Updated U.S. Public Health Service Guidelines for the Management of Occupational Exposures to HIV and Recommendations for Postexposure Prophylaxis*. MMWR Recomm Rep. 2005 Sep 30; 54(RR09); 1-24. Available online at aidsinfo.nih.gov/Guidelines/GuidelineDetail.aspx?GuidelineID=10.

If the HIV status of the source patient is unknown, a rapid HIV test may help in determining the need for PEP (see chapter *Rapid Testing*). Although a positive rapid test requires confirmation before the individual is diagnosed as HIV infected, for the purposes of PEP, it should be considered a true positive until proven otherwise, and the exposed worker should be counseled accordingly. If, upon further testing, the source patient is determined to be HIV uninfected, PEP can be discontinued. A negative rapid test is considered reliable unless the source reports recent high-risk HIV exposure or symptoms of primary HIV (see chapter *Primary HIV Infection*). If a rapid test is not available, PEP is considered "generally not warranted" for exposures involving source patients whose HIV status is unknown. However, PEP can be considered if the source patient has risk factors for HIV infection. PEP should not be delayed (beyond 1-2 hours) while awaiting information about the source patient. PEP is not recommended for exposures to HIV-seronegative source patients.

If the source patient is known or suspected to have infection with HIV that is resistant to ARV medications, seek expert consultation in selecting an appropriate PEP regimen. However, PEP should not be delayed while consultation is obtained.

Additional alternative ARVs are included in the USPHS guidelines, but certain ARVs are not recommended for PEP, including abacavir, delavirdine, nevirapine, and the combination of didanosine + stavudine. Refer to the appendix in the updated USPHS guidelines for a more complete discussion of the dosing, advantages, and disadvantages of the various ARV agents available for PEP.

Begin ARV prophylaxis as soon as possible after the exposure, but always within 72 hours. Treatment should be continued for 28 days.

Provide counseling about the efficacy of PEP, including the importance of protection against future HIV exposures, timely initiation of PEP medications, and adherence to these medications for 28 days. Counsel exposed workers to use latex barriers with their sexual partners until HIV infection has been ruled out.

Follow-Up

Exposed workers should be evaluated at 1 week for review of all test results. For patients taking PEP, adherence assessment and evaluation of any side effects also should be included. At 2 weeks, blood testing (eg, CBC, LFTs) should be done for patients on a 28-day PEP regimen to monitor for PEP toxicity, as indicated by the particular ARV regimen. PEP is discontinued at 4 weeks, and generally no laboratory studies should be repeated unless there is a need to recheck an abnormal result. Follow-up HIV antibody testing should be done at 6 weeks, 3 months, and 6 months after the exposure. In addition to health-education counseling, some patients may need emotional support during their follow-up visits.

Symptoms of primary HIV infection such as fever, rash, and lymphadenopathy (see chapter *Primary HIV Infection*) may occur in HCWs who have been infected with HIV through occupational exposure. Every exposed HCW should be counseled about the symptoms of primary HIV infection and instructed to return for reevaluation as soon as possible if symptoms develop. If symptoms consistent with primary HIV appear within 4-6 weeks after an occupational exposure, the HCW should be evaluated immediately. If the worker is found to be infected with HIV, he or she should be referred immediately to an HIV specialist for further evaluation and care.

Expert Consultation

For consultation on the treatment of occupational exposures to HIV and other bloodborne pathogens, the clinician managing the exposed patient can call the National Clinicians' Post-Exposure Prophylaxis Hotline (PEPline) at 888-HIV-4911 (888-448-4911). This service is available 24 hours a day, at no charge (additional information on the Internet is available at http://www.ucsf.edu/hivcntr). PEPline support may be especially useful in challenging situations, such as when drug-resistant HIV strains are suspected or the HCW is pregnant.

Prophylaxis against HBV and HCV

Prophylaxis against hepatitis B is recommended for patients with potential exposure to HBV who have not been vaccinated against HBV. Give hepatitis B immune globulin (HBIG) as a 0.06-mL/kg intramuscular injection and initiate the vaccination series. For patients who received the vaccine series but did not develop protective antibody (HBV surface antibody positive), give HBIG at the time of the postexposure workup and repeat in 1 month. For patients with immunity to hepatitis B, no treatment is indicated.

For hepatitis C, no recommended prophylactic treatments are available. After potential exposure, conduct a baseline HCV antibody test. If the source is known to have HCV infection, consider alanine aminotransferase (ALT) and HCV viral load testing at 4-6 weeks. HCV antibody testing should be repeated at 4-6 months. If HCV seroconversion occurs (indicated by ALT elevation, detectable HCV viral load, or confirmed positive HCV antibody test), refer the patient to a hepatologist because early treatment of HCV may be indicated.

Addendum: Workplace Obligations

The health care institution has certain obligations to an exposed employee.* The institution should do the following:

- Evaluate the circumstances of the exposure, the type of fluid, and possible entry points.
- Evaluate the source patient.
- Perform baseline HIV antibody testing of the exposed worker, after appropriate pretest counseling.
- Counsel the exposed employee about the possible risks and benefits of PEP.
- Offer or recommend PEP as soon as possible after the exposure, preferably within the first several hours.
- Counsel the worker about avoiding secondary transmission to others (safer sex and other risk-reduction practices, as indicated).
- Support and maintain the confidentiality of the worker.
- For workers taking PEP, monitor for medication toxicity and adherence.
- Repeat HIV testing at 6 weeks, 3 months, and 6 months.
- Report the exposure as required by federal and state regulations (including Occupational Safety and Health Administration requirements).

* *Legal issues vary from state to state. In many states, institutions and clinics have no obligation toward students or non-employees who have HIV exposures in their settings. In such situations, clinical supervisors or school or university officials often are the first contact for notification. However, anyone working in a health care setting should be familiar with the procedures and financial responsibility for HIV exposure management to avoid delays in HIV PEP treatment.*

Patient Education

- Persons who have possible exposures to HIV in the work setting should contact the PEP service of their employer or a qualified medical provider as soon as possible after the exposure, or they should go to an emergency room. Although PEP may be effective if it is started within 72 hours of exposure, the sooner medications are initiated, the better the chance for preventing HIV transmission.
- PEP medications should be taken as directed for the full 28 days. Adherence to PEP medications is essential for successful teratment.
- PEP recipients should be advised to contact their providers if they experience uncomfortable side effects. Providers may prescribe medications to alleviate the side effects, or may prescribe different PEP medications.
- Until HIV infection has been ruled out, exposed workers should be advised to use latex barriers to prevent transmission of HIV to their sex partners.
- Exposed workers should be counseled about the symptoms of primary HIV infection and instructed to contact their care providers immediately if symptoms develop.

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Preventing HIV Transmission/Prevention with Positives

Background

Helping patients to reduce the risk of transmitting HIV to others is an important aspect of medical care for HIV-infected individuals. Most people with HIV infection want to prevent others from being infected with HIV, but they may practice sexual or injection drug behaviors that put others at risk of infection. Most HIV-infected patients also want to protect themselves from acquiring sexually transmitted infections. This chapter offers recommendations for discussing HIV transmission and prevention with HIV-infected patients, with the goal of reducing HIV transmission. This aspect of care is often referred to as "prevention with positives" (PWP).

Taking responsibility for preventing HIV transmission is an important concern for most people with HIV, as well as for their health care providers. In fact, many HIV-infected individuals report that they want to discuss prevention with their health care providers. It is clear that information alone, especially on subjects such as sexual activity and drug use, cannot be expected to change patients' behavior. However, health care providers can help patients understand the transmission risk of certain types of behavior and help patients establish personal prevention strategies (sometimes based on a harm-reduction approach) for themselves and their partners. Some patients may have difficulty adhering to their safer sex goals. In these cases, referrals to mental health clinicians or other professional resources such as prevention case management may be helpful.

Patient-education needs are variable and must be customized. Providers must assess the individual patient's current level of knowledge as part of developing a prevention plan. All the information that a patient needs cannot be covered during a single visit. A patient's prevention strategy should be reinforced and refined at each visit with the clinician. Clinicians also should ask patients questions to determine life changes (eg, a new relationship, a breakup, or loss of a job) that may affect the patient's sexual or substance use practices. If the patient can read well, printed material can be given to reinforce education in key areas, but it cannot replace a direct conversation with the clinician. Patient educators, nurses, peer counselors, social workers, and mental health providers also may be used to discuss prevention strategies with patients.

Sexual Transmission and Prevention of HIV

Begin the education process by learning what the patient and his or her immediate family (if the family is aware of the patient's HIV status) believe about HIV transmission. Also be sure the patient understands how the virus is *not* transmitted (eg, sharing plates and eating utensils or using the same bathrooms) to allay any unnecessary fear.

Advise the patient not to share toothbrushes, razors, douche equipment, or sex toys to avoid transmitting HIV via blood or sexual secretions. This also will help prevent the transmission of other bloodborne or sexually transmitted infections, including hepatitis C, from coinfected patients. The patient should not donate blood, plasma, tissue, organs, or semen because these can transmit HIV to the recipient.

There is no reason why a person with HIV cannot have an active, fulfilling, and intimate sex life. However, the patient must be counseled properly about the risk of transmission. This discussion between the provider and patient, should be client centered. This means that the provider should let the patient guide the discussion, starting from the patient's current point of knowledge and practice, always addressing any presenting concerns the patient may have prior to proceeding with a discussion about sexual transmission and risk. The provider should ask open-ended questions, in a nonjudgmental manner, to elicit information about the patient's relationships, sexual behaviors, and current means of reducing transmission risk.

It is important to recognize that not every patient seeks the complete elimination of risk (eg, via abstinence) but rather a reduction in risk, chosen after the options are discussed with the provider. The clinician may help the patient select and practice behaviors that are likely to

be less risky. There are many methods for reducing risk, including the following:

- Disclosing HIV status
- Reducing the number of sex partners
- Using condoms, particularly for anal or vaginal intercourse (insertive or receptive)
- Having sex only with other HIV-infected partners (serosorting)
- Avoiding drug use in conjunction with sex
- Using adequate lubrication to avoid trauma to genital or rectal mucosa
- Maintaining maximal suppression of HIV through antiretroviral therapy

If the patient requires more extensive counseling to support behavioral changes, the provider should refer the patient to support groups or prevention case management to meet those needs. Certainly, if the patient is dealing with a dual or triple diagnosis (including substance abuse or mental illness), a referral to address those needs also is indicated.

Several models of PWP are appropriate and realistic for the clinical setting, where prevention discussions must be conducted within severe time constraints. The Partnership for Health model developed by Jean Richardson and colleagues resulted in a 38% reduction in unprotected anal or vaginal sex among patients with multiple and casual partners after the implementation of "consequence frame messaging" in the context of a clinic-wide program. This program is being diffused nationally and soon will be included on the Centers for Disease Control and Prevention (CDC) Diffusion of Effective Behavioral Interventions Web site at: http://www.effectiveinterventions.org. Another model, developed by Fisher and Cornman for use in clinical settings, assesses deficits in HIV information, motivation, or behavioral skills using motivational interviewing techniques, complete with behavioral prescription writing at the end of the visit. This model involves a process that takes 5-10 minutes to complete. More information about the model is available at http://www.chip.uconn.edu/interventions/k-options.pdf. Finally, a model (called Act, Screen, Intervene) was generated from a work group developed in collaboration with the national HIV/STD Prevention Training Centers and the AIDS Education and Training Centers, based on the guidelines "Incorporating HIV Prevention into the Medical Care of Persons Living with HIV" developed by the CDC, Health Resources and Services Administration, and HIV Medical Association. The new curriculum, with the same title, includes 4 modules designed to guide the clinician in implementing prevention and partner notification into clinical work. This model has been pilot tested in 5 U.S. cities and also is being diffused nationally. The guidelines can be found at http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5212a1.htm. Any of these models, or new models that are expected to emerge from the Special Projects of National Significance, may assist the provider in implementing prevention work in the context of clinical care.

Partner Notification

A good way to begin a discussion about HIV prevention and transmission is with an inquiry about any previous experiences disclosing to partners. The provider then can ask whether the patient currently has a need to disclose to one or more partners and whether he or she is ready and motivated to share information about HIV status. The provider should prompt patients to consider several questions about disclosure, including how they might approach the discussion, how their partners might react, what information they might offer their partners, whether partners are likely to keep their status confidential, and whether they have any concerns about personal safety (eg, if they fear a violent reaction). If patients fear a violent reaction or are not ready to share their status but want their partners to know, the provider may offer assistance with partner notification, for example through the local health department, in a confidential manner. As an alternative, patients may want the provider to talk with their partners, and that option can be offered as well. See the U.S. Department of Veterans Affairs HIV Web site at http://www.hiv.va.gov/vahiv?page=sex-01-00 for a patient-oriented discussion of partner notification.

Helping Patients Reduce the Risk of Sexual Transmission

Standard Condom Use

Make sure that the patient understands how HIV is transmitted and which types of sexual acts are more and less risky than others. For vaginal or anal sex, correct use of latex or polyurethane condoms reduces the risk of HIV transmission considerably. Patients should be encouraged to use condoms as much as possible. For HIV-infected individuals, condom use is also is effective in reducing the risk of contracting another illness (such

as hepatitis C or another sexually transmitted disease) and the (apparently low) risk of becoming reinfected with another strain of HIV. It should be noted that condoms are less effective in reducing the transmission of organisms such as human papilloma virus (HPV) and herpes simplex virus (HSV), which may result from viral shedding from skin. In the event of allergy to latex or other difficulty with latex condoms, polyurethane male or female condoms may be substituted. "Natural skin" or "lambskin" condoms are not recommended for HIV prevention.

Of course, condoms must be used correctly to be highly effective in preventing HIV transmission. Be sure that the patient knows exactly how to use a condom. Table 1 provides instructions for condom use.

Table 1. Instructions for Use of Standard Condoms

- Use a new latex or polyurethane condom with each act of sex (oral, anal, or vaginal). Make sure that the condom is undamaged, and that its expiration date has not passed.
- Carefully handle the condom to avoid damage from fingernails, teeth, etc.
- Being sure that the condom roll faces out, unroll the condom onto the erect penis before any genital contact with partner.
- Ensure that the tip of the condom is pinched when applying it to the top of the penis, to eliminate air in the tip that could cause breakage during ejaculation.
- Use only water-based lubricants with latex condoms. Oil-based lubricants (such as mineral oil, cooking oil, massage oil, body lotion, and petroleum jelly) can weaken latex or cause it to break, although they are fine with the use of polyurethane condoms. Adequate lubrication during intercourse helps reduce the risk of condom breakage.

Advise patients to avoid using nonoxynol-9 (N-9) spermicides. Recent data suggest that N-9 may increase risk of HIV transmission during vaginal intercourse and can damage the rectal lining. N-9 should never be used for anal intercourse.

For patients who complain about lack of sensitivity with condom use, the following techniques may help:

- Apply a drop of lubricant inside the condom (not more, because it increases the risk that the condom will come off).
- Use polyurethane condoms instead of latex because they conduct heat and may feel more natural.
- Use insertive (female) condoms, which are not as restrictive to the penis.
- Use specially designed condoms that do not restrict the top of the penis (eg, Inspiral, Xtra Pleasure).

For those patients who are unable or unwilling to use condoms, the following suggestions may help reduce HIV transmission risk:

- Use plenty of lubricant to reduce friction and microtrauma, which create portals of entry for the virus.
- Avoid spermicides that damage the vaginal or anorectal linings.
- Avoid douching products.
- Avoid recreational drugs, especially methamphetamine, which impair the ability to maintain "safer" sex behaviors.
- Avoid the use of drugs such as nitrates (poppers) that enhance blood flow to the genitals.

For HIV-infected women, consider avoiding hormonal birth control methods because of a possible increase in the risk of HIV viral shedding.

Insertive (Female) Condom Use

The insertive "female" condom (Reality) may be used for vaginal or anal intercourse. It is a thin polyurethane pouch with a flexible ring at the opening, and another unattached flexible ring that sits inside the pouch to keep it in position in the vagina (for use in the anus, the inner ring must be removed and discarded). The female condom may be an option for women whose male partners will not use male condoms or for couples who do not like standard condoms. Female condoms are more expensive than male condoms, but may be procured at a lower cost at some health departments or Planned Parenthood clinics. They generally are less well known to patients and may be unacceptable to some women whose culture or religion prohibits or discourages touching one's own genitals. Note that the female condom cannot be used at the same time as a male condom.

Be sure the patient knows how to use the insertive condom before she or he needs it; after teaching, encourage practice when alone at home and unhurried. Women who have used the diaphragm, cervical cap, or contraceptive sponge may find it easy to use the female condom. Illustrated directions are included in each box

of insertive condoms. Table 2 gives instructions on the use of insertive condoms.

Table 2. Instructions for Use of Insertive (Female) Condoms

Vaginal Intercourse

- Open the pouch by tearing at notched edge of packet, and take out the female condom. Be sure that the lubricant is evenly distributed on the inside by rubbing the outsides together.
- Find a comfortable position, such as standing with one foot on a chair, sitting with knees apart, or squatting. Be sure the inner ring is inside, at the closed end of the pouch.
- Hold the pouch with the open end hanging down. While holding the outside of the pouch, squeeze the inner ring with your thumb and middle finger. Still squeezing, spread the labia with your other hand and insert the closed end of the pouch into the vagina.
- Now, put your fingers into the pouch itself, which should be inside the vagina, and push the inner ring and the pouch the rest of the way up into the vagina with your index finger. Check to see that the front side of the inner ring is just past the pubic bone. The back part of the inner ring should be up behind the cervix. The outer ring and about an inch of the pouch will be hanging outside the vagina.
- Until you and your partner become comfortable using the female condom, use your hand to guide the penis into the vagina, keeping it inside the pouch. If, during intercourse, the outer ring is getting pushed up inside the vagina, stop, remove the female condom, and start over with a new one. Extra lubricant on the penis or the inside of the female condom may help keep this from happening.
- After intercourse, take out the condom by squeezing and twisting the outer ring to keep the semen inside the pouch. Throw away in a trash can; do not flush. Do not reuse.
- If there are problems, call the manufacturer's toll-free customer assistance line at 800-274-6601, #230.
- More information is available on the manufacturer's Web site at: http://www.femalehealth.com.

Anal Intercourse

Remove the inner ring and discard it. Put the female condom on the penis of the insertive partner and insert the condom with the penis, being careful not to push the outer ring into the rectum. The outer ring remains outside the anus, for ease of removal after ejaculation.

Prevention with Positives and Oral Sex

Although there is evidence that some people have become infected through receptive oral sex, the risk of HIV transmission via oral sex, in general, is much lower than the risk of transmission by vaginal or anal sex. Thus, most public health and prevention specialists focus their attention on riskier sexual and drug-use behaviors. However, because HIV transmission can occur with oral sex, clinicians should address this issue with patients and help them make informed decisions about risk reduction. Sores or lesions in or around the mouth or on the genitals may increase the risk of HIV transmission, as may a concurrent sexually transmitted infection. Patients (and their partners) should avoid oral-genital contact if they have these conditions. Similarly, patients and partners can further reduce risk by not brushing or flossing teeth before oral sex. Individuals who wish to reduce further the risk of HIV transmission during oral sex may use barriers such as condoms, dental dams, or flexible plastic kitchen wrap.

Individuals who smoke crack cocaine often develop open burns, cracked lips, or damaged mucous membranes inside the mouth and thus may be at elevated risk of HIV transmission via oral sex. HIV-infected crack users should be counseled about the risk of transmitting HIV to uninfected partners through those portals of entry during oral sex and should receive risk-reduction counseling. In addition, they (or their partners) may benefit from techniques such as insulating the end of the crack pipe to reduce burns while smoking (eg, with a rubber band or spark plug cap) and avoiding the brittle or sharp-edged copper scrubbing pads used as screens in the crack pipe.

Influence of Substance Use on Sexual Behavior

Alcohol and drug use can contribute significantly to the risk of sexual transmission of HIV, because of behavioral disinhibition. While intoxicated, substance users may, for example, forgo condom use, practice riskier sexual behaviors, have multiple partners, or use erectile dysfunction agents to sustain sexual activity. Addressing substance use issues is an important aspect of PWP. Patients should be assessed for HIV transmission risks associated with alcohol and injection or noninjection drug use, including crystal methamphetamine, in the context of their sexual behaviors (for injection drug use, see below). As always, it is important to approach the patient in a nonjudgmental manner. If alcohol or other drugs are posing barriers to practicing safer behaviors, the provider should counsel the patient to reduce or avoid substance use before engaging in sex, or refer the patient to prevention case management for more specialized risk reduction. Often, the provider can help the patient identify methods for reducing HIV transmission risk, including means that do not require abstaining from alcohol and drug use.

Injection Drug Use and Prevention of HIV

Clinicians should discuss substance use, including steroid use, and reinforce the patient's understanding of the adverse effects that these drugs can have on the body and the immune system. Assess whether referral

for treatment is appropriate, and be knowledgeable about referral resources and mechanisms. If the patient is using injection drugs, emphasize the fact that HIV is readily transmitted by sharing needles and other injection equipment and that reusing or sharing needles and syringes can cause additional infections (eg, endocarditis, hepatitis C). Assess the patient's readiness to change his or her drug injection practices, and refer to drug treatment programs as appropriate. Refer to an addiction counselor for motivational interviewing or other interventions, if available. After completion of substance abuse treatment, relapse prevention programs and ongoing support will be needed. If the patient continues to use needles, discuss safer needle-use practices (Table 3) and refer to a needle exchange program, if one is available, so that syringes and needles are not reused. A partial listing of needle exchange sites may be found at: http://www.nasen.org, although many states either do not have or cannot list their facilities. Local harm-reduction activists may be aware of specific programs for obtaining clean needles and syringes. Patient-education flyers on safer injection practices, safer stimulant use, overdose prevention, and other topics are available on the Midwest AIDS Education and Training Center's Web site at http://www.uic.edu/depts/matec/resource.html.

Table 3. Needle-Use Practices to Reduce the Risk of HIV Infection and Transmission

- Never reuse or share needles, syringes, water, or drug preparation equipment. If there is a need to reuse syringe equipment, it should be cleaned properly with bleach or water, with care taken not to share the materials (eg, container, water) used for cleaning.
- It is best to use only sterile syringes obtained from a reliable source (pharmacy, needle exchange program). In addition, reusing one's own syringes can lead to various bacterial infections, abscesses, etc.
- Use sterile or boiled water to prepare drugs. If unavailable, use clean water from a reliable source, such as fresh tap water.
- Use a new or disinfected container (cooker) and a new filter (cotton) to prepare drugs. Cooking the drugs before injecting can reduce the chances of transmitting HIV when sharing equipment.
- Clean the skin around the injection site with a new alcohol swab before injecting, and use a sterile or clean cotton pad to stop the blood flow after injecting. Also, using a tourniquet when injecting can help reduce damage to veins and assist the user in controlling the shot and avoiding overdose.
- Safely dispose of syringes after one use, either in a specially made sharps container, or a clean detergent container. Many pharmacies offer disposal programs for used syringes.
- For patient flyers on safer injection practices, safer stimulant use, overdose prevention, and other topics, go to http://www.uic.edu/depts/matec/resource.html.

Noninjection Drug Use and Prevention of HIV Transmission

Exposure to HIV through contaminated blood may also occur during noninjection drug use; for example, by sharing cocaine straws or sniffers through which cocaine is inhaled. These straws can easily penetrate fragile nasal mucosa and become contaminated with blood from one user before being used by another individual, who may then experience mucous membrane exposure or even a cut or break in the mucous membrane from the bloody object. Straws or sniffers should not be shared.

Tattoo, Piercing, and Acupuncture Equipment

Patients should be aware of the risk of contamination of tattoo equipment, inks, and piercing equipment, and avoid situations where they might either transmit HIV or pick up other bloodborne pathogens.

Acupuncturists generally use sterile needles, but clients should verify this before using their services.

Maternal-Infant HIV Transmission

HIV-positive women can have healthy pregnancies, with good health outcomes for both mother and baby. For this to occur, women must know their HIV status as early as possible, preferably before becoming pregnant. Although intervention to reduce the risk of perinatal infection is most effective if begun early in pregnancy, or preferably before pregnancy, it may be beneficial at any point in the pregnancy, even as late as during labor. For further information, see chapter *Reducing Maternal-Infant HIV Transmission*.

Postexposure Prophylaxis for Nonoccupational HIV Exposure

Postexposure prophylaxis (PEP) may be considered for certain sexual exposures, sexual assaults, and other nonoccupational exposures to HIV. As with occupational PEP, a risk assessment must be completed and antiretroviral therapy, if indicated, must be started in a timely manner. The risks and toxicities of antiretroviral drugs must be weighed against potential benefits, and the client's informed consent must be obtained. For further information, see chapter *Nonoccupational Postexposure Prophylaxis*.

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Preventing Exposure to Opportunistic and Other Infections

Background

Patients with HIV are more susceptible than others to certain infections. Exposure to some of the opportunistic pathogens may be minimized or avoided if patients are aware of the possible dangers associated with them.

Grouping transmissible infections by type of exposure is a useful way for patients and providers to conceptualize means of prevention.

Sexual Exposures

Patients should use latex or polyurethane condoms during every act of sexual intercourse to reduce the risk of exposure to cytomegalovirus (CMV), herpes simplex virus, hepatitis C, human papillomavirus, and other sexually transmitted pathogens. Although polyurethane male and female condoms have not been tested as thoroughly as latex condoms, they can greatly reduce risk if properly used. Correct use of condoms and other effective barriers, such as latex dental dams or flexible plastic film (eg, plastic food wrap) during oral sex on women also will prevent the transmission of HIV. Avoiding sexual contact when herpetic lesions are present (on the mouth or genitals) may help to reduce herpes simplex transmission, although herpes can be transmitted when no lesions are visible.

The most effective way to avoid the risk of sexually transmitted intestinal infections such as cryptosporidiosis, shigellosis, campylobacteriosis, amebiasis, and hepatitis A and B is to avoid sexual practices that may result in oral exposure to feces (eg, oral-anal contact, or "rimming"). Persons wishing to reduce their risk of exposure might consider using dental dams or other barrier methods (eg, plastic food wrap) for oral-anal contact; changing condoms after anal intercourse; and wearing latex, nitrile, or other intact waterproof gloves during digital-anal contact. Frequently washing hands and genitals with warm soapy water during and after activity that may bring them in contact with feces may further reduce the risk of illness.

Consistent and correct use of condoms greatly reduces the risk of sexually transmitted infections. See chapter *Preventing HIV Transmission/Prevention with Positives* for specific information on the use of condoms.

Injection Drug Use Exposures

Injection drug use with sharing of needles or other injection equipment puts HIV-infected persons at risk for infection with hepatitis C, additional strains of HIV (some of which may be drug-resistant), and other bloodborne pathogens. Injection drug use also conveys a risk of endovascular infections with skin and environmental flora, such as staphylococci, streptococci, *Candida,* and some gram-negative rods. Certain drugs, such as black-tar heroin, may be contaminated with anaerobic bacteria that can cause life- and limb-threatening anaerobic infections if injected. Finally, drug addiction may predispose patients to commercial sex work or trading of sex for drugs, which may increase their risk of acquiring sexually transmitted infections that are not injection related per se.

Assess each patient's readiness to change his or her practices, and refer to drug treatment programs as appropriate. If the patient continues to use needles, discuss ways to avoid sharing needles and other drug equipment, refer to a needle exchange program so that syringes and needles are not reused, and teach proper cleaning of injection equipment. Specific recommendations about injection and other drug use can be found in the chapter *Preventing HIV Transmission/Prevention with Positives*. All injection drug users should be immunized against hepatitis A and hepatitis B if they are not already immune.

Environmental and Occupational Exposures

No specific measures are recommended to prevent exposure to *Pneumocystis jiroveci* pneumonia (PCP), *Mycobacterium avium* complex, *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Candida* spp, or *Cryptococcus neoformans*.

Contact with Infected Populations

Certain activities or types of employment may increase the risk of exposure to tuberculosis. These include volunteer work or employment in health care facilities, correctional institutions, shelters for the homeless, and other settings identified as high-risk by local health authorities. The patient, along with the health care provider, should decide whether to continue such

activities while taking into account the patient's specific duties in the workplace, the prevalence of tuberculosis in the community, and the degree to which precautions are taken in the workplace to prevent the transmission of tuberculosis. These decisions will affect the frequency with which the patient should be screened for tuberculosis.

Child-care providers and parents of children in child-care facilities have an increased risk of acquiring CMV infection, cryptosporidiosis, and other infections (eg, hepatitis A and giardiasis) from children. Although the prevalence of CMV is high (50-70%) in the general adult population in the United States, it is higher (90%) in injection drug users, hemophiliacs, and men who have sex with men (MSM). Any HIV-infected child-care provider without an elevated risk of CMV (ie, no history of injection drug use, hemophilia, or sex with MSM) should be tested for CMV antibody. CMV-negative individuals can reduce the risk of acquiring infection by good hygienic practices, such as hand washing after contact with feces (eg, during diaper changing), urine, and saliva. Any CMV-negative person with HIV who needs a transfusion should receive blood that is CMV negative or leukocyte reduced.

HIV-infected children and adults who are susceptible to varicella-zoster virus (VZV) (ie, those with no history of chickenpox or shingles) should avoid exposure to persons with chickenpox or shingles. Household contacts, especially children, should be vaccinated against VZV if they are HIV negative and have no history of chickenpox so that they will not transmit VZV to their HIV-infected contact. If a susceptible HIV-infected person is in close contact with someone with chickenpox or shingles, varicella-zoster immune globulin (VZIG) should be administered as soon as possible (ideally within 48 hours, but at least within 96 hours) after the exposure. Anti-varicella titers can be performed after exposure if the HIV-infected person's VZV immunity status is unknown. The U.S. Centers for Disease Control and Prevention (CDC) no longer supports the alternative approach of giving acyclovir, 800 mg orally 5 times a day for 3 weeks instead of VZIG, because no data exist to support the efficacy of this approach.

Contact with Animals

Occupations involving contact with animals (eg, veterinary work and employment in pet stores, farms, or slaughterhouses) may pose a risk of cryptosporidiosis, toxoplasmosis, salmonellosis, campylobacteriosis, and *Bartonella* infection. However, the available data are insufficient to justify a recommendation against work in such settings.

Contact with young farm animals, especially animals with diarrhea, should be avoided to reduce the risk of cryptosporidiosis.

Soil Exposure

Glove use and hand washing after gardening or other contact with soil may reduce the risk of cryptosporidiosis and toxoplasmosis.

In histoplasmosis-endemic areas, patients should avoid activities known to be associated with increased risk, such as stirring up dust when working with surface soil; cleaning chicken coops; disturbing soil beneath bird-roosting sites; cleaning, remodeling, or demolishing old buildings; and exploring caves.

In coccidioidomycosis-endemic areas, patients should consider avoiding activities associated with increased risk, such as extensive exposure to disturbed native soil (eg, at excavation sites, on farms, or in dust storms).

Pet-Related Exposures

Health care providers should inform HIV-infected persons of the potential risks posed by pet ownership. However, they should be sensitive to the possible benefits of pet ownership and should not routinely advise persons with HIV to part with their pets. They should advise their patients about the following.

General

Veterinary care should be sought when a pet develops a diarrheal illness. If possible, HIV-infected persons should avoid contact with animals that have diarrhea. A fecal sample should be obtained from an animal with diarrhea and examined for *Cryptosporidium*, *Salmonella*, and *Campylobacter*.

When obtaining a new pet, HIV-infected persons should avoid animals younger than 1 year, especially those with diarrhea. Because the hygienic and sanitary conditions in pet breeding facilities, pet stores, and animal shelters are highly variable, patients should exercise caution when obtaining a pet from these sources. Stray animals should be avoided. Animals less than 6 months of age, especially those with diarrhea, should be examined by a veterinarian for *Cryptosporidium*, *Salmonella*, and *Campylobacter* before

contact with the patient. Patients should wash their hands after handling pets (especially before eating) and avoid contact with pet feces to reduce the risk of cryptosporidiosis, salmonellosis, and campylobacteriosis.

Cats

Patients should consider the potential risks of cat ownership such as the risk of toxoplasmosis, *Bartonella* infection, and enteric infections. Those who elect to obtain a cat should adopt or purchase an animal that is more than 1 year of age and in good health to reduce the risk of cryptosporidiosis, *Bartonella* infection, salmonellosis, and campylobacteriosis.

Litter boxes should be cleaned daily, preferably by an HIV-negative, nonpregnant person; if the HIV-infected patient performs this task, he or she should wash hands thoroughly afterward to reduce the risk of toxoplasmosis. Also to reduce the risk of toxoplasmosis, cats should be kept indoors, should not be allowed to hunt, and should not be fed raw or undercooked meat. Flea control will help reduce the risk of *Bartonella* infection. Although declawing generally is not advised, patients should avoid activities that may result in cat scratches or bites to reduce the risk of *Bartonella* infection. Patients should wash the sites of cat scratches or bites promptly and should not allow cats to lick the open cuts or wounds.

Testing of cats for toxoplasmosis or *Bartonella* infection is not recommended.

Birds

Screening of healthy birds for *C neoformans*, *M avium*, or *Histoplasma capsulatum* is not recommended. Areas contaminated with bird droppings should be avoided if possible, and soil beneath bird-roosting sites should not be disturbed. Contact with chicks and ducklings has been associated with salmonellosis.

Other

Contact with reptiles (such as snakes, lizards, iguanas, and turtles) should be avoided to reduce the risk of salmonellosis.

Gloves should be used while cleaning aquariums to reduce the risk of infection with *Mycobacterium marinum*.

Contact with exotic pets, such as nonhuman primates, should be avoided.

Food- and Water-Related Exposures

Raw or undercooked eggs (including foods that may contain raw eggs, such as some preparations of hollandaise sauce, Caesar and certain other salad dressings, homemade mayonnaises, eggnog, uncooked cake batter, and cookie dough); raw or undercooked poultry, meat, or seafood, especially raw shellfish; unpasteurized dairy products; unpasteurized fruit juice; and raw seed sprouts (alfalfa, mung bean sprouts) may contain enteric pathogens such as *Salmonella*, pathogenic strains of *Escherichia coli*, and parasites including *Cryptosporidium*. Poultry and meat are safest if the internal temperature is verified with a meat thermometer to be at least 180°F (poultry) or 165°F (red meat). If a thermometer is not available, meats should be cooked until no traces of pink remain; however, color changes do not always correlate with internal temperature. Fruits and vegetables should be washed thoroughly, or cooked, before being eaten.

Cross-contamination of foods should be avoided. Uncooked meats should not be allowed to come into contact with other foods. Hands, cutting boards, counters, and knives and other utensils should be washed thoroughly after contact with uncooked foods.

Although listeriosis is uncommon in the United States, it is a serious disease that occurs more frequently among immunocompromised persons, including those with HIV disease. Persons at increased risk of listeriosis may elect to do the following:

- Avoid soft cheeses (eg, feta, brie, camembert, blue-veined, and Mexican-style cheeses such as queso fresco). Hard cheeses, processed cheeses, cream cheese, cottage cheese, and yogurt generally are safe from listeriosis.
- Cook leftover foods or ready-to-eat foods, such as hot dogs, until they are steaming hot before eating.
- Avoid foods from delicatessen counters, such as prepared meats, salads, and cheeses, or heat these foods until steaming before eating. Canned or shelf-stable pate and meat spreads need not be avoided.
- Avoid raw or unpasteurized milk or milk products, including goat's milk, or foods containing unpasteurized milk or milk products.

Patients should not drink water directly from lakes or rivers because of the risk of cryptosporidiosis and giardiasis. Even accidental ingestion of lake, river, or ocean water while swimming, rafting, boating, skiing, or engaging in other types of recreational activity carries this risk.

During outbreaks or other situations in which a community "boil water" advisory is issued, patients should boil water for 1 minute to eliminate the risk of cryptosporidiosis. Use of submicron personal-use water filters (home or office types) or bottled water may reduce the risk. Not all bottled water can be considered free of oocysts, however. Water is considered safe if it been distilled, filtered with an "absolute" 1-micron or submicron filter, or filtered by reverse osmosis. Current data are inadequate to recommend that all HIV-infected persons boil or otherwise avoid drinking tap water in non-outbreak settings.

Persons who wish to take independent action to reduce the risk of water-borne cryptosporidiosis may choose to take precautions similar to those recommended during outbreaks. Such decisions are best made in conjunction with the health care provider. Persons who opt for personal-use filters or bottled water should be aware of complexities involved in selecting the appropriate products, the lack of enforceable standards for the destruction or removal of oocysts, the cost of the products, and the difficulty of using these products consistently (eg, for toothbrushing, eating out, and travelling).

Patients taking precautions to avoid cryptosporidiosis in drinking water should be advised that ice made from tap water can be a source of infection. In addition, fountain beverages served in restaurants, bars, theaters, and other public places may pose a risk because these beverages, as well as the ice they contain, are made from tap water. Nationally distributed brands of bottled or canned carbonated soft drinks are safe to drink. Commercially packaged noncarbonated soft drinks and fruit juices that do not require refrigeration until after they are opened (eg, those that can be stored unrefrigerated on grocery shelves) also are safe. Nationally distributed brands of frozen fruit juice concentrate are safe if they are reconstituted with water from a safe source. Fruit juices that must be kept refrigerated from the time they are processed to the time of consumption may be either fresh (unpasteurized) or heat treated (pasteurized); only those labeled as being pasteurized should be considered safe. Other pasteurized beverages and beers also are considered safe to drink. No data are available concerning the survival of *Cryptosporidium* oocysts in wine.

Travel-Related Exposures

Travel, particularly to developing countries, may carry significant risks for HIV-infected persons, especially for patients who are severely immunosuppressed, in terms of exposure to opportunistic pathogens. There is little medical evidence to support recommending against travel to developing countries, however, as long as precautions are taken. Consultation with health care providers and/or experts in travel medicine will help patients plan itineraries.

During travel to developing countries, HIV-infected persons are at much higher risk of food-borne and water-borne infections than they are in the United States. Foods and beverages may be contaminated, especially raw fruits and vegetables, raw or undercooked seafood or meat, tap water, ice made with tap water, unpasteurized milk and dairy products, and items purchased from street vendors. Items that generally are safe include steaming-hot foods, fruits that are peeled by the traveler, bottled (especially carbonated) beverages, hot coffee or tea, beer, wine, and water brought to a rolling boil for 1 minute. Treatment of water with iodine or chlorine may not be as effective as boiling but can be used, perhaps in conjunction with filtration, when boiling water is not practical.

Water-borne infections may result from swallowing water during recreational activity. To reduce the risk of cryptosporidiosis and giardiasis, patients should avoid swallowing water during swimming and other recreational activities and should not swim in water that may be contaminated (eg, with sewage, animal waste, or human waste).

Antimicrobial prophylaxis for traveler's diarrhea is not recommended routinely for HIV-infected persons traveling to developing countries. Such preventive therapy can have adverse effects and can promote the emergence of drug-resistant organisms. Nonetheless, several studies (none involving an HIV-infected population) have shown that prophylaxis can reduce the risk of diarrhea among travelers. Under selected circumstances (eg, when the risk of infection is very high and the period of travel is brief), the provider and patient may weigh the potential risks and benefits and decide that antibiotic prophylaxis is warranted.

When prophylaxis is offered, fluoroquinolones such as ciprofloxacin (500 mg daily) can be considered, although fluoroquinolones should not be used for pregnant women or children. Taking 1 double-strength

tablet daily of trimethoprim-sulfamethoxazole (TMP-SMX) has been effective, but resistance to this drug is now common in tropical areas. Persons already taking TMP-SMX for prophylaxis against PCP may gain some protection against traveler's diarrhea. For HIV-infected persons who are not already taking TMP-SMX, the provider should use caution when prescribing this agent for prophylaxis of diarrhea because of the high rate of adverse reactions and the possible need for the agent for other purposes (eg, PCP prophylaxis) in the future.

All HIV-infected travelers to developing countries should carry with them a sufficient supply of an antimicrobial agent to be taken empirically should significant diarrhea develop. One appropriate regimen is 500 mg of ciprofloxacin twice daily for 3-7 days. Alternative antibiotics (eg, TMP-SMX) should be considered as empirical therapy for use by pregnant women. Travelers should consult a physician if their diarrhea is severe and does not respond to empirical therapy, if their stools contain blood, if fever is accompanied by shaking chills, or if dehydration develops. Antiperistaltic agents such as diphenoxylate and loperamide are used to treat diarrhea; however, they should not be used by patients with high fever or with blood in the stool, and their use should be discontinued if symptoms persist beyond 48 hours.

Travelers should be advised about other preventive measures appropriate for anticipated exposures, such as chemoprophylaxis for malaria, protection against arthropod vectors, treatment with immune globulin, and vaccination. They should avoid direct contact of the skin with soil and sand (eg, by wearing shoes and protective clothing and using towels on beaches) in areas where fecal contamination is likely.

In general, live-virus vaccines should be avoided. An exception is measles vaccine, which is recommended for nonimmune persons, although not recommended for those who are severely immunocompromised. Immune globulin should be considered for measles-susceptible, severely immunocompromised persons traveling to measles-endemic regions. Inactivated (killed) poliovirus vaccine should be used instead of oral (live) poliovirus vaccine. Persons at risk for exposure to typhoid fever should be given inactivated parenteral typhoid vaccine instead of the live attenuated oral preparation. Yellow fever vaccine is a live-virus vaccine with uncertain safety and efficacy in HIV-infected persons. Travelers with HIV infection who are unvaccinated and for whom travel is necessary should be advised of the risk, instructed in methods for avoiding the bites of vector mosquitoes, and provided with a vaccination waiver letter. Travelers with asymptomatic HIV infection who cannot avoid potential exposure to yellow fever should be offered the choice of vaccination after disclosure of its limitations.

In general, killed and recombinant vaccines (eg, diphtheria-tetanus, rabies, hepatitis B, hepatitis A, Japanese encephalitis) should be used for HIV-infected persons just as they would be for HIV-uninfected persons anticipating travel. Preparation for travel should include a review and update of routine vaccinations, including diphtheria-tetanus. The currently available cholera vaccine is not recommended for persons following the usual tourist itinerary, even if that includes travel to countries that have reported cases of cholera.

All patients traveling to other countries should be evaluated for both routine and destination-specific immunizations and prophylaxes. Travelers should be told about other area-specific risks and instructed about how to reduce those risks. Geographically focal infections that pose a high risk to HIV-infected persons include visceral leishmaniasis (a protozoan infection transmitted by the sandfly) and several fungal infections (eg, *Penicillium marneffei* infection, coccidioidomycosis, and histoplasmosis). Many tropical and developing areas have high rates of tuberculosis, which is a particular risk for HIV-infected persons.

For further information about health precautions for travelers, including vaccination information, check the CDC Web page at: http://www.cdc.gov/travel/index.htm. The "Special Needs Traveler" section contains a link for HIV-infected travelers. Select the "Travelers' Health" option for regional travel documents and outbreak information. Those without Internet access can call the CDC, toll free, at 1-877-FYI-TRIP or 888-232-3299.

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Opportunistic Infection Prophylaxis

Background

Prophylaxis against opportunistic infections (OIs) is treatment given to HIV-infected individuals to prevent either a first episode of an OI (primary prophylaxis) or the recurrence of infection (secondary prophylaxis). Prophylaxis is recommended to prevent 3 important OIs: *Pneumocystis jiroveci* pneumonia (PCP), *Mycobacterium avium* complex (MAC), and toxoplasmosis. Prophylaxis also is recommended to prevent tuberculosis (TB) in patients with latent *Mycobacterium tuberculosis* infection (See chapter *Latent Tuberculosis*). In certain situations, prophylaxis against some other OIs may be reasonable; see the OI prevention guidelines of the U.S. Public Health Service and the Infectious Diseases Society of America (USPHS/IDSA) (reference below) for additional information.

Pneumocystis jiroveci Pneumonia

Background

PCP remains the most common life-threatening infection among U.S. residents with advanced HIV disease.

Primary Prophylaxis: Indications

- Prophylaxis should be administered to all HIV-infected patients with a CD4 count of <200 cells/μL or a history of oral thrush. PCP prophylaxis may be indicated in patients with CD4 counts of >200 cells/μL in the presence of a CD4 percentage <14%, other OIs, or fever >100°F that persists for >2 weeks.
- In patients whose CD4 counts are declining toward 200 cells/μL, the CD4 count should be monitored closely. PCP prophylaxis should be considered for patients with a CD4 count between 200 and 250 cells/μL if laboratory monitoring will not be possible within 3 months.

Prophylaxis Options: Recommended Regimen

- The recommended regimen is trimethoprim-sulfamethoxazole (TMP-SMX; cotrimoxazole, Bactrim, Septra) 1 double-strength tablet daily. An alternative dosage is TMP-SMX 1 single-strength tablet daily, although the lower dosage may not be as effective. (Note: These regimens also are effective in preventing toxoplasmosis.)
  - Warning: Many patients cannot tolerate sulfa medications. Severe reactions may include persistent neutropenia; rash, including severe erythroderma; and Stevens-Johnson syndrome (bullae and desquamation of the skin). Some patients with milder reactions (eg, rash without fevers or systemic symptoms) may undergo desensitization, but this must be done cautiously and requires diligence from the patient and careful management by the provider (see chapter *Sulfa Desensitization*).

Prophylaxis Options: Alternative Regimens

Other options for prophylaxis include the following:

- Dapsone 100 mg orally daily or 50 mg orally twice daily. (Note: These regimens do not prevent toxoplasmosis.)
- Dapsone 50 mg orally daily + pyrimethamine 50 mg orally once per week + leucovorin 25 mg orally once per week. (Note: This regimen also is effective in reducing the risk of toxoplasmosis.)
- Dapsone 200 mg orally + pyrimethamine 75 mg + leucovorin 25 mg, all once per week. (Note: This regimen also is effective in reducing the risk of toxoplasmosis.)
  - Warning: Glucose-6-phosphate dehydrogenase (G6PD) deficiency can increase the risk of hemolytic anemia or methemoglobinemia in patients receiving dapsone. Screen for G6PD deficiency before starting dapsone. (G6PD deficiency is found in approximately 10% of African American males, and in 1-2% of males of Mediterranean, Indian, and Asian descent.)

- Aerosolized pentamidine 300 mg once per month, via Respirgard II nebulizer. (Note: This regimen does not prevent toxoplasmosis.)
  - Warning: Aerosolized pentamidine may increase the risk of extrapulmonary pneumocystosis, pneumothorax, and bronchospasm. It increases the risk of TB transmission to others if the patient has active pulmonary tubercular disease, unless ventilation (negative pressurized facility with outside venting) is adequate. Do not use in patients in whom TB is suspected. The availability of treatment facilities offering aerosolized pentamidine may be limited.
- Atovaquone suspension 1,500 mg daily. (Note: This is also effective in reducing the risk of toxoplasmosis.) Atovaquone is more expensive than dapsone. It should be taken with high-fat meals for optimal absorption.
- TMP-SMX 1 double-strength tablet orally 3 times per week (eg, Monday, Wednesday, Friday).

Secondary Prophylaxis Indications

Prophylaxis should be given to all patients with a history of PCP.

Discontinuing Prophylaxis

Primary or secondary prophylaxis can be discontinued if the CD4 count has increased to >200 cells/μL for at least 3 months in response to effective antiretroviral therapy (ART), with the following cautions:

- If the patient had PCP in the past and the episode of PCP occurred at a CD4 count of >200 cells/μL, it may be prudent to continue PCP prophylaxis for life, regardless of how high the CD4 count rises as a consequence of ART.
- If PCP prophylaxis is discontinued, the patient's clinical status and CD4 count must be observed closely to determine when to resume prophylaxis.
- PCP prophylaxis should be reinitiated if the CD4 count decreases to <200 cells/μL or the patient meets other criteria as indicated above.

Prophylaxis during Pregnancy

TMP-SMX is the recommended agent for use during pregnancy; dapsone may be used as an alternative. Prophylaxis that includes pyrimethamine generally should be deferred until after pregnancy. During the first trimester, aerosolized pentamidine can be used, if the potential teratogenicity of oral agents is a concern.

Disseminated *Mycobacterium avium* Complex

Background

Disseminated MAC (DMAC) is common in patients with advanced HIV disease and occurs in people with CD4 counts of <50 cells/μL.

Primary Prophylaxis: Indications

Prophylaxis should be administered to all HIV-infected patients with CD4 counts of <50 cells/μL. Before starting prophylaxis, rule out active MAC infection by clinical assessment and, if warranted, by acid-fast bacilli (AFB) blood cultures (see chapter *Mycobacterium avium Complex*). Review the current drug regimen for medications that may interact with DMAC prophylaxis.

Prophylaxis Options: Recommended Regimens

- Azithromycin 1,200 mg weekly or clarithromycin 500 mg orally twice a day.
  (Note: Clarithromycin is not recommended during pregnancy, and it can have significant interactions with efavirenz and other drugs; see chapter *Drug-Drug Interactions with HIV-Related Medications.*)
  Note that if breakthrough DMAC occurs, it may be macrolide resistant.

Prophylaxis Options: Alternative Regimens

- Rifabutin 300 mg daily, or azithromycin 1,200 mg daily + rifabutin 300 mg daily.
  (Note: Rifabutin has significant interactions with many drugs; certain nonnucleoside reverse transcriptase inhibitors and protease inhibitors should be avoided or dose adjusted if used with rifabutin. See chapter *Drug-Drug Interactions with HIV-Related Medications.*)

Secondary Prophylaxis

Patients should receive lifelong chronic maintenance therapy, unless immune reconstitution occurs in response to ART. See chapter *Mycobacterium avium Complex*.

Discontinuing Primary Prophylaxis

Primary prophylaxis for DMAC can be discontinued in persons who have responded to effective ART with sustained increases in CD4 counts to >100 cells/μL for at least 3 months. Careful observation and monitoring are required, and prophylaxis should be restarted if the patient's CD4 count decreases to <50-100 cells/μL.

Secondary prophylaxis can be discontinued in patients who received at least 12 months of treatment for DMAC, are asymptomatic, *and* have sustained (for at least 6 months) CD4 counts of >100 cells/μL during ART.

Prophylaxis during Pregnancy

Azithromycin is the prophylactic drug of choice during pregnancy, although some providers withhold it during the first trimester. Clarithromycin is teratogenic in animals.

Toxoplasmosis

Background

Toxoplasmic encephalitis (TE) is usually is caused by reactivation of latent *Toxoplasma gondii* infection in patients with advanced immunosuppression (especially those with CD4 counts of <100 cells/μL). The USPHS/IDSA guidelines recommend that all HIV-infected patients be tested for toxoplasmosis immunoglobulin G (IgG) antibody soon after the diagnosis of HIV infection. Toxoplasmosis IgG-negative patients should be counseled to avoid sources of infection (see chapter *Preventing Exposure to Opportunistic and Other Infections*), and should be retested for toxoplasmosis IgG when CD4 counts fall to <100 cells/μL to determine whether they have seroconverted and are therefore at risk for TE. (See chapter *Toxoplasmosis* for more information on active disease and secondary prophylaxis.)

Primary Prophylaxis: Indications

Prophylaxis should be administered to all HIV-infected patients with CD4 counts of <100 cells/μL who are seropositive for *Toxoplasma*. IgG-negative patients should avoid exposure to *Toxoplasma*; see "Patient Education" below.

Prophylaxis Options: Recommended Regimen

- TMP-SMX 1 double-strength tablet daily. (Note: This option is also effective in preventing PCP.)

Prophylaxis Options: Alternative Regimens

(Note: The following options also are effective in preventing PCP.)

- TMP-SMX, 1 single-strength tablet daily.
- Dapsone 50 mg daily + pyrimethamine 50 mg weekly + folinic acid 25 mg weekly.
- Dapsone 200 mg weekly + pyrimethamine 75 mg weekly + folinic acid 25 mg orally weekly.
  - Warning: G6PD deficiency can increase the risk of hemolytic anemia or methemoglobinemia in patients receiving dapsone. Screen for G6PD deficiency before starting dapsone. (G6PD deficiency is found in approximately 10% of African American males, and in 1-2% of males of Mediterranean, Indian, and Asian descent.)
- Atovaquone 1,500 mg orally daily, with or without pyrimethamine 25 mg daily + folinic acid 10 mg daily; however, this alternative is quite expensive.
- Neither aerosolized pentamidine nor dapsone alone provides protection against TE.

Secondary Prophylaxis

Patients should receive lifelong chronic maintenance therapy, unless immune reconstitution occurs in response to ART (see chapter *Toxoplasmosis*).

Discontinuing Prophylaxis

Primary prophylaxis for TE can be discontinued in patients who have responded to effective ART with sustained CD4 counts of >200 cells/μL for at least 3 months. CD4 counts should be monitored carefully, and prophylaxis should be restarted in patients whose CD4 counts decrease to <200 cells/μL.

Secondary prophylaxis may be discontinued if TE signs and symptoms have resolved with treatment and if patients have sustained (for at least 6 months) CD4 counts of >200 cells/μL during ART.

Prophylaxis during Pregnancy

TMP-SMX may be used as primary prophylaxis during

pregnancy. Prophylaxis that includes pyrimethamine generally should be deferred until after pregnancy, although pyrimethamine may be used with caution to treat active toxoplasmosis during pregnancy in sulfa-allergic patients.

Patient Education

- Discuss adverse effects of the selected medication(s) and how the patient should respond in the event of rashes, diarrhea, and other complications.
- Explain the purpose of each medication, and be sure that patients understand the dosage and frequency of administration.
- Reinforce the need to continue the medication indefinitely (potentially for life) to reduce the risk of the OI.
- OIs can occur despite prophylaxis. Instruct patients to call their health care providers if they become ill.
- Counsel patients who are *Toxoplasma* IgG negative to avoid exposure to *Toxoplasma*. Specifically, they should avoid eating raw or undercooked meat, especially pork, lamb, game, and venison. Patients should wash hands after handling raw meat and after gardening or contact with soil. Encourage patients not to adopt or handle stray cats, and, if they own cats, to wash hands thoroughly after cleaning litter boxes. (See chapter *Preventing Exposure to Opportunistic and Other Infections*.)
- For women of childbearing potential who are taking clarithromycin, emphasize the need for effective contraception to avoid potential teratogenic effects of clarithromycin.

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Latent Tuberculosis

Background

Latent (or inactive) tuberculosis (TB) infection occurs when an individual has dormant *Mycobacterium tuberculosis* organisms and no active disease, and can be diagnosed by a tuberculin skin test (TST). Persons with HIV or AIDS and latent TB infection (LTBI) have a much higher risk of developing active TB (estimated at 10% per year) than does the general population (estimated at 10% in a lifetime). The risk of developing active TB can be reduced dramatically with treatment of LTBI. Hence, identifying and treating HIV-infected persons for LTBI is a high priority. Treatment of LTBI not only reduces the risk of disease for the individual, but also reduces the risk of further TB transmission should the HIV/TB-coinfected person develop active pulmonary TB. Standard treatment with isoniazid (INH) is effective and safe.

Issues of concern regarding the treatment of LTBI among HIV-infected persons include the following:

- Excluding active pulmonary or extrapulmonary TB disease before treatment with INH alone
- Assessing the risk of latent infection with drug-resistant TB
- Avoiding or managing drug interactions if rifampin or rifabutin regimens are used
- Exercising great caution in the use of rifampin/rifabutin and pyrazinamide combinations for LTBI treatment

S: Subjective

HIV-infected persons who have no symptoms of active TB (ie, afebrile, stable weight, no cough) and who have not been treated previously for active or latent TB are eligible for LTBI treatment. When patients do have symptoms that could represent active TB, active TB must be evaluated and ruled out by appropriate diagnostic methods before initiating treatment (see "Assessment" below).

Persons who have had bacillus Calmette-Guérin (BCG) vaccine should be evaluated in the same way as those who have never had BCG. Immigrants from many countries will have had childhood vaccination.

History

Health care providers should ask about a history of potential exposure to TB, because this might indicate infection with drug-resistant TB. Such risk might occur when there is knowledge of a source patient or when the exposure occurred in a setting with known drug resistance or a location with ongoing TB transmission where others remain at risk for exposure).

O: Objective

Physical Exam

Current U.S. guidelines strongly recommend performing a TST in newly diagnosed HIV-infected persons. Repeat testing is recommended for those whose CD4 lymphocyte count increases from low numbers to counts of >200 cells/μL, and annual testing is suggested for those who initially test negative. The TST is administered as an intradermal injection of 0.1 mL (5 tuberculin units TUs) of purified protein derivative (PPD), which raises a wheal in the skin. This also is known as the Mantoux test. Multiple-puncture tests such as tine tests and the use of other strengths of PPD are considered unreliable. Anergy testing is not recommended routinely because a randomized controlled study in HIV-positive patients in the United States failed to show an advantage to treating anergic, tuberculin-negative persons.

PPD tests are not designed for reading by the patient; a trained health care worker must measure the area of induration (not erythema) 48-72 hours after the test is placed. Induration of 5 mm or more is a positive result in HIV-infected persons, other immunosuppressed persons, anyone with recent TB exposure, and anyone with fibrosis on chest x-ray consistent with previousTB. For HIV-uninfected health care workers, 10 mm of induration is positive; in various other populations, either 10 mm or 15 mm of induration may be considered positive. Many large HIV clinics find it challenging to get their patients to return for the PPD reading. One randomized study found that offering incentives (eg, a fast-food coupon) plus counseling was more effective than counseling alone in obtaining return visits for PPD readings.

Recently licensed tests for gamma-interferon, which is produced by peripheral blood T cells in response to TB antigens, have not been not validated for use in HIV-infected persons and currently are not recommended for this population.

A: Assessment

TST-positive, HIV-infected persons without cough or other symptoms should have a chest x-ray. If the chest x-ray in an asymptomatic patient is negative, the patient should be offered treatment for LTBI. Persons with symptoms consistent with pulmonary or extrapulmonary TB, and those with abnormal findings on chest radiography, require further assessment. This assessment may include sending 3 sputum specimens on 3 separate mornings (using saline mist to induce cough for those not coughing spontaneously) for acid-fast bacilli stain and culture or obtaining other specimens, depending on the suspected site of extrapulmonary TB. If suspicion of TB is low, then those with negative sputum smears (or other biopsy or tissue samples) can begin LTBI treatment. If suspicion of active disease is high, treatment for active disease should be started while the culture results are pending (see chapter *Mycobacterium tuberculosis*: *Treatment in the United States and other High-Income Nations*).

HIV-infected close contacts of patients with active pulmonary TB should receive preventive therapy regardless of PPD results or previous courses of preventive treatment, after active TB has been excluded. Such contacts should be tested with 5 TUs of PPD if previously negative and then started on preventive therapy. If the initial TST result is negative, the individual should be evaluated again 3 months after discontinuation of contact with the infectious source. If the contact is severely immunosuppressed, a full course of preventive treatment usually is provided even if that individual remains PPD negative. Contacts who are not immunosuppressed and who remain PPD negative may discontinue preventive treatment.

P: Plan

As with any treatment of TB, adherence with the regimen is required for success. Treatment regimens for LTBI are presented in Table 1.

Table 1. Treatment Regimens for Latent Tuberculosis

Drug	**Dose** (taken orally)	**Frequency**	**Duration** (minimum number of doses for completion)
Recommended			
Isoniazid*	Adults: 300 mg Children: 5 mg/kg	Daily	9 months **OR** 270 doses in 12 months
Alternative			
Isoniazid*	Adults: 900 mg Children: 15 mg/kg	Twice-weekly DOT**	9 months **OR** 76 supervised doses in 12 months
Exposure to isoniazid-resistant TB or intolerance to isoniazid			
Rifampin***	Adults: 600 mg Children: 10-20 mg/kg	Daily	4 months **OR** 120 doses in 6 months
Use only in special situations			
Rifampin* and pyrazinamide**	Highly toxic; to be used only by persons experienced in LTBI treatment in special situations		
Exposure to multidrug-resistant (MDR) TB			
Consider pyrazinamide with either ethambutol or a fluoroquinolone	Seek expert advice from public health authorities and those experienced in treatment of MDR TB. May be postponed or may be based on resistance pattern of index case, if known.		

*10-25 mg of pyridoxine (vitamin B6) should be given with each isoniazid dose to reduce the risk of isoniazid-induced peripheral neuropathy.
** DOT = directly observed treatment
*** Rifampin has significant interactions with antiretroviral drugs in the nonnucleoside reverse transcriptase inhibitor (NNRTI) and protease inhibitor (PI) classes and with other medications. See text about contraindicated combinations, dosage adjustments, and substitution of rifabutin for rifampin.

INH may cause liver toxicity and its use should be monitored carefully in patients with active alcohol use, liver disease, or chronic hepatitis B or C. INH is contraindicated in patients with acute hepatitis or decompensated liver disease. Before INH use, baseline liver and renal function tests should be checked. Routine monthly clinical monitoring for fever, fatigue, anorexia, nausea, vomiting, abdominal pain, jaundice, peripheral neuropathy, and rash should be performed. Alanine aminotransferase (ALT) should be monitored monthly in HIV-infected patients and others at risk for hepatitis. If patients develop abnormalities in liver transaminases while taking INH (ALT or aspartate aminotransferase >3 times the upper limit of normal with symptoms, or >5 times the upper limit of normal in the absence of symptoms), INH should be withheld. Obtain expert consultation before treating patients with abnormal liver function tests or advanced liver disease.

Before rifampin use, baseline liver and renal function tests and a complete blood count are suggested. Follow-up is the same as for INH use.

Drug Interactions with Antiretroviral Therapy

Rifampin and rifabutin have significant interactions with certain antiretroviral drugs, including nonnucleoside reverse transcriptase inhibitors (NNRTIs) and protease inhibitors (PIs). Rifampin can be used in persons taking efavirenz, although some experts recommend increasing the efavirenz dosage to 800 mg daily. Rifampin decreases the blood concentrations of nevirapine and all unboosted PIs (except ritonavir) and should not be used with these drugs. Standard ritonavir boosting of PIs fails to overcome the drug interaction, causes additional toxicity, or both. Although recommended in the past, rifampin should not be used in combination with ritonavir-boosted saquinavir because of high rates of hepatic toxicity. Adding more ritonavir to the fixed-dose combination of lopinavir/ritonavir (Kaletra) may overcome the pharmacokinetic effects of concurrent rifampin, but the regimen is poorly tolerated. Use of ritonavir-boosted PI regimens in combination with rifampin is best avoided and should be done only in consultation with an expert.

No data are available on the use of rifabutin for the treatment of LTBI. Nevertheless, rifabutin may be considered in place of rifampin for patients taking antiretroviral combinations that include NNRTIs (other than efavirenz) or PIs (other than ritonavir alone). In these cases, the dosages of both rifabutin and the antiretroviral agent usually require adjustment.

Table 2 presents information on combining antiretroviral agents with rifampin or rifabutin.

Other Drug Interactions

Rifampin decreases the blood concentrations of estrogens, anticonvulsants, hypoglycemic agents, and many other drugs. Review all medications a patient is taking before initiating rifampin and make adjustments as necessary. (See Table 12: *Clinically significant drug-drug interactions involving rifamycins* at www.cdc.gov/mmwr/preview/mmwrhtml/rr5211a1.htm#tab12.)

Pregnancy

HIV-infected pregnant women with a positive TST and no evidence of active TB should receive standard prophylaxis as soon as possible, even during the first trimester. The preferred prophylaxis in pregnancy is a 9-month INH regimen (with pyridoxine, as above). Alternative regimens, such as rifampin or rifabutin, should be used with caution because of limited experience. Neonates born to women who received rifampin during pregnancy should be given vitamin K (10 mg) to reduce the risk of hemorrhagic disease. Pyrazinamide generally is avoided during pregnancy because of lack of information about fetal effects.

Table 2. Combinations of Antiretroviral Medications with Rifampin or Rifabutin: Contraindicated Combinations and Dose Adjustments

	Rifampin	Rifabutin*
Nonnucleoside Reverse Transcriptase Inhibitors		
Efavirenz**	Rifampin dose unchanged, efavirenz dose 600-800 mg daily	No change in efavirenz dose Increase rifabutin to 450 mg/day or 600 mg 3 times weekly
Nevirapine	Generally not recommended; despite 25-50% reduction in nevirapine levels, 2 small studies claim standard doses are effective	Use standard dose of nevirapine Rifabutin 300 mg daily or 3 times weekly
Delavirdine	Never combine	Never combine
Protease Inhibitors (Nonboosted)		
Ritonavir	May be used at standard doses; limited clinical experience	Ritonavir at standard dose Rifabutin 150 mg alternate days or 3 times weekly
Amprenavir/fosamprenavir	Never combine	PIs at standard dose Rifabutin 150 mg/day or 300 mg 3 times weekly
Atazanavir	Never combine	Atazanavir at standard dose Rifabutin 150 mg alternate days or 3 times weekly
Indinavir	Never combine	Increase indinavir to 1,000 mg every 8 hours Rifabutin 150 mg/day or 300 mg 3 times weekly
Nelfinavir	Never combine	Increase nelfinavir to 1,000 mg every 8 hours Rifabutin 150 mg/day or 300 mg 3 times weekly
Saquinavir	Never combine	Never combine
Ritonavir-Boosted Protease Inhibitors		
Lopinavir/ritonavir (Kaletra)	Lopinavir/ritonavir (3 capsules twice daily) must be supplemented with additional ritonavir 300 mg twice daily; limited experience, not well tolerated	Standard dose of lopinavir/ritonavir Decrease rifabutin to 150 mg alternate days or 3 times weekly
Saquinavir/ritonavir	Due to high rates of hepatotoxicity this combination should not be used	Standard dose of lopinavir/ritonavir; Decrease rifabutin to 150 mg alternate days or 3 times weekly
All other ritonavir-boosted PIs	Should not be used (adequate dosing regimens not defined)	Standard dose of PI/ritonavir; Decrease rifabutin to 150 mg alternate days or 3 times weekly

Source: Updated Guidelines for the Use of Rifamycins for the Treatment of Tuberculosis Among HIV-Infected Patients Taking Protease Inhibitors or Nonnucleoside Reverse Transcriptase Inhibitors. Updated January 20, 2004. (Nucleoside and nucleotide analogues are given in standard doses with either rifampin or rifabutin.)

* If available, rifabutin may be substituted for rifampin when TB treatment and antiretroviral therapy is combined.

** Avoid efavirenz during pregnancy or in women who may become pregnant during therapy. Both rifampin and rifabutin significantly reduce estrogen and progestin levels for women on hormonal contraceptives; efavirenz raises estrogen levels moderately. Two forms of birth control including one barrier method and either a mid- to high-dose hormonal contraceptive or intrauterine device are most often recommended. Barrier methods are also recommended for reducing HIV transmission in women who are infertile.

Patient Education

- Patients should know that although they have the TB germ in their bodies, they cannot pass the germ to others while TB is latent. However, because they have HIV infection, the TB germ is more likely to make them sick at some point in the future.
- The medicine patients are starting will help kill the TB germ and reduce their chances of getting sick with active TB.
- Patients must take all of their medicine, every day, to prevent the TB germ from spreading and making them sick.
- If patients have adverse effects, such as rash or itching, tell them to contact their health care providers immediately. Occasionally, INH can cause tingling or numbness in the hands or feet. The pyridoxine (vitamin B6) they are taking should help prevent that, but they should let their providers know if it occurs.
- Patients should avoid alcohol while taking these medications. The medicines for TB are processed by the liver and, when combined with alcohol, they easily can overload the liver. Acetaminophen (Tylenol) also is processed by the liver, so patients should keep their intake to a minimum. (Patients with hepatitis C, liver disease, or chronic alcohol use should not take more than 3.5 grams per day.)
- Blood tests will be done regularly to make sure the liver is working well, so it is important for patients to keep their follow-up appointments. They should take all their medications, vitamins, and supplements with them to the clinic so that their health care providers can review them and make sure there are no drug interactions.
- If patients experience nausea, vomiting, poor appetite, or abdominal pain, if they notice their urine darkening or becoming cola-colored, or if they notice their eyes or skin yellowing, they should return to the clinic immediately. These problems may indicate that the liver is being overwhelmed, and it is important to find out before permanent damage is done.
- Rifampin will cause sweat, tears, urine, and plastic contact lenses to turn orange.
- Rifampin will make birth control pills ineffective. Patients should use a backup method of contraception until treatment is complete. Condoms can help prevent HIV transmission and reduce the risk of pregnancy.

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Treatment of Latent Tuberculosis in Resource-Limited Settings

Background

Countries with a high prevalence of tuberculosis (TB), including resource-limited countries, traditionally relied on the bacillus Calmette-Guérin (BCG) vaccination rather than treatment of latent TB infection (LTBI) to prevent active TB. Because of the rapidly increasing rates of both TB and HIV in many countries, and the negative impact of each infection on the other, some pilot projects and national programs in resource-limited settings are now providing treatment of LTBI for HIV-infected persons. (See chapter *Latent Tuberculosis* for a general discussion of latent TB, including treatment options and patient education.)

Several issues should be considered in the treatment of LTBI among HIV-infected patients in resource-limited settings, including the following:

- Access to HIV test and tuberculin skin test (TST)
- The effect of previous BCG vaccination on the TST
- The need for TST before treatment of LTBI
- Criteria for isoniazid (INH) use, including the ability to rule out active TB before INH use
- The duration of treatment and the effectiveness of INH in treating LTBI
- Lack of access to preventive therapy other than INH
- Access to HIV and TB interventions

In some settings, a TST is not a prerequisite for INH use; in these settings the term "INH preventive therapy" (IPT) is used, rather than treatment of LTBI. To distinguish INH preventive therapy from intermittent prophylactic treatment of malaria in pregnancy (also abbreviated IPT), the acronym TB-IPT is used commonly.

Access to HIV Test and Tuberculin Skin Test

Interventions for HIV/TB-coinfected persons can occur only if both infections are diagnosed. Many countries are gradually expanding access to voluntary HIV counseling and testing at low or no cost, using either laboratory-based tests or rapid tests applied in the field. However, importation and use of purified protein derivative (PPD) for TB skin testing have been infrequent in many countries. An adequate supply of PPD and training in skin testing are required for programs that use the TST to identify patients who will be offered INH.

Several studies performed in sub-Saharan Africa have documented that the TST is effective in diagnosing TB infection, even in populations where previous BCG vaccination rates approached 100%.

Obtaining PPD test materials, training staff, and implementing a TST program can be formidable barriers to providing preventive treatment for LTBI. Some countries with very high rates of LTBI in their populations have decided not to require TSTs, but to offer IPT to all HIV-infected persons who meet certain criteria, without the use of TB skin testing.

Treatment with Isoniazid

Criteria for INH treatment of HIV-infected persons with suspected LTBI (positive TST or those from a high-prevalence population) require exclusion of active TB or risk factors for adverse events. Reliance on a chest x-ray to rule out active TB is prohibitively expensive for many resource-limited settings, however, and observational studies have shown that clinical criteria are 95% sensitive in ruling out active TB. Persons with cough, night sweats, fever, weight loss, loss of appetite, and lymphadenopathy are not offered INH preventive therapy. Instead, persons with those symptoms are evaluated for active TB or other conditions that require treatment. Other exclusion criteria include recent treatment for TB, active TB requiring combination therapy, unsatisfactory commitment to adherence with treatment; and preexisting liver disease, preexisting peripheral neuropathy, or previous severe adverse reaction to INH.

Randomized trials in Haiti, Zambia, and Uganda have demonstrated that a 6-month course of INH reduced the risk of active TB among HIV-infected persons by 60% over 1-5 years of follow-up. In resource-limited settings, the usual course of treatment is 6 months of daily INH treatment taken by the patient without observation, but with monthly clinic visits and prescription refills. A minimum of 180 doses taken within 9 months, or 80% of the doses within 6 months, is considered a complete regimen. Often, pyridoxine 10-25 mg daily also is provided. In studies of HIV-negative persons, the benefit of INH lasts 2 years. Current guidelines do not recommend prolonging INH preventive therapy beyond 6 months or repeating IPT in subsequent years; these issues are under study.

INH is the only treatment for LTBI that is available in much of the world. Rifampin and rifabutin combinations are very expensive and are not used for treatment of LTBI in resource-limited settings. The combination of rifampin and pyrazinamide is toxic and is not recommended in either industrialized or resource-limited settings.

Treatment of HIV/TB-coinfected persons requires adequate supplies of HIV test kits, materials for tuberculin testing, INH, pyridoxine, a trained staff, a mechanism for promoting adherence, and a system of record keeping, along with the willingness of patients to participate. In Uganda, only a small proportion of HIV-infected persons who were offered tuberculin testing eventually took a 6-month course of INH. Use of IPT requires substantial resources and planning. Projects and countries using this approach to TB prevention will have to identify resources for all of these requirements.

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Antiretroviral Therapy

Background

Potent combination antiretroviral therapy (ART), consisting of 3 or more antiretroviral drugs (ARVs), has greatly improved the health and survival rates of HIV-infected patients in areas of the world with access to ARVs.

More than 20 individual ARVs are available in the resource-sufficient world, in addition to several fixed-dose combination preparations. These can be combined to construct a number of effective regimens for initial and subsequent therapy. ART is not without limitations, however. ART does not cure HIV infection and it requires that multiple medications be taken for very long periods of time (usually for the duration of life). It is expensive, may cause a variety of adverse effects (some severe), requires close adherence to be effective and to prevent the emergence of resistance, and often fails (because of the patient's imperfect adherence or other factors). The failure of an ARV regimen when accompanied by drug resistance usually means that subsequent regimens are less likely to succeed.

Greatly overshadowing the limitations of ART, however, is the overwhelming evidence that ART saves lives and improves or restores immune system function. Mortality and morbidity benefits are particularly obvious in patients with relatively advanced immune suppression or with symptoms related to HIV infection. For asymptomatic patients with relatively high CD4 cell counts (>350 cells/μL), it is less clear whether or when to start ART. In deciding when to start ART for any patient, practitioners must weigh the expected benefits of ART for that individual (in terms of morbidity and mortality) against the possible risks (eg, toxicity, drug resistance, adverse drug interactions).

Although implementing ART is complex, a number of guidelines from expert panels are available to help practitioners select effective regimens for particular patients. The U.S. Department of Health and Human Services (DHHS) keeps a repository of "living documents" of frequently updated recommendations on the use of ARV medications in children, adults and adolescents, and pregnant women. All clinicians treating HIV-infected patients should be familiar with the most current versions of these treatment guidelines. They are available on the Internet at the AIDSinfo Web site "Clinical Guidelines" section (http://aidsinfo.nih.gov/Guidelines). This chapter frequently references the *Adult and Adolescent ARV Guidelines*. (U.S. Department of Health and Human Services. *Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents*. May 4, 2006. Available online at aidsinfo.nih.gov/Guidelines/GuidelineDetail.aspx?GuidelineID=7.)

S: Subjective

Obtain the patient's history, including the following:

- CD4 cell count history, including nadir
- HIV viral load history, including before therapy if the patient is currently taking ARVs
- History of HIV-related conditions
- Previous and current ARV regimens, including regimen efficacy, toxicity, resistance, start and stop dates
- Current medications, including herbal preparations, supplements, and over-the-counter medications
- Medication allergies, intolerances, or prominent adverse effects
- Comorbid conditions (eg, hepatitis C, hepatitis B, depression)
- Occupation and daily schedule
- Current and previous substance use, including alcohol and recreational drugs
- Self-assessment of adherence to previous regimens
- Desire to start or continue an ARV regimen
- Commitment to adherence (see chapter *Adherence*)
- Indicators of ability to adhere to various types of regimens (eg, once daily, twice daily, every 8 hours, with or without food) given current life situation
- For women of childbearing potential: last menstrual period, current method of birth control (if any), current pregnancy status, thoughts on whether or when to have children

- History and review of systems (see chapter *Initial History*)

O: Objective

Perform the following objective tests:

- Complete physical examination (see chapter *Initial Physical Examination*)
- Current CD4 count and HIV viral load: preferably 2 or more separate results approximately 1 month apart
- Drug resistance profiles (genotype, phenotype, or both), past and present (if available) (see chapter *Resistance Testing*)
- Complete blood count (CBC) and platelet count, liver function tests (LFTs), renal function tests, fasting lipid panel (see chapter *Initial and Interim Laboratory and Other Tests*) fasting glucose, rapid plasma reagin (RPR), tuberculin skin test, hepatitis serologies

A: Assessment

Make the following basic decisions:

- The patient is or is not likely to benefit from ART at this time (ie, do potential benefits outweigh the risks)? See the *Adult and Adolescent ARV Guidelines* noted above, which thoroughly address the issue. A brief summary is included in the tables in the chapter *Determining Risk of HIV Progression* and in the chapter *CD4 Monitoring and Viral Load Testing*.
- The patient is or is not willing to start ARVs at this time (the choice to accept or decline therapy ultimately lies with the patient).
- The patient is or is not likely to adhere to an ARV regimen (an adherence counselor, with or without a mental health clinician, may be able to assist with this assessment and should be called upon if available). No patient should be automatically excluded from consideration of ART; the likelihood of adherence must be discussed and determined individually.

P: Plan

After educating the patient about the purpose and logistics of the proposed regimen and assessing the patient's potential for adherence, the ART regimen can be initiated, changed, or postponed accordingly.

The goals of therapy are to achieve maximal and durable viral suppression, restore or preserve immune function, improve quality of life, and reduce HIV-related morbidity and mortality.

Considerations before Initiating ART

No "average patient" exists. Some patients will do better during treatment and some will do worse than clinical studies would predict. Health care providers must work with each patient to develop a treatment strategy that is both clinically sound and appropriate for that individual's needs, priorities, and circumstances of daily life. Not all patients will be able to tolerate all drugs, and the patients understanding, readiness to commit to the regimen, and history of adherence to previous regimens must be considered when choosing ARV combinations. Major considerations are as follows:

- Willingness of the individual to begin therapy, coupled with understanding of the purpose and the mechanics of the planned regimen, and how it will fit into his or her life
- Degree of immunodeficiency and risk of disease progression as reflected by the CD4 count and HIV RNA level (see tables in the chapter *Determining Risk of HIV Progression* and the chapter *CD4 Monitoring and Viral Load Testing*)
- Potential benefits and risks of ARV drugs
- Likelihood of adherence to the prescribed regimen
- Resistance, if any, to ARV medications (obtain resistance testing prior to ARV initiation in ARV-naive patients)

The patient has the right to decline or postpone ART. This decision should not affect any other aspect of care, and ART should be offered again at each visit to patients who meet the criteria for treatment. If mental health issues, addiction, or the patient's social situation are barriers to adherence, initiate appropriate referrals and reassess adherence barriers at regular intervals.

Initiating Therapy: DHHS ARV Guidelines

The following recommendations have been adapted from the DHHS *Adult and Adolescent ARV Guidelines*.

- ART is *recommended* for all patients with a history of AIDS-defining illness or severe symptoms of HIV infection regardless of the CD4 cell count.

- ART is also *recommended* for asymptomatic patients with a CD4 count of <200 cells/μL.
- Therapy *should be offered* to asymptomatic patients with CD4 counts of 201-350 cells/μL. The urgency of treatment recommendations may be based on various factors, including the following:
  - Rate of CD4 cell decline
  - Plasma HIV RNA >100,000 copies/mL
  - Patient's interest
  - Risk of toxicity
- Therapy should probably be *deferred* for asymptomatic patients with CD4 counts of >350 cells/μL and plasma HIV RNA <100,000 copies/mL.

The question of when to initiate ART in asymptomatic patients remains an area of research and debate. It is clear that ART should be initiated before the CD4 count declines to <200 cells/μL, if at all possible. However, it is not yet known at what CD4 threshold ≥200 cells/μL therapy should be started, because the long-term risks of ARVs may be substantial in some patients. With the increasing availability of ARV regimens that are more tolerable, include fewer pills, and offer easier dosing schedules, some clinicians are choosing to initiate therapy earlier in the course of HIV infection.

Special Situations

- Pregnancy (see chapter *Care of HIV-Infected Pregnant Women*)
- Acute or primary HIV infection (see chapter *Primary HIV Infection*)
- Postexposure prophylaxis (see chapters *Occupational Postexposure Prophylaxis* and *Nonoccupational Postexposure Prophylaxis*)

Preparing the Patient for ART

Before starting ART, it is necessary to have a detailed discussion with the patient about his or her readiness to commit to a difficult, potentially toxic medication regimen, and to return for the required follow-up visits. The patient also must understand that the first treatment regimen offers the best opportunity for effective viral suppression, and immune reconstitution, which are the primary goals of ART.

Supporting Adherence

Numerous strategies are being tested for their effectiveness in supporting patients' adherence to the ART regimen. These may include extensive patient education, telephone contact with office staff members who can answer questions about adverse effects or other difficulties, family meetings, and peer support. Trust and accessibility appear to be important predictors of adherence, and some practitioners see the patient for 2 or 3 appointments before starting ART. Patients also may be given "test regimens" for a few weeks using inactive pills or mints, to help them understand how the medication schedule may fit into their lives before starting the actual ARVs. The choice to accept or decline ART ultimately lies with the patient (see chapter *Adherence*).

Anticipating Difficulties

Choosing an initial regimen that fits the patients lifestyle and that is likely to be tolerable will improve the likelihood of long-term success with that regimen. If patients develop toxicities to 1 or more components of an initial regimen, substitutions typically can be made without limiting the success of the regimen. Close monitoring and "check-in" appointments allow these adjustments to be made under clinical supervision. Close monitoring also can help to identify medication toxicities that may limit treatment and to detect early signs of inadequate medication adherence; early intervention to treat adverse effects and to support adherence may increase the likelihood of treatment success.

Considerations in Regimen Selection

Regimens should be selected with consideration of both patient factors and medication factors. The patient's schedule, adherence history, and self-defined goals of ARV therapy should be considered in selecting a regimen to which the patient will best adhere. The patient's comorbid conditions and potentially interacting medications should be evaluated for potential contraindications or synergism. The ARV history and any available resistance profiles should be reviewed carefully to choose a regimen that will be likely to achieve durable viral suppression. The CD4 cell count should be considered, especially if nevirapine will be used. In women who are pregnant or likely to become pregnant, ARV pregnancy categories and ARV teratogenicity should be taken into account. Table 6

of the *Adult and Adolescent ARV Guidelines* reviews the advantages and disadvantages of various drug classes and individual drugs in initial therapy.

Use of Multiple Classes of Drugs

For initial therapy, the *Adult and Adolescent ARV Guidelines* recommend the use of 2 nucleoside reverse transcriptase inhibitors (NRTIs) in combination with either a nonnucleoside reverse transcriptase inhibitor (NNRTI) or a protease inhibitor (PI). Drug combinations that include only NRTIs generally do not reduce virus levels as effectively as 2-class combinations. The question of whether to use an NNRTI or a PI in initial therapy is a matter of debate. Some clinicians advocate using 2 NRTIs with an NNRTI to preserve the PI class for later and avoid PI-related toxicities. Others are more concerned about the potential toxicities of NNRTIs and their low genetic barrier to resistance and instead recommend starting with a PI-containing regimen. In the end, the regimen should be selected with the individual patient in mind because the only effective combination is the one that the patient is willing and able to take on a consistent basis. See the information on drug resistance and toxicities below as well as the full text of the *Adult and Adolescent ARV Guidelines* for more complete discussions.

Boosted Protease Inhibitors

Ritonavir may be used at low doses in combination with several other PIs to enhance or "boost" the serum level and prolong the half-life. This strategy generally decreases the dosing frequency and the number of pills required, and improves the activity of some PIs.

Preferred Starting Regimens

More than 20 ARVs in 4 drug classes are approved (see Tables 10, 11, and 12 in the *Adult and Adolescent ARV Guidelines*). There are 4 nucleoside or nucleotide fixed-dose combinations and 1 PI coformulation. These guidelines suggest "preferred" and "alternative" regimens for initial therapy (Table 1).

Table 1. Initial Antiretroviral Regimens

Class	Antiretroviral Agents
Preferred Regimens	
NNRTI-Based	• Efavirenz + (lamivudine or emtricitabine) + (zidovudine or tenofovir) [Note: Efavirenz is not recommended for use in first trimester of pregnancy or in women with high pregnancy potential.]
PI-Based	• Lopinavir/ritonavir (coformulation) + (lamivudine or emtricitabine) + zidovudine
Alternative Regimens	
NNRTI-Based	• Efavirenz + (lamivudine or emtricitabine) + (abacavir or didanosine or stavudine) [Note: Efavirenz is not recommended for use in first trimester of pregnancy or in women with high pregnancy potential.] Nevirapine + (lamivudine or emtricitabine) + (zidovudine or stavudine or didanosine or abacavir or tenofovir) [Note: A high incidence of symptomatic hepatic events was observed in women with pre-nevirapine CD4 counts >250 cells/µL and men with CD4 counts >400 cells/µL; nevirapine should not be initiated in these patients unless the potential benefit clearly outweighs the risk.]
PI-Based	• Atazanavir + (lamivudine or emtricitabine) + (zidovudine or stavudine or abacavir or didanosine) or (tenofovir + ritonavir 100 mg/d) • Fosamprenavir + (lamivudine or emtricitabine) + (zidovudine or stavudine or abacavir or tenofovir or didanosine) • Fosamprenavir/ritonavir + (lamivudine or emtricitabine) + (zidovudine or stavudine or abacavir or tenofovir or didanosine) • Indinavir/ritonavir + (lamivudine or emtricitabine) + (zidovudine or stavudine or abacavir or tenofovir or didanosine) • Lopinavir/ritonavir + (lamivudine or emtricitabine) + (stavudine or abacavir or tenofovir or didanosine) • Nelfinavir + (lamivudine or emtricitabine) + (zidovudine or stavudine or abacavir or tenofovir or didanosine) • Saquinavir (hard-gel capsules or tablets)/ritonavir (100-400 mg/d) + (lamivudine or emtricitabine) + (zidovudine or stavudine or abacavir or tenofovir or didanosine)
3 NRTI-Based	• Abacavir + zidovudine + lamivudine (only when a preferred or an alternative NNRTI-based or PI-based regimen cannot or should not be used)

Key to abbreviations: NNRTI = nonnucleoside reverse transcriptase inhibitor; PI = protease inhibitor; NRTI = nucleoside reverse transcriptase inhibitor.

Adapted from U.S. Department of Health and Human Services. Table 6. Antiretroviral Regimens Recommended for Treatment of HIV-1 Infection in Antiretroviral-Naive Patients. In: *Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents*. May 4, 2006.

Practitioners should note that these recommendations change over time as new data regarding efficacy or toxicity become available. Among regimens with adequate potency (taking into account possible ARV resistance), regimen selection should be guided by factors such as anticipated tolerability, pill burden, drug interactions, and the patient's comorbid conditions.

Avoiding Drug Resistance

ARV medications never should be given as single agents, in 2-drug regimens, in suboptimal regimens, or in lower doses than recommended because of the potential for development of resistance. High-level resistance to NNRTIs, as well as to emtricitabine and lamivudine, may develop quickly (ie, within days to weeks) in these situations. It may take longer for high-level resistance to develop with other NRTIs and PIs. Patients must be instructed to take the full dosage of all medications on schedule, and to avoid skipping doses or taking "days off" from their regimens. Careful medication dosing is important because resistance to 1 drug within a particular class may transfer to other drugs in the same class (cross-resistance). Cross-resistance can limit the options for future therapy significantly or require very complicated regimens in the future. Resistant viral strains, once developed, may be transmitted to other people.

Acquired or "primary" resistance, in which a patient is infected with ARV-resistant virus, is common in parts of the United States. Because both multi- and single-class resistance has been found among drug-naive persons in many U.S. cities, it is recommended that individuals with newly diagnosed HIV infection and those new to care should receive a baseline resistance test as early as possible, and before initiation of ART (see chapter *Resistance Testing*).

Drug Interactions

Many of the ARVs interact with one another as well as with other common medications. When starting or changing an ARV regimen, review all the patient's current medications carefully for possible drug interactions. See chapter *Drug-Drug Interactions with HIV-Related Medications* for a summary of this issue and for references and resources to review medication lists and combinations. For further information on drug interactions involving ARVs, see Tables 19, 20, and 21 in the *Adult and Adolescent ARV Guidelines*.

Once-Daily Regimens

Convenient and simplified dosing is an obvious strategy to improve adherence, particularly with the availability of coformulations that reduce pill burden. The *Adult and Adolescent ARV Guidelines* currently include the once-daily combination of efavirenz + tenofovir + lamivudine or emtricitabine as a "recommended" regimen, and list several other possibilities are listed among the "alternative" regimens.

The combinations indicated below (2 NRTIs + 1 NNRTI or PI) are likely to be effective in initial therapy (Table 2). Some of these combinations, however, have not been studied in clinical trials.

Table 2. Once-Daily Regimens for Initial Therapy

NRTI Combinations	NNRTI or PI
• Lamivudine or emtricitabine + abacavir • Lamivudine or emtricitabine + didanosine • Lamivudine or emtricitabine + tenofovir# • Didanosine + tenofovir*#	• Efavirenz* • Nevirapine* • Atazanavir# • Atazanavir/ritonavir • Fosamprenavir/ritonavir • Indinavir/ritonavir • Lopinavir/ritonavir

Key to abbreviations: NRTI = nucleoside reverse transcriptase inhibitor; NNRTI = nonnucleoside reverse transcriptase inhibitor; PI = protease inhibitor

* Didanosine + tenofovir should not be used with efavirenz or nevirapine.

Tenofovir cannot be used with unboosted atazanavir. Adapted from Coffey S. *Options for Once-Daily Dosing of Antiretrovirals*. AETC National Resource Center Web site. Available at http://aidsetc.org/aidsetc?page=et-03-00-01.

Drugs and Drug Combinations That Should Not Be Used

Drugs with similar mechanisms of action and resistance mutations (eg, lamivudine and emtricitabine, or efavirenz and nevirapine) offer no significant advantage when combined and may increase toxicities. Drugs with additive or overlapping toxicities, such as stavudine and didanosine, should not be combined. Zidovudine and stavudine, which compete intracellularly and therefore cause antagonism, should not be used together. Most clinicians in the United States avoid using the NRTI stavudine if other options are available because of the high rate of metabolic abnormalities associated with that drug. Certain 3-drug combinations have suboptimal efficacy and are not recommended (eg, tenofovir + didanosine + NNRTI). Some ARVs require specific dosing intervals in particular patients. For example, once-daily dosing of lopinavir/ritonavir is not

recommended patients receiving concomitant efavirenz or nevirapine, and some once-daily PIs or combinations should not be used in treatment-experienced patients.

Follow-Up of Patients Starting ART

Patients who start a new ARV regimen should be seen at least twice within the first month to assess effectiveness, adherence, tolerability, and adverse effects of the regimen.

At 2 weeks on a new regimen, practitioners should check the following:

- CBC with platelets, especially for patients starting a zidovudine-containing regimen, to monitor for anemia
- LFTs, especially for patients starting a nevirapine-containing regimen, to monitor for hepatotoxicity

At 4-8 weeks on a new regimen, and every 3 months on a stable regimen, check the following:

- HIV viral load, to monitor initial virologic response to therapy
- CD4 cell count, to monitor initial CD4 response to therapy (note that CD4 response may lag behind virologic response)
- CBC with platelets (as above)
- LFTs (as above) and renal function tests

Patients should have glucose and lipid profiles (preferably when fasting) checked at baseline and, if normal, repeated every 4-6 months after starting ART. If the results are abnormal or if the patient has cardiac risk factors, recheck every 3-4 months while on the regimen.

Regimen Failure

A treatment regimen may fail for several reasons.

Inadequate virologic response

- Viral load does not decline below the level of detection (<50-75 copies/mL, especially in patients taking initial therapy) within 6 months of initiating therapy. (In patients with previous treatment experience and in those with ARV resistance, it may not be possible to decrease plasma HIV viral load to undetectable levels, and stabilization of viral load below the previous baseline may be an appropriate goal of therapy.)

Virologic rebound

- Virus is repeatedly detected in plasma after initial suppression to undetectable levels. The degree of increase should be considered, however. Repeat testing is required to rule out "blips" of virus (isolated elevations in viral load of less than about 1,000 copies/mL) that are not clinically significant and to ensure that the increase is not due to infection, vaccination, or problems with test methodology.
- A reproducible, significant increase occurs in viral load, reaching 3-fold or greater from the lowest plasma HIV RNA level, that is not due to intercurrent infection, vaccination, or problems with test methodology.

Immunologic failure

- The CD4 cell count, measured on at least 2 separate occasions, shows a persistent decline.
- The CD4 cell count fails to increase by at least 25-50 cells/μL above baseline in the first year of ART.

Clinical deterioration or progression

- Recurrent, persistent, or new HIV-related illness occurs after at least 3 months on ART. Note that new or recurrent symptoms of opportunistic illness occurring in the first weeks to months after starting ART, especially in patients with severe immunosuppression, may not reflect a failure of ART. Rather, these symptoms could be due to persistence of severe opportunistic infections that may require longer treatment, or they could be due to an immune reconstitution syndrome (see chapter *Immune Reconstitution Syndrome*).

Responding to Apparent Treatment Failure

Refer to the *Adult and Adolescent ARV Guidelines* and consult with HIV-expert clinicians about the use of resistance testing and alternative regimens before discontinuing therapy.

Carefully assess patient adherence, because inadequate adherence to ARVs is a common reason for regimen failure. In some cases, adherence support, treatment of adverse drug effects, substitution for poorly tolerated ARVs, or other measures to enhance adherence may result in virologic suppression. In other cases, ARV resistance may have developed. Poor adherence may affect the decision to change therapy, and adherence issues should be addressed before a new regimen is initiated.

The availability of effective alternative ARVs is critical consideration in deciding whether or when to change therapies. If treatment possibilities are limited or nonexistent, it may be necessary to weigh the value of partial virologic suppression with the current regimen against the likelihood of further resistance. Consultation with an experienced HIV provider and use of HIV resistance testing are appropriate when considering changes in therapy. When no treatment options remain among currently approved drugs, refer the patient to an appropriate clinical trial if possible.

Susceptibility or Resistance Testing

It is fairly common for a first regimen to fail because of resistance to only 1 or 2 drugs in a multidrug combination (see chapter *Resistance Testing*). Resistance testing, although expensive and time consuming, can identify drugs that are less likely to be effective against the patient's virus. During resistance testing, the patient should still be taking the failing regimen so that resistant viral populations will be present in detectable numbers. Resistance testing is recommended before changing regimens because of virologic rebound during ARV therapy or suboptimal suppression of viral load on ARV therapy.

Cross-resistance exists among ARVs, such that resistance to 1 drug in a class of agents often extends to other agents in that class. For example, cross-resistance between efavirenz and nevirapine is almost complete, and resistance mutations to NRTIs and to PIs often decrease viral susceptibility to other drugs in those classes. As a result, selecting a new ARV regimen can be complicated because it requires knowledge of expected resistance patterns. The likelihood of sustained viral suppression is lower when resistant virus is present even if a subsequent regimen contains new ARVs.

Guidelines for Changing an ARV Regimen for Suspected Drug Failure

The following recommendations are adapted from the *Adult and Adolescent ARV Guidelines*.

- Distinguish between the need to change a regimen because of drug intolerance or inability to adhere to the regimen and the failure to achieve the goal of sustained viral suppression. In the event of intolerance, single agents usually can be changed without resistance testing.
- In general, do not change a single drug or add a single drug to a failing regimen; it is important to use at least 2 or, preferably, 3 active drugs. If resistance testing (performed while the patient is taking the failing regimen) shows resistance to only 1 agent in a regimen, it may be possible to replace only that drug; however, this approach requires clinical validation.
- Many patients have limited options for new regimens that will achieve durable virologic suppression. In some of these cases it is rational to continue the same regimen if partial virologic suppression and clinical and immunologic stability were achieved.
- In some cases, it is rational to continue regimens identified as suboptimal for initial therapy in patients with limitations imposed by toxicity, intolerance, or nonadherence, especially in late-stage disease. Even when these patients fail to achieve durable viral suppression on these regimens, they may remain clinically stable, with stable CD4 cell counts. Discontinuing ARVs can lead to reversion of more virulent wild-type virus and to clinical progression.
- Data are limited on the value of restarting a drug that the patient has previously received. Resistant virus can be archived and will reemerge for patients who are rechallenged with regimens on which they had previously developed resistance. As a result, resistance tests from previous regimens should be used with current resistant tests to determine what drugs might be active in a new regimen.
- If virologic failure occurs on an NNRTI-containing regimen, avoid changing among NNRTIs because high-level cross-resistance is likely.
- The decision to change therapy and the choice of a new regimen require that the clinician have considerable expertise in the care of people with HIV infection. Those less experienced in the care of persons with HIV are strongly encouraged to obtain assistance by consulting with or referring to an expert clinician.

For a general strategy for selecting a new regimen after virologic failure of an initial regimen, see Table 25 in the *Adult and Adolescent ARV Guidelines*. Note that other possibilities exist, and resistance testing and expert consultation should be sought to help guide treatment choices.

Follow-Up of Patients Not Started on ART

Patients who may benefit from ART, but are not on therapy

These patients should continue their regular visits for monitoring, prophylaxis, and other medical treatment. Changes in laboratory results and the patients' condition should be taken as opportunities to reassess their decisions about ARVs, to educate them about new medications and research findings, and to discuss the risks of delayed treatment, including the risk of progression to AIDS or death. ARVs should be discussed again and offered at regular intervals to anyone who initially refuses treatment. If lack of readiness or probable adherence difficulties are issues, an adherence counselor (if available) or a mental health provider should be engaged to bolster the patients support and coping mechanisms (see the *Adult and Adolescent ARV Guidelines* or check tables in the chapter *CD4 Monitoring and Viral Load Testing*).

Patients who do not meet the DHHS criteria for starting ARVs

These patients should be monitored regularly with laboratory tests and physical examination (see Section 1, *Testing and Assessment* for chapters on physical examinations and laboratory tests), offered prophylaxis as appropriate, and reassessed for ARV therapy when they do meet the criteria for starting treatment.

Special Situations for ART

ART during acute or primary HIV infection

Patients with acute or primary HIV infection may experience symptoms such as rash, fever, lymphadenopathy, fatigue, weight loss, nausea, and headache within the first few weeks after becoming infected, and still have a negative or indeterminate result on the HIV antibody test. If a careful HIV risk history reveals the patient to be at significant risk for recent HIV infection, an HIV RNA test can be performed to ascertain whether viremia is present. (Note that a low viral load may suggest a false-positive result.) It is not yet known whether ART has a long-term benefit when started during primary HIV infection. However, for the appropriate patient, it is reasonable to consider starting therapy, with the goal of maximal virologic suppression. Before starting an ARV regimen, patients must be counseled carefully about potential limitations, such as toxicity, pill burden, cost, and the possible development of drug resistance. Patients should be monitored with HIV viral load, CD4 counts, and other parameters, as in patients with established infection who are taking ARV therapy. Because no definitive data exist on the clinical benefit of early treatment and because ART involves certain risks, including drug toxicity and resistance, persons with acute HIV infection ideally should be treated in controlled clinical trials. (See chapter *Primary HIV Infection*.)

Pregnant women

Since 1994, zidovudine has been recommended to reduce the risk of mother-to-child transmission of HIV, but zidovudine monotherapy is less effective than combination therapy in reducing perinatal transmission and is inadequate for treatment of the pregnant woman. Combination ARV regimens are now used during pregnancy, if possible, to reduce the risk of transmission to the infant and to treat HIV infection in the mother. Certain ARVs are recommended during pregnancy, whereas others should be avoided. Because of potential teratogenic effects, efavirenz should not be used. (See chapters *Reducing Maternal-Infant HIV Transmission* and *Care of HIV-Infected Pregnant Women*; also refer to CDC. *Public Health Service Task Force Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV-1 Transmission in the United States*. July 6, 2006. Available online at http://aidsinfo.gov/Guidelines/GuidelineDetail.aspx?GuidelineID=9.)

ARV treatment in resource-limited settings

The discussion of ARV management is futile for the majority of people in the world today who are living with HIV/AIDS. According to the Joint United Nations Programme on HIV/AIDS, as of June 2005, only 11% of those needing ARV therapy in low- and middle-income countries were receiving treatment.

ARV medications are becoming available in many parts of the developing world, but the increase in availability is slow and in no way is occurring at the pace and with the efficiency warranted in this dire situation. Medication choices are limited by the availability and cost of drugs. Most resource-limited countries that are able to provide ARVs use an NNRTI-based combination for initial therapy. This regimen typically includes nevirapine or efavirenz plus 2 NRTIs such as zidovudine or stavudine plus lamivudine. Second-line therapies or substitutions needed because of toxicities or intolerance often are not readily available.

Widespread use of nevirapine to prevent mother-to-child transmission of HIV has lowered the rate of HIV

transmission to infants, but the drug resistance that may emerge after even single-dose administration to the mother during labor has raised many concerns regarding effective treatment options for the mother. Without the availability of resistance testing, many women are subsequently started on an ARV regimen that includes an NNRTI. For women who have developed NNRTI resistance during previous nevirapine exposure, these regimens probably will be ineffective. In addition, NRTI resistance is likely to develop, further limiting treatment options.

Concern about adherence in resource-limited settings, although often cited as a treatment-limiting factor, has proven to be less of an issue than it is in the United States and western Europe. Many treatment programs require a lengthy educational process before ARVs are initiated. In addition, the limited availability of treatments paired with the widespread devastation of entire communities and countries has enhanced the motivation for strict adherence to therapies among patients able to acquire ARV therapy.

CD4 count and viral load testing to identify patients who should begin ART, and to monitor ARV effectiveness and potential drug toxicities, are severely limited by the lack of sufficient laboratories, equipment, and funds to perform costly blood tests. In some settings, patients are started on therapy based on clinical presentation alone, and monitoring is based solely on clinical criteria. Success of treatment may be assessed by clinical response, such as resolution of opportunistic infections, weight gain, and improvements in quality of life. ARV toxicity may be assessed by clinical signs and symptoms of adverse effects such as anemia or hepatitis.

Comorbid conditions such as tuberculosis and malaria, and potential drug interactions associated with their treatments, often complicate therapy choices. Competing priorities of poverty, lack of clean water or sanitation, and overburdened health care settings and health care providers combine to complicate the distribution of effective ARV treatment. Regardless of the numerous challenges to treatment in resource-limited settings, human compassion and responsibility dictate that we find a way to provide care for those who require treatment.

Expert Consultation

The National HIV/AIDS Clinicians' Consultation Center (NCCC) is a valuable resource for any clinician seeking expert advice about ART, HIV clinical manifestations, laboratory evaluations, and other issues. Its National HIV Telephone Consultation Service (Warmline) is staffed by HIV-experienced physicians and pharmacists. The Warmline operates Monday through Friday, 8 AM to 8 PM EST and is available free of charge in the United States at 800-933-3413.

Patient Education

- Starting ARVs is rarely an emergency. Before starting ARVs, health care providers must work with patients to determine how important therapy would be for them, what goals of therapy are likely to be achieved, and which personal issues are pertinent for selecting the best regimen to fit their lifestyles.
- Providers should review the proposed drug regimen with their patients. Be sure patients understand the instructions about dosage, scheduling, food requirements or restrictions, drug storage, adverse effects, toxicities, and type of reactions that must be reported immediately, as well as remedies for common adverse effects.
- Providers should explain to patients that ART requires a commitment to taking the medications precisely as prescribed. There is a limited number of ARVs, and if they are taken incorrectly, the virus can quickly become resistant to the medications. This will mean even fewer choices and less effective treatment in the future. It might also mean that they could transmit resistant virus to a partner or, if they are pregnant, to an infant.
- Patients should know that HIV medications do not prevent transmission of infection to others. Safer-sex recommendations must be followed and other high-risk activities (eg, needle sharing) must be carefully avoided to keep from spreading the virus to others (see chapter *Preventing HIV Transmission/Prevention with Positives* for more information).
- Experts recommend using latex barriers during sex (safer sex) and not sharing needles or other drug-using equipment, even with other HIV-infected persons. Patients should know that if their virus develops resistance to some ARVs and they pass that virus on to another person, HIV medications may not be effective in that person. If a patient's partner

happens to have a drug-resistant strain of HIV, it is possible for the patient to become infected with a resistant virus in addition to the one he or she has already, and this may limit treatment options.

- Hepatitis C, hepatitis B, and other sexually transmitted infections such as syphilis and gonorrhea can be transmitted between partners who both have HIV.
- If ARVs must be discontinued, it is usually best to stop all ARVs at once. The exception to this recommendation may be NNRTI-containing regimens; in this case, the NRTIs should be continued for about 1 week after discontinuation of the NNRTI, if possible. Even carefully managed interruptions can cause drug resistance mutations. Again, this will limit future treatment options, and should be avoided if possible.
- Discuss contingencies in the event that the client is unable to take ARVs for a day or more (eg, illness, severe adverse effects, hospitalization, or other unexpected circumstances).

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Adherence

Background

For HIV-infected patients treated with antiretroviral therapy (ART), adherence to ART is a significant determinant of survival. Adherence is second only to the CD4 cell count as a predictor of progression to AIDS and death. Adherence rates approaching 100% are needed for optimal viral suppression, yet the average adherence rate to ART in the United States is approximately 70%. Patients with suboptimal adherence are at risk not only for HIV progression, but also for the development of drug resistance (see chapter *Resistance Testing*). Studies indicate that health care providers' assessments of their patients' adherence often are inaccurate and limited, so individualized assessment and planning for adherence are essential for patients to be successful with ART.

S: Subjective

Adherence assessment is most successful when conducted in a positive, nonjudgmental atmosphere. Patients need to know that their provider understands the difficulties associated with taking an antiretroviral (ARV) regimen. Within a trusting relationship, a provider may learn what is actually happening with the patient's ARV medication regimen rather than what the patient thinks the provider wants to hear. Important questions to ask a patient who is considering ART may be found in Table 1. Table 2 suggests important questions for patients who are receiving ART.

Common reasons for nonadherence include the following: experiencing adverse effects, finding the regimen too complex, having difficulty with the dosing schedule (not fitting into the daily routine), forgetting to take the medications, being too busy with other things, oversleeping and missing a dose, being away from home, not understanding the importance of adherence, and being embarrassed to take medications in front of family, friends, or coworkers. It is important to look for these and other potential barriers to adherence. (See chapter *Initial History.*)

O: Objective

Evaluate the following:

- CD4 cell count
- HIV viral load (indicating the effectiveness of ART in suppressing viremia; an indirect indicator of adherence)
- Current drug list (including over-the-counter medications, vitamins, and herbal remedies); check for adverse drug interactions with ARV medications
- Pharmacy refill records

A: Assessment

Assess adherence at each visit using questions such as those in Tables 1 and 2, and assessment scales such as those found in Tables 4, 5, and 6 (Appendix 1). Ask these questions in a nonjudgmental way and listen carefully to the patient to invite honesty about issues that may affect adherence.

Table 1. Important Questions to Ask Patients Considering Antiretroviral Therapy

- What is your attitude toward antiretroviral therapy?
- Do you believe that antiretroviral therapy is effective?
- What do you hope these medications will do for you?
- Are you ready to take the medication every day, around the same time each day?
- Are you committed and motivated to take the medication every day for the rest of your life?
- Who knows about your HIV status?
- What other medications are you taking: prescription, over-the-counter, herbals?
- Are you a morning or afternoon person?
- What is your daily routine, including waking and bed times?
- How many meals and snacks do you eat per day, and at what times?
- Do you use alcohol, marijuana, cocaine, or injectable drugs? If so, how much do you use and how long have you used them?

Table 2. Important Questions to Ask Patients Taking Antiretroviral Therapy

- Do you manage your own medications? If not, who manages them for you?
- What HIV medications do you take and what is their dosage? When do you take these?
- How do you remember to take your medications?
- How many doses of your HIV medication have you missed in the last 72 hours, last week, last 2 weeks, and last month?
- On a scale of 1 to 10, where would you say you are? A score of 1 indicates that you do not take your medicines right at all; for example, not every day or not at the same time every day; 10 indicates that you take your medications perfectly every day, at the same time every day. (Visual analog scales are also used to assess adherence; see Appendix 1.)
- If not a 10, what causes you not to be a 10?
- When are you most likely to miss doses?
- Do you have any adverse effects to from your HIV medications? If so, what are they?
- Are you comfortable taking medications in front of others?
- What is most difficult about taking your medications?
- How do you like working with your pharmacy?

The patient's self-report has been shown to be the most effective measure of adherence. Although, according to some studies, self-report of good adherence has limited value as a predictor of good adherence, self-report of suboptimal adherence should be regarded as a true predictor of poor adherence.

Before initiating (or changing) ART, it is important to assess the patient's readiness for ART. Patient factors that have been associated with poor adherence in the United States and western Europe include:

- Depression
- Active alcohol or drug use
- Low literacy
- Lack of social support
- Lack of belief in treatment efficacy
- Unstable housing
- Competing priorities (eg, housing, childcare, food, work)

Most of these factors are modifiable. Before starting ART, appropriate interventions should be made, and sources of adherence support should be identified to help patients overcome potential barriers to adherence.

It is important to note that sociodemographic variables such as sex, HIV risk factors, and education level generally are not associated with adherence. In addition, a history of substance or alcohol abuse is not a barrier to adherence.

Assess the patient's support system, and ask who knows about the patient's HIV status. Supportive family or friends can help remind patients to take their medications and assist with management of adverse effects. For patients who have accepted their HIV infection as an important priority in their lives, taking medications can become routine despite other potential adherence barriers such as alcohol or drug use.

Assess patients' willingness to accept and tolerate common adverse effects of ART. Patients may identify some adverse effects that they wish to avoid completely and others that they are willing to accept and manage; this may help in tailoring the selection of ARV medications to the individual patient. Describe strategies for the management of adverse effects before starting a regimen (see chapters *Patient Education* and *Adverse Reactions to HIV Medications*).

Before prescribing ARVs, some clinicians have their patients do adherence trials using placebo tablets or jelly beans to measure the patients' readiness to start therapy and their ability to adhere to a regimen. This trial allows patients to experience what a regimen will entail in real life, how therapy will affect their daily lifestyle, and what changes will be needed to accommodate the regimen. The shortcoming of placebo trials is that patients are not challenged with adverse effects as they might be with a true regimen.

For patients taking ART, it is important to assess adherence at every clinic visit. Tools such as those in Appendix 1 may be useful in predicting adherence. Adverse effects are a common cause of suboptimal adherence to ART. Continue to ask whether the patient has adverse effects from the ARV medications and assess his or her ability to accept and tolerate these. Work closely with the patient to treat adverse effects, and consider changes in ART if adverse effects are not tolerated. Continue to offer support to improve or maintain optimal adherence.

P: Plan

Start the ARV regimen only when the patient is ready. Starting it too early may result in poor adherence, failure of the regimen, and increased risk of ARV resistance. Comorbid conditions that interfere with

adherence, such as mental health issues or depression, must be treated initially. It is important to consider the patient's preferences in selecting the drug regimen. The regimen must fit into the patient's daily routine, and the patient must believe in the potential success of ART. Simplifying the ARV regimen to the extent possible with once-daily regimens and the lowest number of pills, while maintaining efficacy and minimizing adverse effects, is important for maximizing adherence and avoiding pill fatigue. Starting ART is rarely an emergency, so taking time to identify the patient's wishes for care, make a thorough readiness assessment, select the ARV regimen, and plan for adherence support is important in maximizing the likelihood of treatment success. (See Table 3 for additional suggestions.)

Table 3. Strategies to Improve Adherence to Antiretroviral Therapy

- Establish readiness to start therapy
- Provide education on medication dosing
- Review potential adverse effects
- Anticipate and treat adverse effects
- Utilize educational aids including pictures, pillboxes, and calendars
- Engage family, friends
- Simplify regimens, dosing, and food requirements
- Utilize team approach with nurses, pharmacists, and peer counselors
- Provide accessible, trusting health care team

Source: U.S. Department of Health and Human Services. *Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents*. Table 15. May 4, 2006. Available online at http://aidsinfo.nih.gov/Guidelines/GuidelineDetail.aspx?GuidelineID=7. Accessed May 19, 2006.

Patients who can identify their medications (in their own words) and describe the proper dosing and administration have higher adherence rates. Providing patient education before writing a prescription helps ensure adherence to ARV medications. Education can be provided in oral, written, or graphic form to assist the patient's understanding of the medications and their dosing. Basic information, including number of pills, dosages, frequency of administration, dietary restrictions, possible adverse effects, tips for managing adverse effects, and duration of therapy will help patients to understand their ARV regimens. Patients should understand that the success of ART depends upon taking the medications every day and that adherence levels of >95% are important in preventing virologic failure.

Close follow-up by telephone, clinic visits, or other contact with the patient during the first few days of therapy is useful in identifying adverse effects, assessing the patient's understanding of the regimen, and addressing any concerns before they become significant adherence barriers. Individualized interventions should be designed to optimize outcomes for each patient. Pharmacists, peer counselors, support groups, adherence counselors, behavioral interventions, and community-based case managers are useful in supporting adherence for the HIV-infected patient. Multidisciplinary teams that include nurses, case managers, nutritionists, and pharmacists, in which each care provider focuses on adherence at each contact with the patient, are extremely effective in supporting adherence.

Many physical devices can be used to support adherence. The following are simple, inexpensive, and easy to incorporate into the routine of the HIV patient:

- Medication organizers include pillboxes and medisets. These are available in several shapes and sizes to fit the needs of the individual patient. They can be filled weekly so that the patient can easily determine whether a dose of medication was missed.
- Reminder devices include alarm watches, beepers, or cell phone alarms. They are effective in reminding the patient when to take medications. Medication diaries may be used for the patient to record doses that were taken.
- Visual medication schedules: are calendars with pictures of the patient's medications on them to remind the patient to take the doses.

Interventions for successful adherence are an ongoing effort, not one-time events. Studies have suggested that adherence rates decline when patient-focused interventions are discontinued. Therefore, positive reinforcement at each clinic visit or contact is extremely important. Reinforce what the patient has done well and assist the patient in identifying and problem-solving areas for improvement. Whenever possible, share positive information about the patient's health, such as improvements in quality of life, CD4 cell count, and viral load, to encourage a high level of adherence.

Special Populations and Issues

Mental Illness

Patients with mental health issues may have difficulty with adherence. In this population, it is particularly important to incorporate ARV medications into structured daily routines. Medication cassettes, reminder

signs, and calendars have been very effective for these patients. Nursing care providers and family members may be instrumental in filling medication boxes or ordering prescription refills.

Pediatrics

Adherence can be a challenge for young children who rely on parents and caregivers to provide their medications. Adolescents are more likely than younger children to have poor adherence. To improve adherence in this population, it is important to support the family. The *Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection* review some of the adherence issues and considerations for this patient population.

Low Literacy

Health literacy is an important predictor of treatment adherence, particularly in low-income populations. Adherence interventions are necessary in this population to accommodate individuals who have difficulty reading and understanding medical instructions. Providers often fail to recognize this disability. In addition, adherence support is needed for patients who have difficulty navigating the health care system.

Resource-Limited Settings

Early research has shown that the level of adherence in resource-limited countries is at least as good as that in resource-rich settings and that rates of virologic suppression are equivalent or better. Lack of access to a consistent supply of ARV medications, including financial barriers that may cause interruptions in treatment, appears to be the primary obstacle to adherence in resource-limited settings.

Patient Education

- Providers must urge patients to take their ARV medications exactly as prescribed and to take every dose, every day.
- Patients must know that if they miss or skip doses of their ARV medications, they may not work well to fight HIV, and the virus may develop resistance to them.
- Tell patients to notify the clinic if they miss doses of their ARV medications.
- Discuss with patients how to improve their adherence, and support good adherence.
- Warn patients that some people have adverse effects from the medications, and tell them to notify the clinic if they develop adverse effects. Discuss ways to reduce these effects.

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Appendix 1. Scales to Assess Adherence to HIV Medication Regimens

Table 4. Visual Analog Scale Used in a Research Study to Assess Adherence to HIV Medication Regimens

Script for Interviewing Patient about Adherence		
Interviewer	Now I'm going to ask some questions about your HIV medications. Most people with HIV have many pills or other medications to take at different times during the day. Many people find it hard to always remember to take their pills or medicines. For example: • Some people get busy and forget to carry their pills with them. • Some people find it hard to take their pills according to all the instructions, such as "with food" or "on an empty stomach," "every 8 hours," or "with plenty of fluids." • Some people decide to skip taking pills to avoid adverse effects or to just not take pills that day. We need to understand what people with HIV are really doing with their pills or medicines. Please tell us what you are actually doing. Don't worry about telling us you don't take all your pills or medicines. We need to know what is really happening, not what you think we "want to hear." Which antiretroviral medications have you been prescribed to take within the last 30 days?	
INTERVIEWER: LIST CODES FOR ALL ANTIRETROVIRALS THAT SUBJECT WAS PRESCRIBED TO TAKE IN LAST 30 DAYS. IDENTIFY UP TO 4 DRUGS.		
	DRUG A:	**DRUG C:**
	DRUG B:	**DRUG D:**
Interviewer	Now, I am going to ask you some questions about these drugs. Please put an "X" on the line below at the point showing your best guess about how much (DRUGS A-D) you have taken in the last 3-4 weeks. We would be surprised if this were 100% for most people.	
HAND INSTRUMENT AND PEN TO RESPONDENT		
Interviewer	0% means you have taken no (DRUG A) 50% means you have taken half your (DRUG A) 100% means you have taken every single dose of (DRUG A)	
Adherence Self Assessment Instrument		
Instructions for Patient:	Put an "X" on the line below at the point showing your best guess about how much of each drug you have taken in the last 3 to 4 weeks. 0% means you have taken none of the drug 50% means you have taken half of the drug 100% means you have taken every single dose of the drug	
DRUG A:	**0% 10% 20% 30% 40% 50% 60% 70% 80% 90% 100%**	
DRUG B:	**0% 10% 20% 30% 40% 50% 60% 70% 80% 90% 100%**	
DRUG C:	**0% 10% 20% 30% 40% 50% 60% 70% 80% 90% 100%**	
DRUG D:	**0% 10% 20% 30% 40% 50% 60% 70% 80% 90% 100%**	

Adapted from Machtinger EL, Bangsberg DR. *Adherence to HIV Antiretroviral Therapy*. HIV InSite, May 2005. Available online at hivinsite.ucsf.edu. Accessed June 1, 2006.

Table 5. Morisky Scale to Assess Adherence to HIV Medications: Dichotomous Response Options

Subjects were asked: "Thinking about the medications PRESCRIBED to you by your doctor(s), please answer the following questions."		
	NO	**YES**
Do you ever forget to take your medications?		
Are you careless at times about taking your medications?		
When you feel better, do you sometimes stop taking your medications?		
Sometimes, if you feel worse when you take your medications, do you stop taking them?		

Adapted from Morisky DE, Green LW, Levine DM. *Concurrent and predictive validity of a self-reported measure of medication adherence*. Med Care 1986;24: 67-74.

Table 6. Morisky Scale to Assess Adherence to HIV Medications: 5-Point Response Options

Subjects were asked: "Thinking of the medications PRESCRIBED to you by your doctor(s), please answer the following questions."					
Response options: never = 0; rarely = 1; sometimes = 2; often = 3; always = 4					
	0	1	2	3	4
Do you ever forget to take your medications?					
Are you careless at times about taking your medications?					
When you feel better, do you sometimes stop taking your medications?					
Sometimes, if you feel worse when you take your medications, do you stop taking them?					

Adapted from Morisky DE, Green LW, Levine DM. *Concurrent and predictive validity of a self-reported measure of medication adherence*. Med Care 1986;24: 67-74.

Resistance Testing

Background

As of mid 2006, 2 major types of resistance testing are available: genotype tests and phenotype tests.

Genotype Tests

Genotypic testing works by amplifying and sequencing HIV taken from a patient to look for mutations in the HIV reverse transcriptase and HIV protease genes, which are known to correlate with clinical resistance to antiretroviral drugs. This test generally can detect mutations in plasma samples with HIV RNA levels >1,000 copies/mL. Species representing 20% or more of the amplified product usually can be detected by current techniques. Minor species may not be detected. Resistance mutations acquired in the past, under the selective pressure of a previous drug, may be archived in minor species and remain invisible to genotypic testing. These resistance mutations may reemerge and cause drug failure, however, if the previous drug is used again.

A genotype test takes 1-2 weeks to complete. The results are reported as a list of the mutations detected; most reports also include an interpretation that indicates the drug resistance likely to be conferred by those mutations (see "Modifying Factors" below, for a discussion of the limitations of resistance testing).

Genotype results can be difficult to interpret. A thorough antiretroviral history and expert clinical review, therefore, are necessary to put the results of a genotype test in proper perspective and to identify options for further treatment. A compilation of the most common HIV mutations selected by the 3 classes of antiretroviral agents is available at: http://hiv-web.lanl.gov.

A "virtual phenotype" is a genotype that is compared with a databank of patients' samples that have been analyzed by paired genotype and phenotype testing. The patient's genotype is matched to a banked genotype, and the patient's phenotype is then predicted based on the phenotypes paired to the banked genotype. A virtual phenotype can be completed in the same amount of time as a genotype. Results are reported as a genotype (listing the mutations detected) as well as a predicted fold change in the 50% inhibitory concentration (IC50) of each drug to the patient's virus (see "Phenotype Tests" below). The predicted susceptibility of the patient's virus to each drug is then reported, based on biologic and clinical cutoffs.

Phenotype Tests

Phenotypic testing works by splicing the HIV reverse transcriptase and HIV protease genes from a patient's virus into a standardized laboratory strain, which is then grown in the presence of escalating concentrations of antiretroviral drugs. The test measures the IC50 of each drug against the virus in vitro. Results are reported as fold-change in IC50, as compared with a drug-susceptible control strain or with a previous test of the same patient's blood. The predicted susceptibility of the patient's virus to each drug is then reported, based on what is known about the correlation between fold-change in IC50 of that drug and clinical resistance. As with genotypic testing, the phenotype may not be able to detect resistance if the HIV RNA is low (<1,000 copies/mL) and may not detect minor species. A thorough antiretroviral history and expert interpretation are essential in determining the significance of the results. A phenotype takes 2-3 weeks to complete.

Modifying Factors

Table 1 presents an overview of when genotype and phenotype testing is, and is not, recommended.

Limits of Resistance Testing

In a patient taking antiretroviral therapy (ART), drug-resistant HIV evolves in response to selective pressure applied by the antiretroviral drugs in the patient's system. Specific resistance mutations develop in response to the pressure exerted by specific drugs (M184V, for example, evolves in response to lamivudine or emtricitabine). The presence of viral resistance suggests that a particular drug (and drugs with similar resistance patterns, or cross-resistance) is unlikely to be successful in suppressing viral replication.

In contrast, the absence of resistance to a drug does not necessarily indicate that the drug will be successful, particularly if that drug (or drugs sharing cross-resistance) has been used previously. If a particular

Table 1. Resistance Testing Recommendations

Clinical Setting/Recommendation	Rationale
Recommended	
Acute or primary HIV infection, if treatment is to be started	• Determine whether drug-resistant virus was transmitted, to help design an initial regimen or to change a regimen accordingly. • Consider resistance testing if treatment is deferred.
Chronic HIV infection before starting ART	• Determine whether drug-resistant virus was transmitted to help design an initial regimen. • Transmitted drug-resistant virus is more likely to be detected earlier in the course of HIV infection; consider resistance testing early.
Virologic failure during ART	• Determine the role of resistance in drug failure and maximize the number of active drugs in the new regimen, if indicated.
Suboptimal suppression of viral load after starting ART	• Determine the role of resistance and maximize the number of active drugs in the new regimen, if indicated.
Not Usually Recommended	
After discontinuation of drugs	• Drug resistance mutations may decrease in number and become undetectable on assays.
Plasma viral load <1,000 HIV RNA copies/mL	• Resistance assays may not be reliable because of the low number of RNA copies.

Key to abbreviations: ART = antiretroviral therapy.

Source: U.S. Department of Health and Human Services. *Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents*. May 4, 2006. Available online at aidsinfo.nih.gov/Guidelines/GuidelineDetail.aspx?GuidelineID=7.

drug is discontinued, the viral strains harboring the mutations that confer resistance to that drug may decrease below the threshold of detection by the resistance assay, so the resistance test may not reveal certain resistance mutations. In such situations, minority populations of resistant viruses may exist in reservoirs and may emerge rapidly under selective pressure if that drug is restarted, or if drugs with similar or overlapping resistance patterns are used. The implications of archived mutations are 2-fold: 1) Resistance tests are most reliable while the patient is still on the failing regimen; and 2) resistance testing should be interpreted in the context of both the drugs that the patient was taking at the time of the test and the drugs that the patient had been exposed to previously (ie, the patient's antiretroviral history).

Antiretroviral-Naive Patients

In treatment-experienced patients, as indicated above, resistance testing is most reliable when performed while the patients are still taking the failing antiretroviral medications. In treatment-naive patients, resistance testing may reveal resistance mutations that were acquired at the time of infection, through infection with a strain of HIV that had already developed antiretroviral resistance. Current guidelines recommend genotypic testing in recently infected patients and in antiretroviral-naive, chronically infected patients before initiation of therapy. Many experts suggest testing as early as possible in the course of HIV infection, to increase the likelihood of detecting transmitted mutations. The rationale for resistance testing in antiretroviral-naive patients is 2-fold: 1) The incidence of primary resistance is rising, particularly in locations with a high prevalence of persons taking ART; and 2) unknowingly starting a patient on antiretroviral medications to which his or her virus is already resistant may risk failure of the initial regimen, rapid acquisition of additional resistance mutations, and curtailment of future treatment options.

Using Genotype and Phenotype Tests at the Same Time

Genotype and phenotype tests have a few complementary properties that may, in some circumstances, make it desirable to use both tests at the same time. This strategy is especially advantageous when trying to devise a regimen for patients who have been exposed to many antiretroviral agents and have few remaining treatment options, and for whom the development of additional resistance could be particularly dangerous. For example, early mutations may appear on a genotype before detectable increases in inhibitory concentrations, and these would not be detected on a phenotype. Phenotypic testing can detect loss or gain of drug efficacy caused by complex interactions of mutations that, by themselves, would not be predictive.

Resistance Testing in Patients with Virologic Failure

As discussed in the chapter *Antiretroviral Therapy*, factors other than nonadherence and resistance may cause failure of ART; these include drug-drug interactions and malabsorption. Therefore, before assuming that drug failure is due to resistance and ordering a resistance test, it is important to assess the causes of antiretroviral regimen failure. If resistance is still suspected after assessing all possible causes, resistance testing should be done while the patient is taking the failing regimen, for the reasons noted above.

Key Points

- There are 2 major types of resistance testing currently available: genotype and phenotype tests.
- In general, a patient's viral load must be at least 1,000 copies/mL for either test to be reliable.
- Both genotypic and phenotypic testing can detect resistance only if it exists in at least 20% of the viral species present in a patient (known as the dominant species). Minor species may harbor resistance that remains undetected by either test.
- Resistance tests are most reliable when performed while a patient is still taking a failing regimen, or within 4 weeks after stopping. Neither test predicts which drugs will be active in a particular patient, only drugs that are not likely to be active. Nevertheless, studies comparing the use of resistance testing to expert opinion alone have shown that resistance testing can improve virologic control of HIV. Most treatment guidelines recommend resistance testing in certain circumstances.

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Reducing Maternal-Infant HIV Transmission

Background

In the absence of antiretroviral (ARV) prophylaxis or other interventions, the rate of mother-to-child transmission (MTCT) of HIV in the United States ranges from 16% to 25%. Certain interventions, notably antiretroviral therapy (ART), are highly effective in reducing the risk of perinatal transmission of HIV. ART and may reduce the transmission rate to as low as 1.5% in selected groups. Pregnant women with HIV infection who wish to carry their pregnancies to term should be educated about the risks of perinatal HIV transmission and offered appropriate medical management and ARV medications to maintain or improve their own health and to reduce the risk of HIV transmission to their infants.

This chapter describes strategies to reduce the risk of MTCT of HIV and presents information on HIV testing during pregnancy. It is not intended to be a comprehensive discussion of these topics, and all HIV-infected pregnant women should be treated by an HIV-experienced obstetrician and an HIV specialist. For centers that do not have HIV specialists available, experts at the National Perinatal HIV Consultation and Referral Service Perinatal Hotline (888-448-8765) are available for consultation. For more information on caring for pregnant women, see chapter *Care of HIV-Infected Pregnant Women*.

Overview of Prevention of Perinatal HIV Transmission

In 1994, an interim analysis of Pediatric AIDS Clinical Trial Group study 076 (PACTG 076) found that ARV treatment during pregnancy could significantly reduce the risk of HIV transmission to the infant. Pregnant women in the intervention group took zidovudine (ZDV) orally during the last weeks of pregnancy, received it intravenously during labor and delivery, and gave it to their newborns for 6 weeks. Only 7.6% of those infants were infected with HIV, compared with 22.6% of infants whose mothers in the control group did not receive ZDV. ART for pregnant women with HIV infection rapidly became the standard of care in the United States and other high-income countries. A task force of the U.S. Public Health Service (USPHS) issued recommendations in August 1994 for the use of ZDV for the reduction of perinatal transmission. Those recommendations were expanded to include guidelines for the medical management of pregnant women with HIV infection, including ARV treatment during pregnancy, as well as recommendations regarding other interventions that can further decrease transmission risk, such as cesarean section. The USPHS task force now meets regularly to review and update these guidelines as new research is published and new ARV drugs are approved. These guidelines, the *Public Health Service Task Force Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV-1 Transmission in the United States* are available online and in print (see "References" below).

Studies subsequent to PACTG 076 in resource-limited countries as well as resource-abundant areas found that other ARV regimens also reduced the risk of HIV transmission from mother to infant. The Petra study, a placebo-controlled trial in a breast-feeding population in Uganda, South Africa, and Tanzania, found a transmission rate of 9% among women who received oral ZDV plus lamivudine (3TC) intrapartum and for 1 week postpartum and whose infants also received 1 week of ZDV/3TC, compared with a rate of 15% in the placebo group. The HIV NET 012 trial in a breast-feeding population in Uganda compared the efficacy of a single dose of nevirapine (NVP) given to the mother at the onset of labor plus a single dose given to the newborn 48 hours postpartum with oral ZDV given to the mother during labor and to the newborn. The transmission rate was 9% in the NVP arm compared with 21% in the ZDV arm. The results of this study and the low cost of NVP led a number of resource-limited countries to institute NVP prophylaxis as the standard of care for preventing MTCT of HIV. Numerous other trials have demonstrated the efficacy of various ARV strategies, combining different ARVs with different treatment durations, and given to mothers, newborns, or both, in both breast-feeding and non-breast-feeding populations. Some trials have suggested that even late ARV interventions may decrease the infant's risk of HIV infection. A retrospective study of subjects in New

York found that the rate of perinatal HIV transmission was 9.3-10% if ZDV was given to both the mothers intrapartum and their newborns or only to the newborn, compared with 26.6% if no ARV medication was given. This study supports the importance of offering ARV interventions to pregnant women with HIV infection whenever they are identified.

In the United States, the PACTG 076 regimen remains the standard of care for preventing perinatal HIV transmission, and usually is incorporated into combination ARV therapy for pregnant women. For international settings, other guidelines have been developed by global agencies such as the World Health Organization (see "References" below) and by individual governments.

Unless otherwise referenced, the information in this chapter is based on the most recent USPHS perinatal guidelines available at the time this chapter was written. The reader should consult the AIDSInfo Web site (http://aidsinfo.nih.gov) for the most current recommendations.

HIV Testing during Pregnancy

The success of interventions to reduce the risk of perinatal HIV transmission has underscored the importance of HIV testing and counseling of all pregnant women. Interventions to interrupt transmission can be effective only if women know their HIV status and can access treatment. The USPHS first recommended universal HIV counseling and testing for pregnant women in 1995. Many nationwide professional and governmental organizations, including the American Academy of Pediatrics, the American College of Obstetricians and Gynecologists, and the U.S. Preventive Services Task Force, have endorsed those recommendations. Current recommendations from the U.S. Centers for Disease Control and Prevention (CDC) urge 3 approaches to HIV testing during pregnancy:

- An "opt-out" approach to HIV testing during pregnancy, whereby a pregnant woman is tested unless she specifically declines testing
- Routine testing with a rapid HIV test for women with unknown or undocumented HIV status who present in labor, in order to offer those testing HIV positive ARV prophylaxis during labor
- Rapid HIV testing for newborns of mothers of unknown HIV status so that they can receive postexposure ARV prophylaxis, if indicated.

State laws regarding HIV testing during pregnancy vary widely, and many are under review. Clinicians should be familiar with their state laws regarding HIV testing during pregnancy, opt-out or consent provisions, and regulations about rapid HIV testing during the intrapartum or newborn period.

HIV Education and Counseling of Pregnant Women

Educating pregnant women about the importance of HIV testing is a critical element in preventing perinatal HIV transmission. However, extensive pretest counseling is not essential. A woman must be told that HIV testing is a standard part of prenatal care, that the clinician recommends the tests, and that all pregnant women should be tested for HIV because knowing about HIV infection is important for their health and the health of their babies. Research has shown that a provider's strong endorsement of HIV testing is a major predictor of whether a woman receives an HIV test. Testing should be voluntary and free of coercion, and a woman should know that she can decline testing without the risk of being denied care. A woman's age, cultural background, educational level, and primary language may influence her knowledge about HIV transmission and her willingness to be tested; the clinician should consider these factors carefully when providing education and information.

The following minimum information should be provided through an educational session with a health care provider or through written or electronic media (eg, brochures, videos):

- HIV is the virus that causes AIDS. Approximately 25% of women with HIV who are not treated can transmit the virus to their babies through pregnancy, during labor and delivery, or by breast-feeding.
- A woman could be at risk for HIV infection and not know it.
- Highly effective treatment can protect the infant from being infected with HIV and can improve the mother's health.
- HIV testing is recommended for all pregnant women.
- Women who decline testing will not be denied care.

Women should also be told that test results are confidential to the extent allowed by law and that medical and other services are available for women with HIV infection. Reporting requirements for the specific state should be explained.

Some states require written informed consent before an HIV test is done. Others require patient education and a chart note from the providers. More recently, states are moving to the opt-out approach, whereby a woman is informed that an HIV test will be done unless she declines. Whatever the consent process, a woman should know that an HIV test is being done and should receive at least the information outlined above.

HIV testing should be performed as early in pregnancy as possible to allow for interventions to prevent transmission and for effective management of a woman's HIV infection, if the woman is found to be HIV seropositive. Repeat HIV testing is recommended in the third trimester for women at high risk for acquiring HIV (eg, a history of injection drug use, exchange of sex for money or drugs, multiple sex partners, a partner known to be HIV infected). Any pregnant woman with signs or symptoms of seroconversion should be evaluated for acute HIV infection (see chapter *Primary HIV Infection*). Some states, such as Florida, now mandate a third-trimester HIV test for all pregnant women. If a client declines testing, the clinician should ask her reasons and follow up at subsequent visits. If a provider is persistent, the woman may choose to have an HIV test at a later visit.

In the United States, the vast majority of pregnant women who are tested for HIV will be HIV seronegative. While giving test results to an HIV-negative woman, the clinician should take the opportunity to discuss risk-reduction strategies to help ensure that a woman remains uninfected by HIV. Women at high risk for HIV infection should be referred for more extensive counseling because recent research indicates that pregnancy may place her at greater risk for acquiring HIV infection.

Counseling a pregnant woman with a positive HIV test result requires knowledge and sensitivity. The clinician should explain that, even though the woman may feel well, she is infected with the virus. The woman should be told about the importance of medical management of HIV for her own health and for the prevention of perinatal transmission, and she should be guided to the medical and social services available in her local community. She also should be referred to an HIV obstetric specialist who can work closely with her primary obstetric and HIV providers to manage her care during the pregnancy. The patient may be surprised or shocked at the HIV diagnosis, or she may have known her status but been reluctant to disclose it. The clinician should emphasize the importance of emotional and social support, assess the patient's social support resources, and offer her referrals as needed.

Rapid HIV Testing during Labor

As discussed earlier, beginning ART during pregnancy offers the greatest chance for preventing MTCT of HIV, but interventions during the intrapartum and neonatal periods still offer opportunities to decrease the risk of HIV transmission. Rapid HIV testing for women who present in labor with unknown or undocumented HIV status can identify HIV-infected women so that interventions can be offered. Newer rapid HIV antibody tests, which are both sensitive and specific, provide results in less than 1 hour. Women who should receive HIV testing during labor include those who have had little or no prenatal care, those who were not offered testing earlier in pregnancy, those who declined previously, and those whose HIV test results are not available at the time of labor. Education and counseling for the woman in labor who needs an HIV test should incorporate the information for prenatal education discussed earlier, and give consideration to the special circumstances of labor. Special educational formats such as flip charts have been developed to help with patient education. Confidentiality should be assured for the information and consent process and for treatment. If an opt-out approach is used in the labor setting, a woman of unknown serostatus should be told that no HIV test is found on her chart, that HIV testing is part of routine care, and that she can decline if she wishes, but that experts recommend HIV testing because interventions are available that decrease her baby's risk of becoming infected with HIV if she is found to be positive.

Factors Influencing Perinatal HIV Transmission

As stated earlier, the rate of MTCT in the United States ranges from 16% to 25% in the absence of ART or other interventions. Perinatal transmission is most likely to occur in the intrapartum period. Several factors influence the risk of transmission from mother to infant. The most influential factor seems to be the mother's HIV RNA level (viral load). Clinical trials and observational studies have shown a strong positive correlation between maternal HIV viral load during pregnancy or at delivery and the risk of perinatal HIV transmission, even among women treated with ARVs. Even for women with viral loads <1,000 copies/mL, in whom the risk of MTCT is lower than in women with

higher viral loads, ARV prophylaxis is a critical factor in reducing HIV transmission. One metaanalysis found that women with HIV RNA <1,000 copies/mL who were receiving ART had a transmission rate of only 1%, compared with a 9.8% transmission rate among women taking no ARVs. For that reason, ARV prophylaxis is recommended for all pregnant women with HIV infection. Other factors associated with increased risk of perinatal transmission include chorioamnionitis, low CD4 cell count, sexually transmitted infections, illicit drug use, cigarette smoking, and unprotected sex with multiple partners.

Obstetric factors also affect the risk of transmission. The risk of HIV infection increases linearly with the increased duration of ruptured membranes, although the effect of ruptured membranes in women with low viral loads is not known. Invasive procedures performed at any time during pregnancy, such as amniocentesis or placement of scalp electrodes, also increase the risk by exposing the fetus to maternal blood; these procedures should be avoided. The mode of delivery, whether vaginal or cesarean section, also influences the risk of HIV transmission. Cesarean section decreases the rate of perinatal infection, at least in the absence of other interventions (including ART); see "Mode of Delivery and Intrapartum Management" below for further information.

Breast-feeding increases the risk of HIV transmission by 5-20%. In the United States, where replacement foods and clean water routinely are available, women with HIV should not breast-feed. However, some women with HIV will be under tremendous cultural and family pressure to breast-feed and will need the clinician's ongoing support to use substitute formula.

Because many factors that affect the risk of perinatal HIV transmission may be modified, clinicians should educate pregnant women carefully about the importance of ARV prophylaxis and other strategies to reduce the risk of maternal-fetal transmission of HIV.

Antiretroviral Therapy during Pregnancy

The goals of ART for the pregnant woman are the same as those for any person living with HIV:

- To suppress the level of HIV to as low as possible for as long as possible
- To preserve and restore immune function
- To prolong life and improve quality of life

An additional goal in pregnant women is to reduce the risk of perinatal HIV transmission. The USPHS recommendations discuss in detail the multiple issues that must be considered when balancing the woman's need for therapy for her own health and for decreasing the risk of transmission to the infant. Decisions about ART are complex and should be made by the woman and her health care provider after discussing of the risks and benefits. Clinicians are urged to consult an HIV specialist as well as the most current USPHS recommendations when making therapeutic decisions. The following discussion addresses some of the issues in determining ARV treatment and is taken from the current USPHS *Perinatal ARV Guidelines.*

A fundamental principle of the guidelines is that therapies of known benefit should not be withheld during pregnancy unless they may cause adverse effects to the woman, fetus, or infant and these adverse effects outweigh the potential benefit to the woman. The woman's clinical, virologic, and immunologic status should be the most important factor in guiding treatment decisions. Combination therapy with 3 ARVs, including agents from at least 2 ARV classes, is the standard therapy for adults and should be discussed with the pregnant woman. Special considerations in choosing drug regimens during pregnancy include changes in dosing requirements because of physiologic changes, the potential effects of ARVs on the woman, and the known and unknown potential effects or ARVs on the fetus or infant.

Safety and Toxicity of Antiretroviral Medications during Pregnancy

Only limited data are available on the safety of ARV drugs in pregnancy, particularly when ARVs are used in combination. The existing safety and toxicity information is derived from animal data, clinical trials, registry data, and anecdotal experience. A few drugs are of special concern when used during pregnancy (Tables 1-2). Efavirenz (Sustiva) is classified by the U.S. Food and Drug Administration (FDA) as a Pregnancy Class D drug because malformations have occurred in monkeys receiving efavirenz during the first trimester. Several cases of neural tube defects have been reported in humans after first-trimester exposure to efavirenz. Efavirenz should be avoided during the first trimester, and women taking efavirenz should be counseled about the risks and the importance of avoiding pregnancy. Use of efavirenz can be considered after the second trimester if other alternatives are unavailable. Amprenavir (Agenerase) oral solution is

contraindicated during pregnancy because the high levels of propylene glycol may not be metabolized well during pregnancy. The combination of didanosine (ddI) and stavudine (d4T) should be avoided unless no alternatives are available. Hydroxyurea, a drug previously thought to boost the response to ARVs, is a potent teratogen in various animal species and should not be used in the first trimester. Information on ARV toxicity during pregnancy should be consulted carefully before treatment choices are made.

The *USPHS Perinatal ARV Guidelines* maintain information on each ARV drug, including preclinical and clinical data, pharmacokinetic and toxicity data, and recommendations regarding use in pregnancy. These guidelines are updated routinely as information is received (Tables 1-2). Of course, numerous other medications are contraindicated during pregnancy, and potential toxicity should be considered carefully before any medication is given to a pregnant woman.

Table 1. Preclinical and Clinical Data Relevant to the Use of Antiretrovirals during Pregnancy

Antiretroviral Drug	FDA Pregnancy Category*	Placental Passage (Newborn-to-Mother Drug Ratio)	Long-Term Carcinogenicity Studies in Animals	Teratogen Studies in Animals
Nucleoside and Nucleotide Analogue Reverse Transcriptase Inhibitors				
Abacavir (Ziagen, ABC)	C	Yes (rats)	Positive: malignant and nonmalignant tumors of liver, thyroid in female rats, and preputial and clitoral gland of mice and rats	Positive: rodent anasarca and skeletal malformations at 1,000 mg/kg (35x human exposure) during organogenesis; not seen in rabbits
Didanosine (Videx, ddI)	B	Yes (human) [0.5]	Negative: no tumors, lifetime rodent study	Negative
Emtricitabine (Emtriva, FTC)	B	Unknown	Not completed	Negative
Lamivudine (Epivir, 3TC)	C	Yes (human) [~1.0]	Negative: no tumors, lifetime rodent study	Negative
Stavudine (Zerit, d4T)	C	Yes (rhesus monkey) [0.76]	Positive: liver and bladder tumors in mice and rats, at very high-dose exposure	Negative: but sternal bone calcium decreases in rodents
Tenofovir DF (Viread)	B	Yes (rat and monkey)	Positive: hepatic adenomas in female mice at high doses	Negative: but osteomalacia when given to juvenile animals at high doses
Zalcitabine (Hivid, ddC)	C	Yes (rhesus monkey) [0.30 - 0.50]	Positive: thymic lymphomas in rodents	Positive: hydrocephalus at high doses in rodents
Zidovudine†(Retrovir, AZT, ZDV)	C	Yes (human) [0.85]	Positive: noninvasive vaginal epithelial tumors in rodents	Positive at near lethal dose in rodents
Nonnucleoside Reverse Transcriptase Inhibitors				
Delavirdine (Rescriptor)	C	Unknown	Positive: hepatocellular adenomas and carcinomas in male and female mice but not rats; bladder tumors in male mice	Positive: ventricular septal defect in rodents
Efavirenz (Sustiva)	D	Yes (cynomolgus monkey, rat, rabbit) [~1.0]	Positive: hepatocellular adenomas and carcinomas and pulmonary alveolar/ bronchiolar adenomas in female but not male mice	Positive: anencephaly, anophthalmia, microphthalmia in cynomolgus monkeys
Nevirapine (Viramune)	C	Yes (human) [~1.0]	Positive: hepatocellular adenomas and carcinomas in mice and rats	Negative

Protease Inhibitors				
Amprenavir (Agenerase)	C	Unknown	Positive: hepatocellular adenomas and carcinomas in male mice and rats	Negative, but deficient ossification and thymic elongation in rats and rabbits
Atazanavir (Reyataz)	B	Unknown	Positive: hepatocellular adenomas in female mice	Negative
Fosamprenavir (Lexiva)	C	Unknown	Positive: benign and malignant liver tumors in male rodents	Negative for fosamprenavir, but deficient ossification with amprenavir
Indinavir (Crixivan)	C	Minimal (humans)	Positive: thyroid adenomas in male rats at highest dose	Negative, but extra ribs in rodents
Lopinavir/Ritonavir (Kaletra)	C	Unknown	Positive: hepatocellular adenomas and carcinomas in mice and rats	Negative, but delayed skeletal ossification and increase in skeletal variations in rats at maternally toxic doses
Nelfinavir (Viracept)	B	Minimal (humans)	Positive: thyroid follicular adenomas and carcinomas in rats	Negative
Ritonavir (Norvir)	B	Minimal (humans)	Positive: liver adenomas and carcinomas in male mice	Negative, but cryptorchidism in rodents
Saquinavir (Fortovase)	B	Minimal (humans)	Negative	Negative
Tipranavir (Aptivus)	C	Unknown	In progress	Negative, but decreased ossification and weights in rats at maternally toxic doses
Fusion Inhibitors				
Enfuvirtide (Fuzeon)	B	Unknown	Not done	Negative

Key to abbreviations: FDA = U.S. Food and Drug Administration.

*Food and Drug Administration Pregnancy Categories:

A–Adequate and well-controlled studies of pregnant women fail to demonstrate a risk to the fetus during the first trimester of pregnancy (and no evidence exists of risk during later trimesters).

B–Animal reproduction studies fail to demonstrate a risk to the fetus, and adequate but well-controlled studies of pregnant women have not been conducted.

C–Safety in human pregnancy has not been determined; animal studies are either positive for fetal risk or have not been conducted, and the drug should not be used unless the potential benefit outweighs the potential risk to the fetus.

D–Positive evidence exists of human fetal risk that is based on adverse-reaction data from investigational or marketing experiences, but the potential benefits from the use of the drug among pregnant women might be acceptable despite its potential risks.

X–Studies among animals or reports of adverse reactions have indicated that the risk associated with the use of the drug for pregnant women clearly outweighs any possible benefit.

Source: Centers for Disease Control and Prevention. *Table 2: Preclinical and Clinical Data Relevant to the Use of Antiretrovirals in Pregnancy*. In: *Public Health Service Task Force Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV-1 Transmission in the United States*. July 6,2006. Available online at http://aidsinfo.nih.gov/Guidelines/GuidelineDetail.aspx?GuidelineID=9.

Table 2. Antiretroviral Drug Use in Pregnant HIV-Infected Women: Pharmacokinetics, Toxicity Data, and Recommendations

Nucleoside/ Nucleotide Reverse Transcriptase Inhibitors			
Antiretroviral Drug	**Pharmacokinetics during Pregnancy**	**Concerns during Pregnancy**	**Rationale for Recommended Use during Pregnancy**
Class concerns and comments		See text for discussion of potential maternal and infant mitochondrial toxicity.	NRTIs are recommended for use as part of combination regimens, usually including 2 NRTIs with either an NNRTI or 1 or more PIs. Use of single or dual NRTIs alone is not recommended for treatment of HIV infection (zidovudine alone may be considered for prophylaxis of perinatal transmission in pregnant women with HIV RNA <1,000 copies/mL).
Recommended Agents			
Zidovudine* **(Retrovir, AZT, ZDV)**	Pharmacokinetics not significantly altered in pregnancy; no change in dose indicated.	No evidence of human teratogenicity. Well-tolerated, short-term safety demonstrated for mother and infant.	Preferred NRTI for use in combination antiretroviral regimens during pregnancy based on efficacy studies and extensive experience; should be included in regimen unless significant toxicity or stavudine use
Lamivudine* **(Epivir, 3TC)**	Pharmacokinetics not significantly altered in pregnancy; no change in dose indicated.	No evidence of human teratogenicity. Well-tolerated, short-term safety demonstrated for mother and infant.	Because of extensive experience with lamivudine in pregnancy in combination with zidovudine, lamivudine plus zidovudine is the recommended dual NRTI backbone for pregnant women.
Alternative Agents			
Didanosine **(Videx, ddI)**	Pharmacokinetics not significantly altered in pregnancy; no change in dose indicated.	Cases of lactic acidosis, some fatal, have been reported in pregnant women receiving didanosine and stavudine together.	Alternate NRTI for dual nucleoside backbone of combination regimens. Didanosine should be used with stavudine only if no other alternatives are available.
Emtricitabine **(Emtriva, FTC)**	No studies in human pregnancy.	No studies in human pregnancy.	Alternate NRTI for dual nucleoside backbone of combination regimens.
Stavudine **(Zerit, d4T)**	Pharmacokinetics not significantly altered in pregnancy; no change in dose indicated.	No evidence of human teratogenicity. Cases of lactic acidosis, some fatal, have been reported in pregnant women receiving didanosine and stavudine together.	Alternate NRTI for dual nucleoside backbone of combination regimens. Stavudine should be used with didanosine only if no other alternatives are available. Do not use with zidovudine because of potential for antagonism.
Abacavir* **(Ziagen, ABC)**	Phase I/II study in progress.	Hypersensitivity reactions occur in ~5-8% of nonpregnant persons; a much smaller percentage are fatal and are usually associated with repeat challenge. Rate of such reactions during pregnancy is unknown. Patient should be educated regarding symptoms of hypersensitivity reaction.	Alternate NRTI for dual nucleoside backbone of combination regimens. See footnote regarding use in triple NRTI regimen.[#]
Insufficient Data to Recommend Use			
Tenofovir DF **(Viread)**	No studies in human pregnancy. Phase I study in late pregnancy in progress.	Studies in monkeys show decreased fetal growth and reduction in fetal bone porosity within 2 months of starting maternal therapy. Clinical studies in humans (particularly children) show bone demineralization with chronic use; clinical significance is unknown.	Because of lack of data on use in human pregnancy and concern regarding potential fetal bone effects, tenofovir should be used as a component of a maternal combination regimen only after careful consideration of alternatives.
Not Recommended			
Zalcitabine (Hivid, ddC)	No studies in human pregnancy	Rodent studies indicate potential for teratogenicity and developmental toxicity (see Table 1).	Given lack of data and concerns regarding teratogenicity in animals, zalcitabine is not recommended for use in human pregnancy unless alternatives are not available.

Nonnucleoside Reverse Transcriptase Inhibitors			
Antiretroviral Drug	**Pharmacokinetics in Pregnancy**	**Concerns in Pregnancy**	**Rationale for Recommended Use in Pregnancy**
Recommended Agents			
Nevirapine (Viramune)	Pharmacokinetics not significantly altered in pregnancy; no change in dose indicated.	No evidence of human teratogenicity. Increased risk of symptomatic, often rash-associated, and potentially fatal liver toxicity among women with CD4 counts >250 cells/µL when first initiating therapy; unclear whether pregnancy increases risk.	Because of the increased risk of potentially life-threatening hepatotoxicity in women with high CD4 counts, nevirapine should be initiated in pregnant women with CD4 counts >250 cells/µL only if benefit clearly outweighs risk. Women who begin pregnancy on nevirapine regimens and are tolerating them well may continue therapy, regardless of CD4 count.
Not Recommended			
Efavirenz (Sustiva)	No studies in human pregnancy.	FDA Pregnancy Class D; significant malformations (anencephaly, anophthalmia, cleft palate) were observed in 3 (15%) of 20 infants born to cynomolgus monkeys receiving efavirenz during the first trimester at a dose giving plasma levels comparable to systemic human therapeutic exposure. Three cases were reported of neural tube defects in humans after first-trimester exposure; relative risk is unclear.	Use of efavirenz should be avoided in the first trimester, and women of childbearing potential must be counseled regarding risks and avoidance of pregnancy. Because of the known failure rates of contraception, alternate regimens should be strongly considered in women of childbearing potential. Use after the second trimester of pregnancy can be considered if other alternatives are not available and if adequate contraception can be assured postpartum.
Delavirdine (Rescriptor)	No studies in human pregnancy.	Rodent studies indicate potential for carcinogenicity and teratogenicity (see Table 1).	Given lack of data and concerns regarding teratogenicity in animals, delavirdine is not recommended for use in human pregnancy unless alternatives are not available.

Protease Inhibitors			
Antiretroviral Drug	**Pharmacokinetics in Pregnancy**	**Concerns in Pregnancy**	**Rationale for Recommended Use in Pregnancy**
Class concerns		Hyperglycemia, new onset or exacerbation of diabetes mellitus, and diabetic ketoacidosis reported with PI use; unclear if pregnancy increases risk. Conflicting data regarding preterm delivery in women receiving PIs.	
Recommended Agents			
Nelfinavir (Viracept)	Adequate drug levels are achieved in pregnant women with nelfinavir 1,250 mg, given twice daily.	No evidence of human teratogenicity. Well-tolerated, short-term safety was demonstrated for mother and infant. Nelfinavir dosing at 750 mg 3 times daily produced variable and generally low levels in pregnant women.	Given pharmacokinetic data and extensive experience with use in pregnancy compared with other PIs, nelfinavir is the preferred PI for combination regimens in pregnant women, particularly if antiretrovirals are being given solely for perinatal prophylaxis. In clinical trials of initial therapy in nonpregnant adults, nelfinavir-based regimens had a lower rate of viral response compared with lopinavir/ritonavir or efavirenz-based regimens, but similar a viral response compared with atazanavir or nevirapine-based regimens.

Saquinavir-SGC (Fortovase)/ Ritonavir	Adequate drug levels are achieved in pregnant women with saquinavir-SGC 800 mg boosted with ritonavir 100 mg, given twice daily. Recommended adult dosing of saquinavir-SGC 1,000 mg plus ritonavir 100 mg may be used. No PK data exist on saquinavir hard-gel capsule/ritonavir in pregnancy, but better gastrointestinal tolerance in nonpregnant adults.	Well-tolerated, short-term safety was demonstrated for mother and infant. Inadequate drug levels were observed in pregnant women with saquinavir-SGC given alone at 1,200 mg 3 times daily.	Given pharmacokinetic data and moderate experience with use in pregnancy, ritonavir-boosted saquinavir-SGC can be considered a preferred PI for combination regimens during pregnancy.
Alternative Agents			
Indinavir (Crixivan)	Two studies including 18 women receiving indinavir 800 mg 3 times daily showed markedly lower drug levels during pregnancy compared with postpartum, although suppression of HIV RNA was seen.	Theoretical concern exists about increased indirect bilirubin levels, which may exacerbate physiologic hyperbilirubinemia in the neonate, but minimal placental passage. Use of unboosted indinavir during pregnancy is not recommended.	Alternate PI to consider if unable to use nelfinavir or saquinavir-SGC/ritonavir, but would need to give indinavir as ritonavir-boosted regimen. Optimal dosing for the combination of indinavir/ritonavir during pregnancy is unknown.
Lopinavir/Ritonavir (Kaletra)	Phase I/II safety and pharmacokinetic study is in progress using twice-daily lopinavir 400 mg and ritonavir 100 mg.	Limited experience in human pregnancy.	Preliminary studies suggest increased dose may be required during pregnancy, though specific dosing recommendations not established. If used during pregnancy, monitor response to therapy closely. If expected virologic result is not observed, consult with a specialist with expertise in HIV during pregnancy.
Ritonavir (Norvir)	Phase I/II study during pregnancy showed lower drug levels during pregnancy compared with postpartum.	Minimal experience in human pregnancy.	Given low levels in pregnant women when used alone, ritonavir is recommended for use in combination with a second PI as low-dose "boost" to increase levels of second PI.
Insufficient Data to Recommend Use			
Amprenavir (Agenerase)	No studies in human pregnancy.	Oral solution is contraindicated in pregnant women because of high levels of propylene glycol, which may not be adequately metabolized during pregnancy.	Safety and pharmacokinetics data in pregnancy are insufficient to recommend use of capsules during pregnancy.
Fosamprenavir (Lexiva)	No studies in human pregnancy.	No experience in human pregnancy.	Safety and PK data in pregnancy are insufficient to recommend use during pregnancy.
Atazanavir (Reyataz)	No studies in human pregnancy.	Theoretical concern exists about increased indirect bilirubin levels, which may exacerbate physiologic hyperbilirubinemia in the neonate, although transplacental passage of other PIs has been low.	Safety and pharmacokinetics in pregnancy data are insufficient to recommend use during pregnancy.
Tipranavir (Aptivus)	No studies in human pregnancy.	No experience in human pregnancy.	Safety and pharmacokinetics in pregnancy data are insufficient to recommend use during pregnancy.

Fusion Inhibitor			
Antiretroviral Drug	Pharmacokinetics in Pregnancy	Concerns in Pregnancy	Rationale for Recommended Use in Pregnancy
Insufficient Data to Recommend Use			
Enfuvirtide (Fuzeon)	No studies in human pregnancy.	No experience in human pregnancy.	Safety and pharmacokinetics data in pregnancy are insufficient to recommend use during pregnancy.

Source: Centers for Disease Control and Prevention. *Table 3. Antiretroviral Drug Use in Pregnant HIV-Infected Women: Pharmacokinetic and Toxicity Data in Human Pregnancy and Recommendations for Use in Pregnancy*. In: *Public Health Service Task Force Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV-1 Transmission in the United States*. July 6, 2006. Available online at http://aidsinfo.nih.gov/Guidelines/GuidelineDetail.aspx?GuidelineID=9.

Key to abbreviations: HGC = hard-gel capsule; NNRTI = nonnucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; NtRTI = nucleotide reverse transcriptase inhibitor; PI = protease inhibitor; SGC = soft-gel capsule.

*Zidovudine and lamivudine are included as a fixed-dose combination in Combivir; zidovudine, lamivudine, and abacavir are included as a fixed-dose combination in Trizivir.

Triple NRTI regimens including abacavir have been less potent virologically compared with PI-based ART regimens. Triple NRTI regimens should be used only when an NNRTI- or PI-based ART regimen cannot be used (eg, due to significant drug interactions). A study evaluating use of zidovudine/lamivudine/abacavir among pregnant women with HIV RNA <55,000 copies/mL as a class-sparing regimen is in development.

Adverse Antiretroviral Drug Events during Pregnancy

Concerns have been raised about complications and toxicities related to ART during pregnancy. For example, a European study found a 2-fold increase in preterm birth among mothers who started combination therapy before pregnancy. A metaanalysis of 7 U.S. clinical trials, however, found that ARV use was not associated with preterm labor, low birth-weight, low Apgar scores, or stillbirth. Until more is known, pregnant women who are taking combination regimens should be monitored closely for complications and toxicities and should be educated about the signs of premature labor.

Nucleoside reverse transcriptase inhibitors can cause mitochondrial dysfunction with long-term use. Clinical disorders linked to mitochondrial dysfunction include symptomatic lactic acidosis and hepatic steatosis, which are seen more commonly in women than in men. Three maternal deaths were reported in the United States in women taking ARV regimens that included ddI and d4T in combination with other ARVs. Patients with lactic acidosis with hepatic steatosis often present with 1-6 weeks of symptoms including nausea, vomiting, abdominal pain, dyspnea, and weakness. Because some of the symptoms of lactic acidosis/hepatic steatosis syndrome can mimic those of pregnancy, clinicians must be alert for early signs and symptoms of lactic acidosis and evaluate them promptly. The combination of ddI and d4T should be avoided during pregnancy, and used only when other effective options are not available (Table 2).

Women, including pregnant women, who begin nevirapine therapy when their CD4 count is >250 cells/μL have a 9.8 times higher incidence of hepatotoxicity than women initiated on nevirapine at lower CD4 counts. Symptoms of hepatotoxicity include fatigue, malaise, anorexia, nausea, jaundice, liver tenderness, and hepatomegaly. Nevirapine should be initiated as part of an ARV regimen in pregnant women with CD4 cell counts >250 cells/μL *only* if the benefits clearly outweigh the risks (Table 2).

Hyperglycemia, new-onset diabetes, worsening diabetes, and diabetic ketoacidosis have been reported in patients taking protease inhibitors. In addition, pregnancy itself is a risk factor for hyperglycemia. Clinicians should monitor closely the glucose level of pregnant women taking PIs and should educate them about the symptoms of hyperglycemia. (See chapter *Care of HIV-Infected Pregnant Women*.)

Recommendations for Antiretroviral Chemoprophylaxis to Reduce Perinatal HIV Transmission

The Perinatal HIV Working Group has offered recommendations on ARV prophylaxis to reduce perinatal HIV transmission based on 4 clinical scenarios:

- HIV-infected women who have not received previous ARV therapy
- HIV-infected women receiving ARV therapy during the current pregnancy
- HIV-infected women in labor who have had no previous therapy
- Infants born to HIV-infected women who received no ARV therapy during pregnancy or intrapartum

Recommendations for ART in these 4 clinical scenarios are listed in Table 3.

Table 3. Clinical Scenarios and Recommendations for the Use of Antiretroviral Drugs to Reduce Perinatal HIV-1 Transmission

SCENARIO #1: HIV-1-infected pregnant women who have not received previous ARV therapy	SCENARIO #2: HIV-1-infected women receiving ARV therapy during the current pregnancy
• Pregnant women with HIV-1 infection must receive standard clinical, immunologic, and virologic evaluations. Recommendations for initiation and choice of ARV therapy should be based on the same parameters used for persons who are not pregnant, although the known and unknown risks and benefits of such therapy during pregnancy must be considered and discussed. • The 3-part ZDV chemoprophylaxis regimen, initiated after the first trimester, is recommended for all pregnant women with HIV-1 infection regardless of antenatal HIV RNA copy number to reduce the risk of perinatal transmission. • The combination of ZDV chemoprophylaxis with additional ARV drugs for treatment of HIV-1 infection is recommended for infected women whose clinical, immunologic, or virologic status requires treatment or who have HIV-1 RNA >1,000 copies/mL regardless of clinical or immunologic status, and can be considered for women with HIV-1 RNA <1,000 copies/mL. • Women who are in the first trimester of pregnancy may consider delaying initiation of therapy until after 10-12 weeks' gestation.	• HIV-1-infected women receiving ARV therapy in whom pregnancy is identified after the first trimester should continue therapy. ZDV should be a component of the antenatal ARV treatment regimen after the first trimester whenever possible, although this may not always be feasible. • For women receiving ARV therapy in whom pregnancy is recognized during the first trimester, women should be counseled regarding the benefits and potential risks of ARV administration during this period, and continuation of therapy should be considered. If therapy is discontinued during the first trimester, all drugs should be stopped and reintroduced simultaneously to avoid the development of drug resistance. • Regardless of the antepartum ARV regimen, ZDV administration is recommended during the intrapartum period and for the newborn.
SCENARIO #3: HIV-1-infected women in labor who have had no previous therapy	**SCENARIO #4: Infants born to HIV-1-infected mothers who have received no ARV therapy during pregnancy or intrapartum**

• Several effective regimens are available (see *USPHS Perinatal ARV Guidelines*,Table 5). These include:
  ◦ Intrapartum intravenous ZDV followed by 6 weeks of ZDV for the newborn;
  ◦ Oral ZDV and 3TC during labor, followed by 1 week of oral ZDV-3TC for the newborn;
  ◦ A single dose of nevirapine at the onset of labor followed by a single dose of nevirapine for the newborn at 48 hours postpartum;
  ◦ The single-dose maternal and infant nevirapine regimen combined with intrapartum intravenous ZDV and 6-week ZDV for the newborn.
• If single-dose nevirapine is given to the mother, alone or in combination with ZDV, consideration should be given to adding maternal ZDV/3TC starting as soon as possible (intrapartum or immediately postpartum) and continuing for 3- 7 days, which may reduce the development of nevirapine resistance.
• In the immediate postpartum period, the woman should have appropriate assessments (eg, CD4 count and HIV-1 RNA copy number) to determine whether ARV therapy is recommended for her own health.
	• The 6-week neonatal ZDV component of the ZDV chemoprophylactic regimen should be discussed with the mother and offered for the newborn.
	• ZDV should be initiated as soon as possible after delivery—preferably within 6-12 hours of birth.
	• Some clinicians may choose to use ZDV in combination with other ARV drugs, particularly if the mother is known or suspected to have ZDV-resistant virus. However, the efficacy of this approach for prevention of transmission has not been proven in clinical trials, and appropriate dosing regimens for neonates are incompletely defined for many drugs.
	• In the immediate postpartum period, the woman should undergo appropriate assessments (eg, CD4 count and HIV-1 RNA copy number) to determine whether ARV therapy is required for her own health. The infant should undergo early diagnostic testing so that, if HIV infected, treatment can be initiated as soon as possible.

Key to abbreviations: ARV = antiretroviral; ZDV = zidovudine; USPHS = U.S. Public Health Service; 3TC = lamivudine.

Adapted from: Centers for Disease Control and Prevention. *Table 4. Clinical Scenarios and Recommendations for the Use of Antiretroviral Drugs to Reduce Perinatal Human Immunodeficiency Virus Type 1 (HIV-1) Transmission.* In: *Public Health Service Task Force Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV-1 Transmission in the United States*. July 6, 2006. Available online at http://aidsinfo.nih.gov/Guidelines/GuidelineDetail.aspx?GuidelineID=9.

The *USPHS Perinatal ARV Guidelines* emphasize that the PACTG 076 regimen is effective not only for women whose clinical status is similar to that of the participants in the original study, but also for women with advanced HIV disease, low CD4 counts, and previous ZDV therapy.

Because the goals of ART in a pregnant woman are not only to maintain her health, but also to prevent transmission to her infant, the considerations in ART differ from those in nonpregnant adults. Because the HIV viral load strongly influences the risk of HIV transmission, a primary goal of therapy should be to suppress the viral load to very low levels (preferably to undetectable levels) during pregnancy and throughout delivery; this goal guides treatment decisions. For nonpregnant adults, the *Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents* recommend that treatment be deferred in certain persons, depending on the CD4 cell count and the HIV viral load. (See chapter *Antiretroviral Therapy*.) In contrast, the *USPHS Perinatal ARV Guidelines* recommend that all pregnant women, regardless of CD4 cell count, receive the 3-part ZDV prophylaxis regimen used in PACTG 076, that is, ZDV orally (200 mg 3 times a day or 300 mg twice a day) beginning after the first trimester, intravenous ZDV during labor, and ZDV given orally to the newborn for 6 weeks. The guidelines also recommend that women with an HIV RNA level >1,000 copies/mL (regardless of CD4 cell count) or with immunologic, virologic, or clinical indications for treatment be offered a combination ART regimen that includes ZDV and other ARV drugs. Even women with HIV RNA levels <1,000 copies/mL should be considered for combination therapy.

The specific ART regimen should be selected with a view to the limited information available about the efficacy and potential toxicities of ARV combinations during pregnancy. The USPHS offers recommendations on the use of specific ARV agents during pregnancy (Table 2).

Mode of Delivery and Other Intrapartum Management

All pregnant women with HIV infection should receive the intrapartum and neonatal components of ZDV prophylaxis used in the PACTG 076 protocol, as outlined earlier. ZDV should be given to the woman intravenously during labor in a 1-hour initial loading dose of 2 mg per kilogram body weight followed by a continuous infusion of 1 mg/kg body weight per hour until delivery. The newborn should receive ZDV syrup at a dose of 2 mg/kg body weight per dose every 6 hours beginning 8-12 hours after birth and continuing for the first 6 weeks of life.

Early studies before the availability of viral load testing found that cesarean delivery performed before the onset of labor or rupture of membranes significantly reduced the risk of perinatal transmission. However, now that many HIV-infected pregnant women in the United States and other high-income settings are receiving combination ART, transmission rates of 1.2-1.5%, unadjusted for mode of delivery, have been reported). Because the transmission rate is so low in women taking effective ART, it is difficult to determine whether cesarean section offers any additional benefit. For women with a viral load <1,000 copies/mL, it is unlikely that cesarean section would provide additional benefit.

The American College of Obstetricians and Gynecologists recommends consideration of cesarean section at 38 weeks for HIV-infected women with a viral load >1,000 copies/mL at or near the time of delivery. The woman and her health care providers should decide about mode of delivery before the onset of labor, based on her current viral load, her health status, and discussion about other concerns. Pregnant women who have not achieved optimal virologic control and whose viral load remains >1,000 copies/mL in the weeks before delivery, should be counseled about the risks and benefits of cesarean section. A planned cesarean section should be scheduled for 38 weeks' gestation, because the benefits of cesarean section once the membranes have ruptured are unknown. Intravenous ZDV should be started 3 hours before the scheduled cesarean section. Prophylactic antibiotics are recommended at the time of cesarean section in HIV-infected women, to decrease the risk of maternal infection. The *USPHS Perinatal ARV Guidelines* outline 4 scenarios in which the clinician must decide whether cesarean section is needed (Table 4). The data on the benefits of cesarean section are complex and must be balanced with the increased risk to the mother after surgery. The clinician may want to consult an obstetric/HIV specialist to discuss specific situations.

Questions remain about the management of labor when a vaginal delivery is planned. Because the duration of ruptured membranes is a risk factor for perinatal transmission, pregnant women with HIV infection should be counseled to go to a hospital for care at the first signs of labor or rupture of membranes. If the membranes rupture spontaneously before labor occurs or early in labor, the clinician should consider interventions to decrease the interval to delivery, such as administration of oxytocin. Procedures that increase the neonate's exposure to maternal blood, such as the use of scalp electrodes or artificial rupture of membranes, should be avoided.

Table 4. Clinical Scenarios and Recommendations regarding Mode of Delivery to Reduce Perinatal HIV-1 Transmission

Mode of Delivery Clinical Scenario	Recommendations
Scenario A: An HIV-1-infected woman presenting in late pregnancy (after about 36 weeks of gestation), known to be HIV-1-infected but not receiving ART, and who has HIV-1 RNA level and lymphocyte subsets pending but unlikely to be available before delivery	Therapy options should be discussed in detail. The woman should be started on ART, including at least the PACTG 076 ZDV regimen. The woman should be counseled that scheduled cesarean section is likely to reduce the risk of transmission to her infant. She should also be informed of the increased risks to her of cesarean section, including increased rates of postoperative infection, anesthesia risks, and other surgical risks. If cesarean section is chosen, the procedure should be scheduled at 38 weeks of gestation, based on the best available clinical information. When scheduled cesarean section is performed, the woman should receive continuous intravenous ZDV infusion beginning 3 hours before surgery and her infant should receive 6 weeks of ZDV therapy after birth. Options for continuing or initiating combination ART after delivery should be discussed with the woman as soon as her viral load and lymphocyte subset results are available.
Scenario B: An HIV-1-infected woman who initiated prenatal care early in the third trimester, is receiving highly active combination ART, and has an initial virologic response, but has HIV-1 RNA levels that remain substantially >1,000 copies/mL at 36 weeks of gestation	The current combination ARV regimen should be continued because the HIV-1 RNA level is dropping appropriately. The woman should be counseled that, although she is responding to ART, it is unlikely that her HIV-1 RNA level will fall below 1,000 copies/mL before delivery. Therefore, scheduled cesarean section may provide additional benefit in preventing intrapartum transmission of HIV-1. She also should be informed of the increased risks to her of cesarean section, including increased rates of postoperative infection, anesthesia risks, and surgical risks. If she chooses scheduled cesarean section, it should be performed at 38 weeks' gestation according to the best available gestational dating parameters, and intravenous ZDV should be begun at least 3 hours before surgery. Other ARV medications should be continued on schedule as much as possible before and after surgery. The infant should receive oral ZDV for 6 weeks after birth. The importance of adhering to therapy after delivery for the woman's own health should be emphasized.
Scenario C: An HIV-1-infected woman taking combination ART with an undetectable HIV-1 RNA level at 36 weeks of gestation	The woman should be counseled that her risk of perinatal transmission of HIV-1 with a persistently undetectable HIV-1 RNA level is low, probably 2% or less, even with vaginal delivery. There is no information currently available to evaluate whether performing a scheduled cesarean section will decrease her risk further. Cesarean section increases the risk of complications for the woman as compared with vaginal delivery, and these risks must be balanced against the uncertain benefit of cesarean section in this case.
Scenario D: An HIV-1-infected woman who has opted for scheduled cesarean section but presents in early labor or shortly after rupture of membranes	Intravenous ZDV should be started immediately because the woman is in labor or has ruptured membranes. If labor is progressing rapidly, the woman should be allowed to deliver vaginally. If cervical dilatation is minimal and a long period of labor is anticipated, some clinicians may choose to administer the loading dose of intravenous ZDV and proceed with cesarean section to minimize the duration of membrane rupture and avoid vaginal delivery. Others might begin oxytocin augmentation to enhance contractions and potentially expedite delivery. If the woman is allowed to labor, scalp electrodes and other invasive monitoring and operative delivery should be avoided if possible. The infant should be treated with 6 weeks of ZDV therapy after birth.

Key to Abbreviations: ART = antiretroviral therapy; PACTG 076 = Pediatric AIDS Clinical Trial Group study 076; ZDV = zidovudine; ARV = antiretroviral.

Adapted from: Centers for Disease Control and Prevention. *Table 7. Clinical Scenarios and Recommendations Regarding Mode of Delivery to Reduce Perinatal Human Immunodeficiency Virus Type 1 (HIV-1) Transmission.* In: *Public Health Service Task Force Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV-1 Transmission in the United States.* July 6, 2006. Available online at http://aidsinfo.nih.gov/Guidelines/GuidelineDetail.aspx?GuidelineID=9.

Postpartum Follow-Up of the Woman with HIV Infection

Women with HIV infection who have delivered recently need access to a comprehensive array of services for themselves and their infants. The clinician should refer the postpartum woman not only to her primary obstetric and HIV providers for family planning and HIV management, but also to a pediatric HIV specialist for care for her infant. She should also be referred as needed for mental health, substance abuse, and social support services. The clinician should be alert for indications of postpartum depression and should offer treatment promptly. Adherence to ARV regimens may be particularly difficult in the immediate postpartum period because of the physical changes postpartum and the demands of a new baby.

Women should be evaluated for their ongoing need for ART postpartum. If combination ART was given only or primarily to reduce the risk of perinatal transmission, the woman and her clinician may wish to consider discontinuing therapy after pregnancy, with the option to resume ART when she meets the criteria for treatment. Generally, all drugs should be stopped at once, but if the drugs have very different half-lives, their discontinuation should be staggered to decrease the risk of resistance, (eg, in regimens containing nevirapine, which has a long half-life). Drugs with a short half-life should be continued for several days to 1 week after the nevirapine is discontinued.

Follow-Up of the HIV-Exposed Infant

The HIV-exposed infant should be referred to a pediatric HIV specialist for diagnostic testing and monitoring of health status. Newborns should be discharged home with a supply of ZDV oral syrup. The newborn should receive ZDV syrup at a dose of 2 mg/kg body weight per dose every 6 hours beginning 8-12 hours after birth and continuing for 6 weeks.

Traditional HIV antibody testing cannot be used in infants because maternal antibodies may persist for up to 18 months. Diagnosis of HIV infection in infants requires virologic testing with HIV DNA polymerase chain reaction (PCR) or HIV RNA PCR. The *DHHS Pediatric ARV Guidelines* recommend testing at birth to 14 days, at 1-2 months, and at 3-6 months. HIV DNA PCR is a sensitive test that detects viral DNA in the patient's peripheral monocytes. Although the sensitivity of DNA PCR is <40% if performed at <48 hours of age, by 2-4 weeks of age, the sensitivity is >90%. HIV RNA PCR detects extracellular viral RNA in the plasma and is as sensitive as DNA PCR for early diagnosis in infants. Some clinicians recommend using the HIV RNA assay as a confirmatory test for an infant with a positive DNA PCR result. This approach confirms the diagnosis and can help guide treatment decisions. HIV viral culture is also sensitive, but it is expensive and results may not be available for 2-4 weeks.

HIV can be diagnosed in an infant on the basis of 2 positive virologic tests done on separate blood samples at any time. HIV reasonably can be excluded in an infant with 2 negative virologic tests done at >1 month of age, with 1 being done at >4 months of age. Antibody testing is recommended at age 12-18 months to document seroreversion.

Infants should have a baseline complete blood count and should be monitored for anemia while they are taking ZDV. The *DHHS Perinatal ARV Guidelines* recommend *Pneumocystis jiroveci* pneumonia (PCP) prophylaxis for HIV-exposed infants beginning at 6 weeks (when the ZDV is completed) and continuing until age 6 months or until HIV infection can be ruled out.

Parents and family care givers need to be educated that the infant must be monitored closely until an HIV diagnosis is made or is ruled out. They also need to know that the infant's exposure to ARV agents in utero is an important part of the infant's medical history and should be shared with future health care providers. Although no long-term consequences of ARV exposure have been confirmed, the child may be at risk for long-term problems.

Antiretroviral Pregnancy Registry

To improve tracking of pregnancy-related adverse effects and fetal effects, an Antiretroviral Pregnancy Registry has been established as a collaborative project among the pharmaceutical industry, pediatric and obstetric providers, the CDC, and the National Institutes of Health. The registry collects observational data on HIV-infected pregnant women taking ARV medications to determine whether patterns of fetal or neonatal abnormalities occur. Pregnant women taking ARVs can be placed in this confidential follow-up study by calling 800-258-4263, 8:30 AM to 5:30 PM eastern time; the fax number is 800-800-1052. Information is confidential and patients' names are not used. Providers are encouraged to add to the available information on fetal risk by using this registry at first contact with a pregnant woman taking ARVs. More information can be obtained at http://www.APRegistry.com.

Patient Education

- The clinician should provide the pregnant woman with the most current information on the risk of mother-to-child HIV transmission and the importance of ARV prophylaxis.
- The clinician and the pregnant woman should have a detailed discussion about whether she needs ART for her health and the ARV regimen that would be most appropriate for her to decrease the risk of perinatal transmission.
- The clinician should review the critical importance of adherence to ARV regimens before prescribing a regimen.
- Once a regimen is begun, the clinician should review possible adverse effects of the drugs and give the woman specific instructions about managing them if they are mild or getting medical advice if they represent a more serious adverse effect, such as ongoing fatigue, persistent nausea and vomiting, or signs of hyperglycemia.
- Early in the third trimester, the clinician and patient should discuss the risks and potential benefits of cesarean section based on her viral load and clinical status.
- Intrapartum management, including intrapartum ZDV, should be discussed with the patient so that she knows that she should tell the delivery team about her HIV status when she presents in labor.
- The signs of early labor should be explained to the pregnant woman and she should know that she should seek care immediately if her membranes rupture or she believes she is in labor.
- The clinician should discuss infant feeding plans with the mother and reinforce that she should not breast-feed. The clinician may need to provide ongoing support for formula feeding.
- The clinician should discuss follow-up plans and make referrals for the pregnant woman and her infant. If at all possible, the woman should meet the pediatric HIV team before delivery or in the postpartum period. The importance of ARV prophylaxis and follow-up for the newborn should be stressed.

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Care of HIV-Infected Pregnant Women

Background

This chapter describes the elements involved in caring for the pregnant woman with HIV infection, whether the woman was known to be HIV infected before conception or was found to be HIV infected during pregnancy. It is not intended to be a comprehensive discussion of this topic, and an HIV-experienced obstetrician and an HIV specialist should be involved in the management of all HIV-infected pregnant women. For centers that do not have HIV specialists available, experts at the National Perinatal HIV Consultation and Referral Service are available for consultation through the Perinatal Hotline (888-448-8765).

The first task in caring for an HIV-infected woman who is pregnant or is considering pregnancy is to provide counseling that will allow her to make informed reproductive choices. Taking a careful reproductive history and providing preconception counseling should be part of any woman's routine primary care. To make informed choices about pregnancy, the patient needs education and information about the risk of perinatal transmission of HIV, potential complications of pregnancy, continuation or modification (or possible initiation) of antiretroviral therapy (ART), and the support she will need to optimize maternal and fetal outcomes.

The goals of HIV management during pregnancy are to maintain and support the woman's health, provide optimal ART to preserve or restore her immune system and suppress viral replication, and offering interventions that decrease the risk of perinatal HIV transmission. ART has proven highly effective in preventing mother-to-child HIV transmission. After the results of the Pediatric AIDS Clinical Trial Group study 076 were released in 1994, ART tailored to the specific patient has been recommended to decrease perinatal transmission and optimize outcomes (see chapter *Reducing Maternal-Infant HIV Transmission*). In the United States, ART should be offered according to the U.S. Public Health Service (USPHS) Task Force guidelines (see "Antiretroviral Therapy" below).

Preconception Evaluation of the HIV-Infected Woman

Ideally, the evaluation of reproductive issues with an HIV-infected woman begins before pregnancy. The preconception evaluation should include the following elements:

- Reproductive history, including number of pregnancies, number of partners, pregnancies with each partner, and outcomes of each pregnancy
- Length of relationship with current partner, HIV serostatus of partner, and couple's sexual history, including condom use and sexual decision making or control of reproductive choices
- Patient's and partner's reproductive desires, and discussion of options

Any history of infertility or low fertility in either the patient or her partner also should be evaluated and discussed, including current information on gamete donation, other assisted reproductive techniques, and adoption. For a woman (or a couple) who has decided to try to conceive, several issues must be considered. Prominent among these is the HIV serostatus of both partners. If HIV infection is present in only one of the partners, the risk of transmission to the uninfected partner and techniques to minimize the risk should be discussed. (For further discussion and patient-education materials for HIV-discordant couples, see Aaron and Mercurius in "References" below.)

If ART is indicated, an appropriate regimen should be started before pregnancy, avoiding agents with increased risk for teratogenicity (eg, efavirenz), hepatotoxicity (eg, nevirapine), or metabolic complications such as lactic acidosis (eg, didanosine, stavudine, and zalcitabine). See chapter *Reducing Maternal-Infant HIV Transmission* and the *Public Health Service Task Force Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV-1 Transmission in the United States.* Centers for Disease Control and Prevention. July 6, 2006. (http://aidsinfo.nih.gov/Guidelines/GuidelineDetail.aspx?GuidelineID=9) for further information. It should be noted that most fetal organogenesis occurs in the early weeks of pregnancy, before most women know that they are pregnant. Thus,

any medication with potential teratogenicity or fetal toxicity, whether an antiretroviral (ARV) or another drug, should be avoided in women who are intending to become pregnant or are at risk of pregnancy. Certain medications (eg, ribavirin) also should be avoided by male partners of women who may become pregnant.

Folate supplementation to reduce the risk of neural tube defects in the developing fetus should be started at least 1 month before conception, if possible, because the neural tube forms in the early weeks of pregnancy (see below).

Evaluation and Counseling of Pregnant Women

All HIV-infected pregnant women should receive thorough education and counseling about perinatal transmission risks, strategies to reduce those risks, and potential effects of HIV infection or HIV treatment on the course or outcomes of pregnancy.

- The goals of therapy for pregnant women treated with ART, as for all persons being treated for HIV infection, are to suppress the HIV viral load maximally (preferably to undetectable levels) for as long as possible, to improve quality of life, to restore or preserve immune function, and, for pregnant women specifically, to reduce the risk of perinatal transmission as much as possible.
- Therapy-associated adverse effects, including hyperglycemia, anemia, and hepatic toxicity, may have a negative effect on maternal and fetal health outcomes. Pregnant woman should be advised about possible ARV-related adverse effects and should be monitored regularly for these events.
- HIV-infected women should receive evaluation and appropriate prophylaxis for opportunistic infections (OIs), as well as vaccinations as indicated for persons with HIV infection (eg, pneumococcus vaccination) (see below).
- Some medications, both ARVs and other drugs, may cause fetal anomalies or toxicity when taken during pregnancy. These should be avoided in pregnant women, unless the anticipated benefit outweighs the possible risk. Consult with an HIV or obstetric specialist, a pharmacist, or the drug labeling information before prescribing medications for pregnant women.

Other evaluation and support for pregnant women should include the following:

- Screening for other potential maternal health problems, such as diabetes and hypertension
- Maternal nutritional evaluation and support, including initiation of a prenatal multivitamin containing folate (0.4-0.8 mg orally once daily) to reduce the risk of fetal neural tube defects. Pregnant women who are taking trimethoprim-sulfamethoxazole (Septra, Bactrim, cotrimoxazole) and women who may become pregnant who are taking trimethoprim-sulfamethoxazole should be given higher doses of folate. Some experts recommend a folate dose of 4 mg daily for women receiving trimethoprim-sulfamethoxazole.
- Screening for psychiatric and neurologic disease
- Counseling about the risks of tobacco smoking; smoking cessation support as indicated
- Counseling about the risks of alcohol or drug use and support for discontinuation of these substances as needed
- Domestic violence screening
- Review of medications, including over-the-counter and nutritional agents; discontinuation of medications with the potential for fetal harm
- Immunizations (eg, influenza, hepatitis B) as indicated
- Institution of the standard measures for evaluation and management (eg, assessment of reproductive and familial genetic history, screening for infectious diseases or sexually transmitted diseases [STDs])
- Planning for maternal-fetal medicine consultation, if desired or indicated
- Selection of effective and appropriate postpartum contraceptive methods if desired

Comprehensive Care of Pregnant Women with HIV Infection

Comprehensive care is important for pregnant women with HIV infection to achieve a healthy pregnancy and delivery. A multidisciplinary approach is the most effective way to address the medical, psychological, social, and practical challenges. For example, while her medical care is being managed by her obstetrician and an HIV specialist, the pregnant woman may need help from a social worker to find appropriate

social services for food, housing, child care, and parenting issues. The pregnant woman may need counseling and psychological support for herself and her partner, as well as referrals for substance abuse and detoxification programs. Peer counselors may be of particular assistance. Some patients may need legal or domestic violence services during and after pregnancy. Cooperation and communication between the obstetrician or nurse/midwife and the primary HIV provider are imperative throughout the pregnancy and early postpartum period. Referral to a maternal-fetal medicine specialist may be needed in complicated obstetric cases.

Prenatal Care

All of the pregnancy-related complications seen in HIV-uninfected women, such as hypertensive disorders, ectopic pregnancy, psychiatric illness, multiple gestation, preterm delivery, and STDs also can occur in HIV-infected women. These problems must be recognized quickly and treated appropriately to avoid life-threatening complications. Ideally, HIV-infected pregnant women are managed by both an experienced obstetrician-gynecologist and an HIV specialist. Communication between these specialists about medications, expectations, and complications is vital for the health and well-being of both mother and baby. If complications occur or abnormalities are detected, they should be evaluated and treated as indicated by the condition, and referral should be made to a maternal-fetal medicine specialist, if possible. Antenatal fetal surveillance and testing to identify fetal abnormalities should be carried out using guidelines established by the American College of Obstetricians and Gynecologists.

Tables 1-3 present the suggested testing and monitoring practices for pregnant women with HIV infection, from the first trimester to labor and delivery.

Table 1. Recommended Evaluation and Routine Monitoring of the Pregnant Woman with HIV Infection: Initial and Subsequent Visits

Initial Visit		Frequency/Subsequent Visits
History		
HIV History	Date of diagnosis	-
	Signs and symptoms	Every visit
	Nadir CD4 and current CD4 cell count; HIV viral load	-
	ARV history, including regimen efficacy, toxicity, and ARV resistance	-
	Opportunistic infections and malignancies	Every visit
	History of genital herpes (HSV-2)	-
	Adherence	Every visit
Obstetric History	Number of pregnancies; complications and outcomes	-
	History of genetic disorders	-
	Use of ARV prophylaxis during previous pregnancies	-
	HIV status of children	-
Current Pregnancy	Last menstrual period (LMP)	-
	Pregnancy: intended or not	-
	Contraceptive methods used, if any	-
	Gestational age (can be calculated in a woman with regular menses, counting weeks from LMP)	Every visit
	Estimated date of delivery	-
	Signs or symptoms of maternal complications: elevated blood pressure, headache, significant edema, gastrointestinal or genitourinary symptoms, vaginal discharge or bleeding, decreased fetal movement	Every visit
	Screen for intimate-partner violence	Every visit

Physical Examination		
General	Vital signs and weight, funduscopy, breast exam	Every visit
Gynecologic	Pelvic exam, STD screening, examination for perineal or vaginal lesions (discoloration, condyloma, ulcerative lesions, vaginal discharge), cervical lesions, discharge or bleeding	As indicated
	Fundal height, correlating with gestational age (concordant between 18 and 30 weeks)	Every visit
	Fetal heart beat and rate: audible with DeLee fetal stethoscope between 16 and 19 weeks, earlier with Doppler devices	Every visit
	Fetal movements and position in third trimester	Every visit
Laboratory Tests		
HIV	HIV enzyme-linked immunosorbent assay (ELISA) with Western blot confirmation (if HIV status is not known) or rapid test and confirmatory test	-
	HIV viral load and CD4 count (total and %)	Every 3 months (at least every trimester) or as indicated
	Fasting lipid measurement	As indicated
	Genotype if ARV naive or detectable HIV RNA while on ART	As indicated
	Cytomegalovirus (CMV) immunoglobulin G (IgG) if CD4 count <100 cells/µL or if at low risk for CMV	-
	Toxoplasmosis IgG	-
	Consider HSV-2 serology, if history suggests	-
General	Complete blood count (CBC); chemistries, liver enzymes (LFTs)	Every 3 months or more frequently based on ARV regimen or symptoms
	Blood group	-
	Rh antibody screen	-
	Rubella antibody	-
	Varicella IgG, if history unclear	As indicated
	Screening for syphilis: rapid plasma reagin (RPR) or Venereal Diseases Research Laboratory (VDRL)	As indicated
	Screening for gonorrhea and chlamydia	As indicated
	Urinalysis and clean-catch urine culture	As indicated
	Papanicolaou smear	As indicated
Hepatitis Serologies	Hepatitis A virus (HAV) antibody (IgG)	-
	Hepatitis B virus (HBV): HBsAg, HBcAb, HBsAb	-
	Hepatitis C virus (HCV) antibody	-
TB Screening	Tuberculin skin test (PPD); more reliable if CD4 >200 cells/µL (induration >5 mm is positive)	-
Disease Specific	G6PD level, especially if anemic	-
	Consider hemoglobin electrophoresis, if anemic and/or at increased risk for hemoglobinopathies	-
	Serum screening for Tay-Sachs disease—both partners—if at increased risk	-
	Urine toxicology screen	As indicated

Table 2. Recommended Evaluation and Routine Monitoring of the Pregnant Woman with HIV Infection: Second and Third Trimesters

Test	Comment
Weeks 16-20	
Ultrasound	Confirm gestational age, screen for malformations, multifetal pregnancy.
Maternal serum alpha-fetoprotein (AFP) or triple screen (human chorionic gonadotropin [HCG], serum estriol, and AFP)	Screen for neural tube and abdominal wall defect, trisomy 21, trisomy 18. Abnormal test requires further investigation—consider amniocentesis only if abnormality is detected on expanded triple screen or level-2 sonogram. Voluntary and requires counseling.
STD screening: gonorrhea, chlamydia, wet mount	Repeat as indicated, according to the woman's risk factors.
Weeks 24-28	
Complete blood count	
Syphilis serology	
Diabetes screening	Consider at 20 weeks: check glucose 1 hour after a 50 g glucose load; perform 3-hour glucose tolerance test if screen is abnormal. If 3-hour test abnormal, perform regular glucose monitoring, especially in women taking protease inhibitors.
Bacterial vaginosis (BV) screening	BV increases the risk of preterm labor.
Weeks 32-36	
Streptococcus B screening	If positive, offer intrapartum chemoprophylaxis.
STD screening: gonorrhea, chlamydia, syphilis	Repeat tests to rule out risk of perinatal transmission of these infections.
CD4 count, HIV viral load	Results obtained at 35-36 weeks guide decisions on the mode of delivery.

Table 3. Recommended Evaluation and Routine Monitoring of the Pregnant Woman with HIV Infection: Labor and Delivery

Test	Comment
Record Review	• Documentation of HIV serostatus, blood type and Rh, hepatitis serologies, rapid plasma reagin (RPR) • Review of antiretroviral therapy, if any, during pregnancy • Review of HIV viral load results during pregnancy
Physical Evaluation	• Vital signs and fetal heart rate • Frequency and intensity of contractions • Fetal lie, presentation, attitude, and position • Vaginal examination: rule out herpes simplex virus (HSV) lesions; detect ruptured membranes; determine cervical effacement, dilatation, and position • **Avoid procedures that increase the risk of perinatal HIV transmission (eg, fetal scalp electrodes, scalp sampling, or assisted rupture of membranes)**
Admission Laboratory Tests	• Complete blood count • Liver function tests • RPR or Venereal Diseases Research Laboratory (VDRL), if not done recently • Repeat hepatitis B and C testing, if at risk for acquisition of hepatitis B or C, to prevent perinatal transmission of these infections

Immunizations and Opportunistic Infection Prophylaxis

Immunizations during Pregnancy

Immunizations should be given before pregnancy, if possible. Immunizations should be considered during pregnancy when the risk of exposure to an infection is high, the risk of infection to the mother or fetus is high, and the vaccine is unlikely to cause harm. Some vaccinations (such as measles/mumps/rubella) are contraindicated, and others should be given only if the anticipated benefit of the vaccination outweighs its possible risk. Special considerations for immunizations in HIV-infected individuals are discussed in chapter *Immunizations for HIV-Infected Adults and Adolescents*.

Some clinicians avoid giving immunizations during the third trimester of pregnancy because vaccinations may cause a transient increase in the HIV viral load and theoretically may increase the risk of perinatal HIV transmission. An increase in viral load may be prevented with effective ART, and some clinicians defer immunizations until ART is under way.

Recommendations related to immunizations during pregnancy are shown in Table 4.

Table 4. Immunizations and Postexposure Prophylaxis in Pregnant Women with HIV Infection

Immunization	Comment
Hepatitis A virus (HAV)	Recommended for susceptible patients at high risk of infection, those with chronic HBV or HCV, those traveling to endemic areas, injection drug users, or in the setting of a community outbreak
Hepatitis B virus (HBV)	Generally recommended for susceptible patients
Influenza	Generally recommended; give before flu season
Measles/Mumps/Rubella (MMR)	*Contraindicated*
Pneumococcus	Generally recommended, repeat every 5-7 years
Tetanus-diphtheria	Recommended; give booster every 10 years
Immune globulins (For postexposure prophylaxis in susceptible individuals)	**Comment**
Measles	Recommended after measles exposure, for symptomatic HIV-infected persons
Hepatitis A	Recommended after exposure to a close contact or sex partner, or in case of travel to endemic areas
Hyper immune globulins	**Comment**
Varicella-zoster virus immune globulin (VZIG)	Recommended after significant exposure to varicella-zoster virus (give within 96 hours)
Hepatitis B immune globulin (HBIG)	Recommended after needlestick or sexual exposure to a person with hepatitis B infection

Opportunistic Infection Prophylaxis

Some OIs can have an adverse effect on pregnancy In turn, pregnancy can affect the natural history, presentation, treatment, and significance of some OIs. Women should be monitored carefully for OIs during pregnancy, with special attention given to nonspecific symptoms such as fatigue, back pain, and weight loss, which may be due to HIV-related illness rather than to pregnancy. Respiratory symptoms in particular merit rapid, aggressive investigation. Clinicians should follow the most current recommendations of the USPHS and the Infectious Diseases Society of America, which give special consideration to pregnant women for each OI discussed. (*Guidelines for Prevention of Opportunistic Infections among HIV-Infected Persons—2002*. June 14, 2002. Available online at http://aidsinfo.nih.gov/Guidelines/GuidelineDetail.aspx?GuidelineID=13.) The indications and recommendations for OI prophylaxis generally should follow the guidelines for adults (see chapter *Opportunistic Infection Prophylaxis*). However, because of the risks of teratogenicity or harm to the developing fetus, some drugs routinely used for prophylaxis of OIs in nonpregnant adults are contraindicated during pregnancy.

Special Considerations for OI Prophylaxis during Pregnancy

Trimethoprim-sulfamethoxazole

Trimethoprim inhibits the synthesis of metabolically active folic acid. In pregnant women, folate deficiency increases the risk of neural tube defects in the developing fetus. Pregnant women, or women who may become pregnant, who are taking trimethoprim-sulfamethoxazole (Septra, Bactrim, cotrimoxazole) have an increased risk of folate deficiency and should be given folate supplementation to reduce the risk of neural tube defects. Some experts recommend high doses of folate (eg, 4 mg daily) to overcome the folate antagonism of trimethoprim-sulfamethoxazole. Because neural tube development occurs very early in pregnancy, folate supplementation should be started at least 1 month before conception, if possible.

Genital herpes

Women with HIV infection are more likely than HIV-uninfected women to experience outbreaks of herpes. If herpes simplex virus (HSV) is transmitted to the infant, neonatal infection can be severe, even if it is detected and treated early. Strongly consider obtaining HSV-2 serologies in a woman whose clinical history is unclear. Treatment for symptomatic HSV infections should be offered during pregnancy, and suppressive therapy should be given to women with frequent recurrences. If a woman has an active outbreak of genital HSV or experiences prodromal symptoms at the time of labor or membrane rupture, delivery by cesarean section is indicated. Prophylaxis with oral acyclovir late in pregnancy to prevent neonatal herpes transmission is controversial and is not routinely recommended.

Tuberculosis

Prophylaxis is recommended for any woman with either a positive purified protein derivative (PPD) skin test (≥5 mm induration) or a history of exposure to active tuberculosis, after active disease has been ruled out. Because of concern about possible teratogenicity from drug exposure, clinicians may choose to delay prophylaxis until after the first trimester. Patients receiving isoniazid also should receive pyridoxine to reduce the risk of neurotoxicity.

Toxoplasmosis

All HIV-infected persons should be tested for immunoglobulin G (IgG) antibodies to *Toxoplasma* soon after HIV diagnosis, and this should be a part of antenatal testing for pregnant women with HIV infection. Women with a negative IgG titer should be counseled to avoid exposure to *Toxoplasma* (eg, by avoiding raw or undercooked meats, unwashed or uncooked vegetables, and cat feces). Women with previous exposure to *Toxoplasma* (positive IgG titer) may be given prophylaxis during pregnancy, if indicated. For women who require prophylaxis, trimethoprim-sulfamethoxazole is the preferred agent; some specialists advise against giving pyrimethamine during pregnancy.

Antiretroviral Therapy

Current USPHS guidelines for the use of ARV agents in pregnant women with HIV infection recommend treating HIV infection in pregnant women using the same principles and modalities as for nonpregnant individuals. The 3-part zidovudine (ZDV) regimen (antenatal, intrapartum, and neonatal) should be recommended as the minimum intervention to reduce the risk of perinatal HIV transmission. In addition to the 3-part ZDV regimen, the guidelines recommend offering effective combination ART to all pregnant women to maximally suppress viral replication, minimize the risk of developing resistant virus, and reduce the risk of perinatal transmission. The choice of ARV regimen should take into account the optimal regimen for the woman's health, the potential effect on the fetus and infant, the woman's previous experience, if any, with ARV treatment, and her stage of pregnancy. In most cases, the regimen should include ZDV, if possible. ARV agents with known teratogenic effects, such as efavirenz, should be avoided, especially in the first trimester. Some clients and HIV care providers may elect to withhold ARV therapies during the first trimester, because this is a period of rapid organogenesis and an increased risk of birth defects if teratogen exposure occurs. For women already taking ART at the time they become pregnant, the ARV regimen should be reevaluated for its appropriateness during pregnancy to avoid potentially toxic medications and to ensure maximal virologic suppression. If a decision is made to interrupt ART during the first trimester, the woman should be instructed how and when to stop and to restart ART and should be made aware of the risk of viral rebound during the ARV interruption.

Discussion of treatment options should include the known and unknown effects of ARV drugs on the fetus and newborn, recommendations for the woman's health,

and the known efficacy of ZDV in preventing perinatal transmission. Recommendations should be noncoercive, and the woman herself must make the final decision regarding the use of ARV drugs. A decision to decline ART should not result in punitive action or denial of care; nor should ART be denied to any woman who wishes to minimize the fetus's exposure to drugs and therefore chooses to receive only ZDV to reduce the risk of perinatal transmission. The woman should be informed that ZDV alone does not reduce the baby's HIV risk as much as a potent triple-drug therapy, and also that monotherapy with any ARV drug confers a risk of drug resistance that may affect the success of future treatment for her and for the infant (if HIV infected).

The *USPHS Perinatal ARV Guidelines* are updated regularly as clinical trial results are reported and ARVs are approved by the U.S. Food and Drug Administration. The guidelines include recommendations regarding ARV regimens, modes of delivery (vaginal vs cesarean section), and potential adverse events, as well as a detailed discussion of individual ARV agents. Pregnant women with HIV infection should be managed as a collaboration between an HIV specialist and the obstetric provider.

For further information about ARV treatment during pregnancy, see the chapter *Reducing Maternal-Infant HIV Transmission* and the *USPHS Perinatal ARV Guidelines*.

Antiretroviral Pregnancy Registry

To improve tracking of pregnancy-related adverse effects and fetal effects, an Antiretroviral Pregnancy Registry has been established as a collaborative project among the pharmaceutical industry, pediatric and obstetric providers, the CDC, and the National Institutes of Health. The registry collects observational data on HIV-infected pregnant women taking ARV medications to determine whether patterns of fetal or neonatal abnormalities occur. Pregnant women taking ARVs can be placed in this confidential follow-up study by calling 800-258-4263, 8:30 AM to 5:30 PM eastern time; the fax number is 800-800-1052. Information is confidential and patients' names are not used. Providers are encouraged to add to the available information on fetal risk by using this registry at first contact with a pregnant woman taking ARVs. More information can be obtained at http://www.APRegistry.com.

Pregnancy-Specific Complications and Management

Nutrition Risk and Inadequate Weight Gain

Maternal nutrition and weight must be monitored throughout the pregnancy. A food diary may be a useful tool in assessing intake, and nutritional counseling is recommended.

Nausea and Vomiting

Women with signs of dehydration should be assessed and treated appropriately in collaboration with the obstetrician or nurse-midwife. Any medication used for nausea and vomiting must be assessed for drug-drug interactions with all HIV-related medications the patient is already taking. Women who are not taking ART at the beginning of their pregnancy usually are assessed and placed on an ARV regimen at the end of the first trimester, when the nausea and vomiting of early pregnancy have improved.

Hyperglycemia

Pregnancy is a risk factor for hyperglycemia, and women treated with protease inhibitors (PIs) may have an even higher risk of glucose intolerance than other pregnant women and must be monitored carefully. New-onset hyperglycemia and diabetes mellitus, and exacerbation of existing diabetes, all have been reported in patients taking PIs. Clinicians should educate women taking PIs about the symptoms of hyperglycemia and closely monitor glucose levels. Some clinicians check glucose tolerance at 20-24 weeks and again at 30-34 weeks if the woman is taking PIs. The baby should be checked for neonatal hypoglycemia at 1 and 4 hours.

Lactic Acidosis

Lactic acidosis is a rare but life-threatening complication that has been reported in pregnant women taking nucleoside reverse transcriptase inhibitors, particularly didanosine and stavudine. The combination of didanosine and stavudine should be avoided during pregnancy and prescribed only when the potential benefit clearly outweighs the potential risk. Clinical suspicion of lactic acidosis should be prompted by vague symptoms such as malaise, nausea, or abdominal discomfort or pain. Lactate levels, electrolytes, and liver function tests should be monitored carefully, particularly in the third trimester.

Hyperbilirubinemia

Women who are taking indinavir may have an increased risk of nephrolithiasis, but evidence of harm to the newborns has not been demonstrated. Women taking indinavir or atazanavir frequently develop elevated indirect bilirubin, but it is not known whether treatment during pregnancy exacerbates physiologic hyperbilirubinemia in the newborn.

Pain Management

Pain management during labor and delivery may be complicated by drug interactions with ARVs and by the higher medication tolerance in women who have addictions. Additional pain medication may be needed for women with histories of drug use.

Perinatal Considerations

The risk of HIV infection of the fetus during invasive procedures (eg, amniocentesis, chorionic villus sampling, percutaneous or umbilical cord blood sampling) must be balanced against the possible benefits of these procedures. Invasive procedures should be performed only after discussion with and consent from the pregnant woman.

Postpartum Considerations

Because HIV can be transmitted to the infant through breast-feeding, breast-feeding is contraindicated in the United States and other resource-adequate countries where safe replacement feeding is available. Breast-feeding information should be removed from patient educational material pertaining to labor and delivery. Breast binding and ice packs can be used as needed to reduce lactation discomfort. Clinicians should recognize that women in some cultural groups are expected to breast-feed and they may need additional support to use formula rather than breast-feed.

ART should be continued as indicated by the *USPHS Perinatal ARV Guidelines*. Maternal and infant medication adherence must be discussed with the new mother. Adherence barriers for the mother during the postpartum period may be different from those during pregnancy (eg, because of changes in daily routine, sleep/wake cycles, and meals).

New mothers should be observed carefully for signs of bleeding or infection. If the mother's glucose tolerance test was abnormal during pregnancy, she should be reevaluated (by 2-hour glucose tolerance test) 6 weeks postpartum and should be screened yearly for diabetes.

At the 2-week postpartum follow-up visit, the clinician should address the patient's concerns, screen for postpartum depression, assess adherence to her own and the infant's ARV medications, and ensure follow-up with the primary HIV care provider, pediatrician, and obstetric provider. This visit also affords an opportunity to address the woman's contraceptive needs and options, if this was not done previously.

Contraception

Many contraceptive choices are available for HIV-infected women; some considerations are discussed in Table 5. Depending on the woman's risk factors, consistent condom use should be emphasized, with or without other methods of contraception, to prevent the transmission of HIV and the acquisition or transmission of other STDs.

Table 5. Advantages and Disadvantages of Various Contraceptives

Contraceptive Type	Advantages	Disadvantages
Barrier Methods		
Male and female condom	• Protect against transmission of HIV and STDs	• Requires partner cooperation and correct technique • High failure rate when used incorrectly
Diaphragm and cervical cap		• Requires partner cooperation and correct technique • High failure rate when used incorrectly
Sponge		• Does not prevent STD or HIV transmission
Hormonal Methods		• Do not prevent STD or HIV transmission
Oral*	• Very effective • Lighter menstrual flow	• May have significant drug-drug interactions with protease inhibitors (PIs) and nonnucleoside reverse transcriptase inhibitors (NNRTIs) that may affect the efficacy and toxicity of estradiol and norethindrone, and of certain PIs* • Consider alternative methods for women taking PIs or NNRTIs • Some concern about increased cervical proviral shedding
Injectable depot medroxyprogesterone acetate (DMPA, Depo-Provera)	• Effective contraception for 3 months	• Possible increased risk of genital tract HIV shedding • Long-term concern about osteoporosis
Transdermal/Patch	• Effective • Lighter menstrual flow	• No studies to document pharmacokinetic interactions, but possible significance • Possible increased risk of HIV viral shedding
Vaginal ring	• Effective • Lighter menstrual flow	• No studies to document pharmacokinetic interactions, but possible significance • Possible increased risk of HIV viral shedding
Intrauterine devices (IUDs)	• Effective for long-term use • No evidence of increased HIV viral shedding	• Possible blood loss with Copper T IUD
Surgical Methods		
Bilateral tubal ligation (female)	• Effective; permanent	• Does not prevent STD or HIV transmission • No future fertility (usually not reversible)
Vasectomy (male)	• Effective; permanent	• Does not prevent STD or HIV transmission • No future fertility (usually not reversible)
Spermicides		
Spermicides		• Not currently recommended • Nonoxynol-9 increases risk of HIV transmission • Do not prevent STD or HIV transmission

* See chapter *Antiretroviral Medications and Oral Contraceptive Agents* and U.S. Department of Health and Human Services. *Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents*. May 4, 2006. Available online at aidsinfo.nih.gov/Guidelines/GuidelineDetail.aspx?GuidelineID=7.

Patient Education

- Reinforce regularly and clearly the notion that, when the mother cares for herself, she is caring for her infant. Talk with the patient about stress, the importance of adequate mild-to-moderate exercise, and sufficient rest.
- Emphasize that regular prenatal care is extremely important to prevent complications of pregnancy.
- Use of a prenatal vitamin supplement is important, but cannot replace healthy food intake. Develop a plan with the patient for attaining the desired weight gain during pregnancy, while maintaining a healthy nutritional intake.
- Cigarette, alcohol, and drug use contribute to poor maternal nutrition and can harm the developing fetus. Illicit drug use also increases the risk of transmitting HIV to the infant. Injection drug use can transmit hepatitis B and C and cytomegalovirus (CMV) to the mother as well as to the baby. Encourage cessation of cigarette, alcohol, and drug use, and offer referrals for treatment, as needed.
- Be sure the woman understands all planned procedures and treatments and understands their potential risks and benefits both to herself and to the fetus.
- Discuss the risks and benefits (to the woman and fetus) of each medication to be taken during pregnancy, including those for which there are limited data on teratogenicity.
- Discuss ART as part of the strategy to reduce the risk of perinatal HIV transmission to the newborn. Allow the woman to choose whether to add ZDV to her combination ARV regimen (if applicable), or take it alone. The risk of developing ZDV-resistant HIV should be discussed if ZDV is used alone.
- For women at risk, diligent use of "safer sex" during pregnancy is important to prevent STDs and CMV, which can cause more complications when HIV is present. STDs can harm fetal development and may increase the risk of HIV transmission to the baby. New genital herpes infections during pregnancy can cause severe complications and even death in neonates.
- For women with negative *Toxoplasma* titers, explain the need to avoid undercooked meats, soil, and animal feces.
- Teach the pregnant woman how to obtain medical attention quickly at the first signs of OI or other complication. Discuss what to watch for and how to get help when emergencies arise in the evenings or on weekends or holidays.
- Help the patient clarify her child care options and encourage her to begin putting in place long-term child care and guardianship plans in case she becomes too sick to care for her child or children.

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Antiretroviral Medications and Oral Contraceptive Agents

Background

This chapter highlights the interactions between currently available antiretroviral agents and oral contraceptives.

The oral contraceptives ethinyl estradiol and norethindrone may interact in complex ways with protease inhibitors (PIs) and nonnucleoside reverse transcriptase inhibitors (NNRTIs). The mechanism of these interactions may be multifactorial and includes the activity of these agents on cytochrome P450 enzymes. Pharmacokinetic studies have shown changes (either increases or decreases) in levels of ethinyl estradiol and norethindrone in women who are taking certain PIs or NNRTIs. Other studies have shown decreases in levels of amprenavir (a PI) in women taking oral contraceptives.

The clinical significance of these drug interactions has not been evaluated thoroughly, but may cause oral contraceptive failure or antiretroviral failure, or medication toxicity, depending on whether drug levels are lowered or raised by the interacting drug.

Table 1 summarizes the available pharmacokinetic data. A more comprehensive review of oral and nonoral contraceptives for HIV-infected women can be found in the chapter *Care of HIV-Infected Pregnant Women*.

Table 1. Interactions between Antiretroviral Agents and Oral Contraceptives

Antiretroviral Agent	Pharmacokinetic Changes with Oral Contraceptives	Comments
Protease Inhibitors		
Atazanavir (ATV, TAZ, Reyataz)	• EE AUC increased 48% • NE AUC increased 110%	• Use lowest effective dose of each OC component and monitor for adverse effects. • Consider alternative methods of contraception to avoid OC adverse effects.
Fosamprenavir (FPV, Lexiva), Amprenavir (AMP, Agenerase)	• C_{min} of EE/NE increased 32-45%; no significant change in AUC • Amprenavir AUC decreased 22% and C_{min} decreased 20%	• To avoid risk of ARV failure, do not coadminister amprenavir or fosamprenavir with OCs. • Consider alternative methods of contraception.
Indinavir (IDV, Crixivan)	• EE AUC increased 24% • NE AUC increased 26%	• No dose adjustment is recommended.
Lopinavir/ritonavir (LPV/r, Kaletra)	• EE AUC decreased 42% • NE AUC decreased 17%	• Use of alternative or additional method of contraception is recommended.
Nelfinavir (NFV, Viracept)	• EE AUC decreased 47% • NE AUC decreased 18%	• Use of alternative or additional method of contraception is recommended to avoid contraceptive failure.
Ritonavir (RTV, Norvir)	• EE AUC decreased 40%	• Use of alternative or additional method of contraception is recommended to avoid contraceptive failure.
Saquinavir (SQV, Invirase, Fortovase)	• No data available regarding effect of SQV on EE or NE levels • SQV kinetics not affected by OC	• Until more data are available alternative methods of contraception is recommended.
Tipranavir/ritonavir (TPV/r, Aptivus)	• EE C_{max} and AUC decreased approximately 50%	• Use of alternative or additional method of contraception is recommended to avoid contraceptive failure.
Nonnucleoside Reverse Transcriptase Inhibitors		
Efavirenz (EFV, Sustiva)	• EE levels increased 37% • No data available on NE component	• Use of alternative method of contraception is recommended to avoid OC side effects.
Nevirapine (NVP, Viramune)	• EE AUC decreased 20% • NE AUC decreased 20%	• Use of alternative or additional method of contraception is recommended to avoid contraceptive failure.

Key to abbreviations: EE = ethinyl estradiol; NE = norethindrone; AUC = area under the curve (drug concentration); C_{min} = minimum concentration; C_{max} = maximum concentration.

Adapted from U.S. Department of Health and Human Services. *Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents*. May 4, 2006.

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- U.S. Department of Health and Human Services. *Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents. May 4, 2006*. Available online at aidsinfo.nih.gov/Guidelines/GuidelineDetail.aspx?GuidelineID=7. Accessed May 19, 2006.

Abnormalities of Body-Fat Distribution

Background

Body-fat abnormalities are a recognized complication of antiretroviral therapy (ART). These include central fat accumulation, subcutaneous fat atrophy, and the development of lipomas. Taken together, these abnormalities in fat distribution and body shape have been noted in up to 40-50% of patients treated with ART. The etiology of these changes in body habitus is not well understood, but research to date suggests that it is multifactorial, with components related to specific antiretroviral (ARV) medications, HIV-related immune depletion and immune recovery, hormonal influences, individual genetic predispositions, and non-HIV-related factors such as diet and obesity. In fact, lipodystrophy probably is not a single syndrome, but rather several separate but interrelated clinical presentations.

Lipodystrophy may present as isolated fat accumulation (lipoaccumulation), fat wasting (lipoatrophy), or a combination of both. The most common morphologic changes seen in fat accumulation are an enlarged abdomen from central or visceral fat accumulation, breast enlargement (gynecomastia), and development of a dorsocervical fat pad ("buffalo hump"). Lipoatrophy is seen most commonly as the loss of subcutaneous fat in the face, arms, legs, and buttocks. Lipoatrophy differs from the generalized wasting seen in advanced AIDS, because lean cell mass generally is preserved.

Severe lipoaccumulation can cause discomfort and, in some cases, impairment of breathing or other bodily functions. It also may be associated with other metabolic abnormalities, including dyslipidemia and the metabolic syndrome. Both lipoaccumulation and lipoatrophy can be disfiguring, can damage self-image and quality of life, and can negatively influence ARV adherence.

Research into the causes and manifestations of lipodystrophy has yielded varying results, in part because there is no standard clinical case definition of lipodystrophy. The prevalence of and risk factors for lipodystrophy are not well understood. The condition seems to develop more frequently in patients who are older and have longer exposure to ART. In some studies, lipodystrophy has been associated with lower nadir CD4 count as well as with sex (central lipoaccumulation may be more common in women). It has been associated with protease inhibitors (PIs) and with nucleoside reverse transcriptase inhibitors (NRTIs), but does not appear to be associated with nonnucleoside reverse transcriptase inhibitors (NNRTIs). However, it may develop in patients who have never received PIs, and occasionally in ARV-naive individuals. PIs appear to be associated more commonly with fat accumulation, whereas NRTIs, most notably stavudine, are associated with lipoatrophy.

S: Subjective

The patient may report any of the following: abdominal fat accumulation with change in waist size, increased neck size, "buffalo hump," and enlarged breasts; women may note an increase in bra size. The patient also may report sunken cheeks, temporal wasting, decreased arm or leg circumference, prominence of veins in the arms or legs, buttock flattening, and even pain in walking because of atrophy of fat padding around the soles of the feet. The patient may volunteer that these changes are causing emotional distress.

Inquire about CD4 nadir, ARV medication history, duration of and response to each regimen, and recent medication adherence. Ask about past medical and family history, specifically regarding hyperlipidemia, diabetes or insulin resistance, other metabolic disorders, and cardiovascular disease. Elicit the patient's emotional responses to the body shape changes.

O: Objective

Compare past and current weights. Calculate body mass index. Measure and document waist and hip circumferences; check waist-to-hip ratio. An abdominal circumference >102 cm (39 inches) in men and >88 cm (35 inches) in women is the clinical definition of abdominal obesity and is associated with the metabolic syndrome. Waist-to-hip ratios >0.95 in men and >0.85 in women are associated with an increased risk of coronary heart disease.

Examine the head, neck, back, breasts, and abdomen for fat accumulation, especially looking for dorsocervical fat

pad and facial, neck, or breast enlargement. Examine the face and extremities for subcutaneous fat loss (eg, in the cheeks, temples, limbs, and buttocks).

Review laboratory history (glucose, lipid panel), to identify other metabolic disorders. *(*See chapters *Dyslipidemia* and *Insulin Resistance and Hyperglycemia on Antiretroviral Therapy.)*

A: Assessment

No uniform standard criteria are available for defining or grading lipodystrophy in clinical practice. Clinicians must base their assessment on physical examination (for characteristic body-shape changes) and lipodystrophy-associated symptoms and psychological consequences.

In research settings, modalities such as dual-energy x-ray absorptiometry (DEXA), computed tomography (CT), and magnetic resonance imaging (MRI) have been used to characterize lipodystrophy. Anthropometric measurements may be made in the clinic by trained personnel (eg, nutritionists), but do not measure visceral fat directly. Although measurements such as waist circumference cannot be used to assess lipodystrophy, they have been validated (in non-HIV-infected individuals) as an assessment of cardiovascular risk. Bioelectrical impedance analysis (BIA) does not measure regional body composition and thus is not used to measure abnormal body-fat changes.

P: Plan

Laboratory

Check for other metabolic abnormalities associated with the use of ART, such as dyslipidemia and impaired glucose metabolism. See chapters *Dyslipidemia* and *Insulin Resistance and Hyperglycemia on Antiretroviral Therapy* for further information about workup and treatment.

Evaluate the effect of body-shape changes on the patient's self-esteem, medication adherence, and interpersonal relationships. Refer the patient for psychological or adherence support and counseling, if indicated. If the patient is distressed enough to consider discontinuing or interrupting ART, review with the patient any gains he or she has made on ART and discuss treatment options (see below). In some cases the patient may insist on discontinuing ARV medications; in this situation, carefully review the risks and benefits of treatment interruption, as well as the alternatives to discontinuing treatment.

Treatment

Consistently effective treatments for lipodystrophy have yet to be identified. In general, patients with marked or severe lipodystrophy have shown poor or inconsistent responses to interventions. The best approaches to lipodystrophy are prevention and early intervention.

Clinicians can help to prevent lipodystrophy by avoiding, whenever possible, ARV agents known to confer a greater risk of this disorder (particularly stavudine). All patients who take ARVs should be monitored carefully for the development of lipodystrophy. If lipodystrophy is noticed, intervention should be initiated, if possible.

The optimal management of lipodystrophy is not known, although the following approaches can be considered. Also consider referring the patient to clinical studies of lipodystrophy treatment.

Drug Substitutions

Avoiding thymidine analogue NRTIs, particularly stavudine, and avoiding the NRTI combination stavudine + didanosine have been shown to reduce the risk of lipoatrophy. In patients with lipoatrophy, modest long-term improvement has been demonstrated after switching from thymidine analogues (stavudine and zidovudine) to nonthymidine analogues (such as abacavir or tenofovir) or to NRTI-sparing regimens. Before switching therapies, carefully assess the potential risk to the patient's long-term HIV management.

Nonpharmacologic Measures

Diet

The effects of diet on lipodystrophy have not been evaluated thoroughly. If overall weight reduction is needed, recommend dietary changes and exercise. Avoid rapid weight loss plans, as lean body mass is often lost disproportionately. Refer to a dietitian, to help the patient decrease his or her intake of saturated fat, simple sugars, and alcohol.

Exercise

Regular, vigorous cardiovascular exercise may help control central fat accumulation, whereas muscle-building (strength training) will improve the ratio between fat and muscle. Some studies of exercise have shown a reduction in visceral fat accumulation with minimal or no changes in peripheral lipoatrophy. Moderate aerobic exercise should be encouraged in all patients.

Pharmacologic Measures

Recombinant Human Growth Hormone

Treatment with recombinant human growth hormone (rHGH), 3-6 mg/d for 12 weeks followed by maintenance therapy with lower doses of 1-2 mg/d, has been shown to reduce visceral fat with minimal impact on peripheral fat wasting. However, the high cost of rHGH, the high rate of adverse effects (including insulin resistance), and the frequent recurrence of morphologic abnormalities once rHGH is discontinued have resulted in a limited role for this treatment.

Insulin-Sensitizing Agents

In diabetic and non-HIV lipodystrophy, treatment with thiazolidinediones may decrease visceral fat, increase peripheral fat, and improve glycemic control. Unfortunately, studies of rosiglitazone as treatment for lipoatrophy in HIV-infected patients have shown mixed results. Some small studies have reported improvement in peripheral fat loss; however, a larger, 48-week randomized trial of rosiglitazone in HIV-infected patients with lipoatrophy found no improvement in fat mass. Therefore, rosiglitazone cannot be recommended currently for the treatment of lipoatrophy.

Metformin has been somewhat effective in treating lipoaccumulation in patients with insulin resistance, but may cause worsening of lipoatrophy. Metformin should not be given to patients with an elevated risk of lactic acidosis.

Studies of insulin-sensitizing agents continue.

Plastic and Reconstructive Surgery

Various techniques have been investigated, but generally have limited applicability and efficacy. These include liposuction and breast reduction for lipoaccumulation, and cheek implants and autologous fat transfer for facial lipoatrophy. Poly-L-lactic acid (Sculptra, New-Fill) is approved by the U.S. Food and Drug Administration as a treatment for facial lipoatrophy. This injectable material has shown to good cosmetic results, at least in the short term.

Although plastic surgery can help some people with lipodystrophy, the treatments are expensive, may need to be repeated, and usually are not covered by private or public-payer sources. In some cases, they may be only a temporary solution, because abnormalities may reappear after treatment.

Patient Education

- Instruct patients who are receiving ARV medications to inform their health care providers if they notice changes in the shape or appearance of their bodies.
- Review the importance and benefits of ART and assess adherence to the regimen.
- For patients with lipoaccumulation, recommend aerobic and resistance exercise to build muscle and reduce fat. Assess resources in your area for safe muscle-strengthening possibilities.
- If weight reduction is needed, refer to a dietitian for consultation. Remind the patient that quick weight loss diets may result in excessive muscle loss.

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Dyslipidemia

Background

In HIV-infected people treated with antiretroviral therapy (ART), improved life expectancy and the aging process are likely to increase morbidity and mortality from coronary heart disease (CHD). Thus, identification and reduction of modifiable risk factors for CHD are important aspects of primary care for HIV-infected patients. Several risk factors for CHD are common among HIV-infected populations in the United States and Europe. Dyslipidemia is a well-described independent risk factor for CHD that occurs in a high proportion of patients treated with antiretroviral (ARV) medications. Other metabolic abnormalities such as insulin resistance and diabetes may be caused or compounded by ARVs. In addition, some traditional CHD risk factors, including smoking, hypertension, and inactivity, are prevalent in many HIV-infected populations.

Before the widespread use of ARV medications, increases in triglyceride (TG) levels and decreases in total cholesterol (TC), high-density lipoprotein (HDL) cholesterol, and low-density lipoprotein (LDL) cholesterol were reported in individuals with HIV disease. The introduction of combination ART, particularly the use of protease inhibitors (PIs), increased the prevalence of dyslipidemia in HIV-infected patients. In fact, dyslipidemia is associated with certain agents in each of the 3 major classes of ARVs. In the PI class, ritonavir and ritonavir-boosted PIs (with the exception of atazanavir) are particularly likely to cause marked elevations of TG and LDL levels. Nonnucleoside reverse transcriptase inhibitors (NNRTIs) also may contribute to increases in TC, LDL, and TG levels although the effects, particularly with efavirenz, are more variable. Nucleoside analogue reverse transcriptase inhibitors (NRTIs), specifically stavudine, may increase TC and TG levels.

The pathogenesis of ARV-induced dyslipidemia is not well understood. Current research suggests that the dyslipidemia observed in patients taking ART is caused by a combination of factors related to HIV disease, ARV regimens, and individual patient characteristics. Lipid abnormalities may appear or worsen within a few weeks to months after starting ART. Not all ARV-treated patients experience lipid abnormalities to the same degree. Patients with a personal or family history of dyslipidemia, glucose intolerance, diabetes, obesity, or a combination of these health problems may be genetically predisposed to lipid abnormalities that become evident once ART is initiated.

Published research regarding the relationship between ARVs and the risk of cardiovascular disease has not been conclusive. The largest prospective study of CHD events related to ARVs (the DAD study), showed a small but significant increase in the risk of myocardial infarction among HIV-infected patients treated with ART; moreover, the effect increased with cumulative years of ARV exposure. While awaiting definitive results from this and other studies, it is important to screen and treat patients for lipid abnormalities and for other known CHD risk factors. For patients with CHD or CHD risk equivalents (see below), ARV regimens should, if possible, be selected to minimize the risk of hyperlipidemia.

Guidelines for the evaluation and management of dyslipidemia have been developed by the National Cholesterol Education Program (NCEP). These recommendations and follow-up reports are based on studies of HIV-uninfected patients and may not be entirely applicable to HIV-infected patients. Despite this limitation, expert panels generally recommend similar treatment goals when evaluating and managing dyslipidemia in patients with HIV infection. (For recommendations on screening, see chapter *Initial and Interim Laboratory and Other Tests*.)

S: Subjective

The history should focus on factors indicating coronary artery disease or cardiovascular risk. CHD risk factors are conditions associated with a greater risk of serious cardiac events. A CHD risk equivalent, such as diabetes, is considered to be equal in risk to known CHD. Both CHD risks and CHD equivalents should be the focus of lifestyle modification strategies and lipid-normalizing treatment.

- Assess for CHD or CHD equivalents.
  - CHD includes a history of myocardial infarction, unstable angina, stable angina, CHD procedures, or evidence of clinically significant myocardial ischemia.
  - CHD equivalents include diabetes, peripheral vascular disease, carotid artery disease, abdominal aortic aneurysm, transient ischemic attacks, or 2 or more CHD risk factors with a 10-year risk of CHD >20% (see "Calculations to Estimate the 10-Year Risk of Cardiac Events for Men and Women", below, or the online risk calculator at http://hin.nhlbi.nih.gov/atpiii/calculator.asp?usertype=prof).
- Assess CHD risks. Major risk factors include hypertension, diabetes, smoking, low HDL, age, and family history of CHD.
- Assess for causes of secondary dyslipidemias, including diabetes, hypothyroidism, obstructive liver diseases, chronic renal failure, and medications such as corticosteroids or progestins.
- Screen for other factors that contribute to hyperlipidemia, including obesity, chronic liver diseases, alcohol abuse, high-fat or high-carbohydrate diet, and prothrombotic or proinflammatory states.
- Screen for health behaviors that increase CHD risk, including smoking, high-fat diet, sedentary lifestyle, and use of recreational drugs such as cocaine or methamphetamine.
- Review the patient's family history for premature CHD, obesity, diabetes, and lipid abnormalities.
- Review the patient's medications, with special attention to ARVs known to increase LDL or TG levels (particularly ritonavir and ritonavir-boosted PIs) or decrease HDL.

O: Objective

Check vital signs, weight, and height. Calculate body mass index (BMI). (See chapter *Initial Physical Examination* for information on BMI.)

Perform a focused physical examination with particular attention to signs of hyperlipidemia, such as xanthelasma, and to the cardiovascular system.

Table 1. Low-Density Lipoprotein Cholesterol Goals and Thresholds for Treatment*

Risk Category	Initiate Therapeutic Lifestyle Changes	Consider Drug Therapy	LDL Goal*
Lower risk: No CHD or CHD equivalents and <0-1 risk factor	LDL ≥160 mg/dL (≥4.1 mmol/L)	≥190 mg/dL (≥4.9 mmol/L) (at 160-189 mg/dL, LDL drug therapy is optional)	<160 mg/dL (<4.1 mmol/L)
Moderate risk: No CHD or CHD equivalents and ≥2 risk factors, with 10-year estimated risk <10%	LDL ≥130 mg/dL (≥3.4 mmol/L)	≥160 mg/dL (≥4.1 mmol/L)	<130 mg/dL (<3.4 mmol/L)
Moderately high risk: No CHD or CHD equivalents and ≥2 risk factors and 10-year estimated risk 10-20%	LDL ≥130 mg/dL (≥3.4 mmol/L)	≥130 mg/dL (≥3.4 mmol/L)	<130 mg/dL (<3.4 mmol/L) (optional goal of <100 mg/dL)
High risk: CHD or CHD equivalent	LDL ≥100 mg/dL (≥2.6 mmol/L)	≥100 mg/dL (≥2.6 mmol/L)	<100 mg/dL (<2.6 mmol/L) (optional goal of <70 mg/dL)

*Non-HDL cholesterol target levels are 30 mg/dL higher than corresponding LDL cholesterol levels.

Adapted from: Adult Treatment Panel III, National Cholesterol Education Program. Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. May 2001; NIH publication 01-3670. http://www.nhlbi.nih.gov/guidelines/cholesterol/

Table 2. Classification of Triglyceride Levels

Risk Category	Triglyceride Measurement
Normal triglycerides	<150 mg/dL
Borderline-high triglycerides	150-199 mg/dL
High triglycerides	200-499 mg/dL
Very high triglycerides	≥500 mg/dL

Hypertriglyceridemia is an independent risk factor for CHD. In addition, severe hypertriglyceridemia (eg, TG >1,000 mg/dL) increases the risk for pancreatitis. Patients with marked TG elevations should be treated to reduce this risk.

A: Assessment

Determine whether intervention is appropriate based on the patient's lipid values and identified CHD risks, as indicated in Tables 1 and 2. Aside from LDL, the following major CHD risk factors are listed by the NCEP as requiring intensive lipid management.

- Cigarette smoking
- Hypertension (systolic blood pressure ≥140 mm Hg or taking antihypertensive medication)
- HDL <40 mg/dL (if HDL is ≥60 mg/dL, subtract 1 risk factor)
- Patient age ≥45 for men, or ≥55 for women

Family history of premature CHD in first-degree relatives aged <55 (men) or <65 (women)

For patients who do not have diabetes or preexisting CHD and who have 2 or more CHD risk factors, calculate the "10-year risk of cardiovascular events" by using the risk-estimate page at the end of this chapter or the online tool at the National Institutes of Health Web site: http://hin.nhlbi.nih.gov/atpiii/calculator.asp.

P: Plan

Laboratory

Before starting ART, obtain baseline fasting lipid panel, fasting glucose, and comprehensive metabolic panel.

- Measure serum lipids after the patient has fasted at least 8 hours (ideally 12 hours). Include TC, HDL, TGs, non-HDL cholesterol with calculated LDL, and TC/HDL cholesterol ratio.

Repeat the fasting lipid panel within 3-6 months after starting an ARV regimen, and sooner (1-2 months) for patients who have abnormalities at baseline. Patients with normal lipid values should receive annual screening. Those with abnormal values may need more intensive monitoring (eg, every 4-6 weeks) until the LDL goal is met, after which monitoring every 4-6 months is adequate. If a new ARV regimen is begun, repeat the fasting lipid panel at 3-6 months.

Treatment of dyslipidemia usually involves a multimodal approach, including diet and exercise in all cases, and potentially including lipid-modifying medication, changes in ARV medication, or both as indicated. The primary goal of lipid-lowering therapy is to reduce LDL to target levels. Very high TG levels, may have to be reduced before LDL is treated directly (see below). Table 1 shows the LDL levels at which either therapeutic lifestyle change (TLC) or drug therapy should be initiated, as well as the target goals for LDL cholesterol. The response to therapy should be monitored and therapeutic interventions should be intensified or augmented until lipid targets are met.

Therapeutic Lifestyle Change

TLC, consisting of diet modification and exercise, is fundamental to the management of dyslipidemia in HIV-infected patients. Target goals for lipid abnormalities will be difficult to achieve without prioritizing these efforts. Although TLC is hard to maintain, it can yield significant results in reducing CHD risk and improving quality of life. Effective TLC is best achieved with a multidisciplinary team approach. HIV/AIDS primary care providers can be instrumental in identifying TLC as a treatment priority and providing referrals to nutritionists for dietary counseling, to mental health professionals for assessment of treatable mood disorders, and to social workers, peer counselors, or clinical nurse specialists for assistance with health-behavior changes, self-care strategies, and identification of resources in the community for smoking cessation support and exercise programs.

Treatment for Hypercholesterolemia

All patients with elevated lipid levels should initiate TLC. If pharmacologic intervention is indicated, hydroxymethylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) are the first-line treatment for most patients. These agents can be effective in reducing TC, LDL, and non-HDL cholesterol levels in HIV-infected patients (Table 3).

In patients with serum TGs >400 mg/dL, the LDL cholesterol calculation is unreliable. In this situation,

non-HDL cholesterol (TC minus HDL) can be used as a surrogate target of therapy; the non-HDL goal is 30 mg/dL higher than the LDL goal. For these individuals, dietary intervention is warranted, and drug therapy to decrease LDL (or non-HDL) can be considered if TC is >240 mg/dL or HDL cholesterol is <35 mg/dL. For those with TG levels of 200-500 mg/dL, achieving the LDL cholesterol target is the primary goal and lowering non-HDL cholesterol levels is a secondary goal (see Table 1 for LDL intervention levels). (For treatment of high TGs, see "Treatment of Hypertriglyceridemia" below.)

Clinicians should note that PIs interact with most statins and can significantly increase serum statin levels, thus increasing the risk of rhabdomyolysis. Of the statin drugs, pravastatin is the least affected by PIs and is the recommended statin for patients with hypercholesterolemia without hypertriglyceridemia. Atorvastatin, if used, must be initiated cautiously and at a low dosage (note that atorvastatin may lower TGs as well as TC and LDL levels). Lovastatin and simvastatin should not be used in patients taking PIs (Table 4). Cerivastatin has been removed from the market in the United States because of reports of fatal rhabdomyolysis. Other available HMG-CoA reductase inhibitors include rosuvastatin and fluvastatin. These agents have not been as well studied as the others, but given their metabolic pathway, no significant interactions with PIs would be expected. Be aware that various formulations and combination products contain these statins. Check the generic name of components in new or unfamiliar cardiac prescriptions to determine whether they contain lipid-lowering agents.

Recommended starting dosages of statins in patients taking PIs are as follows:

- Pravastatin: 20 mg orally daily
- Atorvastatin: 10 mg orally daily

Niacin may be effective as adjunctive therapy, but may worsen insulin resistance. Ezetimibe (Zetia) has not been studied thoroughly in HIV-infected individuals, but in HIV-uninfected patients, it has been effective in combination with statins for patients whose cholesterol is not controlled adequately with a statin alone. Bile acid sequestrants generally should be avoided because they may interfere with the absorption of other drugs, and may increase TG levels. When given concomitantly, statins and fibrates increase the risk of rhabdomyolysis; these must be used cautiously and with careful monitoring.

Treatment of Hypertriglyceridemia

Patients with TG levels between 200 and 500 mg/dL should begin non-drug interventions such as diet modification, reduction in alcohol consumption, aerobic exercise, and smoking cessation. When TG level is >500 mg/dL, a low-fat diet (≤15% of caloric intake) is recommended to help prevent pancreatitis, and pharmacologic therapy will probably be required. Patients with CHD or CHD equivalents, those at high risk of CHD, and those with TG levels >200 mg/dL may need pharmacologic therapy.

Fibrates are the first-line drug option for isolated hypertriglyceridemia and are an alternative treatment for combined hypertriglyceridemia and hypercholesterolemia. Fenofibrate or gemfibrozil reduce TG levels effectively in patients on ARVs. Because they are not metabolized by the cytochrome P450 hepatic enzyme system, they do not have significant drug interactions with ARVs. Fibrates are contraindicated in patients with renal failure. Recommended dosages of these agents are as follows:

- Fenofibrate: 50-200 mg orally daily
- Gemfibrozil: 600 mg orally twice daily, 30 minutes before meals

If a fibrate alone is inadequate in reducing TGs, several options are possible. A statin (notably atorvastatin, which acts on TGs as well as cholesterol) could be added cautiously, although there is an increased risk of skeletal muscle toxicity with concomitant use of a fibrate and a statin. N-3 (omega-3) fatty acid supplements, administered at 2 g 3 times a day, have decreased TG levels in patients taking ART. Niacin also decreases both TG and TC levels, although its clinical utility is restricted because of associated insulin resistance and flushing.

Switching Antiretroviral Therapy

In patients with CHD or CHD equivalents, ARV medications should, if possible, be selected to minimize the risk of hyperlipidemia. In patients with dyslipidemia caused by ARV agents, data suggest that it may be beneficial to discontinue the offending ARVs if reasonable alternatives exist. Substituting atazanavir or nevirapine in place of a lipogenic PI, or replacing stavudine with abacavir or tenofovir, may improve the lipid profile. Before making ARV substitutions, however, consider carefully the possible effect of the substitution on HIV virologic control and the potential adverse effects of new ARVs. In some cases, antihyperlipidemic agents may still be necessary after ARV substitution.

Table 3. Drug Treatments for Lipid Abnormalities

Lipid Abnormality	First Choice	Second Choice	Comments
Isolated high LDL, non-HDL cholesterol	Statin	Fibrate	Start with pravastatin or atorvastatin. Use low statin dosages and titrate upward; patients taking PIs may have increased risk of myopathy.
Isolated high triglycerides	Fibrate	Statin, N-3 (omega-3) fatty acids	Start with gemfibrozil or fenofibrate. Combined statin and fibrate may increase myopathy risk.
High cholesterol and triglycerides (TG level 200-500 mg/dL)	Statin	Fibrate	Start with pravastatin or atorvastatin. Use fluvastatin, rosuvastatin, gemfibrozil, or fenofibrate as alternative. Combined statin and fibrate may increase myopathy risk.
High cholesterol and triglycerides (TG level >500 mg/dL)	Fibrate	N-3 (omega-3) fatty acids, niacin, statin	Start with gemfibrozil or fenofibrate. Niacin is associated with insulin resistance. May need to add statin if cholesterol is not controlled adequately.

Table 4. Interactions between Statin Agents and Antiretroviral Medications*

Statin	Considerations
Atorvastatin	• Some CYP3A4 metabolism. • Large increase in atorvastatin levels when given with protease inhibitors (PIs). Use lowest possible dosage. Monitor antilipid activity and titrate the statin dosage cautiously. • Monitor closely.
Fluvastatin	• Metabolized by CYP2C9, so no significant interactions with PIs or nonnucleoside reverse transcriptase inhibitors (NNRTIs) are expected. Decreased levels of nelfinavir are likely.
Lovastatin; Simvastatin	• Extensively metabolized by CYP3A4. Statin levels are increased substantially if coadministered with PIs. **These should not be used in patients taking PIs.**
Pravastatin	• Renal excretion and some hepatic metabolism. Levels of pravastatin are increased 30% when it is given with lopinavir/ritonavir. Levels of pravastatin are decreased 35% when it is given with ritonavir/saquinavir and decreased 40% when it is given with efavirenz. The clinical significance of these changes in pravastatin levels is unknown. • PI and NNRTI concentrations are not affected. Titrate pravastatin dosage based on antilipid activity.
Rosuvastatin	• Metabolized by CYP2CP and CYP2C19. Mostly excreted in bile. No significant interactions with PIs or NNRTIs expected. Studies are ongoing.

* Note that various formulations and combination products contain statins and other lipid-lowering agents. Check the generic name of components in new or unfamiliar cardiac prescriptions to determine whether they contain lipid-lowering agents.

Calculations to Estimate the 10-Year Risk of Cardiac Events for Men and Women

To calculate the 10-year risk of cardiac events, add up points from the following 5 tables pertaining to age, HDL, systolic blood pressure, TC, and smoking status (Tables 5.1-5.5). Note that in Tables 5.3-5.5, women's points are in parentheses. After adding points from all of the tables, consult Table 5.6. (Alternatively, an online calculator is available at http://hin.nhlbi.nih.gov/atpiii/calculator.asp.)

Table 5.1. Estimate of 10-Year Risk of Cardiac Events: Age

Age (year)	Points–Men	Points–Women
20-34	-9	-7
35-39	-4	-3
40-44	0	0
45-49	3	3
50-54	6	6
55-59	8	8
60-64	10	10
65-69	11	12
70-74	12	14
75-79	13	16

Table 5.2. Estimate of 10-Year Risk of Cardiac Events: High-Density Lipoprotein Cholesterol

HDL (mg/dL)	Points–Men	Points–Women
≥60	-1	-1
50-59	0	0
40-49	1	1
<40	2	2

Table 5.3. Estimate of 10-Year Risk of Cardiac Events: Systolic Blood Pressure

Systolic Blood Pressure	Points if Untreated–Men (Women)	Points if Treated–Men (Women)
<120	0 (0)	0 (0)
120-129	0 (1)	1 (3)
130-139	1 (2)	2 (4)
140-159	1 (3)	2 (5)
≥160	2 (4)	3 (6)

Table 5.4. Estimate of 10-Year Risk of Cardiac Events: Total Cholesterol

Total Cholesterol (mg/dL)	Points for Men (Women)				
	Age 20-39	Age 40-49	Age 50-59	Age 60-69	Age 70-79
<160	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
160-199	4 (4)	3 (3)	2 (2)	1 (1)	0 (1)
200-239	7 (8)	5 (6)	3 (4)	1 (2)	0 (1)
240-279	9 (11)	6 (8)	4 (5)	2 (3)	1 (2)
≥280	11 (13)	8 (10)	5 (7)	3 (4)	1 (2)

Table 5.5. Estimate of 10-Year Risk of Cardiac Events: Smoking Status

Smoking Status	Points for Men (Women)				
	Age 20-39	Age 40-49	Age 50-59	Age 60-69	Age 70-79
Nonsmoker	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Smoker	8 (9)	5 (7)	3 (4)	1 (2)	1 (1)

Table 5.6. Estimate of 10-Year Risk of Cardiac Events: Calculating Risk

Men		Women	
Point Total	10-Year Risk (%)	Point Total	10-Year Risk (%)
<0	<1	<9	<1
0	1	9	1
1	1	10	1
2	1	11	1
3	1	12	1
4	1	13	2
5	2	14	2
6	2	15	3
7	3	16	4
8	4	17	5
9	5	18	6
10	6	19	8
11	8	20	11
12	10	21	14
13	12	22	17
14	16	23	22
15	20	24	27
16	25	≥25	≥30
≥17	≥30		

Tables are adapted from: Adult Treatment Panel III, National Cholesterol Education Program. *Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults.* May 2001. NIH publication 01-3670.

Patient Education

- Review the importance of reducing cardiovascular risk factors.
- Educate patients about the benefits of diet and exercise in improving lipid levels and reducing cardiovascular risk.
- If lipid-lowering medications are prescribed, advise patients on possible adverse effects, and advise them to call the clinic if these develop.

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Insulin Resistance and Hyperglycemia on Antiretroviral Therapy

Background

Patients taking antiretroviral therapy (ART), particularly certain regimens containing a protease inhibitor (PI), appear to have an increased risk of hyperglycemia and diabetes mellitus. Hyperglycemia with or without diabetes has been reported in 3-17% of patients and has occurred at a median of about 60 days, with a range of 2 days to more than a year, after starting therapy. Disorders of glucose metabolism may present as the following:

- Insulin resistance, in which higher concentrations of insulin are required to exert normal effects; blood glucose levels may be normal but fasting insulin levels will be high because of compensatory insulin secretion by the pancreas
- Impaired glucose tolerance (ie, a glucose level of 140-199 mg/dL 2 hours after a 75-g oral glucose load)
- Impaired fasting glucose (ie, 110-125 mg/dL)
- Diabetes mellitus, which is diagnosed when the fasting blood sugar is ≥126 mg/dL, or the confirmed 2-hour glucose level is ≥200 mg/dL during glucose tolerance testing

The incidence of new-onset hyperglycemia in HIV-infected patients taking ART has been reported as about 5%, on average. Even if fasting glucose levels remain normal in patients taking ART, up to 40% of those on a PI-containing regimen will show impaired glucose tolerance. The etiology of insulin resistance and hyperglycemia in HIV-infected patients is probably multifactorial, with varying contributions from traditional risk factors (eg, obesity, family history), comorbid conditions (eg, hepatitis C virus infection), and antiretroviral-related factors (eg, direct effects of PIs, hepatic steatosis, and fat redistribution).

Patients who have preexisting diabetes must be monitored closely when starting ART; some experts would consider a PI-sparing regimen for these patients. Alternatively, PIs with favorable metabolic profiles (eg, atazanavir) may be preferred for such patients. Those with no history of diabetes should be advised about the warning signs of hyperglycemia (polydipsia, polyuria, and polyphagia) and the need to use diet and exercise to maintain an ideal body weight.

S: Subjective

The patient is about to begin ART, has been on an antiretroviral (ARV) regimen that includes a PI, or is overweight, has central fat accumulation, or has lipoatrophy. Although most patients with hyperglycemia are asymptomatic, some may report polydipsia, polyuria, and polyphagia.

History

Include the following in the patient's history:

- Fat redistribution on ART (see chapter *Abnormalities of Body Fat Distribution*)
- Family history of diabetes
- Obesity, or habitual physical inactivity
- Racial or ethnic heritages at higher risk: African, Hispanic, Native American, Asian-Pacific Islander
- Hypertension
- History of low level of high-density lipoprotein
- History of elevated triglycerides
- Gestational diabetes or delivery of infant weighing >9 lbs
- Current pregnancy
- Hepatitis C virus coinfection
- Polycystic ovary syndrome

O: Objective

Review previous or baseline blood glucose levels. Document weight and any weight changes or fat redistribution.

A: Assessment

Determine whether the patient has normal blood glucose, impaired fasting glucose, or diabetes (see laboratory recommendations and definitions below).

P: Plan

Laboratory

Most experts (eg, the International AIDS Society-USA) recommend monitoring routine fasting blood glucose levels at baseline and 3-6 months after starting therapy if baseline results are normal. Some recommend 2-hour postprandial measurements or a 75-g oral glucose tolerance test within the first 3-4 months of starting therapy and every 3-4 months thereafter. Monitoring should be more frequent if abnormalities are detected, or any additional risk factors exist, as noted earlier. Patients with these risk factors must be counseled about prevention of hyperglycemia before starting ART.

Treatment

Patients with insulin resistance

For patients with insulin resistance (impaired glucose tolerance) and normal blood glucose levels, current evidence is inadequate to recommend drug treatment. However, lifestyle modifications can be recommended, including exercise, weight loss, and diet changes. Weight loss is strongly recommended if the patient is overweight. Refer the patient to a dietitian. Some studies of insulin resistance in HIV-infected individuals are under way, and patients with access to clinical trials may be interested in these studies.

Patients with hyperglycemia and insulin resistance require treatment. A trial of lifestyle modifications may be attempted, including weight loss (if indicated), diet changes, and exercise. When drug treatment is required, because patients meet the diagnosis of diabetes and lifestyle changes are not adequate, the insulin sensitizers metformin or thiazolidinediones (pioglitazone or rosiglitazone) should be considered. Oral antidiabetic agents may increase the risk of hepatic and renal abnormalities, so patients should be monitored for hepatic toxicity (thiazolidinediones) and lactic acidosis (metformin). Thiazolidinediones should be avoided in patients with significant liver disease. Patients with elevated serum creatinine (>1.5 mg/dL in men or >1.4 mg/dL in women), hepatic impairment, or metabolic acidosis should not take metformin. In some cases, insulin may be the safest drug therapy for symptomatic hyperglycemia, although episodes of hypoglycemia are much more common with insulin than with most oral agents. For hyperglycemia that is associated with the use of PIs, switching to an alternative agent (eg, a nonnucleoside reverse transcriptase inhibitor or a different PI) may be effective if the HIV treatment history and resistance profile permit.

Patients with diabetes

Treatment should be instituted to control blood sugar and to modify other cardiovascular risk factors, with the aim of preventing heart disease and other end-organ disease.

- Control glucose: maintain the glycosylated hemoglobin (HbA1c) level at <7%.
- Treat dyslipidemia: maintain low-density lipoprotein (LDL) at <100 mg/dL and maintain triglycerides at <200 mg/dL.
- Treat hypertension: maintain systolic blood pressure at <130 mm Hg and diastolic blood pressure at <85 mm Hg.
- Reduce cardiovascular risk with lifestyle modifications: smoking and alcohol cessation, exercise, weight loss, nutritional counseling.
- Decrease the risk of end-organ complications:
  - Measure urine microalbumin and creatinine; if the urine albumin/creatinine ratio is >30 mg/g, treat with an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker to slow the progression of nephropathy.
  - Schedule annual retinal examination by an ophthalmologist.
  - Perform an annual foot exam.
- Start aspirin therapy if the patient has evidence of macrovascular disease, a family history of coronary artery disease, a history of smoking, or previous vascular events.

For further information, see the American Diabetes Association, *Clinical Practice Recommendations, Diabetes Care*, at: http://care.diabetesjournals.org.

Patient Education

- Antiretroviral therapy can increase the risk of diabetes in some individuals. Patients should report any difficulty with excessive hunger and thirst and increased urination. Health care providers will monitor blood glucose when doing laboratory work, but it is important for the patient to call if any symptoms are present.
- Review exercise possibilities to determine what activities might be realistic and acceptable for the patient.
- Review the patient's eating habits and explain the need to work with a dietitian to keep blood glucose (and triglycerides) within normal limits. A proper diet can reduce the risk of permanent damage to the blood vessels of the eye, the kidney, the brain, and can reduce the risk of a heart attack.
- Emphasize other lifestyle modifications, such as weight loss (if appropriate).
- Provide medication-specific education, especially if the patient will be taking metformin or insulin.
- Consider referral to a diabetic clinic for specialty needs.

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Drug-Drug Interactions with HIV-Related Medications

Background

Drug-drug interactions are common concerns of both patients with HIV and their health care providers. The issues involved in evaluating and drug interactions are complex. Although many questions can be articulated simply (eg, "What antidepressant is least likely to have drug interactions with HIV medications?"), the responses to these questions involve more complex concerns (eg, "In choosing an antidepressant for my patient with HIV, I must consider efficacy, adverse effects, and tolerability as well as drug interactions.").

This complexity is increased because antiretroviral agents, particularly protease inhibitors (PIs) and nonnucleoside reverse transcriptase inhibitors (NNRTIs), can cause and be affected by alterations in the activity of the cytochrome P450 enzymes in the liver. These enzymes are responsible for metabolizing many medications. Understanding the relevance of the influence of P450 enzymes is challenging because of several factors, including the following:

- Different drugs affect different P450 enzymes.
- Some medications have dosage-related responses that influence their effects on P450 enzymes.
- Formal pharmacokinetic studies on drug combinations are limited.
- Even when pharmacokinetic data exist for specific drug combinations, the clinical significance of any changes in pharmacokinetic parameters may not be clear.
- Patients taking HIV medications often have complex drug regimens. The interaction of only 2 drugs is rarely the concern; more often, patients are taking 3 or more medications that could influence interactions. Pharmacokinetic studies that evaluate the clinical significance of drug interactions involving more than 2 medications are less likely to be available.
- The P450 system is not the only influence on medication activity. Other influences include absorption, food-drug interactions, protein binding, altered activation of medications intracellularly, and altered efflux-pump activity.

Information on various drug-drug interactions is available in guidelines and via the Internet (see "Resources" below). Such resources can provide data regarding 2-drug combinations, but rarely consider all the complexities outlined above. What follows, therefore, is a suggested approach to considering drug-drug interactions in the management of HIV-infected patients and making patient-specific decisions.

S: Subjective

A new patient arrives for his clinic intake appointment. The patient receives his medical care from a local infectious-disease physician who has only a handful of HIV-infected patients in her practice. The patient was recently released from the hospital with a discharge diagnosis of pneumonia and *Mycobacterium avium* complex (MAC). He is not yet taking HIV medications, but is likely to start them in the next several weeks after the establishment of care and adherence support programs. Other problems include hyperlipidemia, erectile dysfunction, diabetes, depression, and herpes. The clinician wants to review the patient's medication list to check for any potential drug-drug interactions.

O: Objective

Review the patient's pharmacy records for current medications. As requested, the patient has brought in all his medications from home for review. His current medication list includes the following:

- Clarithromycin 500 mg twice daily
- Ethambutol 1,000 mg daily
- Rifabutin 300 mg daily
- TMP-SMX (Septra, Bactrim) DS 1 tablet daily
- Lovastatin 20 mg daily
- Metformin 500 mg twice daily
- Bupropion 150 mg daily
- Acyclovir 400 mg twice daily
- Milk thistle *(silymarin)*
  (patient takes as needed for energy and liver health)

A: Assessment

Step 1: Identify interactions and classify them as follows:

- Definite interactions
- Probable interactions
- Possible interactions

Definite Drug Interactions

A drug interaction is definite if a high level of evidence is available regarding the drug combination, the clinical significance of the interaction is well understood, and consensus exists regarding the management strategy (eg, dosage adjustments). Common definite interactions for HIV patients include:

- Certain combinations of HIV agents (eg, boosted PIs, NNRTI + PI combinations)
- Rifamycins and PIs or NNRTIs
- Statins and PIs + NNRTIs
- Erectile dysfunction agents and PIs
- Methadone and PIs

Probable Drug Interactions

A drug interaction is probable if the limited available evidence suggests that an interaction may occur, even if the clinical outcome or significance may not be clearly established. Effective management of a probable interaction is based on assessment and clinical judgment about the risks and benefits of a particular combination for that patient. Examples of probable interactions with HIV-related medications include:

- Antidepressants and PIs or NNRTIs
- Oral contraceptives and PIs
- Warfarin and PIs or NNRTIs
- Proton pump inhibitors or H-2 blockers and atazanavir

Possible Drug Interactions

Possible drug interactions may be difficult to distinguish from probable drug interactions, but in these cases, only theoretical evidence is available. The proper management of such an interaction requires weighing the risks and benefits of the combination and making sound clinical judgments. Examples of possible drug interactions with HIV medications include:

- Herbal products and PIs or NNRTIs (except in the case of St. John's wort, for which definite information on interactions is available)
- Antidiabetic medications and PIs or NNRTIs
- Antifungal agents and PIs or NNRTIs (except in the case of voriconazole, for which definite information on interactions is available)
- Antiseizure medications and PIs or NNRTIs
- Antipsychotic agents and PIs or NNRTIs

Memorizing all the potential drug interactions is impossible. It is possible, however, to remember a few commonly used drug combinations with the potential for clinically significant interactions. The above examples of definite, probable, and possible interactions are reasonable "red flag" drug combinations that can be recalled easily. In addition, certain Internet resources allow you to submit all of a patient's current medications and planned additions (eg, lopinavir/ritonavir as part of a new antiretroviral regimen) and receive feedback on potential interactions (see "Resources" below). Finally, consultation with clinical pharmacists can aid in identifying and classifying potential interactions.

P: Plan

Step 2: The patient described above will start an antiretroviral regimen of lopinavir/ritonavir + zidovudine + lamivudine. The PI may cause problematic drug-drug interactions with some of his other medications. Develop a plan for management when lopinavir/ritonavir is added to this regimen.

For this patient, the following definite interactions should be of concern:

- Rifabutin and lopinavir/ritonavir
- Lovastatin and lopinavir/ritonavir

Refer to available references for management suggestions. Such references include:

- DHHS Adult and Adolescent Antiretroviral Treatment Guidelines *http://www.aidsinfo.nih.gov/Guidelines/GuidelineDetail.aspx?MenuItem=Guidelines&GuidelineID=7*
- HIV InSite Database of Antiretroviral Drug Interactions: *http://hivinsite.ucsf.edu/arvdb?page=ar-00-02*

- Toronto General Hospital Drug Interaction Tables *http://tthhivclinic.com/interact_tables.html*
- Discover Drug Interaction Checker *http://health.discovery.com/encyclopedias/checker/checker.jsp*
- Check my Meds on AIDSMeds.com *http://aidsmeds.com/cmm/DrugsNewContent.asp*

Most of these sites include specific dosage adjustments or alternative agents to consider when managing these drug combinations. The following are suggestions for the above interactions:

- The rifabutin dosage should be 150 mg every other day with standard lopinavir/ritonavir dosing. Alternatively, discuss with the patient's primary care provider whether rifabutin is important to the current MAC regimen or whether the patient could be treated adequately with just clarithromycin + ethambutol to avoid the above interactions.
- Lovastatin should be discontinued in this patient when lopinavir/ritonavir is begun. To manage hyperlipidemia, the patient should be switched to safer statins such as pravastatin or low-dose atorvastatin.

Although this patient's current medication list does not contain an erectile dysfunction agent, the patient should be educated about the definite interactions and dosage adjustments recommended for patients using those agents with PIs. Some patients may obtain erectile dysfunction agents outside the care of their physician and, if unaware of the interactions and suggested dosage adjustments, may be at risk for life-threatening consequences.

Some additional probable or possible interactions should be considered if PIs are begun, including:

- Bupropion with lopinavir/ritonavir
- Milk thistle with lopinavir/ritonavir

The Web sites and references listed above include some information about these potential interactions, but no specific management or dosage adjustments are given. This patient should be monitored for increased effects of bupropion and educated about potential interactions with milk thistle. Clinical judgment and decision making with the primary care provider and other subspecialists (eg, psychiatrists) may be required. Consultation with clinical pharmacy services also may assist in evaluating the potential significance of an interaction and developing management strategies.

Patient Education

- Instruct patients that HIV medications, in particular PIs and NNRTIs, have a high potential for significant drug interactions.
- Tell patients to take all their medicines, including any herbal supplements and over-the-counter remedies, with them to all medical appointments. If they cannot take the actual bottles with them, they should make a list of current prescribed medications, supplements, and over-the-counter medications.
- Patients should have their primary care provider or pharmacist review any newly prescribed medications along with their current list of medicines. This is especially important if another physician prescribes a new medication.
- Patients should not "borrow" medications from friends or family. Assure patients that if they have a problem that needs medical treatment, their primary care provider will discuss it and choose the safest treatments for them.
- Tell patients that if they are considering buying a new nutritional or herbal supplement or an over-the-counter product, they should consult their pharmacist or primary care provider about interactions with drugs on their current medication list.
- Not all drug interactions are cause for alarm. Some drug combinations are safe for certain people, but less safe for others. Warn patients not to stop taking any medicines without the advice of their primary care provider.

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Resources

- *HIV InSite Database of Antiretroviral Drug Interactions:* http://hivinsite.ucsf.edu/arvdb?page=ar-00-02
- *Toronto General Hospital Drug Interaction Tables:* http://tthhivclinic.com/interact_tables.html
- *Discover Drug Interaction Checker:* http://health.discovery.com/encyclopedias/checker/checker.jsp
- *Check my Meds on* AIDSMeds.com*:* http://aidsmeds.com/cmm/DrugsNewContent.asp

Adverse Reactions to HIV Medications

Background

Clinicians and patients face many challenges associated with antiretroviral (ARV) therapy. These include decisions about when to start therapy, what regimen to start with, when to change medications, and how to switch if a regimen is failing. Although clinical research should guide the selection of ARV regimens, it is important to remember that the best regimen for any individual patient is the regimen he or she is willing and able to take. No regimen, no matter how potent, will be effective if the patient does not take it properly. Adherence to ARV therapy is one of the most important predictors of treatment efficacy. Although many factors may interfere with adherence to ARV therapy, adverse reactions to the medications are among the most important. In one trial, patients with adverse events were 13 times less likely than those without adverse events to have 95-100% adherence. Monitoring and managing adverse reactions to ARVs are crucial to establishing a successful HIV regimen.

Although adverse reactions are common and often predictable, their management must be individualized. Several factors will affect the management of adverse reactions, including comorbid conditions, the patient's other current medications, the availability of alternative regimens, and the patient's history of medication intolerance. In addition, the patient's report of severity can be inconsistent with the clinical interpretation (ie, some patients may overemphasize symptoms, whereas others underemphasize symptoms), and this must be considered when determining the management of adverse reactions.

This chapter reviews some of the most common adverse effects noted as patients start an ARV regimen and suggests strategies for the management of adverse effects. It is not intended as a comprehensive guide to adverse effects. For detailed information regarding assessment of symptoms, see the complaint-specific chapters found in Section 5 of this manual. For information on common adverse reactions to ARV agents and to medications used to prevent and treat opportunistic infections, see Section 10 of this manual. Consultation with an HIV expert also can help in determining the best management when symptoms may have multiple and overlapping causes. Finally, in each case of suspected medication adverse effects, the patient should be evaluated for other possible causes of his or her symptoms.

S: Subjective

A patient presents 2 weeks after starting her new ARV regimen complaining of fatigue, nausea, and rash. Her current ARV medications include a combination of zidovudine (ZDV), lamivudine (3TC), and abacavir (ABC) (ie, Trizivir)—and nevirapine (NVP). She has continued her prophylactic medications, which include trimethoprim-sulfamethoxazole (TMP-SMX) and fluconazole. Although she reports that she had not missed any doses of her medications and she likes the low pill burden of this regimen, she does not want to continue because she has been feeling so sick that she cannot adequately care for her children. She is asking to stop her ARV therapy because of "too many side effects."

The patient should be evaluated in the clinic for her complaints about adverse effects.

O: Objective

The following are suggestions for this evaluation; they are not intended to be a complete review of the workup and management of each symptom or objective finding. For more detailed information, refer to the complaint-specific chapters of this manual, as noted above.

- Vital signs: Fever may indicate a hypersensitivity reaction (HSR), acute hepatitis, or immune reconstitution syndrome related to starting ARV medications. See the chapter *Fever* for a more complete discussion about fever workup and considerations. Tachycardia or hypotension may suggest anemia, HSR, dehydration, or another illness.
- Physical examination: Pay special attention to the skin (rash, pallor), mucous membranes, and liver (enlargement or tenderness). Positive physical examination findings should be evaluated for severity and extent of involvement.

- Laboratory tests: Complete blood count is important when monitoring drugs that may cause bone marrow toxicity (eg, anemia, neutropenia). Perform a complete metabolic panel including electrolytes and liver function tests (LFTs). If the history suggests pancreatitis, evaluate amylase or lipase.
- Other studies: Perform as indicated by symptoms and examination (eg, chest x-ray if respiratory symptoms are present).

A: Assessment

Step 1: Clarify reports of adverse reactions by requesting the following information for each symptom the patient describes:

- Characterize the symptoms by asking about severity, onset, and frequency. It is also helpful to have the patient describe whether the symptom(s) have been improving or worsening over time.
- Ask whether the patient has tried any remedies to alleviate the symptom(s) and whether they were helpful.
- Explore how the patient is currently taking the regimen. Open-ended questions such as: "What are your current medications?" "How often do you take them?" "How many pills of each medicine do you take?" and "Do you take your medicines with or without food?" can be helpful in determining whether the patient has been taking medications correctly. Incorrect administration of medications (eg, taking higher dosages than recommended) can lead to adverse effects and is often overlooked by providers.

Step 2: Assess the severity of the reaction against the need to continue the current regimen. An understanding about the relative availability of alternative ARV regimens is important in this assessment

- Most adverse effects are self-limited and mild-to-moderate in severity. With supportive care, patients often are able to continue their current medications. This is particularly true for gastrointestinal symptoms (eg, nausea, vomiting, bloating). Supportive care for gastrointestinal adverse effects includes reminding the patient to take medications with food (if appropriate), suggesting the use of ginger-containing beverages or foods to relieve symptoms (see "Nausea," below), and prescribing antiemetics if needed. Other symptoms that can be monitored carefully with supportive care include: fatigue, malaise, mild rashes, abdominal pain, and bloating.
- More severe reactions often require discontinuation of the offending medication. These include fever, LFT abnormalities, or severe systemic symptoms. Determining which of the medications is causing the reaction is often challenging, because patients are commonly taking several medications with overlapping toxicities.
- The threshold for stopping a medication depends in part on the availability of alternative agents for any given patient. Some patients have limited alternatives because their virus is resistant to other ARV agents (eg, patients on salvage ARV regimens). For other patients, alternatives are limited by past adverse effects. For patients who develop significant adverse effects when starting their first ARV regimen, substituting alternative ARV medications that are better tolerated should be considered as early as possible during therapy to avoid nonadherence due to adverse effects. For these situations, single-drug substitutions often improve tolerance and achieve long-term viral suppression.
- Some patients may refuse to attempt supportive care and refuse to continue treatment. In these situations, it may be best to discontinue all ARV medications and return to an adherence-readiness assessment (see chapter *Adherence*) to determine when to restart medications and what medications to restart (see chapter *Antiretroviral Therapy*).

Clarified Subjective and Objective Information

For the patient who reported nausea, fatigue, and rash 2 weeks after starting ZDV/3TC/ABC (Trizivir) and NVP (see above), additional history, physical examination, and laboratory work yielded the following information:

- Nausea: This was present since she started ARVs 2 weeks ago. She has had difficulty taking medications with food, because of nausea. No actual vomiting or other abdominal pain has occurred. She has not tried any remedies. The nausea is not worsening and perhaps has improved slightly over the past few days.
- Fatigue: This was present since she started ARVs 2 weeks ago. She is able to exercise and perform normal daily activities.

- Vital signs: Normal; no fever or signs of hemodynamic changes.
- Skin: Skin and conjunctival pallor is noted, along with mild to moderate maculopapular rash on the trunk, back, and extremities. These are associated with slight itching, but no pain. No mucous membrane involvement is noted. The rash has been present for 4 days, with slight improvement over the past day.
- Abdomen: Nontender, with normal liver size.
- Complete Blood Count: Normal, except for a slight increase in mean corpuscular volume (MCV), probably from ZDV therapy and not indicating macrocytic anemia.
- LFTs: Normal.

Availability of Alternative Regimens

A clarified ARV history yielded the following information. The patient took ZDV alone for 3 months a few years ago, during 1 of her pregnancies, and recalls similar feelings of nausea and fatigue that caused her distress at the time. She was able to continue ZDV through the end of her pregnancy. Otherwise, the patient is ARV naive and has many treatment options.

Assessment and Conclusion

The patient's symptoms are mild and are most likely related to starting ARV therapy. Thus, no additional workup is needed at this time. Careful monitoring is important because, if symptoms do not improve over the next few days, the patient should have a more extensive workup for other possible causes of the various symptoms. If other causes of her symptoms are ruled out and she is unable to tolerate supportive care, alternative ARV medications (eg, didanosine, tenofovir, protease inhibitors) can be substituted for medications in her current regimen. Given her ARV history, substitutions are likely to be effective.

P: Plan

Following is a suggested treatment plan for the mild adverse effects exhibited by the patient described above:

Fatigue

Fatigue is a common adverse effect among patients who are starting ARV therapy. It is usually self-limited, and, with reassurance that symptoms should improve over a few weeks, most patients are able to continue their regimens without any changes. If fatigue does not resolve within the first weeks of treatment, it is important to rule out other causes of fatigue, including depression. For ZDV-containing regimens, practitioners should also rule out ZDV-induced anemia, especially when patients are also taking other medications that can cause bone marrow toxicity (eg, TMP-SMX). Some patients experience fatigue from ZDV even without anemia. If fatigue persists for several weeks or becomes debilitating and other causes are ruled out, consider replacing ZDV in this regimen. (See also chapter *Fatigue.*)

Nausea

Nausea is another common adverse effect described by patients starting a new ARV regimen. Like fatigue, it is usually self-limited, and patients without other systemic symptoms, acute hepatitis, or pancreatitis usually can continue their regimens. Supportive care is often helpful, however, in allowing patients to continue their ARVs. For example, patients should take their medications with food. Small, frequent snacks may be helpful for patients with significant nausea that prevents substantial meals. Clinical trials have suggested that ginger extract may relieve nausea symptoms. Patients can take ginger in a variety of forms, including ginger ale, tea, cookies, and candies. Among the medications that the current patient is taking, ZDV is the most likely culprit to cause persistent nausea. If nausea symptoms persist for several weeks despite taking medications with food, using ginger, or taking other antiemetics, and if other underlying causes are ruled out, consider replacing ZDV in this regimen. (See also chapter *Nausea and Vomiting.*)

Rash

Rash is a common adverse effect of certain ARVs and many other medications. It may present with a wide range of severity:

- Mild rash occurs with no other related symptoms and resolves over days or weeks.
- Moderate rash may be accompanied by systemic symptoms (eg, fever, LFT abnormalities, myalgias).
- Life-threatening rashes (eg, Stevens-Johnson syndrome) associated with pain, mucous membrane involvement, fever, LFT changes, and myalgias.

If a patient is taking 2 or more medications that have rash as a possible adverse effect, it may be difficult to

determine which of the medicines is the most likely cause of the rash. In the case of the patient described above, rash may be related to the following:

- Mild ABC rash: Usually a self-limited reaction that can be treated symptomatically
- Moderate to severe ABC HSR: Resolution of symptoms requires discontinuation of ABC, but repeat challenge can be life threatening (see below for more details)
- Mild NVP rash: Usually a self-limited reaction that can be treated symptomatically
- Moderate to severe NVP rash accompanied by hepatitis: Requires discontinuation of NVP
- Mild TMP-SMX reaction: Either delayed or part of an immune reconstitution reaction
- Other reactions: can be caused by other medications, contact dermatitis, folliculitis, immune reactivation or reconstitution effect and other causes

If the clinician discontinues all of the suspect medications and the rash resolves, the patient will be relieved, but the clinician will not be able to determine which medication caused the rash. In cases of mild rash, it is reasonable to try to identify the offending medication by discontinuing 1 medication at a time (generally, a substitution should be made for the discontinued ARV). This situation would require careful clinical judgment or consultation with an expert regarding the advantages or disadvantages of discontinuing each of the suspect medications.

Abacavir hypersensitivity reactions

Abacavir hypersensitivity reactions are a common cause of rash. The initial symptoms of possible ABC HSR are not life threatening, and it is important to try to distinguish true ABC HSR from isolated rash (without other hypersensitivity symptoms), self-limited adverse medication effects, or other illness (eg, influenza). This is often best accomplished by asking a patient who complains of mild gastrointestinal symptoms with or without rash to continue taking all medications while being monitored closely. Careful assessment of symptoms for a few days should clarify whether symptoms are lessening (indicating self-limited effects) or worsening (suggesting of ABC HSR). The pattern of symptom onset is also helpful. For patients with ABC HSR, symptoms usually begin after 10 days of therapy and worsen approximately 30-60 minutes after each ABC dose administration. When ABC is discontinued because of suspected HSR, patients should never be rechallenged. Initial flulike symptoms are uncomfortable for patients, but not life-threatening. If, however, ABC is discontinued when HSR symptoms are present and is then restarted, life-threatening HSRs may occur.

Clinicians should report ABC HSRs to the following agencies:

- Abacavir Hypersensitivity Reaction Registry at Glaxo Wellcome at 1-800-270-0425
- FDA MedWatch program by telephone at 800-FDA-1088, via fax at 800-FDA-0178, via the Internet at *http://www.fda.gov/medwatch/report/hcp.htm*, or by mail at MedWatch HF-2, FDA, 5600 Fishers Lane, Rockville, MD 20857

Other Adverse Reactions

Patients may describe any number of adverse effects after starting new medications. Although some adverse effects are directly caused by the medications themselves, some symptoms may occur simply in the process of starting ARVs. The start of ARV therapy may precipitate a significant psychological shift in a patient's perception of self, in living with HIV infection, and in daily routine. In particular, patients who have kept their HIV infection distant from their "everyday" lives may notice significant internal changes as they take medications every day, go to the pharmacy to pick up medications, and make frequent visits to the clinic for evaluation and laboratory work. Some patients become depressed upon realizing that the severity of their illness now requires them to be on treatment. These psychological changes can cause significant symptoms that should be assessed and managed similarly to the pharmacologic adverse reactions.

These psychological effects can be considered "process" effects from starting ARVs, rather than adverse effects of the medications themselves. As with the self-limited adverse effects of early ARV therapy, process effects should become more tolerable over time as the medication regimen becomes routine for the patient. One of the most common process effects is fatigue. Many patients hope that their ARV regimen will give them increased energy and health, and they become frustrated when they notice increasing fatigue after starting the regimen. These patients must be evaluated to rule out common adverse effects that contribute to fatigue (eg, anemia, hepatitis, lactic acidosis). Equally important, especially for patients beginning a new

regimen, symptoms of fatigue could indicate depression or signal that the "process" of taking medications is emotionally difficult. Counseling, peer support, and antidepressant medications can be used to treat this type of fatigue. Often, once patients realize some of the goals of treatment (eg, the CD4 count increases, the HIV viral load becomes undetectable, or symptoms of HIV infection resolve), they recognize the benefits of ARV medications, and their fatigue or other adverse symptoms associated with the process of starting the regimen may lessen.

Clinicians are encouraged to report adverse reactions to medications to the FDA MedWatch program by telephone at 800-FDA-1088, via fax at 800-FDA-0178, via the Internet at *http://www.fda.gov/medwatch/report/hcp.htm*, or by mail at MedWatch HF-2, FDA, 5600 Fishers Lane, Rockville, MD 20857.

Patient Education

- All medications have potential to cause adverse reactions, which are defined as negative, unintended effects of medication use.
- Patients should be advised to report any adverse reaction to their medical care provider as soon as possible.
- Before starting a new medication, patients should be counseled by their medical care provider or pharmacist about the most common adverse effects and about any remedies available to minimize the severity of those effects.
- Nausea is one of the most common adverse effects. Nausea can be minimized by taking medications with food (if indicated, some medications should be taken on an empty stomach) or using ginger-based food or beverages (eg, ginger ale, tea, cookies). If these measures do not work, patients should talk with their medical care provider; they may need medications to treat the symptoms.
- Patients should not stop taking any medications unless instructed to do so by their medical care provider.

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Recreational Drugs and Antiretroviral Therapy

Background

Very few data are available on interactions between antiretroviral (ARV) medications and recreational drugs. No controlled trials have investigated this issue because of the legal and ethical issues regarding the use of illicit agents. Most available information on interactions between ARVs and recreational drugs has been derived from pharmacokinetic studies and from case reports. In addition, projections about ARV-drug interactions have been based on what is known about interactions between ARVs and similar agents.

Most phenomena related to drug-drug interactions arise from the pharmacokinetic properties of each interacting agent, specifically their metabolism and excretion. One relevant issue is enzyme induction or inhibition, explained as follows:

- Different agents have different effects on the liver enzyme systems, specifically cytochrome p450 enzymes, used to metabolize the active form of many agents.
- Inducers are agents that *increase* the activity of these enzymes, resulting in increased metabolism and *decreased* serum concentration of the active drug form. This lower drug concentration could cause a loss of therapeutic efficacy of the interacting drug.
- Inhibitors are agents that *decrease* the activity of these enzymes, resulting in decreased metabolism and *increased* serum concentration of the active drug form. This higher drug concentration could lead to increased drug toxicity.
- Some agents have both inhibiting and inducing activity, making assessment of drug interactions more complicated.

Some agents exert most of their pharmacologic activity through their active metabolites, in which case inhibition and induction could affect the parent compound and the active metabolite in different or even opposite ways. For example, an agent that inhibits the metabolism of a parent drug would increase levels of the parent drug but decrease the concentration of active metabolites. If the parent compound has little pharmacologic effect compared with the active metabolite, the net effect could be decreased pharmacologic activity. This consideration further complicates drug-drug interactions and the understanding of their clinical significance. Further considerations include the following:

- Some agents are not metabolized by the liver, but instead are cleared by the kidneys and excreted in the urine.
- In the presence of hepatic or renal impairment, the metabolism and excretion of certain agents may be impaired, thus possibly increasing the amount of drug in the body or the amount of its toxic metabolites. Hepatic or renal dysfunction also may worsen drug-drug interactions.
- Street drugs are often impure, and sometimes are not what they are thought to be. They are frequently cut with substances that may themselves interact with ARVs or other drugs, and their potency can vary widely, even within the same batch.

Table 1 lists potential and documented drug interactions associated with commonly used recreational drugs. Pharmacokinetic properties and the interacting agents are discussed briefly.

Table 1. Potential and Documented Drug Interactions between Recreational Drugs and Antiretroviral Agents

Pharmacokinetics	Interactions	Significance	Comments
Alcohol			
Principally metabolized by alcohol dehydrogenase, but acute use can lead to enzyme inhibition, and chronic use may induce activity of CYP2E1 and CYP3A .	With induction of CYP3A, alcohol may increase the metabolism of PIs and NNRTIs. Because a common metabolic pathway is used by abacavir, there is theoretical concern that alcohol may compete for metabolism, thus increasing abacavir serum concentrations.	Inducing metabolism of specific medications may result in subtherapeutic levels, predisposing to resistance and decreasing efficacy.	Although the possibility of CYP3A induction is of theoretical concern, there may be little or no actual interaction between alcohol and ARV agents. Alcohol abuse and concomitant use of hepatotoxic agents may increase the risk of early and severe liver damage. Additionally, chronic alcohol abuse in the presence of didanosine markedly increases the risk of pancreatitis. There is no evidence of increased risk of abacavir-related toxicity or hypersensitivity reaction.
Amphetamine Compounds (crystal methamphetamine)			
Primarily metabolized by cytochrome P450 (CYP2D6). Under normal conditions, approximately 15% of a dose is eliminated renally, but as urine becomes more acidic, the proportion excreted renally may increase to 55%.	Inhibition of CYP2D6 can interfere significantly with hepatic metabolism of the amphetamine compound. Such inhibitors include: • Ritonavir (increases amphetamine levels 2- to 3-fold) • Delavirdine • Selective serotonin reuptake inhibitors (SSRIs) (primarily fluoxetine, fluvoxamine, sertraline, paroxetine)	Inhibition of amphetamine metabolism leads to increased levels of the compound. Effects similar to those seen with large doses may be anticipated. Response is variable from patient to patient and may include intense exhilaration, euphoria, agitation, panic, angina, cardiovascular collapse, convulsions, and cerebral hemorrhage. Amphetamines do not have any significant effect on ARV agents.	Patients who are taking ritonavir or other potent CYP2D6 inhibitors should be strongly urged to avoid using amphetamine compound(s).
Amyl Nitrate (poppers)			
Completely and rapidly metabolized in the liver by first-pass mechanism.	Pharmacodynamic property of this agent creates rapid and systemwide vasodilation. Agents that also cause vasodilation may create an additive effect. The use of erectile dysfunction (ED) agents such as sildenafil (Viagra), tadalafil (Cialis), vardenafil (Levitra), and amyl nitrate may significantly decrease cardiac circulation.	Combinations of nitrates and ED agents can cause severe hypotension and may lead to loss of consciousness, ischemic angina, unstable angina, and myocardial infarction.	Nitrates and nitric oxide compounds are contraindicated with ED agents. Caution should be exercised with concomitant use of other vasodilators.

Benzodiazepines, Group I (alprazolam, clorazepate, clonazepam, diazepam, midazolam, triazolam)			
These agents are metabolized extensively in the liver by CYP3A4 isoenzymes.	Drugs inhibiting CYP3A4 could theoretically interfere with metabolism of these agents, causing a large increase in the area under the time-concentration curve (AUC). Ritonavir is the most potent CYP3A4 inhibitor.	Large increases in the AUC (>3-fold) of some of these compounds could have serious consequences, including sedation and respiratory depression.	Midazolam and triazolam are contraindicated for use with ritonavir; other PIs should be used with extreme caution. Other benzodiazepines may be administered safely with PIs, with close monitoring and dose adjustment.
Benzodiazepines, Group II (lorazepam, oxazepam, temazepam)			
These benzodiazepines are metabolized primarily by conjugation with glucuronic acid, which is mediated by glucuronosyltransferase enzymes.	Agents that increase glucuronosyltransferase enzyme activity may increase the metabolism of these compounds. Ritonavir may increase the metabolism of these drugs by this mechanism.	Concomitant use of these agents with ritonavir may decrease their therapeutic effectiveness. In patients who are abusing these agents, reduction in serum levels may cause symptoms of withdrawal, including: rebound insomnia, tremors, irritability, dysphoria, panic/paranoia, and convulsions.	Patients receiving these benzodiazepine agents for therapeutic purposes should be monitored for loss of effectiveness in the presence of ritonavir therapy. These benzodiazepine agents are likely to have less toxicity than the above (group I) agents. Patients who are known to be actively abusing these agents should be given an alternate PI or monitored for withdrawal.
Caffeine			
Thought to be extensively metabolized by the CYP1A2 enzyme group. Minor pathways include CYP2D6 and CYP3A4.	Drugs most likely to affect the metabolism of caffeine include those that inhibit its major metabolizing isoenzymes: ciprofloxacin (and potentially other fluoroquinolones) and macrolide antibiotics.	Elevations in caffeine levels may result in accentuated effects: increased blood pressure, increased central nervous system stimulation, tremors, and atrial dysrhythmias. CYP3A4 inhibitors such as ritonavir potentially elevate caffeine levels, but this is unlikely as it involves a very minor pathway in caffeine metabolism.	Recommend decreasing caffeine intake while concomitantly using agents that inhibit CYP1A2. No documented interaction between caffeine and PIs has been reported.
Cocaine			
Primarily metabolized by tissue and plasma enzymes. Small amount (10%) is metabolized by P450 enzymes (CYP3A3/4, CYP2B1) to hepatotoxic metabolite. Cocaine may induce some P450 enzymes with chronic use, and inhibit others with acute use. The isoenzymes involved are not related to ARV drug metabolism.	Potential interaction with: • Protease inhibitors (PIs) • Nonnucleoside reverse transcriptase inhibitors (NNRTIs) (nevirapine, efavirenz) • Macrolide antibiotics (erythromycin, clarithromycin)	Both inhibition and induction of P450 enzymes can lead to increased effects or toxicities of cocaine because of increased levels of the drug or active metabolites. However, given the minor role these enzymes play in overall cocaine metabolism, clinical significance is unlikely. Cocaine is unlikely to have any significant effects on ARV agents.	Monitor for increased cocaine effects and hepatotoxicity. Cocaine is also a known immunotoxic agent, significantly decreasing $CD4^+$ cell production by as much as 3- to 4-fold, and increasing the rate of HIV reproduction up to 20-fold.

Ecstasy (X, MDMA) and GHB (gamma hydroxybutyrate)			
Ecstasy is an amphetamine-like compound that has similar metabolism as amphetamine compounds, with the major portion metabolized by CYP2D6. GHB is also thought to be metabolized through the CYP2D6 isoenzyme.	Inhibition of CYP2D6 is likely to impair detoxification of ecstasy and GHB because of large increases in serum levels. Such inhibitors include: • Ritonavir (increases ecstasy levels by 5- to 10-fold) • Delavirdine • SSRIs	At least 2 deaths from the combination of ritonavir and ecstasy have been reported. Ritonavir can increase the risk of life-threatening adverse effects from ecstasy (eg, heatstroke and dehydration) and GHB (eg, seizures, bradycardia, respiratory depression, loss of consciousness). Dehydration effects of these medications could increase the risk of renal stones in patients taking indinavir.	Strongly recommend avoiding the combination of ecstasy or GHB with ritonavir or other potent CYP2D6 inhibitors. Recent research has shown that ecstasy affects serotonin levels and can increase the potential for depression and anxiety disorders in individuals at risk. At least 68 deaths have been attributed to the combination of ecstasy and alcohol.
Heroin, Morphine, Hydromorphone, and Codeine			
Morphine and hydromorphone are extensively metabolized to glucuronides, mediated by glucuronosyltrans-ferases. Codeine is mainly metabolized by glucuronidation, but minor pathways include a process mediated by CYP2D6. Heroin is converted to morphine in the blood rapidly and is metabolized similarly.	Plasma concentrations of all these agents may be decreased by agents that increase the activity of glucuronosyltransferases (eg, ritonavir). In the presence of ritonavir, heroin serum concentrations are reduced by as much as 50%. Administration of codeine with a CYP 2D6 inhibitor may inhibit the bioactivation of codeine into morphine.	Decreased levels of all these agents may result in loss of therapeutic effect when administered with ritonavir. Patients abusing these agents who add ritonavir may develop withdrawal symptoms, including lacrimation, rhinorrhea, irritability, tachycardia, elevated blood pressure, chills, flushing, sweating, seizures, myalgias, and arthralgias. There is also potential for an increase in a glucuronide metabolite, which is 45 times more potent than the parent compound. This increase in active metabolite could offset the above-described decreases in parent opiates.	Patients taking these agents with ritonavir or a CYP2D6 inhibitor (of codeine) should be monitored either for loss of therapeutic effect (in the case of prescribed opiates) or for withdrawal symptoms.
Ketamine (Special K)			
Undergoes extensive demethylation and hydroxylation in the liver, possibly via CYP3A4, and is excreted in the urine. Ketamine is structurally similar to phencyclidine and may undergo similar metabolism.	CYP 3A4 inhibitors could inhibit the metabolism of ketamine, resulting in elevated serum concentrations of the compound. A wide range of CYP3A4 inhibitors can play a significant role in interactions with ketamine, including: • Protease inhibitors • Macrolide antibiotics • Delavirdine	Ketamine has a reported wide margin of safety; however, elevated serum concentrations could result in increased heart rate, increased blood pressure, or respiratory depression. Chronic use of ketamine in the presence of ritonavir may increase ketamine concentrations and the potential for hepatotoxicity and drug-induced hepatitis.	Caution should be exercised with concomitant use of ketamine and agents that are CYP3A4 inhibitors. Two cases of drug-induced hepatitis have been reported in patients concomitantly using ketamine and ritonavir. Ketamine is often added to other illegal psychoactive substances such as ecstasy, marijuana, and others.

LSD, Mescaline, Psilocin, and Methyltryptamine			
Information about P450 metabolism is not available. LSD is structurally similar to serotonin and thus may be metabolized similarly. This means that LSD might be eliminated by the enzymes monoamine oxidase (MAO), aldehyde dehydrogenase, and alcohol dehydrogenase. Mescaline, psilocin, and dimethyltryptamine may have similar metabolic pathways.	Based on the postulated metabolism of LSD, MAO inhibitors could cause serious interactions by decreasing LSD metabolism and increasing serum levels. Because the metabolism of both abacavir and LSD involves alcohol dehydrogenase, it is possible that levels of either drug may be affected by the other; the clinical significance of any possible interactions is unknown.	Possible adverse effects of increased serum levels of LSD include respiratory insufficiency, acute anxiety, fear, vascular spasm, and potentially fatal malignant hyperthermia. The clinical significance of this possible interaction is unknown.	Because no data confirm these interactions in humans, the clinical significance of combining LSD with MAO inhibitors or abacavir is unknown.
Phencyclidine (PCP)			
PCP is mainly metabolized in the liver, mediated by CYP2C11. It is also speculated that PCP may inhibit CYP2B1.	Given the potential bidirectional effect on P450 enzymes, it is difficult to predict significant drug interactions.	The effects of PCP or PIs may increase with concomitant use. The clinical significance of this potential interaction is unknown.	No case reports have described interactions between PCP and P450 inhibitors. Caution should be exercised if combining PCP with ritonavir because of possible increased effects of both PCP and PIs.
Tetrahydrocannabinol (THC, marijuana, hashish, and hashish oil)			
Rapidly metabolized in the liver to an active metabolite (11-hydroxyl THC), which is then converted to inactive metabolites and excreted in the urine and stool. Levels of the active metabolite vary with route of administration. The oral route produces more of the active metabolite than either the intravenous or inhaled route. P450 isoenzymes are thought to be important in THC metabolism (CYP3A3/4, 2C9, 2C6).	Inhibiting agents that affect CYP3A3/4 could affect THC metabolism, thus increasing parent compound THC levels: • PIs • Macrolide antibiotics • Delavirdine Inducing agents of the same isoenzymes could reduce THC levels: • Efavirenz, nevirapine • Rifampicin compounds Fluconazole is an inhibitor of 2C9 and potentially increases THC levels. Clinical trials of THC in patients taking nelfinavir and indinavir suggested no change in THC levels, but some decrease in nelfinavir and indinavir levels. It is possible that more potent CYP3A3/4 inhibitors (eg, ritonavir) may change THC levels significantly.	Inhibition of selected isoenzymes may increase THC levels, producing higher parent THC levels but a lower amount of the active THC metabolite. The net effect on THC pharmacology is unknown. Symptoms of higher THC levels include frank hallucinations, delusions, paranoia, altered time sense, anxiety, panic, orthostatic hypotension, and increased heart rate. In the same way, medications that induce CYP3A4, 2C9 and 2C6 may increase or decrease THC effects. The clinical significance of changes in nelfinavir and unboosted indinavir with THC is unknown.	Recommend close monitoring of response to THC in patients who also take inhibitors and inducers of THC metabolism. To date, no clinically significant effects have been reported, despite widespread concomitant use of these agents.

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Anemia

Background

Anemia is usually characterized by a hemoglobin level of <14 g/dL in men and <12 g/dL in women. In people with HIV infection, anemia has been linked to poor quality of life and decreased survival, and correction of anemia can improve these parameters.

Anemia has many potential causes and, in HIV-infected individuals, several of these may occur concomitantly. Common causes include:

- Anemia of chronic disease
- Bone marrow suppression due to medications
- Bone marrow infiltration by infection or malignancy (eg, *Mycobacterium avium* complex, tuberculosis, cytomegalovirus, lymphoma, myelodysplasia)
- Nutritional deficiencies (eg, vitamin B12 or folate)
- Iron deficiency (eg, from blood loss)
- Hypogonadism

Anemia of chronic disease, due to HIV infection itself, is very common in patients with low CD4 counts (<200 cells/μL) and high HIV viral loads, as well as in those with low body mass index, and in women, African Americans, and older people (aged >50 years).

Medication-induced anemia, particularly from zidovudine (AZT) and trimethoprim-sulfamethoxazole (TMP-SMX), is also common and may occur quickly after initiation of these medications. The risk of anemia with a AZT-containing regimen is of particular concern in resource-limited settings where access to alternative antiretroviral (ARV) medications may be limited and the likelihood of advanced disease when starting AZT is substantial. Careful monitoring of hemoglobin at 2-4 weeks after initiation of AZT and regularly thereafter, and continued access to affordable alternatives, are crucial to the success of antiretroviral therapy (ART) in these settings.

S: Subjective

Patients who have gradual declines in hemoglobin may be able to compensate and remain asymptomatic even at very low hemoglobin levels. Others may complain of weakness, fatigue, shortness of breath, pallor, dizziness, syncope, nausea, anorexia, headache, palpitations, chest pain, sleep disturbance, anxiety, malaise, or confusion.

History

Take a careful history, asking about symptoms listed above, as well as the following:

- Onset and duration of symptoms
- Previous anemia (and family history of anemia)
- Blood transfusions received (if any)
- HIV disease status, including CD4 cell count, history of opportunistic infections, other illnesses
- Abnormal bleeding; dark or tarry stools
- For women, date of last menses and amount of menstrual blood loss
- Jaundice
- Other symptoms: fever, sweats, weight loss, diarrhea, lymph node enlargement
- Current and recent medications (prescribed or over-the-counter), nutritional supplements, and herbal preparations
- Use of aspirin or nonsteroidal antiinflammatory drugs
- Dietary habits
- Alcohol abuse

O: Objective

Measure vital signs, with special attention to heart rate and blood pressure. Perform orthostatic measurements. Compare current weight with previous values. Perform a careful physical examination, including the following:

- General appearance (nutritional status, appearance of health or illness)
- Skin, conjunctivae: pallor, jaundice, icterus
- Mouth: stomatitis or glossitis (vitamin B12 or folate deficiency)
- Abdomen: liver or spleen enlargement, masses
- Lymph nodes

- Extremities: edema
- Neurologic: vibratory sensations, balance and gait, deep tendon reflexes, Babinski reflexes
- Rectal: check for occult blood

A: Assessment

Remember that more than one cause of anemia may be present. A partial differential diagnosis includes:

- Chronic disease: HIV/AIDS; other comorbid conditions
- Medications
  - AZT or AZT-containing drugs (Combivir, Trizivir)
  - TMP-SMX (Septra, Bactrim, cotrimoxazole)
  - Other hematotoxic medications (see list, below)
- Iron deficiency
- Vitamin B12 or folate deficiency
- Malnutrition
- Alcoholism
- Malignancy
- Renal disease
- Liver disease
- Blood loss (eg, gastrointestinal)
- Hemolysis (eg, in patients with glucose-6-phosphate dehydrogenase [G6PD] deficiency who are exposed to dapsone, TMP-SMX, or other oxidants)
- Parvovirus B19
- Tuberculosis
- *Mycobacterium avium* complex (MAC)
- Histoplasmosis, cryptococcosis
- Malaria
- Sickle cell disease
- Thalassemia
- Hypogonadism
- Hypothyroidism
- Pregnancy
- Rheumatoid arthritis
- Systemic lupus erythematosus
- Inflammatory bowel disease
- Hookworm infection

P: Plan

Diagnostic Evaluation

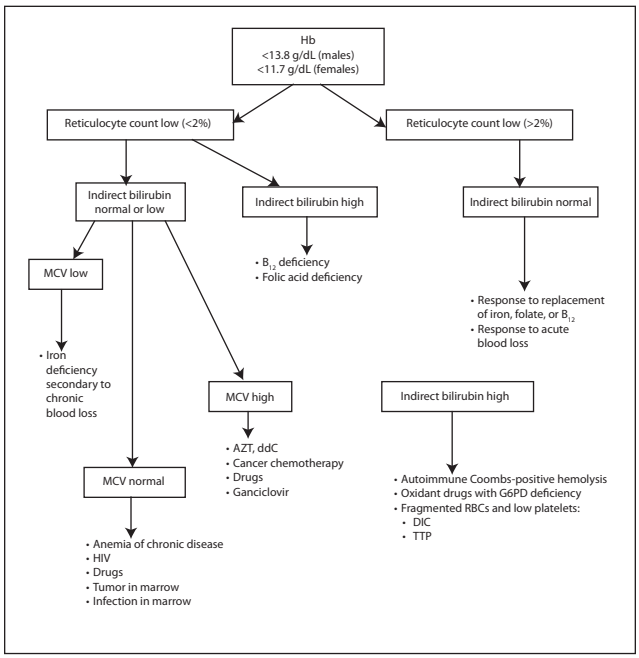
Recheck the hematocrit and hemoglobin to confirm anemia, and perform a complete blood count with differential to determine whether other cytopenias are present.

Perform laboratory work and other diagnostic studies as suggested by the history, physical examination, and differential diagnosis. Consider the following as initial tests to determine the cause of anemia:

- Mean corpuscular volume
- Peripheral blood smear
- Reticulocyte count
- Bilirubin (total and direct)
- Iron studies: ferritin, iron, transferrin, total iron-binding capacity
- Hemoccult testing for fecal blood
- Pregnancy test if indicated

See Figure 1 for a possible diagnostic approach.

Figure 1. Diagnostic Evaluation for Anemia



Key to abbreviations: AZT = zidovudine; ddC = dideoxycytidine; DIC = disseminated intravascular coagulation; HB = hemoglobin; MCV = mean cell volume; RBCs = red blood cells; TTP = thrombotic thrombocytopenic purpura

Adapted from: Volberding PA, Levine AM, Deiterich D, et al. Anemia in HIV infection: clinical impact and evidence-based management strategies (Figure 4. Simplified diagnostic approach to anemia in HIV-infected individuals). Clin Infect Dis. 2004 May 15;38(10):1454-63. Used with permission of the University of Chicago Press.

Check the testosterone level in individuals (both men and women) with anemia of uncertain cause, particularly if they have other signs or symptoms of hypogonadism. Perform further testing if indicated by the clinical presentation and results of the initial workup (eg, evaluation for parvovirus B19 or other infection, vitamin B12 deficiency, G6PD deficiency, malignancy, or gastrointestinal blood loss).

Consider bone marrow biopsy if the diagnosis is unclear, if the anemia is chronic or severe, if the initial evaluation does not determine the cause, or if the anemia is accompanied by pancytopenia. Bone marrow biopsy may also be performed to confirm a diagnosis.

Review the patient's medication list for drugs that may cause anemia. Some common medications that may cause anemia are the following:

- AZT
- Ganciclovir, valganciclovir
- Sulfonamides
- Pyrimethamine
- Dapsone
- Ribavirin
- Interferon-alfa
- Antineoplastic agents

Refer the patient to hematology or oncology specialists as appropriate.

Treatment

The appropriate treatment depends on the cause and severity of the anemia. Refer to pertinent chapters in *Section 6: Disease-Specific Treatment* or primary care management guidelines as appropriate.

- Patients with severe anemia may require transfusion (unless hemolysis is suspected) with or without hospitalization for evaluation and treatment.
- Consider treating anemia of chronic disease with ART, if it is otherwise indicated, while avoiding medications associated with bone marrow toxicity. Mild anemia often resolves without intervention after the start of ART as the immune system is reconstituted.
- If drug-induced anemia is suspected, discontinue the offending medication, if possible. For example, for patients taking AZT in whom other causes of anemia have been excluded, consider substituting another nucleoside/nucleotide analogue in place of AZT. If it is not possible to alter therapy, consider using erythropoietin (EPO) or red blood cell transfusion to increase the hematocrit.
- EPO may be used to stimulate red blood cell production. A typical dosage of recombinant human EPO is 40,000 units weekly by subcutaneous injection. Note that EPO replacement is ineffective if the erythropoietin level is >500 international units per liter (check serum EPO levels before treatment) or if iron levels are low. For patients in whom EPO is started, monitor the hemoglobin and hematocrit regularly (eg, every week until stabilized, then every 4 weeks) and adjust the dosage as required.
- Treat hypogonadal patients with testosterone.
- Treat iron deficiency with ferrous sulfate 325 mg orally 3 times daily.
- Treat nutritional deficiencies as indicated. For folate deficiency, give folic acid 1-5 mg daily for 1-4 months; for vitamin B12 deficiency: administer cobalamin 1 g intramuscularly once daily for 7 days, then once weekly for 4 weeks, then once monthly, or 1-2 g orally once daily.

Patient Education

- Symptoms such as fatigue, weakness, and shortness of breath may be signs of anemia. Patients should notify their health care providers if they develop these or other symptoms.
- Anemia may be caused by an opportunistic infection or other illness; further evaluation may be necessary.
- Anemia often responds to treatment. For many patients, ART may be a successful treatment; encourage them to adhere to ART.
- Counsel patients to take their medications exactly as directed and to call their health care providers if they experience new or worsening symptoms.

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Diarrhea

Background

Diarrhea is a common condition in HIV-infected individuals that may have a variety of causes. Episodes may be acute and brief, intermittent or recurrent, or, in some cases, chronic and severe. If diarrhea persists, it may cause poor nutrition, dehydration, and weight loss. Diarrhea may diminish patients' quality of life significantly, and may interfere with adherence to and efficacy of antiretroviral (ARV) medications.

Diarrhea is defined in various ways, but commonly as more than 4 loose stools or watery stools per day for more than 3 days. Duration is classified as follows:

- Acute: <2 weeks
- Persistent: 2-4 weeks
- Chronic: >4 weeks

The causes of diarrhea, both infectious and noninfectious, found in HIV-positive individuals with normal or mildly depressed CD4 cell counts are likely to be similar to those in HIV-uninfected persons. Among the noninfectious causes of diarrhea, adverse effects of ARVs and other medications are particularly common. Persons with advanced immunodeficiency are more likely to have infections, including opportunistic infections, as the cause of diarrhea.

Infectious diarrhea typically involves either the small or the large intestine, and the patient's history often suggests the site of the problem. Infections of the small intestine commonly produce generalized abdominal cramps, large-volume diarrhea without blood, and possibly dehydration. Large-intestine infections (colitis) often produce lower abdominal pain, an unproductive urge to defecate, and frequent small-volume stools with blood and pus.

S: Subjective

The patient complains of diarrhea. Take a thorough history, including the following:

- Onset of diarrhea
- Frequency (times per day, last episode)
- Stool consistency (soft vs liquid)
- Stool color (gray, white, or greasy stools: possible cholelithiasis or pancreatitis; dark stools: possible gastrointestinal bleeding)
- Bloody stools (possibly caused by invasive organisms, inflammation, ischemia, or neoplasm)
- Rectal bleeding
- Nausea or vomiting (if beginning within several hours of ingesting food, possible gastroenteritis)
- Weight loss: quantify amount and time frame
- Abdominal pain or cramping, and location if present
- Fever
- Other associated symptoms
- Allergies (to foods or medications)
- Aggravating factors
- Alleviating factors
- Treatments tried
- Contact with others with similar symptoms
- Previous episodes of diarrhea
- History of cytomegalovirus (CMV), *Mycobacterium avium* complex (MAC) or other infections involving the gastrointestinal tract
- Family history of inflammatory bowel disease, celiac disease
- Oral-anal sexual contact (males and females)
- Receptive anal intercourse
- Exposure to unsafely prepared food (eg, raw, undercooked, spoiled), unpasteurized milk or juices
- Exposure to possibly contaminated water (swimming in or drinking from well, lake, or stream)
- Exposure to non-toilet-trained infants and children (eg, daycare), pets, farm animals, reptiles

- Recent travel
- Antibiotic use or exposure in recent weeks or months
- ARV medications, especially ritonavir or nelfinavir; check relationship of diarrhea onset to initiation of ARVs
- Other current and recent medications, including supplements (prescribed or over-the-counter) and herbal preparations
- Dietary factors, especially "sugar-free" foods (containing nonabsorbable carbohydrates), fat substitutes, milk products, and shellfish, or heavy intake of fruits, fruit juices, or caffeine
- Alcohol and recreational drug use; withdrawal

O: Objective

Record vital signs, including temperature, orthostatic heart rate, blood pressure measurements, and weight. Compare these with recent or baseline values. Perform a thorough physical examination, including evaluation of the following:

- Hydration status (skin turgor, mucous membrane moistness)
- Nutritional status (body habitus, muscle mass, skin and hair integrity)
- Oropharynx (lesions, candidiasis, ulcerations, Kaposi sarcoma)
- Optic fundi (signs of CMV infection)
- Abdomen (distention, bowel sounds, tenderness, organomegaly, masses, adenopathy)
- Rectum (masses, tenderness, bloody stool)

Review recent CD4 cell counts. Low CD4 counts increase the risk of chronic or systemic illnesses and opportunistic infections.

A: Assessment

The differential diagnosis is broad, and includes the following infectious and noninfectious causes:

Infectious Causes

Acute diarrhea, any CD4 count

- Viruses (especially Norwalk virus)
- Viral hepatitis
- Herpes enteritis
- *Clostridium difficile* (suspect in patients who have recently been treated with antibiotics)
- *Salmonella*
- *Shigella*
- *Campylobacter*
- *Escherichia coli* O157:H7

Chronic diarrhea, any CD4 count

- *C difficile* (suspect in patients who have recently been treated with antibiotics)
- *Giardia lamblia*
- *Entamoeba histolytica*

Chronic diarrhea, CD4 count <300 cells/μL

- *Microsporidia*
- *Cryptosporidia*
- *Mycobacterium avium* complex (MAC) (CD4 count <50 cells/μL)
- *Isospora belli*
- CMV (CD4 count <100 cells/μL)

Adapted from: Infectious Causes of Diarrhea in Patients with HIV, Table 8-8. In: Bartlett JG, Cheever LW, Johnson MP, et al, eds. A Guide to Primary Care of People with HIV/AIDS. Rockville, MD: U.S. Department of Health and Human Services, Health Resources and Services Administration; 2004.

Noninfectious Causes

- Medication adverse effects, common with many medications including some ARVs:
  - Protease inhibitors (especially ritonavir and nelfinavir)
  - Didanosine buffered tablets (no longer available in the United States)
- Irritable bowel syndrome
- Inflammatory bowel disease (ulcerative colitis, Crohn disease)
- Lymphoma
- Lactose intolerance
- Celiac disease
- Small-bowel overgrowth
- Pancreatic insufficiency
- Diverticulitis
- Fecal incontinence

P: Plan

Diagnostic Evaluation

For suspected infections, perform laboratory studies including complete blood count with differential, electrolyte measurements, and liver function tests. Check stool for white blood cells and blood. Perform stool studies as indicated by the patient's presentation (bacterial culture, ova and parasites, *Microsporidia, Cryptosporidia*, and giardia: *C difficile* toxin assay). Order additional studies as suggested by the history (eg, blood cultures, MAC cultures, hepatitis serologies, retinal examination for CMV).

If the patient is febrile, perform a complete fever workup as appropriate (see chapter *Fever*).

Check the CD4 cell count and HIV viral load, if not checked recently.

If stool study results are negative (ova and parasite negative in 3 successive samples) and the patient has severe symptoms, particularly in the case of advanced immunodeficiency, refer to a gastroenterologist for colonoscopy or flexible sigmoidoscopy with biopsy. Endoscopy is the best procedure to identify certain conditions, including CMV colitis, and inflammatory bowel disease. If all studies are negative and the diarrhea persists, repeat endoscopy in 6-8 weeks regardless of the level of immunodeficiency. Pathogens may be difficult to identify.

Treatment

Once a diagnosis is made, initiate appropriate treatment. In seriously ill patients, presumptive treatment may be started while diagnostic tests are pending. See the appropriate chapter in *Section 6: Disease-Specific Treatment* or relevant treatment guidelines. If the cause of the diarrhea cannot be identified, consult with an HIV expert or a gastroenterologist.

For moderate to severe diarrhea, including dysentery (bloody diarrhea), empiric treatment can be given pending stool study results or in settings with limited resources for workup. Use fluoroquinolones in a 3-day regimen, including ciprofloxacin 500 mg twice daily, norfloxacin 400 mg twice daily, or levofloxacin 500 mg once daily. Monitor effectiveness and adjust therapy according to the results of diagnostic studies and clinical response.

For patients whose diarrhea is suspected to be due to ARV agents or other medications, symptomatic treatment may be tried (see below). Diarrhea from protease inhibitors often decreases after a few weeks without treatment. If the diarrhea cannot be controlled, a change in ARV regimen should be considered.

Symptomatic treatments

- Antimotility agents such as loperamide (Imodium) in over-the-counter or prescription strengths and atropine/diphenoxylate (Lomotil) are useful for many patients. The suggested dosage is 2 tablets after each loose bowel movement, not to exceed 8 tablets per day. These agents should not be used if patients have bloody diarrhea or if *C difficile* is suspected.
- Pharmaconutritional approaches include the use of calcium supplementation (500 mg 2-3 times daily). Patients with diarrhea related to protease inhibitors may find that taking calcium with each dose can decrease or prevent diarrhea. Note that magnesium supplements may worsen diarrhea.
- Pancrelipase (eg, Cotazym, Creon, Ultrase) can be useful in managing chronic diarrhea due to malabsorption. The dosage is 2-3 caplets 3 times daily with meals, titrated downward according to response.
- Cholestyramine (Questran) or psyllium (Metamucil) may reduce diarrhea by slowing peristalsis and adding bulk to stools. Avoid administering cholestyramine with other medications because it may impair their absorption.
- A combination of these treatments may be needed to control chronic diarrhea and can be continued for patients after an infectious process has been ruled out.

Nutrition and hydration

Encourage frequent intake of soft, easily digested foods such as bananas, rice, wheat, potatoes, noodles, boiled vegetables, crackers, and soups. Encourage hydration with fruit drinks, tea, "flat" carbonated beverages, and water. Patients should avoid high-sugar drinks, caffeinated beverages, alcohol, high-fiber foods, greasy or spicy foods, and dairy products. Many patients may benefit from a trial of a lactose-free, low-fiber, or low-fat diet. Patients should use nutritional supplements as needed or as recommended by a dietitian. In case of chronic or severe diarrhea, or significant weight loss, refer to a dietitian for further recommendations.

Patients with severe diarrhea must maintain adequate hydration, by mouth if possible. In severe cases, intravenous administration of fluids may be necessary. Oral rehydration solutions include the World Health Organization formula, Pedialyte, Rehydralyte, Rice-Lyte, and Resol. Homemade alternatives include the following:

- Combine 1/2 teaspoon of salt, 1 teaspoon of baking soda, 8 teaspoons of sugar, and 8 ounces of orange juice; add water to make l liter and drink.
- Drink 1 glass containing 8 ounces of apple, orange, or other juice; 1/2 teaspoon of corn syrup or honey; and a pinch of salt; then drink 1 glass containing 8 ounces of water and 1/4 teaspoon of baking soda.
- Mix 1/2 cup of dry, precooked baby rice cereal with 2 cups of water (boil first in areas with poor water quality); add 1/4 teaspoon of salt and drink.

Patient Education

- Diarrhea can have many causes. Instruct patients to notify their health care providers if they develop new or worsening symptoms.
- Instruct patients to take their medications exactly as directed and to call their health care providers if they experience worsening diarrhea, or other symptoms such as fever, nausea, vomiting, or pain.
- Patients must stay nourished and well hydrated even if they are having diarrhea. Instruct patients to eat small, frequent meals and to avoid dairy products, greasy food, and high-fat meals.

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Ear, Nose, Sinus, Mouth

Background

HIV-infected individuals frequently experience infections and neoplasms that affect the ears, nose, sinuses, and mouth. The degree of immunosuppression, as reflected by a patient's CD4 cell count, can affect the severity, likelihood of recurrence, and response to therapy for various infections and neoplasms.

Patients may present with ear, nose, sinus, or mouth complaints early in the course of HIV infection, perhaps even before they are aware of their infection. Some conditions arise more commonly in patients with advanced HIV infection. Certain complaints (eg, oral candidiasis) should prompt consideration of HIV testing in patients without known infection.

Ears

HIV-infected patients may experience recurrent acute otitis media and serous otitis media. Nasopharyngeal lymphoid hyperplasia, sinusitis, or allergies may contribute to dysfunction of the eustachian tubes. Unilateral and bilateral sensorineural hearing loss has been reported and may be caused by HIV infection involving the central nervous system (CNS) or the auditory nerve. Hearing loss may also be due to syphilis, other CNS infections, chronic otitis media, neoplasms, and certain medications (including some nucleoside analogues in rare cases). The pathophysiology, causative organisms, and incidence of external-ear infections appear to be the same in HIV-infected patients as in HIV-uninfected individuals.

S: Subjective

The patient may complain of ear pain, decreased hearing or hearing loss, a feeling of fullness in the ear, vertigo, or a popping or snapping sensation in the ear.

Obtain the following information during the history:

- Medications (prescription and over-the-counter), and herbal supplements, current and past
- Current or recent sinus infection
- Associated symptoms
- Drainage or blood from the ear
- Head or ear trauma

O: Objective

Recent CD4 count and HIV viral load are important measures of immunosuppression to determine whether the patient is at risk for opportunistic infections as causes of ear complaints.

Perform visual and otoscopic inspection, including evaluation for skin abnormalities, lesions, cerumen impaction or foreign body, lymphadenopathy, adenotonsillar hypertrophy, etc.

Evaluate hearing and refer for an audiogram. Perform a neurologic examination and draw rapid plasma reagin (RPR) or Venereal Disease Research Laboratory (VDRL) test.

A: Assessment and Plan

Otitis Externa/Interna

Proceed with care as with an immunocompetent patient. A chronic or atypical presentation in an HIV-infected patient warrants a thorough evaluation, including cultures, biopsy, radiographic scans, and referral to an ear, nose, and throat (ENT) specialist.

Hearing Loss

A patient with hearing loss should be referred for evaluation or treated depending on the cause. Avoid ototoxic medications (eg, furosemide, aminoglycosides).

Nose and Sinuses

Nasal and paranasal sinus conditions occur frequently in HIV-infected patients. Nasal obstruction, allergic rhinitis, nasal lesions, and sinusitis are common. Epistaxis can occur in patients with platelet disorders (eg, idiopathic thrombocytopenic purpura [ITP]).

S: Subjective

The patient may complain of "stuffy nose," rhinorrhea, epistaxis, frontal or maxillary headaches (worse at night or early morning), pain in the nostrils, persistent postnasal drip, mucopurulent nasal discharge, general malaise, aching or pressure behind the eyes, or toothache-like pain.

Obtain the following information during the history:

- Medications (prescription and over-the-counter) and herbal supplements, current and past
- Current or recent sinus infection
- Previous sinus surgery
- Recent or current upper respiratory infection (URI)
- Nasal bleeding or discharge
- Facial trauma
- Allergic rhinitis
- Positional pain; worse when patient bends forward?
- Tobacco use
- Fever
- Headache
- Mucopurulent nasal drainage

O: Objective

Recent CD4 count and HIV viral load are important measures of immunosuppression to determine whether the patient is at risk for opportunistic infections as causes of nasal and sinus complaints.

Examine the nose and sinuses. Check the nasal mucosa with a light and a speculum, looking for areas of bleeding, purulent drainage, ulcerated lesions, or discolored areas. Palpate or percuss the sinuses for areas of tenderness, look for areas of swelling over the sinuses, and visualize the posterior pharynx for mucopurulent drainage. Transillumination may be helpful. Examine the teeth and gums for caries and inflammation of the gingivae. Check maxillary teeth with the use of a tongue blade (5-10% of maxillary sinusitis is due to dental root infection). Refer to a dentist for tooth sensitivity or caries.

A: Assessment

Possible causes of epistaxis include coagulopathy, ITP, tumor, lesions of herpes simplex virus (HSV), and Kaposi sarcoma (KS). Suspect ITP if the platelet count is low and bleeding is difficult to control. HSV appears as painful, ulcerated vesicles in the nasal mucosa. Tumors may be caused by KS, squamous papilloma, or lymphoma; biopsy is necessary to determine the cause.

Acute infection of 1 or more of the paranasal sinuses is common. *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis* are seen in both HIV-uninfected and HIV-infected patients, whereas *Staphylococcus aureus* and *Pseudomonas aeruginosa* are found more often in HIV-infected patients. Fungi may be the causative agents, especially in patients with severe immunosuppression.

Chronic sinusitis occurs frequently in patients with HIV infection and may be polymicrobial or anaerobic. In patients with low CD4 cell counts, fungal sinusitis may occur.

Nasal obstruction may be caused by adenoidal hypertrophy, chronic sinusitis, allergic rhinitis, or neoplasm.

P: Plan

Epistaxis

Epistaxis caused by coagulopathy or tumor is managed the same as in the immunocompetent patient with these conditions. Cauterization of an identified bleeding point or packing may be necessary. ITP may be treated with antiretroviral therapy (ART) as chronic management, or with corticosteroids for acute management. Refer to a hematologist.

Acute Sinusitis

Combination therapy with antibiotics, decongestants, mucolytics, saline nasal spray, and topical nasal steroids may be effective. See chapter *Sinusitis* for details. Note: Avoid fluticasone (Flonase) and budesonide (Rhinocort Aqua) nasal spray in patients taking ritonavir or ritonavir-boosted protease inhibitors (eg, Kaletra), because significant increases in serum levels of these glucocorticoids may occur.

Chronic Sinusitis

Treat with a systemic decongestant (guaifenesin), saline nasal spray twice daily, and topical nasal saline spray. Patients with exacerbations of sinusitis should be treated as for acute sinusitis. For more detailed information, see chapter *Sinusitis*. Note: Avoid fluticasone (Flonase) and budesonide (Rhinocort Aqua) nasal spray in patients taking ritonavir or ritonavir-boosted protease inhibitors (eg, Kaletra), because significant increases in serum levels of these glucocorticoids may occur.

Nasal Obstruction

Perform magnetic resonance imaging (MRI) or computed tomography (CT) scan with biopsy for mass lesions or asymmetric nasal lymphoid tissue. Refer to an ENT specialist.

Mouth and Throat

The oral cavity is one of the most common areas of symptoms in patients with HIV infection. Conditions that arise in the oral cavity may be infectious, benign inflammatory, neoplastic, or degenerative processes.

S: Subjective

The patient may complain of white patches and red areas on the dorsal surface of the tongue and the palate, decreased taste sensation, white lesions along the lateral margins of the tongue, ulcerated lesions, nonhealing lesions at the corners of the mouth, sore gums, loose teeth, dysphagia, or odynophagia.

Obtain the following information during the history:

- Medications (prescription and over-the-counter) and herbal supplements (note that zalcitabine, dapsone, and other drugs may cause aphthous ulcers)
- Usual oral hygiene (toothbrushing, tongue brushing or scraping, flossing, use of mouthwash)
- Date of last dental examination
- Involuntary weight loss

O: Objective

Recent CD4 count and HIV viral load are important measures of immunosuppression to determine whether the patient is at risk for opportunistic infections as causes of oral complaints.

Thorough examination of the mouth and throat with a tongue depressor and a good light is mandatory. Observe for white patches or plaques on the mucous membranes that can be partially removed by scraping with a tongue blade (candidiasis). Examine the dorsal surface of the tongue and hard and soft palates for red, flat, subtle lesions (erythematous candidiasis). Check for ulcerations, inflamed gums, and loose teeth. Look for discoloration or nodular lesions on the hard palate (Kaposi sarcoma). Look for ribbed, whitish lesions on the lateral aspects of the tongue that cannot be scraped off (oral hairy leukoplakia). Check the pharynx for adenotonsillar hypertrophy. Rule out HIV-unrelated causes of pharyngitis, including streptococci or respiratory viruses.

A: Assessment and Plan

Perform biopsy, culture, and potassium hydroxide (KOH) preparation of lesions as indicated.

Oral Candidiasis (Thrush)

Oral candidiasis is most likely to occur when the CD4 count is <300 cells/μL, but it can occur at any CD4 level and in HIV-uninfected individuals. It may appear as creamy white plaques on the tongue or buccal mucosa or as erythematous lesions on the dorsal tongue or the palate. The most common treatment strategy is empiric therapy with topical or systemic antifungal agents. For more details, see chapter *Candidiasis, Oral and Esophageal*.

Angular Cheilitis

Angular cheilitis is also caused by *Candida* species, and is characterized by fissuring at the corners of the mouth. For treatment, see chapter *Candidiasis, Oral and Esophageal*.

Oral Hairy Leukoplakia

Oral hairy leukoplakia (OHL) is caused by Epstein-Barr virus and appears as raised, ribbed, "hairy" white lesions along the lateral margins of the tongue. Lesions are primarily asymptomatic, and treatment is generally not needed. Lesions often resolve with successful ART. For more details, see chapter *Oral Hairy Leukoplakia*.

Kaposi Sarcoma

Kaposi sarcoma appears as red, blue, or purplish lesions that are flat or nodular, and solitary or multiple. Lesions appear most commonly on the hard palate but may also occur on the gingival surfaces and elsewhere in the mouth. A definitive diagnosis requires biopsy and histologic examination. KS often resolves with ART and successful immune reconstitution. If lesions do not respond to ART or are severe or numerous, refer to an oncology specialist for chemotherapy. For more details, see chapter *Kaposi Sarcoma*.

Gingivitis

See chapters *Linear Gingival Erythema* and *Necrotizing Ulcerative Periodontitis and Gingivitis* for more details.

Herpes Simplex Virus

HSV lesions occur on the palate, gingivae, or other mucosal surfaces. They appear as single or clustered vesicles and may extend onto adjacent skin of the lips and face to form a large herpetic lesion. Lesions tend to be more common, persist longer, recur more often, and be larger and more numerous in HIV-infected patients, especially those with significant immunosuppression, than in healthy individuals. Empiric treatment with famciclovir, valacyclovir, or acyclovir is appropriate. For more details, see chapter *Herpes Simplex, Mucocutaneous*.

Aphthous Ulcers

Aphthous ulcers are eroded, well-defined lesions surrounded by erythema, ranging in size from <6 mm to several centimeters in diameter. The ulcers an appear anywhere in the oral cavity or pharynx and may be recurrent; they are extremely painful. Treatment may involve topical steroids or other methods. For more details, see chapter *Oral Ulceration*.

Oral Warts (human papillomavirus)

Oral warts may appear as solitary or multiple nodules. The lesions may be smooth, raised masses resembling focal epithelial hyperplasia, or small papuliferous or cauliflower-like projections. See chapter *Oral Warts*.

Other Conditions

Most of these complications also can occur in the esophagus. See chapters *Esophageal Problems, Candidiasis, Oral and Esophageal*, and *Cytomegalovirus Disease*.

If patient is having mouth pain, anorexia, or problems with taste, treat the condition appropriately and refer to an HIV-experienced dentist for evaluation and further treatment as needed. Refer to a dietitian for assistance with dietary needs (eg, nutritional supplements).

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Esophageal Problems

Background

Esophageal problems in HIV-infected patients include difficulty swallowing (dysphagia) or midline retrosternal pain when swallowing (odynophagia). Pain may be diffuse throughout the esophagus or localized in specific areas.

Several conditions may cause esophageal problems. Of the infectious causes of dysphagia in HIV-infected patients, *Candida* is the most common (50-70%). Drug-induced dysphagia, gastroesophageal reflux disease (GERD), vomiting, and hiatal hernia can also cause esophagitis. Less commonly, neoplasm or another cause of stricture may produce symptoms. Neuromuscular or neurological causes may be seen in patients with advanced AIDS.

If untreated, esophageal problems may result in esophageal ulcers, scarring of the esophagus, dehydration, and weight loss.

S: Subjective

The patient may complain of difficulty swallowing, a feeling of something being "stuck in the throat," retrosternal pain when eating, "hiccups," indigestion ("heartburn"), acid reflux, nausea, vomiting, or abdominal pain.

History

The history should include the following:

- Medications (prescription and over-the-counter) and herbal supplements, current and past
- Concurrent gastrointestinal (GI) symptoms, such as abdominal pain or diarrhea
- Recent dietary history
- Location and characteristics of pain (diffuse or focal)
- Oral thrush
- Aphthous ulcers
- Cytomegalovirus (CMV)
- *Candida* esophagitis
- GERD
- Hiatal hernia

O: Objective

Include the following in the physical examination:

- Measure vital signs (temperature may be elevated with certain infections, such as CMV, but not with herpes simplex virus [HSV], candidiasis, or idiopathic ulcers).
- Record weight (and compare with previous weights).
- Assess for oral candidiasis, lesions, and masses.
- Examine optic fundi to evaluate for CMV retinitis (in patients with CD4 counts of <50-100 cells/μL).
- Palpate for thyroid enlargement.
- Palpate the neck for lymphadenopathy.
- Assess the abdomen for masses, tenderness, and organomegaly.
- Perform a rectal examination to obtain stool for occult blood.
- Perform a neurologic examination.
- Check the CD4 count and HIV viral load to determine the level of immunosuppression and assess the risk of opportunistic infections as causes of esophageal complaints.

A: Assessment

Common causes of esophageal problems are as follows:

- Candidiasis (common with a CD4 count of <250 cells/μL or recent exposure to steroids or antibiotics)
- Most medications, including antiretroviral agents, can cause nausea and GI-related symptoms. The following medications are commonly associated with difficulty swallowing or heartburn: aspirin, nonsteroidal antiinflammatory drugs, potassium chloride, iron, tetracycline, theophylline, anticholinergic agents, calcium channel blockers, meperidine, and progesterone tablets.
- Foods can irritate the esophagus, including citrus fruits, mints, coffee, chocolate, and spicy foods.
- GERD

Less common causes of esophageal problems include:

- CMV; HSV; idiopathic or aphthous ulcers
- Kaposi sarcoma, lymphoma, tuberculosis, *Mycobacterium avium* complex (MAC), histoplasmosis
- Cardiac chest pain

P: Plan

Diagnostic Evaluation

Diagnosis often can be made on clinical grounds; in this case, empiric treatment may be initiated (see below). If the diagnosis is unclear, consider endoscopy or radiographic imaging (eg, CT or barium swallow).

Treatment

Determine whether the patient is able to swallow pills before giving oral medications. If pills are not tolerated, the patient may need liquids or troches.

For patients with severe oral or esophageal pain, viscous lidocaine 1% 5-10 mL 2-4 times daily (with swallowing precautions) or Magic Mouthwash (viscous lidocaine 1%, tetracycline, Benadryl, and nystatin compounded 1:1:1:1) may be tried.

Other treatments may depend on the underlying cause:

- Esophageal candidiasis: Fluconazole (Diflucan) is the drug of choice. If symptoms resolve within 7-10 days, no further testing is required. See chapter *Candidiasis, Oral and Esophageal* for more options and for dosing.
- Medication-related: Remove the offending drug(s), and institute a trial of H2 blockers or proton pump inhibitors (PPIs) as appropriate.*
- Food-related: Modify the diet and institute a trial of H2 blockers or PPIs as appropriate.*
- GERD: For nonpharmacologic treatment, in cases of obesity, counsel patients to lose weight, stop smoking, elevate the head of the bed, eat smaller meals, avoid eating food 2-3 hours before bedtime, and reduce fat in the diet to ≤30% of calorie consumption.
- "Heartburn" or reflux: Patients whose primary symptoms are more typical of "heartburn" or reflux, especially those with a history of GERD, should receive a trial of H2 blockers or PPIs as appropriate.* Some patients will require both an H2 blocker and a PPI to control symptoms. Reevaluate after 1-2 weeks; if symptoms are controlled, treat for 8 weeks, then reduce the dosage to the lowest effective amount. Patients may require maintenance therapy for an indefinite period because of the high likelihood of recurrence.
- CMV: Treat with anti-CMV medications (eg, oral valganciclovir). See chapter *Cytomegalovirus Disease* for details.
- HSV: Treat with antiviral medications including acyclovir (Zovirax), famciclovir (Famvir), or valacyclovir (Valtrex). See chapter *Herpes Simplex, Mucocutaneous*.
- Aphthous ulcers: These may respond to oral corticosteroids (prednisone 40 mg/d for 7-14 days, tapered to 10 mg per week for 4 weeks; a shorter course may be effective for small ulcers). Alternatively, a combination of H2 blockers* and sucralfate (Carafate) may be effective. In some circumstances, thalidomide 200 mg every 24 hours may be used. (Note: Thalidomide is teratogenic, and women of childbearing potential are not candidates for this therapy unless the benefits clearly outweigh the risks and appropriate prevention of pregnancy is undertaken.) Up to 40-50% of patients with aphthous ulcers experience relapse and require repeat treatment.
- Neoplastic disease requires referral to an oncologist.

* *Caution: PPIs and H2 blockers interfere with the absorption of atazanavir. PPIs are contraindicated in patients taking atazanavir (Reyataz). H2 blockers may be used cautiously in patients on ritonavir–boosted atazanavir, if they are separated from the atazanavir doses by 12 hours.*

Esophageal conditions that do not resolve with treatment require referral to a GI specialist for diagnostic endoscopy, with biopsy and brushing for histopathology and cultures as appropriate.

Diet

It is important that patients maintain adequate caloric intake, preferably with foods and liquids that can be swallowed easily. Nutritional supplements along with soft, bland, high-protein foods are recommended. Refer to nutritionist as needed.

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Eye Problems

Background

The immunosuppression caused by HIV infection increases the incidence of eye infections. However, serious eye problems associated with advanced immunosuppression, such as blindness due to cytomegalovirus (CMV) retinitis, are less common in patients treated with effective antiretroviral therapy (ART). Common problems not unique to HIV-infected patients include dry eye, blepharitis, keratitis, and presbyopia. Infectious processes affecting the eye include herpes simplex virus (HSV), herpes zoster virus (HZV), and syphilis. More severely immunocompromised patients (CD4 count <100 cells/μL) may experience CMV retinitis, *Toxoplasma* retinochoroiditis, cryptococcal chorioretinitis, and other conditions. Retinal detachment can result. Kaposi sarcoma (KS) also can affect the eye.

Immune reconstitution disease (IRD) may affect the eye in patients with advanced HIV disease soon after the initiation of effective ART. IRD may lead to exacerbation of a previously treated opportunistic infection or a new presentation (often with unusual manifestations) of a previously subclinical infection. In the case of CMV, IRD may present as retinitis, or less commonly as uveitis or vitreitis. IRD retinitis typically occurs in patients whose CD4 counts have increased from <50 cells/μL to 50-100 cells/μL during ART.

Drug-induced ocular toxicity can be caused by rifabutin (Mycobutin), ethambutol (Myambutol), and cidofovir (Vistide), and less often by high-dose didanosine (ddI, Videx), intravenous ganciclovir (Cytovene), intravenous acyclovir (Zovirax), and atovaquone (Mepron).

S: Subjective

The patient complains of dry eyes, blurred vision, floaters, sharp pains, flashing lights, central vision loss ("black holes"), vision field defects ("can only see half the page"), or peripheral vision loss ("looks like I'm in a tunnel").

Ascertain the following during the history:

- Pain: clarify type and characteristics
- Unilateral or bilateral problem
- Visual defects (central or peripheral vision loss or distortion), scotomata (an area of lost or depressed vision surrounded by an area of less depressed or normal vision). Occurs with reading, distance, or both?
- Fever
- Headache
- Previous eye or vision problems
- Medications (prescription and over-the-counter), and herbal supplements, current and past
- Use of corrective lenses
- Date of last eye examination
- Recent or current varicella-zoster virus (VZV) or HZV infection

O: Objective

Recent CD4 count and HIV viral load are important measures of immunosuppression to determine whether patient is at risk for opportunistic infections as causes of eye complaints. Also do the following:

- Consider the patient's age
- Check vital signs, including blood pressure and temperature
- Administer a visual acuity examination using the Snellen chart. Test the patient's ability to read small print, such as classified ads.
- Consider using an Amsler grid to locate areas of retinal pathology.
- Examine the eyelids for lesions, inflammation, and swelling.
- Examine the external eye for edema, ptosis, conjunctival injection, and corneal clarity.
- Test cranial nerves II, III, IV, and VI.
- Perform funduscopic examination with pupillary dilatation if available. Note retinal appearance, lesions, and condition of the disc, vessels, and macula.

A: Assessment and Plan

Refer to an HIV-experienced ophthalmologist for dilated retinal or slit-lamp examination and definitive diagnosis. If symptoms raise suspicion of serious or vision-threatening conditions such as herpes ophthalmicus, CMV retinitis, or retinal necrosis, ophthalmologic evaluation should occur within 24-72 hours.

The differential diagnosis includes the following conditions:

Dry Eye (Keratoconjunctivitis Sicca)

The patient may complain of intermittent eye pain, intermittent blurred vision that clears with blinking, and mild eye irritation. The condition worsens with extended reading or computer use. Keratoconjunctivitis sicca is related to HIV-mediated inflammation with damage to the lacrimal glands. It occurs in 10-20% of HIV-infected patients, most often in those with advanced HIV disease. In patients with a CD4 count of >400 cells/μL and no other signs or symptoms, confirm that a recent eye examination was normal or refer for same, prescribe artificial tears, and monitor.

Blepharitis

Blepharitis is inflammation of the eyelids, a common condition with dry eyes. The patient may complain of discharge and erythema of the eyes or eyelids. Of the bacterial causes, *Staphylococcus aureus* is the most common. Treatment includes cleaning of the eyelashes with warm water and mild shampoo, and applying antibiotic ointment if indicated.

Infectious Keratitis

The patient may complain of photophobia, eye pain, decreased vision, and irritation. Infectious keratitis may be caused by VZV, HSV, CMV, bacteria, fungi, or *Microsporidia*. VZV and HSV are the most common infectious causes of keratitis in HIV-infected patients. Bacterial and fungal causes occur equally in HIV-infected and HIV-uninfected persons. Fungal infections are caused most frequently by *Candida* species, especially in intravenous drug users. Keratitis may be more severe and may recur more frequently in HIV-infected patients than in HIV-uninfected persons. Evaluation should include slit-lamp examination by an ophthalmologist.

Refraction Problems

The patient may complain of blurring vision with near or distance vision. Other findings include an abnormal Snellen test or inability to read fine print. The condition may be due to presbyopia or other causes. Refer for ophthalmologic examination.

Iridocyclitis/Anterior Uveitis

The patient may complain of redness or watering of the eyes, constriction of the pupil, and blurred vision. Anterior-chamber inflammation is fairly common among patients with HIV infection and is often associated with CMV or HSV retinitis. Ocular bacterial infections, syphilis, toxoplasmosis, and tuberculosis can cause severe symptoms. Fungal retinitis rarely causes iridocyclitis. Other causes include other systemic conditions (eg, reactive arthritis, sarcoidosis) and drug toxicity (eg, rifabutin, cidofovir, ethambutol). Evaluation should include slit-lamp examination by an ophthalmologist.

Treatment should be directed at the causative pathogen or illness. If drug toxicity is suspected, the offending drug should be discontinued or reduced in dosage. Topical steroids may be indicated as an adjunctive measure. CMV IRD may present as posterior uveitis; for suspected IRD, consult an HIV-experienced ophthalmologist.

HIV Retinopathy

The patient typically has no symptoms, but may complain of blurred vision, visual field defects, floaters, or flashing lights. Cotton wool spots on the retina appear as small fluffy white lesions with indistinct borders and without exudates or hemorrhages. Usually, these findings are benign and do not progress. Refer for ophthalmologic examination to rule out other causes.

CMV Retinitis

Patients with retinitis caused by CMV infection may be asymptomatic or may experience blurred vision, floaters, scotomata, or central or peripheral vision loss or distortion. Retinal examination shows creamy to yellowish lesions, white granular areas with perivascular exudates, and hemorrhages ("cottage cheese and ketchup"). The abnormalities initially appear in the periphery, but progress if untreated to involve the macula and optic disc. CMV is a common complication of advanced HIV infection in patients with CD4 counts

of <50 cells/μL. Vision loss is usually permanent. Urgent ophthalmology consultation and initiation of anti-CMV therapy are required. See chapter *Cytomegalovirus Disease*.

Acute Retinal Necrosis

The patient may complain of eye pain, decreased visual acuity, and floaters. Rapidly progressing peripheral necrosis frequently causes blindness. Retinal necrosis is usually caused by VZV, although HSV and CMV have also been implicated. Treatment should be initiated urgently.

Toxoplasma Retinochoroiditis

Toxoplasma retinochoroiditis may occur in patients with CD4 counts of <100 cells/μL and cause blurred vision, visual field defects, floaters, or flashing lights. In HIV-infected patients, ocular manifestations often appear after the infection of the central nervous system with toxoplasmosis (see chapter *Toxoplasmosis*). Retinal examination may reveal yellow-white infiltrates without hemorrhage and active vitreous inflammation. Evaluation requires consultation with an HIV-experienced ophthalmologist. If toxoplasmosis is confirmed or strongly suspected, treatment should be initiated as quickly as possible.

Neuro-Ophthalmologic Manifestations

Symptoms or signs of papilledema, optic neuritis, cranial nerve palsies, and visual field defects may indicate encephalopathy, increased intracranial pressure, neurosyphilis, toxoplasmosis, multifocal leukoencephalopathy, meningitis, or central nervous system lymphomas. A thorough neurologic examination is required to determine whether additional diagnostic testing, such as imaging studies or cerebrospinal fluid testing, is needed in addition to ophthalmologic evaluation.

Retinal Detachment

The patient may complain of flashes of light, sudden loss of vision or both. This condition requires immediate referral to an emergency department.

Patient Education

- Patients should report any changes in vision to their health care provider as soon as possible.
- Routine eye examinations should be part of the patient's primary care.

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Fatigue

Background

Fatigue is defined by Aaronson et al as "a decreased capacity for physical and/or mental activity due to an imbalance in the availability, utilization, and/or restoration of resources needed to perform activity." Fatigue is one of the most common and debilitating complaints of HIV-infected people, with an estimated prevalence of 20-69%. The consequences of severe fatigue may include curtailment of work and other activities, need for frequent breaks, limitations in involvement with family and friends, and difficulty completing even the simplest household chores.

In HIV-infected individuals, fatigue may be caused by several comorbid conditions or by HIV itself. HIV-related fatigue is a broad term referring to fatigue that begins or significantly worsens after the patient is infected with HIV and that has no other identifiable causes. HIV-infected people with fatigue should be evaluated carefully for reversible causes, such as depression, anemia, hypogonadism, insomnia, and medication adverse effects, and should be treated aggressively if these are found. In some patients, fatigue may be related to advanced immunosuppression (with low CD4 cell counts) or to high levels of circulating HIV virus. Unfortunately, a specific cause of fatigue is not identified in many patients. Research to date suggests that fatigue in many HIV-infected individuals may result from a complex interplay between physiologic and psychosocial variables, and ongoing studies are being conducted to define factors related to the onset or worsening of fatigue.

S: Subjective

The patient complains of tiredness, easy fatigability, a need for frequent rest or naps, or waking in the morning feeling unrefreshed. The patient may complain of difficulty working, difficulty concentrating, inability to exercise without experiencing profound fatigue, or impairment in social relations because of fatigue.

Consider the following during the history:

- No objective clinical indicators exist for fatigue; thus, the diagnosis of fatigue rests on subjective data.
- Fatigue assessment tools may help to diagnose and estimate the severity of fatigue. One such tool, the HIV-Related Fatigue Scale, was developed specifically for use with seropositive individuals (see Barroso and Lynn reference below). The scale includes 56 items that assess the intensity of fatigue (on the day of the assessment and during the previous week), the circumstances surrounding fatigue (including patterns), and the consequences of fatigue.
- Take a thorough history of the fatigue symptoms, including onset, duration, exacerbating and alleviating factors, and associated symptoms. Evaluate for symptoms of other conditions that cause fatigue (eg, hypothyroidism, hypogonadism, anemia, heart failure, poor nutrition).
- Depression can cause significant fatigue and is common in HIV-infected patients with fatigue. Screen the patient for depression. A single question—"Are you depressed?"—has been shown to be as valid and reliable as most depression instruments. See the chapter *Depression* for further information.
- Evaluate the patient's sleep patterns. HIV infection can interfere with sleep architecture early in the illness.
- Inquire about substance use or abuse.
- Obtain a list of all current medications, including herbal and over-the-counter preparations.
- Conduct a nutritional assessment.

O: Objective

Check vital signs and orthostatic blood pressure and heart rate measurements, if indicated. Perform a physical examination including evaluation of nutritional status, affect, conjunctivae and skin (for pallor), thyroid, lungs and heart, and deep tendon reflexes.

A: Assessment

The differential diagnosis includes the following:

- Anemia
- Hypothyroidism
- Hypogonadism
- Depression
- Insomnia or poor-quality sleep
- Substance use or abuse
- Malnutrition
- Medication adverse effects (eg, zidovudine, interferon)
- Opportunistic infections, malignancy, chronic hepatitis B or C, other illnesses

P: Plan

Diagnostic Evaluation

To rule out reversible causes of fatigue, perform laboratory tests, including:

- Hemoglobin and hematocrit
- Thyroid function tests
- Testosterone (in both men and women)

Fatigue assessment tools, as mentioned above, may be used to assess the intensity of fatigue, the circumstances surrounding fatigue, and the consequences of fatigue.

Treatment

If testing reveals a specific cause of fatigue, treat appropriately. For example:

- Treat anemia, hypothyroidism, or hypogonadism, as indicated. (See chapter *Anemia.*)
- Treat depression with antidepressant medication, psychotherapy, or both. (See chapter *Depression.*)
- Treat insomnia and review good sleep-hygiene practices with the patient. (See chapter *Insomnia.*)
- Refer for treatment of substance use or abuse, if possible.
- Treat malnutrition, ideally in conjunction with a nutritionist.
- Treat opportunistic infections and other illnesses. (See section *Disease-Specific Treatment.*)
- Control other symptoms that could be causing fatigue (eg, diarrhea).
- If fatigue seems to be related to antiretroviral medication(s), weigh the benefits of the medication(s) against the possible adverse effects, and discuss these with the patient.

If, after appropriate evaluation, the fatigue is thought to be related to HIV infection or no specific cause is identified, consider the following:

- If HIV infection is inadequately controlled, particularly if the CD4 count is low or the HIV viral load is high, consider antiretroviral therapy (ART), if otherwise appropriate.
- Patients taking effective ART may still experience HIV-related fatigue. Providers should not dismiss these symptoms or tell these patients that, because their CD4 counts are high or HIV viral loads are low or undetectable, they should be feeling fine.
- Encourage patients to track their patterns of fatigue with a fatigue diary if necessary. Once patients recognize their individual patterns, they can better cope with fatigue by planning their daily activities accordingly (eg, performing the most strenuous tasks during times of peak energy or staggering activities to avoid excessive fatigue).
- Recommend moderate exercise and frequent rest.
- Refer the patient to community-based agencies for assistance with housekeeping.
- Evaluate the need for occupational therapy (eg, energy conservation techniques) or physical therapy (eg, reconditioning and strengthening exercises).
- Medications, such as stimulants, may be helpful for some patients with severe or debilitating fatigue.

Patient Education

- Fatigue is often not related to the CD4 count or HIV viral load. Avoid telling patients that, because their CD4 counts are high or HIV viral loads are low or undetectable, they should be feeling well.
- Encourage patients to keep a fatigue diary to identify patterns of fatigue that may have gone unrecognized. This information can help patients cope with fatigue and plan activities appropriately.
- Patients should be asked what seems to aggravate their fatigue. This information, too, will help patients determine their patterns of fatigue and identify self-care actions they might take to avoid triggers that will worsen the fatigue.
- Screen fatigued patients for depression. If they are depressed, help them get appropriate treatment because this might reduce fatigue.
- Talk to patients about their sleep habits and recommend changes, as appropriate, to improve their sleep hygiene.

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Fever

Background

Although fever may accompany HIV infection at various stages of disease, fever in a patient with a low CD4 count (<200 cells/μL) should prompt the clinician to rule out opportunistic infections.

S: Subjective

The patient complains of persistent fever, or new-onset fever of >101°F (38.3°C).

Assess the following during the history:

- Duration of fever
- Associated symptoms, including chills, sweats, weight loss
- Visual disturbances (see chapter *Eye Problems*)
- Nasal or sinus symptoms
- Asymmetric, tender, or new lymphadenopathy
- Cough or shortness or breath (see chapter *Pulmonary Symptoms*)
- Diarrhea, tenesmus (see chapter *Diarrhea*)
- Vaginal or urethral discharge
- Rash, lesions, soft-tissue inflammation
- Pain (for headache, see chapter *Headache*)
- Neurologic symptoms (see chapter *Neurologic Symptoms*)
- Other localizing symptoms
- Unprotected sexual contacts
- Recent injection drug use
- Travel within the past 6-12 months
- Intravenous line or venous access device
- Medications (as a cause of fever)
- Use of antipyretic agents including acetylsalicylic acid, nonsteroidal antiinflammatory drugs (NSAIDs), and acetaminophen; when was most recent dose?
- Hepatitis history

O: Objective

Document fever. Check other vital signs, including orthostatic measurements. Check weight and compare with previous values. Search for evidence of an infectious focus. Perform a complete physical examination, including evaluation of the eyes (including fundus), sinuses, oropharynx, lymph nodes, lungs and heart, abdomen, joints, genitals, uterus, rectum, and neurologic system. Review recent CD4 measurements, if available, to determine the patient's risk for opportunistic illnesses as a cause of fever.

A: Assessment

The differential diagnosis varies depending on the CD4 count. Partial lists are as follows.

Conditions More Likely with Low CD4 Count

- Aspergillosis
- Cryptococcosis
- Cytomegalovirus infection (CMV)
- Disseminated *Mycobacterium avium* complex (MAC)
- Disseminated histoplasmosis
- HIV infection itself
- Lymphoma, other neoplasms
- *Pneumocystis jiroveci* pneumonia (PCP)
- Sinusitis
- Toxoplasmosis
- Tuberculosis (atypical or extrapulmonary)

Conditions That May Occur at Any CD4 Count

- Acute hepatitis
- Bacterial pneumonia or bronchitis
- Tuberculosis (pulmonary)
- Urinary tract infection (UTI)
- Otitis
- Endocarditis
- Abscess, cellulitis
- Bacteremia or sepsis
- Disseminated herpes simplex virus; chicken pox

- Malaria
- Pelvic inflammatory disease (PID)
- Sexually transmitted infections
- Autoimmune process
- Immune reconstitution syndromes, related to opportunistic infections, are often associated with fever. (See chapter *Immune Reconstitution Syndrome.*)
- Drug-induced fever (common culprits include abacavir, nevirapine, sulfonamides, dapsone, amphotericin, pentamidine, thalidomide, penicillin, clindamycin, carbamazepine, phenytoin, barbiturates, and bleomycin)

P: Plan

Perform laboratory work and other diagnostic studies as suggested by the history, physical examination, and differential diagnosis. These may include the following:

- CD4 count (if not done recently) to help with risk stratification for opportunistic illnesses
- Complete blood count (CBC) with differential
- Blood cultures (bacterial, mycobacterial, fungal)
- Urinalysis, urine culture if UTI symptoms are present
- Liver enzymes, renal panel
- Chest x-ray; sinus films if indicated by symptoms and physical examination findings
- If respiratory symptoms and signs are present: sputum evaluation (Gram stain and acid-fast bacilli smear, evaluation for PCP), with culture of sputum for bacterial pathogens, acid-fast bacilli, and fungi as indicated; consider sputum induction or bronchoscopy if indicated
- Serum cryptococcal antigen if CD4 count is <200 cells/μL and symptoms are consistent with cryptococcosis
- For new lymphadenopathy: aspirate with culture, including acid-fast bacilli and fungal; cytology
- For cytopenias: bone marrow aspirate and biopsy may be needed. See applicable treatment guidelines
- For fever of unknown origin (FUO), defined as persistent fever >101° F, for >3 weeks without findings on initial workup, more intensive workup may be needed, such as lumbar puncture, other scans or biopsies; consult with a specialist in infectious diseases or an HIV expert to determine whether hospitalization or other laboratory tests are needed.
- For patients taking abacavir or nevirapine, rule out hypersensitivity reactions (see chapter *Adverse Reactions to HIV Medications*).

Once a diagnosis is made, appropriate treatment should be initiated. In seriously ill patients, presumptive treatment may be started while diagnostic tests are pending. In some cases, the source of fever cannot be identified. Consult with an HIV expert.

Symptomatic treatment may include NSAIDs, particularly naproxen (Naprosyn, Aleve) because it can be administered twice daily; acetaminophen; and analgesics. Monitor for gastrointestinal adverse effects with NSAIDs. Cold compresses also can be used to relieve fever symptoms. Refer to a dietitian to avoid weight loss during the hypermetabolic state. See *Section 6: Disease-Specific Treatment*, in this manual if an HIV-related cause is identified.

Patient Education

- Patients should report any new fever to their health care providers. They should measure their temperatures using a thermometer at home in order to report actual temperatures.
- Patients should know that fever is usually a sign that their bodies are battling an infection. Their health care providers may need to do special tests to find out what could be causing the fever.
- Many over-the-counter remedies are available to treat fevers. Patients should check with their care providers before taking these. Acetaminophen-containing products (eg, Tylenol) are generally well tolerated. Persons with liver disease should use acetaminophen only as prescribed. NSAIDs (eg, ibuprofen, naproxen, Advil, Motrin, Aleve) may also be used, but can cause gastrointestinal adverse effects, especially if taken without food. Patients should let their care providers know if they need to take these medicines for more than 2 or 3 days.

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Headache

Background

Headache may have many causes in HIV-infected persons, particularly those with low CD4 counts. Possible causes include infections (opportunistic and other) and central nervous system malignancies, HIV-related systemic illnesses, and medication toxicity. In addition, of course, headache may be caused by any of the processes that cause headaches in HIV-uninfected individuals. New or severe headache should be evaluated carefully.

S: Subjective

The patient complains of a new type of headache.

Determine the following during the history:

- History of headaches or migraines
- Characteristics of the headache (location, quality of pain, timing, duration, etc)
- Recent head trauma
- Allergies
- History of sinusitis
- Fevers
- Visual changes
- Dizziness, vertigo, nausea
- Mental status changes
- Seizures
- Focal or other neurologic symptoms (see chapter *Neurologic Symptoms*)
- New rashes or ulcerations
- Other symptoms
- Usual versus recent caffeine intake
- New medications (eg, zidovudine)
- Relief of headache by any medication
- Unprotected sex, new sex partner

O: Objective

Perform a physical examination as follows:

- Check vital signs. Look for fever, orthostasis, and hypertension.
- Examine the head and neck for trauma, sinus tenderness, and neck mobility; check lymph nodes.
- Check the eyes, including funduscopic examination, for lesions or papilledema.
- Look for oral lesions, dental abscess, thrush, and pharyngeal drainage.
- Examine the lungs for abnormal sounds.
- Check the skin, including palms and soles, for rashes or lesions.
- Perform a complete neurologic examination, including mental status examination.
- Review recent CD4 measurements, if available, to determine the patient's risk for opportunistic illnesses as a cause of headache.

A: Assessment

A partial differential diagnosis includes the following:

- Cryptococcal meningitis
- Neurosyphilis
- Tuberculous meningitis; other meningitis
- Progressive multifocal leukoencephalopathy (PML)
- Toxoplasmic encephalitis
- Cytomegalovirus (CMV) meningoencephalitis or retinitis
- Other encephalitis
- Central nervous system lymphoma
- Systemic infection
- Sinusitis
- Anemia
- Fever
- Depression, anxiety disorder
- Medication adverse effect
- Stress or tension headache

- Migraine or cluster headache
- Caffeine withdrawal
- Hypertension
- Dehydration

Other causes of headache unrelated to HIV should be considered.

P: Plan

Diagnostic Evaluation

Evaluation should include the following:

- CD4 count (if not done recently), to help with risk stratification for opportunistic illnesses
- Complete blood count (CBC) with differential (if fever or suspected anemia); see chapters *Anemia* and *Fever*
- Blood chemistries, including liver function tests, electrolytes, creatinine, glucose
- Serum cryptococcal antigen (if fever is present and CD4 count is <200 cells/μL); see chapter *Cryptococcosis*
- Toxoplasma immunoglobulin G (IgG) (if previously negative and CD4 count is <200 cells/μL); see chapter *Toxoplasmosis*
- Syphilis testing: rapid plasma reagin (RPR) or Venereal Diseases Research Laboratory (VDRL) test; see chapter *Syphilis*

When indicated, also consider:

- Sinus imaging
- Computed tomography (CT) scan with contrast or magnetic resonance imaging of the head; see chapter *Neurologic Symptoms*
- Lumbar puncture with cerebrospinal fluid (CSF) studies to include cell count, chemistries, bacterial cultures; fungal and acid-fast bacilli (AFB) evaluations and cultures; India ink stain; cryptococcal antigen, VDRL, as indicated

Treatment

- Once diagnosis is made, appropriate treatment should be initiated. In seriously ill patients, presumptive treatment may be initiated while diagnostic test results are pending. In some cases, the source of headache cannot be identified. Consult with an HIV expert or a neurologist.
- Refer to disease-specific treatment guidelines or primary care management guidelines as appropriate.
- Treat symptomatically with nonsteroidal antiinflammatory drugs (NSAIDs), acetaminophen, or narcotics, if indicated, to control pain.

Patient Education

- Headaches can be a sign of an opportunistic infection, especially in patients with low CD4 cell counts. Patients should notify their health care providers if they develop a new headache.
- Providers should inform patients that they may have to do additional tests to determine the cause of the headaches.
- Many over-the-counter remedies are available for headache. Patients should check with their health care providers before taking these. Acetaminophen-containing products (eg, Tylenol) are generally well tolerated. Persons with liver disease should use acetaminophen only as prescribed. NSAIDs (eg, ibuprofen, naproxen, Advil, Motrin, Aleve) may also be used, but can cause gastrointestinal adverse effects, especially if taken without food. Patients should inform their care providers if they need to take these medicines for more than 2 or 3 days.

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Lymphadenopathy

Background

Lymphadenopathy is very common in HIV-infected individuals and may occur at any stage of HIV infection. It may be the first indication of a serious local or systemic condition, and should be evaluated carefully. Rapid enlargement of a previously stable lymph node or a group of nodes requires evaluation to identify the cause and to determine whether treatment is needed. Similarly, nodes that are abnormal in consistency, tender to palpation, fluctuant, asymmetrical, adherent to surrounding tissues, or accompanied by other symptoms should be evaluated promptly.

Lymphadenopathy may be generalized or localized and is usually characterized by lymph nodes that are >1 cm in diameter. A multitude of conditions can cause lymphadenopathy, including HIV itself, opportunistic or other infections, and malignancies. The likely causes of lymphadenopathy, and thus the diagnostic workup, will depend in part on the patient's degree of immunosuppression. The risk of opportunistic and certain malignant conditions increases at lower CD4 cell counts (see chapter *CD4 Monitoring and Viral Load Testing*).

Many individuals with primary HIV infection (see chapter *Primary HIV Infection*) may have generalized lymphadenopathy that may resolve or may persist for months to years. If lymphadenopathy of >2 cm in size occurs in 2 or more noncontiguous sites and persists for more than 3 months, and if appropriate evaluation reveals no other cause, the patient is diagnosed with persistent generalized lymphadenopathy (PGL). PGL is usually due to follicular hyperplasia from chronic HIV infection. As long as enlarged nodes are stable in number, location, and size, persons with PGL require no management other than monitoring of nodes at each physical examination. Changes in the character of the lymph nodes should prompt further evaluation. Rapid involution of PGL may occur with advanced HIV disease and is a poor prognostic sign.

S: Subjective

The patient complains of new, worsening, or persistent glandular swellings in the neck, axilla, groin, or elsewhere.

Ascertain the following during the history:

- Symptoms that accompany the lymphadenopathy, particularly constitutional symptoms such as fever, sweats, fatigue, and unintentional weight loss.
- Localized symptoms or conditions that involve areas of the body with lymphatic drainage into the area of abnormal lymph nodes (eg, in the case of axillary lymphadenopathy, ask about breast masses and skin conditions or trauma involving the arm)
- A full review of systems
- HIV-related or other malignancies, opportunistic illnesses
- Recent travel, country or region of origin, disease exposures (eg, tuberculosis [TB], sexually transmitted infections), and risk behaviors (eg, injection drug use)
- Trauma or injury (including cat scratches)
- Exposure to household pets
- Current medications

Review recent CD4 cell counts and HIV viral load measurements.

O: Objective

Check vital signs. Perform a complete examination of lymph nodes, including the cervical, submandibular, supraclavicular, axillary, epitrochlear, and inguinal sites. Document the location, size, consistency, mobility, and presence or absence of tenderness of all abnormal nodes. In cases of localized lymphadenopathy, examine the area drained by the node. Check for hepatosplenomegaly. Perform a focused examination (eg, lung, breast, skin, genitals) to identify signs of local or systemic illness.

A: Assessment

The differential diagnosis of lymphadenopathy in HIV-infected patients depends in part on the degree of immunosuppression. For further information, see chapter *CD4 Monitoring and Viral Load Testing*.

Infectious Causes

Generalized lymphadenopathy

- HIV infection, including PGL
- Mononucleosis; Epstein-Barr virus
- *Mycobacterium avium* complex
- TB
- Cytomegalovirus
- Secondary syphilis
- Toxoplasmosis
- Histoplasmosis, other fungal diseases
- *Bartonella* infection
- Hepatitis B
- Lyme disease
- Chlamydia (Lymphogranuloma venereum [LGV])
- Widespread skin infections
- Immune reconstitution syndrome
- Follicular hyperplasia

Localized lymphadenopathy

- Any of the above
- Oropharyngeal and dental infections
- Cellulitis or abscesses
- Chancroid
- TB (scrofula)

Neoplastic causes

- Lymphoma
- Acute and chronic lymphocytic leukemias
- Other malignancy; metastatic cancer
- Kaposi sarcoma

Other causes

- Reactive process (benign)
- Sarcoidosis
- Hypersensitivity reaction to medications
- Serum sickness
- Rheumatoid arthritis
- Castleman disease

P: Plan

Diagnostic Evaluation

After the history and physical examination, the cause of lymphadenopathy may be clear and further diagnostic testing may not be necessary. If the cause of the lymphadenopathy is still uncertain, perform diagnostic testing as indicated by the patient's presentation. This may include the following tests:

- CD4 count (with or without HIV viral load), to determine the risk of opportunistic illnesses
- Complete blood count with differential; liver function tests; urinalysis
- Chest x-ray
- Tuberculin skin test (purified protein derivative, or PPD)
- Rapid plasma reagin (RPR) or Venereal Disease Research Laboratory (VDRL) test
- Blood cultures, if patient is febrile (bacterial, mycobacterial, and fungal, as indicated)
- Testing for specific infections if suspected (eg, *Bartonella* or LGV)

If a node is large, fixed, nontender, or otherwise worrisome, or if the diagnosis is unclear after initial evaluation, fine-needle aspiration (FNA) biopsy may provide a diagnosis. If FNA is nondiagnostic (false-negative results are relatively common), obtain an open biopsy for definitive evaluation. Biopsy specimens should be sent for bacterial, mycobacterial, and fungal cultures; acid-fast staining for mycobacteria; and cytologic examination.

If a node is large, inflamed, tender, or fluctuant, and a bacterial infection is suspected, consider initiating empiric antibiotic treatment and monitoring the patient over 1-2 weeks. If the node does not respond to antibiotic treatment or the patient becomes more symptomatic, arrange for FNA or open biopsy to establish the diagnosis.

Treatment

Treatment will depend on the cause of lymphadenopathy. Refer to the guidelines in *Section 6: Disease-Specific Treatment* or primary care management guidelines as appropriate. In the case of HIV-related lymphadenopathy, antiretroviral therapy may be effective.

Patient Education

- Lymphadenopathy may come and go throughout the course of HIV infection, but it may be a sign of a serious condition.
- Advise patients to notify their clinician if lymph nodes increase in size or change in character.

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Nausea and Vomiting

Background

Nausea with or without vomiting, and occasionally vomiting without nausea, can occur at any stage of HIV infection. Nausea is a common adverse effect of many antiretroviral (ARV) and other medications and often occurs within weeks of starting new medications. In some cases, nausea causes significant discomfort and may interfere with medication adherence. Nausea and vomiting may also be symptoms of a serious complication of ARV therapy, or a sign of an opportunistic infection or neoplasm in patients with late-stage AIDS. Clinicians must identify the cause of nausea and vomiting and institute appropriate treatment.

S: Subjective

The patient complains of nausea with or without vomiting, or vomiting without nausea.

Ascertain the following during the history:

- Duration of symptoms
- Characteristics, timing, and precipitating factors
- Fever
- Hematemesis
- Jaundice
- Abdominal pain
- Lightheadedness, dizziness, vertigo, or orthostatic symptoms
- Polyuria
- Polydipsia
- Headache
- Changes in vision
- Neck stiffness
- Pruritus
- Hepatitis history
- Pancreatitis history
- Toxoplasmosis encephalitis history
- Cytomegalovirus history
- Cryptococcal (or other chronic meningitis) history
- Central nervous system (CNS) lymphoma history
- Renal failure history
- Unprotected sex or missed menses in women
- Medications, new and ongoing
- Nutritional supplements and nonprescription medications
- Alcohol intake, substance use or abuse

O: Objective

Check vital signs, including orthostatic blood pressure and heart rate measurement.

Conduct a thorough physical examination, including evaluation of the following:

- Skin turgor
- Eyes and fundi (retinal abnormalities such as papilledema)
- Oropharynx (dryness of oral mucosa, thrush, ulcerations)
- Neck (stiffness or other signs of meningeal irritation)
- Abdomen (tenderness, distention, masses, organomegaly)
- Pelvis (tenderness, masses)
- Neurologic system (mental status, focal neurologic abnormalities)

Review recent CD4 measurements, if available, to determine the patient's risk for opportunistic illnesses.

A: Assessment

A partial differential diagnosis includes the following conditions:

- Medication effect or reaction
- Drug-drug interactions
- Foodborne illness
- Pancreatitis
- Meningitis
- Pregnancy

- Adrenal insufficiency
- Toxoplasmosis encephalitis (see chapter *Toxoplasmosis*)
- Uremia
- Diabetic ketoacidosis
- Lactic acidosis due to nucleoside analogues
- Esophagitis (see chapter *Esophageal Problems*)
- CNS lymphoma
- Hepatitis, infectious or drug related (see chapters *Hepatitis B Infection* and *Hepatitis C Infection*)
- Appendicitis
- Pelvic inflammatory disease (see chapter *Pelvic Inflammatory Disease*)
- Myocardial infarction

P: Plan

Diagnostic Evaluation

Perform laboratory work and other diagnostic studies as suggested by the history, physical examination, and differential diagnosis. Tests may include the following:

- Complete blood count (CBC) with differential
- Blood urea nitrogen (BUN), creatinine, electrolytes
- Glucose
- Amylase and lipase if symptoms of pancreatitis are present
- Liver function tests (LFTs) and hepatitis serologies for possible acute hepatitis
- Blood cultures and other fever workup as needed (see chapter *Fever*)
- Computed tomography (CT) scan of the brain if neurologic symptoms are present (see chapter *Neurologic Symptoms*)
- Cortisol and cortrosyn stimulation test if indicated (eg, fatigue, weakness, unexplained abdominal pain, weight loss, orthostasis; usually in late-stage AIDS)
- If odynophagia or dysphagia is present, see chapter *Esophageal Problems*
- Electrocardiogram if patient has chest pain or suspicious symptoms
- Lactic acid levels if lactic acidosis is suspected
- Pregnancy test if indicated
- Consult with an HIV expert to determine whether hospitalization or other laboratory tests are needed.

Treatment

Once the diagnosis is made, appropriate treatment should be initiated. In seriously ill patients, presumptive treatment may be started while diagnostic test results are pending. See appropriate chapters in *Section 6: Disease-Specific Treatment* or other relevant guidelines.

In the case of significant adverse effects from ARVs or other medications, use a substitute for the offending medications, if possible (without compromising the efficacy of the treatment regimen). In the case of serious or life-threatening medication toxicities (eg, lactic acidosis or abacavir hypersensitivity reaction), discontinue the offending medication (see chapter *Adverse Reactions to HIV Medications*).

After the workup and exclusion of life-threatening illness, symptomatic treatment can be considered. If nausea and vomiting are due to medications that are vital to the patient, and these complications are not life-threatening, antiemetic therapy may be the best treatment. Chronic therapy is not always necessary. Some patients obtain adequate relief by breaking the "nausea cycle" with effective antiemetics for 1-2 days and then establishing meals or snacks with medications. Patients with dehydration may require administration of fluids (oral or intravenous) to relieve nausea. For patients with chronic nausea resulting in weight loss, refer to a nutritionist for assessment and nutritional support.

Symptomatic treatment

Consider the following strategies for symptomatic treatment:

- Ginger capsules have proven effective in clinical trials for the management of pregnancy-related and chemotherapy-related nausea. Foods and beverages containing ginger (eg, tea, cookies, ginger ale, candies) may help provide relief.
- Promethazine (Phenergan) may be given as a 25-mg oral tablet or a 12.5-mg rectal suppository, every 8-12 hours as needed.
- Prochlorperazine (Compazine) may be given as a 5-mg or 10-mg oral tablet, or a 25-mg rectal suppository, every 6-8 hours as needed. Extended-release Spansule, 10 mg every 12 hours or 15 mg every morning, can also be considered.

- Lorazepam (Ativan) may be given as a 0.5mg oral tablet one half hour before medications for symptoms of anticipatory nausea. Patients with anticipatory nausea develop significant nausea or vomiting when even thinking about medications or reaching for the medications.
- Dronabinol (Marinol) may relieve nausea, especially when nausea is accompanied by a loss of appetite. This remedy is best tolerated by patients who have tolerated inhaled marijuana. The starting dosage is 5mg 2 or 3 times daily.
- 5-Hydroxytryptamine (5-HT_3) receptor antagonists such as dolasetron (Anzemet) 50 mg and 100 mg, granisetron (Kytril) 1mg, and ondansetron (Zofran) 4-mg, 8-mg, and 24-mg tablets are highly effective in relieving severe nausea and vomiting due to chemotherapy and other causes. However, access to these medications is limited by their cost. Their use should be considered a short-term strategy.

Patient Education

- Nausea and vomiting can have many different causes. Patients should let their health care providers know if they are having these symptoms so that the most likely cause can be determined.
- Patients should stay nourished and well hydrated even if they are having nausea and vomiting. Eating small, frequent meals may be best tolerated, while avoiding dairy products, greasy foods, and high-fat meals.
- Tell patients not to stop taking any of their medications without first discussing it with their health care providers. Many medications must be continued despite nausea.
- Many patients wonder whether they should take their medicines again if they vomit after taking their dose. Generally, the medicines are still in the system unless the pills actually come back up. Patients should call their health care provider if they have any questions.
- Ginger may help to relieve nausea. Ginger can be taken in a variety of ways, including ginger ale, tea, cookies, candies, or ginger capsules. Patients can choose the form of ginger that works best for them.

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Neurologic Symptoms

Background

The nervous system may be a site of complications throughout the course of HIV infection, and neurologic complaints are common in people living with HIV/AIDS. Neurologic symptoms may be caused by many factors, including infections (opportunistic and other), central nervous system (CNS) malignancies, medication toxicities, comorbid conditions (eg, diabetes, cerebrovascular disease, chronic hepatitis, mental illness), and nervous system injuries related to HIV itself.

The risk of some conditions, such as CNS infection, malignancy, and dementia, increases with advancing immunosuppression, and the CD4 cell count will help to stratify the patient's risk of opportunistic illnesses (see Table 1 in chapter *CD4 Monitoring and Viral Load Testing*). This chapter presents a general approach to neurologic symptoms in HIV-infected patients, with reference to other chapters in this manual for more detailed reading. For information on peripheral neuropathy, see chapter *Pain Syndrome and Peripheral Neuropathy*.

S: Subjective

The patient, or a friend or family member on his or her behalf, reports new neurologic symptoms such as pain, headache, seizures, altered mental status, or weakness.

Ascertain the following during the history:

- Onset and duration: rapid (hours to days), subacute, chronic
- Characteristics of the symptoms (eg, location, quality, timing)
- Progression or stability of symptoms
- Constitutional symptoms: fever, night sweats, unintentional weight loss
- Associated symptoms, including other neurologic, muscular, psychiatric, or behavioral symptoms
- Recent trauma to the head or other area
- Visual changes, photophobia
- Dizziness, vertigo
- Mental status changes (including changes in behavior, personality, or cognition; short-term memory loss; mental slowing; reading comprehension difficulties; changes in personal appearance and grooming habits)
- Seizures (description, duration, number)
- Pain
- Sensory symptoms
- Weakness (distinguish weakness from fatigue or pain; determine whether bilateral or focal, proximal or distal)
- Bowel or bladder changes
- Rash or ulcerations
- Medications: current, past, and recently initiated medications, including antiretroviral therapy (ART)
- Alcohol or drug use; date of last use
- Exposures (sexual, environmental), travel history
- Psychiatric history and past psychiatric care
- Most recent CD4 cell count and HIV viral load, previous AIDS-defining illnesses
- Functional impact of the symptoms: social functioning, ability to work and perform activities of daily living

Differentiate delirium from dementia. Delirium presents as acute onset of clouded sensorium, disturbed and fluctuating level of consciousness, disorientation, cognitive deficits, and reduced attention, sometimes with hallucinations. Delirium is often due to medication toxicities, infections, hypoxia, hypoglycemia, electrolyte imbalances, or mass lesions, and is frequently is correctable. Dementia emerges more gradually and is characterized by cognitive impairment and behavioral, motor, and affective changes. See chapter *HIV-Associated Dementia and Minor Cognitive Motor Disorder*.

O: Objective

- Check vital signs (temperature, blood pressure, heart rate, and respiratory rate, oxygen saturation) and orthostatic measurements.
- Perform a careful physical examination as guided by the history, with special attention to the following:
  - General appearance: mood, affect, mannerisms
  - Head and neck: signs of trauma, sinus tenderness, lymph node status, neck mobility
  - Eyes, including fundi: lesions, papilledema
  - Lungs, heart: abnormal sounds
  - Extremities: muscle tone and bulk
  - Skin, mucous membranes: rash, lesions
- Conduct a thorough neurologic examination, including cranial nerves, motor function, sensory function, coordination, gait, and deep tendon reflexes.
- Conduct a mental status examination.
- Review recent CD4 measurements, if available, to determine the patient's risk for opportunistic illnesses.

A: Assessment

The differential diagnosis of neurologic abnormalities in patients with HIV infection may be broad, particularly if the CD4 count is low. Both HIV-related and HIV-unrelated causes should be considered; remember that more than one cause of symptoms may be present.

Causes related to the cerebrum or cranial nerves

- Toxoplasmic encephalitis
- Primary CNS lymphoma
- Cryptococcal meningitis
- Cytomegalovirus (CMV) encephalitis
- Other meningitis (bacterial, tuberculous, fungal, viral)
- Progressive multifocal leukoencephalopathy (PML)
- Neurosyphilis
- CNS coccidioidomycosis, histoplasmosis
- HIV-related dementia
- Alcohol or drug intoxication or withdrawal (medications or illicit drugs); chronic alcohol abuse
- Depression, mania, anxiety, psychosis
- Cerebrovascular accident; stroke
- Metabolic abnormalities, including hypo- or hyperglycemia, electrolyte abnormalities

Causes related to the spinal cord, nerve roots, peripheral nerves, and muscle

- Inflammatory demyelinating polyneuropathy (eg, Guillain-Barré syndrome)
- Polyradiculitis (eg, CMV, herpes simplex virus)
- Vitamin deficiency
- Myositis
- Myopathy (eg, due to zidovudine)
- Myelopathy (HIV vacuolar myelopathy)
- Epidural abscess or mass
- Mononeuritis multiplex
- Lactic acidosis
- Electrolyte abnormality (eg, hypokalemia)
- Peripheral neuropathy
- Distal sensory polyneuropathy
- Antiretroviral toxic neuropathy (especially stavudine, didanosine)
- Other neuropathy (eg, due to diabetes, alcohol, medications [isoniazid, dapsone, many others])

Note that organic causes of neurologic symptoms must be ruled out before concluding that symptoms are psychiatric in nature.

P: Plan

Diagnostic Evaluation

Unstable or seriously ill patients should be hospitalized for evaluation and treatment. Criteria for hospitalization include acutely altered mental status, fever with focal neurologic findings, and new or unstable seizures.

Perform laboratory work and other diagnostic studies as suggested by the history, physical examination, and differential diagnosis. This may include the following:

- Establish the CD4 count (if not done recently) to help with risk stratification for opportunistic illnesses.
- Determine which laboratory tests are appropriate depending on the patient's presentation. The initial evaluation often includes a complete blood count with differential and monitoring of electrolyte and glucose levels.

  - In patients with CNS symptoms or signs and low CD4 counts (<100 cells/μL), check serum levels of toxoplasma antibody (IgG) if not previously checked. Check serum cryptococcal antigen (CrAg) titer.
  - In patients with symptoms of neuropathy or dementia, check serum levels of vitamin B12 and thyroid-stimulating hormone (TSH).
  - In patients with cranial nerve abnormalities, meningoencephalitis, symptoms of dementia, or any symptoms of neurosyphilis, check syphilis serology by rapid plasma reagin (RPR) or Venereal Disease Research Laboratory (VDRL) test.
- When CNS symptoms or signs are present, brain imaging by computed tomography (CT) scan with contrast is usually adequate as the initial test. Magnetic resonance imaging (MRI) is the modality of choice if the neurologic examination is nonfocal or if physical examination suggests a lesion in the posterior fossa.
- For patients with fever and CNS findings, perform lumbar puncture (LP) with cerebrospinal fluid (CSF) sampling. CT or MRI should be performed before the LP, if possible, to rule out a mass lesion that could cause herniation.
- Record the opening pressure, and send CSF for cell count and differential with protein and glucose measurements. Depending on the clinical suspicion, the fluid should also be sent for bacterial culture, India ink stain for fungal organisms (75-85% sensitive), acid-fast bacilli smear and culture, VDRL test, and CrAg titer (95% sensitive).
- If CMV is suspected, perform polymerase chain reaction (PCR) for CMV DNA (62-100% sensitivity; 89-100% specificity).
- If PML is suspected, perform CSF PCR analysis for JC virus DNA (sensitivity approximately 80%; specificity 92-100%).
- For suspected drug or alcohol use, perform urine or serum toxicology screen. (Note that alcohol usually has been metabolized by the time withdrawal symptoms set in, typically 7-48 hours after the last alcohol intake).
- For new-onset seizures, perform an electroencephalogram (EEG)
- Consult with neurology specialists if the workup or the diagnosis is in question.

Treatment

Specific treatment will depend on the cause of neurologic symptoms. Consult relevant chapters in this manual. For complex cases, consult with an HIV-experienced neurologist.

Patient Education

- Inform patients that keeping the CD4 count above 200 cells/μL with ART is the best way to prevent most HIV-associated neurologic diseases.
- Advise patients to take prophylaxis, as appropriate, to prevent opportunistic infections.
- When an antibiotic treatment is prescribed, advise patients to complete the entire regimen to prevent relapse of symptoms. Long-term treatment (prophylaxis) will be needed to prevent recurrence of certain infections.
- Advise patients who have seizures that driving and other potentially dangerous activities will be prohibited until the condition is stable.
- Counsel patients to avoid substances that impair the nervous system, such as alcohol and recreational drugs.
- If a patient is forgetful, educate other members of the household about the medication regimen and help devise a plan for adherence to medications and appointments.

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Pulmonary Symptoms

Background

Shortness of breath or cough may be common manifestations of acute or chronic respiratory diseases, but also may be symptoms of HIV-related opportunistic infections. Further, these symptoms may indicate nonpulmonary conditions such as anemia, cardiovascular disease, and sinusitis, or adverse effects of medications such as angiotensin-converting enzyme (ACE) inhibitors.

The onset and duration of symptoms, and the presence or absence of other factors such as sputum production, fever, and weight loss, will guide the evaluation. In addition, the patient's CD4 cell count will establish a context for the evaluation, because it will help to stratify the risk of opportunistic infections.

S: Subjective

The patient complains of dyspnea or cough. Determine the following factors relating to the patient's history.

Recent History

- Onset and duration of symptoms: rapid (hours to days), subacute, chronic
- Progression or stability of symptoms
- Dyspnea at rest or with exertion?
- Cough: productive (character of sputum), hemoptysis?
- Associated symptoms (chest pain, pleuritic pain, etc)
- Constitutional symptoms: fever, night sweats, unintentional weight loss
- Sinus congestion, facial tenderness, postnasal discharge, sore throat
- Orthopnea, paroxysmal nocturnal dyspnea (PND), peripheral edema
- Wheezing

Past History

- CD4 nadir (lowest documented CD4 cell count), current CD4 count
- If the CD4 count is <200 cells/μL, ask whether the patient is taking *Pneumocystis jiroveci* pneumonia (PCP) prophylaxis (primary or secondary); if taking PCP prophylaxis and adhering to the regimen, the diagnosis of PCP is less likely.
- Tuberculosis (TB): date and result of tuberculin skin test (purified protein derivative, or PPD), risk factors for *Mycobacterium* TB
- PCP, bacterial or other pneumonia, bronchitis
- Smoking
- Cardiovascular diseases, including congestive heart failure, coronary heart disease, arrhythmia, pulmonary hypertension
- Asthma, emphysema
- Pollen, dander, or dust allergies
- Drug allergies, specifically to penicillins and sulfa drugs
- Medications (eg, ACE inhibitors)
- Use of inhaled stimulants, injection drugs

O: Objective

Check vital signs, oxygen saturation (resting and after exercise), weight.

Conduct a thorough physical examination, to include evaluation of the following:

- Ears, nose, oropharynx
- Neck
- Lungs
- Heart
- Extremities

Note: If patients are coughing, strongly consider having them wear a surgical mask in the clinic or office until TB or other transmissible infection is ruled out. Covering both the nose and the mouth should prevent the discharge of large infectious droplets into the environment.

A: Assessment

The differential diagnosis of pulmonary symptoms is broad (Table 1). Both HIV-related and HIV-unrelated causes should be considered; the patient's risk of HIV-related causes is strongly influenced by the CD4 count. More than 1 cause of symptoms may be present.

Table 1. Partial Differential Diagnosis of Pulmonary Symptoms

CD4 Cell Count	Possible Cause

Any Count	• Upper respiratory tract illness
	  ◦ Upper respiratory tract infection (URI)
	  ◦ Sinusitis
	  ◦ Pharyngitis
	• Acute or chronic bronchitis
	• Bacterial pneumonia
	• TB
	• Influenza
	• Chronic obstructive pulmonary disease
	• Reactive airway disease, asthma
	• Non-Hodgkin lymphoma
	• Pulmonary embolus
	• Congestive heart failure
	• Pulmonary hypertension
	• Pneumothorax
	• Bronchogenic carcinoma
	• Anemia
	• Gastroesophageal reflux (may cause cough)
	• Lactic acidosis
	• Medication adverse effect

≤500 cells/µL	• Bacterial pneumonia (recurrent) • Pulmonary *Mycobacterium* pneumonia (nontuberculous)
≤200 cells/µL	• PCP • *Cryptococcus neoformans* pneumonia or pneumonitis • Bacterial pneumonia (associated with bacteremia or sepsis) • Disseminated or extrapulmonary TB
≤100 cells/µL	• Pulmonary Kaposi sarcoma • Bacterial pneumonia (risk of gram-negative bacilli and *Staphylococcus aureus* is increased) • *Toxoplasma* pneumonitis
≤50 cells/µL	• Disseminated histoplasmosis • Disseminated coccidioidomycosis • Cytomegalovirus pneumonitis • Disseminated *Mycobacterium avium* complex • Disseminated *Mycobacterium* (nontuberculous) • *Aspergillus* pneumonia • *Candida* pneumonia

Adapted from: Huang L. *Pulmonary Manifestations of HIV* (Table 4). In: Peiperl L, Coffey S, Volberding PA, eds. HIV InSite Knowledge Base [textbook online]; San Francisco: UCSF Center for HIV Information; May 1998. Available online at http://hivinsite.ucsf.edu/InSite?page=kb-04-01-05.

P: Plan

Diagnostic Evaluation

Perform laboratory work and other diagnostic studies as suggested by the history, physical examination, and differential diagnosis. This may include the following:

- Chest x-ray, especially if the patient has abnormal findings on chest examination, fever, or weight loss, or if the CD4 cell count is <200 cells/µL.
- Arterial blood gas (ABG) on room air, particularly if PCP is suspected.
- Complete blood count and white blood cell (WBC) count with differential, metabolic panel, and lactate dehydrogenase (LDH).
- If fever is present (especially temperature >38.5°C), obtain routine blood cultures (2 specimens) for bacteria. If the CD4 count is <50 cells/µL, obtain blood culture for acid-fast bacilli (AFB); if <100 cells/µL, check the serum level cryptococcal antigen (CrAg).
- Induced sputum (outside, or in negative-pressure room or area that is safely vented to the outside, to prevent TB aerosolization) for AFB smear and cultures (3 specimens), Gram stain and bacterial cultures, PCP stains, fungal stains and cultures, and cytology, as indicated.
- CD4 count and HIV viral load, if recent values are not known.
- Bronchoscopy with bronchoalveolar lavage (BAL) or biopsy if sputum studies are negative, if the diagnosis is unclear after initial evaluation, or the patient is not responsive to empiric therapy.
- Pulmonary function tests if no infectious or HIV-related pulmonary diagnosis is suspected and symptoms persist.
- Lactate level if lactic acidosis is suspected (eg, nausea, tachypnea, abdominal pain, fatigue, in the setting of long-term nucleoside analogue therapy).

Treatment

Once the diagnosis is made, appropriate treatment should be initiated. In seriously ill patients, presumptive treatment may be started while diagnostic test results are pending. See the appropriate chapter in *Section 6: Disease-Specific Treatment* or relevant guidelines. In some cases, the source of dyspnea or cough cannot be identified. In these cases, consult with an HIV expert or a pulmonologist.

Patient Education

- Shortness of breath and cough can be signs of an opportunistic illness, especially in patients with low CD4 counts. Patients should notify their health care providers if they develop new or worsening symptoms.
- Patients taking antibiotics should be instructed to take their medications exactly as directed and to call their care providers if they experience worsening fevers, shortness of breath, inability to take the prescribed medications, or other problems.
- Counsel smokers about the importance of smoking cessation; refer to tobacco cessation programs and prescribe cessation supports, as indicated.

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Vaginitis/Vaginosis

Background

Vaginitis is defined as inflammation of the vagina, usually characterized by a vaginal discharge containing many white blood cells (WBCs); it may be accompanied by vulvar itching and irritation. Vaginosis is characterized by increased vaginal discharge without WBCs or inflammation. Vaginal infections are common in HIV-infected women. This chapter focuses on 2 of the most common types of vaginal infections: trichomoniasis and bacterial vaginosis (BV). For information on the topic of vulvovaginal candidiasis, see the chapter *Candidiasis, Vulvovaginal*.

S: Subjective

The patient complains of vaginal discharge, with or without odor, itching, burning, pelvic pain, vulvar pain, or pain during intercourse.

Take a focused history, including the following:

- Duration of symptoms
- Sexual history, especially recent new partner(s), unprotected sex
- Relationship of symptoms to sexual contacts
- Contraceptive use, especially:
  - Vaginal contraceptive film
  - Other products containing nonoxynol-9 (N-9)
  - Condoms; type of condoms
- Use of feminine hygiene products (eg, sprays, deodorants)
- Douching
- Use of perfumed toiletries (eg, bath salts, scented toilet tissue or sanitary napkins)
- Use of any vaginal creams
- Postcoital bleeding
- Vulvar pain
- Pain or burning during urination
- Pain with intercourse
- Recent antibiotic use
- History of sexually transmitted infections (STIs), pelvic inflammatory disease (PID)
- Medications, including supplements

O: Objective

Perform a focused physical examination of the external genitalia, including perineum and anal area, for the following:

- Inflammation
- Edema
- Excoriation
- Lesions

Perform speculum examination for:

- Discharge (note color, quality)
- Erythema, edema, erosions, lesions
- Cervical friability
- Foreign body

Perform a bimanual examination for masses or tenderness, if indicated.

A: Assessment

A partial differential diagnosis includes the following:

- Bacterial vaginosis (BV)
- Candidiasis
- Trichomoniasis
- Pelvic inflammatory disease (PID)
- Latex or condom allergy
- Urinary tract infection (UTI)
- Condyloma
- Herpes simplex virus (HSV)
- Contact dermatitis from irritants, perfumes, etc
- Chlamydia
- Gonorrhea
- Normal vaginal discharge

P: Plan

Diagnostic Evaluation

- Obtain a cervical sample for STI testing, if indicated.
- Obtain smears from the vaginal wall for wet mounts and pH.
- Wet mounts: Perform microscopic examination of saline and potassium hydroxide (KOH) preparations for the following:
  - WBCs, clue cells, motile trichomonads (saline slide)
  - Yeast forms (KOH)
- Perform a whiff test of KOH preparation; if positive, check pH (if >4.5, presume BV).

Treatment depends on the specific diagnosis, and in general is the same as for HIV-negative women.

Trichomoniasis

Trichomoniasis is caused by the protozoan *Trichomonas vaginalis*. Many infected women have a diffuse, malodorous, yellow-green discharge. Most men who are infected with *T vaginalis* have no symptoms; others have symptoms of nongonococcal urethritis. The diagnosis is usually made by visualization of motile trichomonads on microscopic examination of wet mounts.

The sex partners of patients with trichomoniasis should be treated. Patients should avoid sexual intercourse until they and their partners have completed treatment and symptoms have resolved.

Treatment: Recommended regimen

- Metronidazole 2 g orally in a single dose

Treatment: Alternative regimen

- Metronidazole 500 mg orally twice a day for 7 days

Note: Patients must avoid alcohol while taking metronidazole. This combination may cause a disulfiram-like reaction. Patients taking ritonavir or tipranavir may also experience symptoms because of the small amount of alcohol in the capsules.

Treatment failure

Certain strains of *T vaginalis* have diminished susceptibility to metronidazole and must be treated with higher doses. If treatment failure occurs with either regimen, repeat treatment using metronidazole 500 mg orally twice daily for 7 days. If treatment failure occurs again, the patient should be treated with metronidazole 2 g once daily for 3-5 days. If this regimen is not effective, consult with a specialist.

Bacterial Vaginosis

BV is a clinical syndrome resulting from loss of the normal vaginal flora, particularly *Lactobacillus*, and replacement with anaerobic bacteria such as *Gardnerella vaginalis* and *Mycoplasma hominis.* BV appears as a homogeneous, white, noninflammatory discharge on the vaginal walls. The diagnosis is made by the detection of clue cells on the wet-mount slide, a vaginal fluid pH of >4.5, and a fishy odor to the vaginal discharge before or after the addition of KOH (whiff test).

Many studies have documented an association between BV and infections such as endometritis, PID, and vaginal cuff cellulitis after gynecologic procedures. Therefore, the U.S. Centers for Disease Control and Prevention (CDC) recommends screening for and treating BV before invasive gynecologic procedures.

The sex partners of women with BV do not need to be treated.

Treatment: Recommended regimen

- Metronidazole 500 mg orally twice daily for 7 days
- Metronidazole gel 0.75%, 1 full applicator (5 g) intravaginally at bedtime for 5 days
- Clindamycin cream 2%, 1 full applicator (5 g) intravaginally at bedtime for 7 days

Treatment: Alternative regimens

- Metronidazole 2 g orally in a single dose
- Clindamycin 300 mg orally twice daily for 7 days
- Clindamycin ovules 100 g intravaginally at bedtime for 3 days

Note: Patients must avoid alcohol while taking metronidazole. This combination may cause a disulfiram-like reaction. Patients taking ritonavir or tipranavir may also experience symptoms because of the small amount of alcohol in the capsules.

Treatment Failure

Multiple conditions or pathogens may present concurrently. Perform testing for other conditions as suggested by symptoms, or if symptoms to do not resolve with initial treatment:

- Perform herpes culture if indicated by lesions; see chapter *Herpes Simplex, Mucocutaneous*.
- Test for chlamydia and gonorrhea if indicated; see chapter *Chlamydia and Gonorrhea.*
- Perform urinalysis (with or without culture and sensitivities) if urinary symptoms are prominent.
- If an irritant or allergen is suspected, including N-9, discontinue use.
- If symptoms are related to the use of latex condoms, switch to polyurethane male or female condoms.
- For tenderness on cervical motion or other symptoms of PID, see chapter *Pelvic Inflammatory Disease*.
- Perform workup or obtain referral as needed for other abnormalities found on bimanual examination.

For information on other STIs or related conditions, see the CDC's treatment guidelines at http://www.cdc.gov/std/treatment.

Patient Education

- Patients must avoid any form of alcohol while taking metronidazole and for 24 hours after the last dose. Alcohol and metronidazole together can cause severe nausea, vomiting, and other immobilizing symptoms.
- Patients taking ritonavir may experience symptoms because of the small amount of alcohol in the capsules and should call their health care providers if nausea and vomiting occur.
- Clindamycin cream and ovules are oil based and will weaken latex condoms, diaphragms, and cervical caps. Patients should use alternative methods to prevent pregnancy and HIV transmission.
- Recurrence of BV is common. Patients should contact their health care providers and return for repeat treatment if symptoms recur.
- Instruct patients to avoid douching.
- To avoid being reinfected by *Trichomonas*, patients should bring their sex partners to the clinic for evaluation and treatment.

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Anal Dysplasia

Background

Anal cancer is a squamous cell cancer associated with human papilloma virus (HPV), the same virus that is associated with cervical cancer (see chapter *Cervical Dysplasia*). In the United States, the current incidence of anal cancer in the general population is approximately 1:100,000 per year, and rising. The incidence of anal cancer is significantly higher in HIV-infected women and men than in the general population. Rates are also higher in men who have sex with men (MSM), whether HIV infected or uninfected. Before the HIV epidemic, the anal cancer incidence in an MSM population was 35:100,000. Current rates in an HIV-infected MSM population are as high as 70-80:100,000. Thus, the incidence of anal cancer in this population is greater than the incidence of cervical cancer in women before the introduction of cervical cytology screening.

The cervical canal and anal canal share a common embryologic origin: Both have a squamocolumnar transition zone and are prone to infection with genitotropic HPV, a sexually transmitted virus. HPV infection, in combination with other cofactors, may stimulate dysplastic changes in the cervix or anus that may develop through precursor stages (squamous intraepithelial lesions [SIL]) into squamous cell cancer.

A small but growing body of literature suggests a high prevalence of anal HPV infection and dysplasia in HIV-infected individuals. Some studies have shown that, in HIV-infected individuals, anal HPV infection is present in 93% of MSM and 76% of women, and anal dysplasia (any grade) is present in 56% of MSM and 26% of women. Receptive anal intercourse (RAI) may increase the likelihood of anal HPV infection, but is not a prerequisite for anal HPV or dysplasia. In a study of HIV-positive heterosexual men with no history of RAI, anal HPV infection was found in 46% and anal dysplasia in 32%. Patients with lower CD4 cell counts appear to be at higher risk of developing anal dysplasia. It is not clear whether effective antiretroviral therapy (ART) and immune reconstitution offer protection against dysplasia.

Prevention of HPV infection is difficult. Latex or plastic barrier may be partially effective through bodily contact outside the area covered by the barriers. Vaccines against certain strains of HPV may be available soon, though their efficacy in preventing anal dysplasia (as opposed to cervical dysplasia), and their efficacy in HIV-infected individuals, is unknown.

The field of anal dysplasia and anal cancer is a relatively new area of scientific investigation, and many questions about the disorder and its medical management remain unanswered. Because of the similarities between cervical and anal dysplasia, researchers postulate that many of the paradigms of managing cervical cytologic abnormalities may be translated to the anal canal. No national or international guidelines have been developed for anal cancer screening or the management of anal dysplasia. Further, many centers lack the resources for anal dysplasia screening and treatment. In areas with adequate diagnostic and treatment resources, some specialists recommend screening all HIV-infected individuals for anal dysplasia; and if indicated, intervening to prevent the development of anal cancer. Further investigation is needed to define appropriate screening intervals, diagnostic approaches, indications for therapy, and modalities of treatment.

S: Subjective

Patients with anal dysplasia are usually asymptomatic and the condition cannot be identified without screening tests. Exophytic anal condylomata may cause itching, discomfort, or bleeding, but are usually associated with low-risk phenotypes of HPV and low-grade dysplasia. Anal cancer may cause nonspecific symptoms such as pain, bleeding, and the development of a mass lesion.

Risk factors for anal dysplasia are not well understood, but include the following:

- Receptive anal intercourse (RAI)
- HPV infection
- Genital warts (or history of genital warts)
- HIV infection
- CD4 count <200 cells/μL
- Iatrogenic immunosuppression
- High-grade cervical or vulvar dysplasia
- Cigarette smoking

O: Objective

Examine the perianal and anal region, and perform digital anorectal examination. Look for lesions, masses, condylomata, and other abnormalities. In women, also examine the vulva, vagina, and cervix. Simple anoscopic examination with the naked-eye may not reveal any abnormality because dysplastic tissue tends to be flat and difficult to differentiate from normal anal tissue; application of 3% acetic acid is required (see below).

A: Assessment

HIV-infected individuals with anal dysplasia have an increased risk of progression to anal cancer. If the history or physical examination reveals abnormalities suggestive of anal dysplasia or anal cancer, an appropriate evaluation should be undertaken. Because most patients with anal dysplasia have no symptoms, anal cancer screening should be considered if follow-up evaluation of abnormal cytologic results is available.

P: Plan

Screening

No national or international guidelines for anal cytology screening in people with HIV infection. However, some experts recommend annual or biannual screening regardless of sex or sexual practices. Anal cytologic screening is performed using Papanicolaou (Pap) smears (for technique, see the study by Berry and Palefsky referenced below). Papanicolaou smear testing is sensitive for the detection of dysplastic anal cells, but does not reliably distinguish the grade of abnormality. Like cervical cytology, anal cytology is graded using the Bethesda 2001 system, which categorizes disease in increasing order of severity as follows:

- Negative for intraepithelial lesion or malignancy
- Atypical squamous cells of undetermined significance (ASCUS)
- Atypical squamous cells suggestive of high-grade (ASC-H)
- Low-grade squamous intraepithelial lesion (LSIL)
- High-grade squamous intraepithelial lesion (HSIL)
- Squamous cell carcinoma (SCC)

All individuals with abnormal anal cytology should be referred for high-resolution anoscopy (HRA) and biopsy to grade the lesion. If available, refer to an anal dysplasia specialty center.

Evaluation of Cytologic Abnormalities

HRA of the anal canal should be performed using a colposcope for magnification (x16) and the application of 3% acetic acid with or without Lugol's Iodine solution to aid in visualization of dysplastic lesions. Abnormal areas should be biopsied. Anoscopic features of high-grade disease are similar to those seen in the cervix; these include coarse punctation, mosaicism, and the presence of ring glands.

Treatment

The goal of treatment is to prevent progression to anal cancer. Treatment of high-grade anal dysplasia to prevent anal cancer is biologically plausible, following the model of cervical dysplasia treatment. However, the indications for treatment for anal dysplasia, the efficacy of treatment, and the optimal treatments have not been defined clearly.

The focus of treatment is high-grade, premalignant dysplasia. For patients with HSIL, refer to an anal dysplasia specialty clinic, if possible. If treatment is not available, or is not pursued, patients diagnosed with high-grade anal disease should be informed about the initial symptoms of anal cancer and asked to follow up promptly should these symptoms develop.

The optimal treatment for high-grade dysplasia is not known. Specific treatment may vary depending on the size, location, and extent of the lesions and the available treatment modalities. In some cases, treatment of small intra-anal lesions with 80% trichloroacetic acid or liquid nitrogen has been successful. More promising, infrared coagulation has shown 70% efficacy at 3 months in clinical cohorts. This office procedure involves identifying the lesion by HRA and applying an infrared energy source to destroy the lesion.

For perianal lesions, topical therapy with podophyllotoxin or imiquimod may be considered. For large or extensive lesions, surgical treatments such as cold-scalpel excision and electrofulguration are typically required. Unfortunately, postoperative pain and other complications may occur, and recurrence of dysplastic lesions is common. Low-grade dysplasia is not considered premalignant, but frequently progresses to high-grade dysplasia. Some specialists do not treat LSIL but monitor regularly instead with HRA, whereas others choose to treat LSIL to prevent progression.

Patient Education

- Women and men with HIV infection have an increased risk of developing anal dysplasia and cancer. MSM are at higher risk than other men of developing anal dysplasia.
- Emphasize the importance of keeping follow-up appointments to allow early detection of precancerous lesions and appropriate monitoring and treatment of abnormalities.
- Patients who have anal dysplasia should be informed about anal cancer symptoms, such as new-onset anal pain, bleeding, or the development of a mass. Patients should call their health care providers if these symptoms develop.

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Candidiasis, Oral and Esophageal

Background

Oropharyngeal candidiasis ("thrush"), a fungal disease of the oral mucosa and tongue, is the most common intraoral lesion in persons infected with HIV. In the absence of other known causes of immunosuppression, oral thrush in an adult is highly suggestive of HIV infection. Three clinical presentations of thrush are common in people with HIV: pseudomembranous, erythematous, and angular cheilitis. Thrush usually occurs with CD4 counts of <300 cell/μL and is not an AIDS-defining illness.

Candida may also infect the esophagus in the form of esophageal candidiasis which causes dysphagia (difficulty with swallowing) or odynophagia (pain with swallowing). Esophageal candidiasis is an AIDS-defining condition, generally occurs in individuals with CD4 counts of <100 cell/μL. It is the most common cause of esophageal infection in persons with AIDS.

Oropharyngeal and esophageal candidiasis are most commonly caused by *C albicans*, although occasionally non-albicans species cause disease and may be resistant to first-line therapies.

S: Subjective

Oropharyngeal Candidiasis

The patient may complain of white patches on the tongue and oral mucosa, smooth red areas on the dorsal tongue, burning or painful areas in the mouth, a bad or unusual taste, sensitivity to spicy foods, or decreased appetite.

Esophageal Candidiasis

The patient complains of difficulty or pain with swallowing, or the sensation that food is "sticking" in the retrosternal chest. Weight loss is common, and nausea and vomiting may occur. Fever is not common with candidal esophagitis and suggests another cause.

O: Objective

Patients presenting with oral candidiasis may be totally asymptomatic, so it is important to inspect the oral cavity thoroughly. Lesions can occur anywhere on the hard and soft palates, under the tongue, on the buccal mucosa or gums, or in the posterior pharynx.

Pseudomembranous oral candidiasis appears as creamy white, curdlike plaques on the buccal mucosa, tongue, and other mucosal surfaces. Typically, the plaques can be wiped away, leaving a red or bleeding underlying surface. Lesions may be as small as 1-2 mm, or may form extensive plaques that cover the entire hard palate.

Erythematous oral candidiasis presents as 1 or more flat, red, subtle lesions on the dorsal surface of the tongue or the hard or soft palate. The dorsum of the tongue may show loss of filiform papillae.

Angular cheilitis causes fissuring and redness at 1 or both corners of the mouth and may appear alone or in conjunction with another form of oral *Candida* infection.

Patients with esophageal candidiasis usually have oral thrush and often have weight loss.

A: Assessment

A partial differential diagnosis for the 2 conditions is as follows:

Oropharyngeal Candidiasis

- Oral hairy leukoplakia
- Burn
- Bacterial gingivitis
- Periodontitis

Esophageal Candidiasis

- Cytomegalovirus (CMV)
- Herpes simplex virus (HSV)
- Aphthous ulceration

P: Plan

Diagnostic Evaluation

Oropharyngeal candidiasis

Clinical examination alone usually is diagnostic. If the diagnosis is unclear, organisms may be detected on smear or culture if necessary.

- Potassium hydroxide (KOH) preparation of a smear collected by gentle scraping of the affected area with a wooden tongue depressor. Visible hyphae or blastospheres on KOH mount indicate *Candida* infection.
- Culture is diagnostic and may detect non-*albicans* species in cases resistant to first-line therapies. Sensitivities may also be needed in such cases to diagnose azole-resistant infections.

Esophageal candidiasis

A presumptive diagnosis can usually be made with a recent onset of dysphagia, especially in the presence of thrush, and empiric antifungal therapy may be started. If the patient fails to improve clinically after 3-7 days of therapy, endoscopy should be performed for a definitive diagnosis.

Treatment

Treatment of oropharyngeal candidiasis

- Oral therapy is convenient and very effective as first-line treatment. Note that azole antifungal drugs are not recommended for use during pregnancy.
  - Fluconazole 100 mg once daily for 7-14 days
- Alternative topical therapy is less expensive, safe for use during pregnancy, and effective for mild to moderate disease. Such therapies include:
  - Clotrimazole troches dissolved in the mouth 5 times per day for 2 weeks
  - Nystatin oral suspension 5 mL "swish and swallow" 4 times daily for 2 weeks
- Other alternatives include the following:
  - Itraconazole oral solution 200 mg once daily for 7-14 days
  - Itraconazole capsules and ketoconazole 200 mg once daily for 7-14 days (less effective)

    These agents present a greater risk of drug interactions and hepatotoxicity than do fluconazole or topical treatments.

Treatment of esophageal candidiasis

- Fluconazole 200 mg as an initial dose, then 100 mg by mouth once daily for 14 days. Intravenous therapy can be given if the patient is unable to swallow pills.
- Itraconazole oral suspension 200 mg once daily for 14 days
- Alternative (less effective) treatments include itraconazole capsules 200 mg once daily or ketoconazole 200 mg once daily for 14 days

Treatment of refractory candidiasis

Oral or esophageal candidiasis that does not improve after at least 7-14 days of azole antifungal therapy can be considered refractory to treatment. The primary risk factors for development of refractory candidiasis are CD4 counts <50 cell/μL and prolonged, chronic antifungal therapy (especially with azoles). In such cases, it is important to confirm the diagnosis of candidiasis. As noted previously, other infections such as HSV, CMV, and aphthous ulcerations can cause similar symptoms. Once refractory candidiasis is confirmed, several treatment options are available, including the following:

- Patients with candidiasis refractory to low-dose fluconazole (100-200 mg once daily) may respond to higher dosages (400-800 mg once daily)
- Itraconazole oral suspension 200 mg once daily
- Voriconazole 200 mg intravenously or by mouth twice daily. (Voriconazole therapy is contraindicated for patients taking protease inhibitors because of significant drug interactions.)
- Amphotericin B 100 mg/mL oral suspension, 1 mL 4 times daily
- Amphotericin B 0.5 mg/kg/d intravenously, or amphotericin liposomal complex 3-5 mg/kg/d intravenously
- Caspofungin 50 mg intravenously once daily

The choice of treatment depends upon the patient's preferences and tolerance, convenience, availability of medications, and the provider's experience. Consult with an HIV or infectious disease expert for advice about treatment regimens.

Maintenance therapy

Use caution when considering chronic maintenance therapy, because it has been associated with refractory and azole-resistant candidiasis, as noted above. Fluconazole 100-200 mg daily or weekly, or itraconazole solution, can be effective for patients who have had multiple recurrences of oral or esophageal disease (azole sensitive). Patients who achieve immunologic and virologic responses to antiretroviral therapy may be able to discontinue maintenance therapy.

Patient Education

- Patients should maintain good oral hygiene by brushing teeth after each meal.
- A soft toothbrush should be used to avoid mouth trauma.
- Advise patients to rinse the mouth of all food before using lozenges or liquid medications.
- Tell patients to avoid foods or liquids that are very hot in temperature or very spicy.
- Patients who have candidiasis under a denture or partial denture should remove the prosthesis before using topical agents such as clotrimazole or nystatin. At bedtime, the prosthesis should be placed in a chlorhexidine solution until reinsertion it into the mouth.
- Pregnant women or women who may become pregnant should avoid azole drugs (eg, fluconazole, itraconazole, voriconazole) during pregnancy because they can cause skeletal and craniofacial abnormalities in infants.

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Candidiasis, Vulvovaginal

Background

Vulvovaginal candidiasis is a yeast infection caused by several types of *Candida*, typically *Candida albicans*. This disease is common in all women, but may occur more frequently and more severely in immunocompromised women.

Although refractory vaginal *Candida* infections by themselves should not be considered indicators of HIV infection, they may be the first clinical manifestation of HIV infection, and can occur early in the course of disease (at CD4 counts >500 cells/μL). The frequency of vaginal candidiasis tends to increase as CD4 counts decrease; this may, however, be due in part to increased antibiotic use among women with advanced HIV infection.

Risk factors for candidiasis include diabetes mellitus and the use of oral contraceptives, corticosteroids, or antibiotics.

S: Subjective

The patient may complain of itching, burning, or swelling of the labia and vulva; a thick white or yellowish vaginal discharge; painful intercourse; and pain and burning on urination.

The most important elements in the history include:

- Type and duration of symptoms
- Previous vaginal yeast infection
- Oral contraceptive use
- Recent or ongoing broad-spectrum antibiotic therapy
- Recent corticosteroid therapy
- Sexual exposures (to evaluate for sexually transmitted infections)
- Diabetes history
- Cushing syndrome
- Obesity
- Hypothyroidism
- Pregnancy
- Use of douches, vaginal deodorants, or bath additives

O: Objective

A focused physical examination of the external genitalia may reveal inflammation of the vulva with evidence of discharge on the labial folds and vaginal opening. Speculum examination usually reveals a thick, white discharge with plaques adhering to the vaginal walls and cervix. Bimanual examination should not elicit pain or tenderness and otherwise should be normal.

A: Assessment

Rule out other causes of vaginal discharge and pruritus:

- Bacterial vaginosis
- Atrophic vaginitis
- Pediculosis
- Chemical or mechanical causes
- Trichomoniasis
- Gonorrhea, chlamydia, and other sexually transmitted infections
- Scabies
- Pediculosis

P: Plan

Diagnostic Evaluation

A presumptive diagnosis is made on the basis of the clinical presentation and potassium hydroxide (KOH) preparation:

- Perform microscopic examination of a KOH preparation of vaginal secretions. This exam usually reveals pseudohyphae and *Candida* spores (presumptive diagnosis).
- Definitive diagnosis is rarely needed, but may be made by a culture of vaginal secretions.
- In the presence of urinary tract symptoms (beyond external vulvar burning), perform urinalysis, culture, or both on a clean-catch urine specimen.
- Consider testing for gonorrhea and chlamydia in patients with a history of possible sexual exposure.

Treatment

Uncomplicated infections

Topical medications

- Prescribe topical vaginal antifungal agents in the form of cream or suppositories: miconazole (Monistat), clotrimazole (Gyne-Lotrimin), terconazole (Terazol). Treat for 3-7 days and offer refills depending on the time to the next scheduled clinic visit. The creams may also be used on the vulva for pruritus.
- Nystatin vaginal pastilles 100,000 units; insert 1 daily for 14 days

Note that the mineral-oil base in topical vaginal antifungal preparations may erode the latex in condoms, diaphragms, and dental dams. Advise the patient to use alternative methods to prevent HIV transmission or conception, or to discontinue intercourse while using these medications. Nonlatex condoms (plastic and polyethylene only) or "female" condoms (polyurethane) can be used.

Oral medications

- Fluconazole 150 mg orally, 1 dose (see "Treatment notes" below)
- Itraconazole 200 mg orally twice daily for 1 day, or 200 mg orally once daily for 3 days (see "Treatment notes" below)

Complicated infections

Severe or recurrent candidiasis

Severe or recurrent candidiasis is defined as 4 or more episodes within 1 year. Consider the following treatments:

- Topical therapy as above, for 7-14 days
- Fluconazole 150 mg orally in a single dose; repeat in 72 hours (see "Treatment notes" below)

For severe cases that recur repeatedly, secondary prophylaxis can be considered, eg, clotrimazole vaginal suppository (500 mg once weekly) or fluconazole.

Non-*albicans* candidiasis

- Non-fluconazole azole for 10-14 days (see "Treatment notes" below)
- Boric acid 600 mg intravaginal gelatin capsules once daily for 2 weeks for refractory cases
- Consult with a specialist

Treatment notes

- Systemic azole drugs are not recommended during pregnancy, and women taking azoles should use effective contraception. Topical azoles are recommended or the treatment of pregnant women..
- Itraconazole interacts with some antiretroviral medications; check for adverse drug interactions before prescribing. Itraconazole should not be used by pregnant women or women considering pregnancy.
- Resistance to azole medications may develop, especially with prolonged use of oral agents.
- Avoid ketoconazole: Case reports have associated ketoconazole with a risk of fulminant hepatitis (1 in 12,000 courses of treatment with oral ketoconazole). Experts agree that the risks may outweigh the benefits in women with vulvovaginal candidiasis. Ketoconazole also interacts with many other drugs, including some antiretroviral drugs.

Patient Education

- Advise women to wash external genitals daily with a fresh washcloth or water-soaked cotton balls and to wipe the vulva and perirectal area from front to back after toileting. Women should not use baby wipes on inflamed vulval tissue because they may increase irritation.
- Women should avoid the use of perfumed soaps, bubble baths, feminine hygiene or vaginal deodorant products, and bath powders.
- Advise women not to douche.
- Women should wear cotton underwear and avoid tight, constrictive clothing, particularly pantyhose.
- If women are prescribed medication for vaginal candidiasis, they should take the medication exactly as prescribed and finish the medicine even during a menstrual period.
- Women who continue to have symptoms, can purchase Monistat or Gyne-Lotrimin medication over the counter. Advise patients to start using these as soon as symptoms come back, and to call the clinic if symptoms get worse on these medicines.
- Women taking fluconazole or ketoconazole must avoid pregnancy. Some birth defects have been reported.
- The mineral-oil base in topical vaginal antifungal preparations may erode the latex in condoms, diaphragms, and dental dams. Advise patients to use alternative methods to prevent HIV transmission or conception or to discontinue intercourse while using these medications. Nonlatex condoms (plastic and polyethylene only) or "female" condoms (polyurethane) can be used.
- Sex toys, douche nozzles, diaphragms, cervical caps and other items, can reinfect patients if not properly cleaned and thoroughly dried after use.
- Some studies have suggested that eating yogurt with live cultures (check labels) can reduce the occurrence of vaginal yeast infections.

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Cervical Dysplasia

Background

Cervical dysplasia and cancer are associated with human papilloma virus (HPV), a sexually transmitted virus. Carcinogenic strains of HPV may, in conjunction with other factors, cause dysplasia and cancer not only of the cervix, but also of the vulva, vagina, and anus. HIV-infected women have a higher prevalence of HPV infection than HIV-uninfected women, and are 5 times more likely to develop cervical dysplasia, or squamous intraepithelial lesion (SIL), precursors to cervical cancer. They may also have a higher risk of invasive cervical cancer and tend to have more aggressive forms of cervical cancer. Invasive cervical cancer is an AIDS-defining illness.

The risk of high-grade cervical lesions appears to be higher in women with advanced immunodeficiency than in women with preserved CD4 cell counts. Other risk factors for dysplasia and cervical cancer include African American ethnicity, a history of smoking, younger age at onset of sexual intercourse, and multiple sexual partners. Effective antiretroviral therapy (ART) with immune reconstitution has not been shown to prevent the progression of dysplasia.

Screening for cervical dysplasia and appropriate intervention in women with high-grade dysplasia are effective in preventing cervical cancer. Frequent monitoring and careful follow-up in women with low-grade lesions are essential for preventing progression to invasive disease. Papanicolaou testing should be performed routinely on all HIV-infected women, with testing initiated at diagnosis, repeated 6 months after the first test, then performed annually thereafter if the results are normal. (See chapter *Initial and Interim Laboratory and Other Tests*.) Because the risk of anal dysplasia is also increased in HIV-infected women, many experts recommend concurrent screening for anal dysplasia. For further information, see chapter *Anal Dysplasia.*

Prevention of HPV infection is difficult. Latex or plastic barriers may be partially effective, although infection may occur through bodily contact outside the area covered by the barriers. A vaccine against certain strains of HPV has been approved by the U.S. Food and Drug Administration and others are expected to follow, although their efficacy in HIV-infected women and men is not yet known.

S: Subjective

Patients with cervical dysplasia or early cervical cancer are usually asymptomatic and disease will not be diagnosed unless screening is performed. Genital condylomata (warts) indicate infection with HPV and are typically associated with low-risk types of HPV; however, women with genital warts may have concurrent dysplasia. The classic symptom of early invasive cervical neoplasia is intermittent, painless bleeding between menstrual periods, which may present initially as postcoital spotting. Late symptoms of invasive cervical carcinoma include flank and leg pain, dysuria, hematuria, rectal bleeding, and obstipation.

Ask all female patients about risk factors for, and previous history of, cervical dysplasia and cancer, including the following:

- Genital warts; previous or current HPV infection
- Previous abnormal cervical Papanicolaou smear
- Previous abnormal anal Papanicolaou smear
- Previous cervical cancer; when and how treated
- Sexual activity before age 20
- History of multiple sexual partners
- Cigarette smoking
- CD4 count <200 cells/μL
- Pregnancy
- Oral contraceptive use

O: Objective

Perform a focused examination of the abdomen and pelvis. Examine the external genital and perianal region. Perform speculum and bimanual examinations to evaluate the vagina and cervix. Look for lesions, masses, warts, and cervical inflammation or discharge, as well as exophytic or ulcerative cervical lesions with or without bleeding. Note that simple visual examination may not reveal abnormalities.

A: Assessment

HIV-infected women have an increased risk of cervical dysplasia with progression to cervical cancer. If abnormalities of cervical disease are suspected, an appropriate evaluation should be performed. Because most women with cervical dysplasia have no symptoms, routine screening should be performed in all women.

P: Plan

Screening

Perform screening Papanicolaou smear on all HIV-infected women. The initial smear should be taken at the time of HIV diagnosis, a second should be taken 6 months later, and the procedure should be repeated annually thereafter if all tests are normal. If a smear is abnormal, see below. Also consider screening for anal dysplasia, with an anal Papanicolaou smear (see chapter *Anal Dysplasia*).

Cervical (and anal) cytology is graded using the Bethesda 2001 system (see "References" below), which categorizes disease in increasing order of severity as follows:

- Negative for intraepithelial lesion or malignancy
- Atypical squamous cells of undetermined significance (ASCUS)
- Atypical squamous cells—cannot exclude HSIL (ASC-H)
- Low-grade squamous intraepithelial lesion (LSIL)
- High-grade squamous intraepithelial lesion (HSIL)
- Squamous cell carcinoma (SCC)

Other abnormalities may be noted, including:

- Atypical glandular cells of undetermined significance (AGUS)
- Infectious organisms such as *Trichomonas*

Evaluation of Cytologic Abnormalities

Atypical squamous cells of undetermined significance

If ASCUS is present without inflammation or suspected neoplastic process, several options for management exist. Most experts recommend referral for colposcopy and directed biopsy, regardless of the woman's degree of immunodeficiency. Patients who are considered reliable for follow-up may be monitored closely with repeat Papanicolaou smears every 4-6 months for 2 years until 3 consecutive tests have been negative. If a follow-up smear shows ASCUS (or higher-grade abnormalities), colposcopy with directed biopsy should be done. If the biopsy result is normal, the patient should be monitored as usual with Papanicolaou tests at 6 and 12 months. Another approach, available in some clinic settings, is to perform HPV DNA testing on a cervical sample; if HPV DNA testing shows an oncogenic HPV type, colposcopic examination should be performed.

Atypical squamous cells—cannot exclude HSIL

Women with abnormalities suggestive of high-grade dysplasia should be referred for colposcopy. HPV DNA testing can be considered to detect oncogenic HPV types.

Low-grade squamous intraepithelial lesion

Women with LSIL should be referred for colposcopy and directed biopsy.

High-grade squamous intraepithelial lesion or squamous cell carcinoma

Women with HSIL should undergo colposcopy with endocervical assessment and directed biopsy as soon as possible. Refer to an oncology specialist for treatment.

Atypical glandular cells of undetermined significance

Because of the high rate of significant lesions in patients with AGUS, colposcopy or endocervical curettage is recommended. Refer to an appropriate specialist for evaluation.

Treatment

The optimal management of precancerous cervical lesions has not been identified clearly for all classes of SIL. Consult with an HIV-experienced gynecologist, oncologist, or other dysplasia specialist.

Patient Education

- Patients who smoke should be advised to quit. Cigarette smoking appears to heighten the risk of cervical cancer, and makes HPV more difficult to treat. Discuss options for smoking cessation, and refer patients to the American Lung Association if programs are available in your area.
- Recommend the use of latex or polyurethane male or female condoms for vaginal or anal intercourse and plastic or latex barriers for oral sex to reduce the risk of transmitting HPV (the usual cause of cervical cancer) to partners. Barriers will also reduce the risk of exposure to other sexually transmitted pathogens.
- Emphasize the importance of keeping follow-up appointments for Papanicolaou smear or colposcopy to allow early detection of precancerous lesions and appropriate monitoring of abnormalities.
- For women with dysplasia who require treatment, emphasize that early treatment is essential to manage the disease and prevent the development of cancer. Advise patients to keep all medical appointments.

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Cryptococcal Disease

Background

Cryptococcosis is a systemic or central nervous system (CNS) fungal infection caused by the yeast *Cryptococcus neoformans.* The organism is ubiquitous, but is particularly plentiful in soils enriched with bird droppings. It may also be present in fruit skins or juices, as well as in unpasteurized milk. In immunocompetent patients, cryptococcal infection is usually asymptomatic, self-limited, and confined to the lungs. In persons with advanced HIV infection (eg, those with CD4 counts <100 cells/μL), *Cryptococcus* may cause life-threatening illness, either from a new exposure or through reactivation of a previously acquired latent infection.

In HIV-infected patients, *Cryptococcus* can infect almost all organs in the body, but most commonly causes meningitis or meningoencephalitis. Disseminated disease, pneumonia, and skin lesions may also be seen.

S: Subjective

Symptoms depend upon the locus of infection. In the case of meningitis, the patient typically complains of the subacute onset of fever, headaches, and malaise, which worsen over several weeks. These symptoms may be accompanied by nausea with or without vomiting. Meningeal signs, nuchal rigidity, and photophobia occur in only about 25% of cases. Cryptococcal meningitis may also cause confusion, personality or behavior changes, blindness, deafness, and, if left untreated, coma and death. If the disease involves the lungs, patients may complain of cough or shortness of breath, pleuritic chest pain, and fever. Skin lesions may also be present.

O: Objective

Perform a thorough physical examination with particular attention to the following:

- Vital signs, hydration status
- Funduscopic examination
- Neck (for nuchal rigidity, which is uncommon)
- Lungs, especially if respiratory symptoms are present
- Neurologic examination, including evaluation of cranial nerves, visual acuity, and mental status
- Skin

Cryptococcal meningitis

Physical examination may reveal papilledema with loss of visual acuity and cranial nerve deficits (particularly in cranial nerves III and VI).

Cryptococcal pulmonary disease

Examination may reveal tachypnea or fine rales.

Cutaneous infection

Skin lesions are variable and may appear as papules, nodules, or ulcers; they often resemble molluscum lesions.

A: Assessment

The differential diagnosis for serum cryptococcal meningitis or meningoencephalitis is broad and includes other infectious causes of meningitis (fungal, mycobacterial, bacterial, viral), syphilis, lymphoma, mass lesions, intoxication, HIV encephalopathy, and trauma. (See chapter *Neurologic Symptoms.*)

The differential diagnosis for cryptococcal pneumonia is broad and includes other infectious causes of pneumonia (fungal, mycobacterial, bacterial, viral), malignancy, and congestive heart failure. (See chapter *Pulmonary Symptoms.*)

P: Plan

Diagnostic Evaluation

The workup should include serum cryptococcal antigen (CrAg), which usually is very sensitive, and blood cultures, including acid-fast bacilli (AFB) and fungal cultures. Patients with symptoms of disseminated or pulmonary infection should be evaluated by chest x-ray (which may show diffuse or focal infiltrates, sometimes appearing as nodular or miliary; intrathoracic adenopathy; or pleural effusions), sputum culture (including fungal and AFB culture), and AFB stain. Bronchoscopy and bronchoalveolar lavage may be necessary for diagnosis. For cutaneous lesions, consider biopsy and histopathologic evaluation or culture. As part of the general fever workup, urinalysis and urine cultures should be checked.

Patients with a positive serum CrAg, another positive test for *Cryptococcus*, or signs or symptoms of meningitis should undergo analysis of the cerebrospinal fluid (CSF). If neurologic symptoms or signs are present, obtain a computed tomography (CT) scan of the brain before performing a lumbar puncture (LP) to rule out a mass lesion or increased intracranial pressure (ICP), which could cause herniation upon LP. Always measure the CSF opening pressure; a high ICP contributes to morbidity and mortality and determines the need for serial LPs to manage the increased ICP. Send the CSF for the following:

- CrAg (usually positive at high titer in meningitis)
- Fungal culture
- India ink stain (lower sensitivity than CrAg)
- Cell counts
- Glucose
- Protein

For exclusion of other etiologies, check CSF with the Venereal Disease Research Laboratory (VDRL) test, bacterial culture, AFB culture or polymerase chain reaction (PCR), if tuberculosis is suspected, and other tests as indicated by the patient's symptoms and exposures.

Treatment

Cryptococcal meningitis

Acute treatment of cryptococcal meningitis consists of 2 phases: induction and consolidation. Acute treatment is followed by chronic maintenance (suppressive) therapy.

Induction

Patients with cryptococcal meningitis should be hospitalized to start 2 weeks of induction therapy with amphotericin B (0.7 mg/kg/day) given intravenously plus flucytosine (25 mg/kg) given orally every 6 hours.

Amphotericin B causes many adverse effects, including fever, rigors, hypotension, nausea, nephrotoxicity and electrolyte disturbances, anemia, and leukopenia. The patient's hemoglobin, white blood cell (WBC) count, platelets, electrolytes, magnesium, and creatinine must be monitored closely during treatment. Note that liposomal forms of amphotericin (AmBisome and Abelcet) cause fewer adverse effects and appear to be effective. These liposomal forms should be considered for patients who have difficulty tolerating the standard amphotericin B. Because amphotericin B is highly irritating to the veins, it should be given through a central line. High levels of flucytosine are associated with bone marrow toxicity, and levels should be monitored (target peak 70-80 mg/L; trough 30-40 mg/L). Note that the dosage of flucytosine must be adjusted for patients with renal insufficiency.

If amphotericin is not available, is contraindicated, or is not tolerated by the patient, alternative induction therapies may be considered. The primary alternative to amphotericin-based therapy is fluconazole (400-800 mg orally per day), with or without flucytosine. Of the newer antifungal agents, echinocandins have little activity against *Cryptococcus*. Voriconazole has good in vitro activity, but few clinical data are available and none suggest superiority over fluconazole. The efficacy of alternative regimens is not well defined.

Consolidation

After clinical improvement with 2 weeks of induction therapy (possibly sooner for patients with substantial improvement), the treatment can be switched to oral fluconazole (400 mg once daily to complete 8 weeks of acute treatment). Itraconazole (200 mg orally twice daily) sometimes is used as an alternative for patients who cannot take fluconazole. It should be noted that itraconazole is less effective than fluconazole and has significant drug interactions with commonly used medications.

Maintenance

After completing acute treatment, the patient should receive chronic maintenance therapy with fluconazole (200 mg orally once daily) to prevent recurrence of cryptococcosis. An alternative treatment is itraconazole (200 mg orally once or twice daily)—with the caution as indicated above.

Maintenance therapy should be continued for life, unless the patient has sustained CD4 cell recovery in response to effective antiretroviral therapy (ART) (CD4 count >100-200 cells/μL for at least 6 months during ART). Maintenance therapy should be restarted if the CD4 count declines to <100-200 cells/μL.

Management of elevated ICP

Elevated ICP significantly increases the morbidity and mortality of cryptococcal meningitis and should be treated by the removal of CSF. The CSF opening pressure should be checked on the initial LP. If the initial opening pressure is >250 mm H_2O, remove

up to 30 mL of CSF to lower the ICP by 50%, if possible. LP and CSF removal should be repeated daily as needed for ICP reduction. Ventriculostomy or a ventriculoperitoneal shunt may be needed if the initial opening pressure is >400 mm H2O, or in refractory cases. There is no role for acetazolamide, mannitol, or steroids in the treatment of elevated ICP.

A repeat LP is not required for patients who did not have elevated ICP at baseline and are responding to treatment. If new symptoms develop, a repeat LP is indicated. Serum CrAg titers are not useful in monitoring response to treatment.

Cryptococcal pulmonary disease, with negative CSF CrAg and cultures

Treat with fluconazole (200-400 mg orally) if symptoms are mild or moderate. Otherwise, consider amphotericin induction, as above. Monitor fungal blood cultures and CrAg to verify the effectiveness of therapy. Itraconazole may be used as an alternative (200 mg orally twice daily capsules; 100-200 mg once daily for oral suspension). Therapy should be continued for life, unless the patient has sustained CD4 cell recovery in response to effective ART (CD4 count >100-200 cells/μL for at least 6 months during ART). Therapy should be restarted if the CD4 count declines to <100-200 cells/μL.

Cutaneous infection, with negative CSF CrAg and cultures

Treat with fluconazole 400 mg once daily for 6-10 weeks, then continue with 200 mg once daily for chronic maintenance therapy, as discussed above.

Other treatment notes

- ART: Immune reconstitution through ART is effective for preventing recurrence of cryptococcal infections. However, initiating ART within the first 1-2 months of cryptococcal infection may result in worsening or recurrence of symptoms because of immune reconstitution syndrome. Some experts recommend treating cryptococcosis with effective antifungal therapy for 1-2 months before starting ART. (See chapter *Immune Reconstitution Syndrome.*)
- Pregnancy: Fluconazole and other azole drugs are not recommended during pregnancy, especially in the first trimester. During the first trimester, pregnant women should be treated with amphotericin for both induction and consolidation therapy. Flucytosine is teratogenic at high doses in rats and should be used during pregnancy only if the benefits clearly outweigh the risks.
- Preventive therapy: Studies have suggested that routine primary prophylaxis for cryptococcal disease in patients with CD4 counts of <100 cells/μL is effective at preventing cryptococcal infection but is not cost efficient. Therefore, it is not routinely recommended. Trials of fluconazole prophylaxis in Asia and Africa are under way, but preservation of immune responses by the use of effective ART, when available, is the best form of prevention.

Patient Education

- Cryptococcosis is not curable in persons with low CD4 cell counts and may require lifelong treatment. Patients should be instructed to take their treatment without interruptions.
- Even with therapy, disease may recur. Patients should report fevers or recurrence of other symptoms immediately.
- Patients should avoid pregnancy while taking any oral antifungal drug. Fetal craniofacial and skeletal abnormalities have been reported.

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Cryptosporidiosis

Background

Cryptosporidiosis is caused by a species of protozoan parasite that typically infects the mucosa of the small intestine, causing watery diarrhea. Diarrhea may be accompanied by nausea, vomiting, abdominal cramping, and occasionally fever. The infection is spread by the fecal-oral route, usually via contaminated water, and is highly contagious. The course of infection depends on the immune status of the host. In immunocompetent individuals, cryptosporidiosis is usually self-limited and can cause a mild diarrheal illness. However, in HIV-infected patients with advanced immunosuppression, cryptosporidiosis can cause severe chronic diarrhea, electrolyte disturbances, malabsorption, and profound weight loss. It can also cause cholangitis and pancreatitis, through infection of the biliary tract and pancreatic duct. Those at greatest risk for cryptosporidiosis are patients with CD4 counts of <100 cells/μL.

S: Subjective

The patient may complain of some or all of the following: watery diarrhea (can be profuse), abdominal pain or cramping, flatulence, nausea, vomiting, anorexia, fever, and weight loss.

The history should include questions about the presence and characteristics of the symptoms listed above, as well as the following:

- Stool frequency (typically 6-26 bowel movements daily)
- Stool volume (mean 3.6 L, and up to 10 L/d in some patients with AIDS)
- Duration of symptoms (subacute or acute onset)
- Associated symptoms
- Exposures: recent travel to areas with unsafe water supply; ingestion of possibly contaminated water while swimming, boating, or camping; oral-anal contact
- Recent CD4 cell count (highest risk is in patients with CD4 count <100 cells/μL)

O: Objective

Perform a thorough physical examination with particular attention to the following:

- Vital signs
- Hydration status (eg, orthostatic vital signs, mucous membrane moistness, skin turgor)
- Weight (compare with previous values; document weight loss)
- Signs of malnourishment (eg, cachexia, wasting, thinning hair, pallor)
- Abdominal examination for bowel sounds (usually hyperactive), tenderness (can be diffuse), rebound
- Recent CD4 count (likely to be <150 cells/μL and can be significantly lower)

A: Assessment

In HIV-infected patients with advanced immunosuppression, the differential diagnosis includes other infectious causes of subacute or chronic diarrhea or cholangitis, such as *microsporidia, Isospora, Giardia, cytomegalovirus* (CMV), and *Mycobacterium avium* complex (MAC), as well as lymphoma.

P: Plan

Diagnostic Evaluation

- Test the stool for ova and parasites, including *Cryptosporidium*.
  - Be sure to ask that the laboratory look for *Cryptosporidium*; certain laboratories do not look for these parasites unless requested. For profuse diarrhea, a single sample is usually adequate for diagnosis; repeat sampling can be useful if the first round of test results is negative.
  - Test for fecal leukocytes. This is usually negative in cryptosporidiosis; if positive, consider the possibility of a second enteric infection, especially if the CD4 count is low.
- If the stool is negative for ova and parasites after 3 tests, consider a referral for biopsy of the gastrointestinal mucosa or flexible sigmoidoscopy.

- If cholangitis is suspected, consider abdominal ultrasound to detect biliary ductal dilatation, and endoscopic retrograde cholangiopancreatography (ERCP).
- Check electrolytes; conduct liver function studies including alkaline phosphatase and bilirubin.
- If fever is present, obtain blood cultures.
- Conduct other diagnostic testing as indicated by the history and physical examination (eg, evaluation for CMV, MAC, and other infectious causes of diarrhea or cholangitis) (see chapter *Diarrhea*).

Treatment

- Provide supportive care and symptomatic relief (this may require hospitalization in cases of severe dehydration), including the following:
  - Aggressive fluid and electrolyte replacement as needed
  - Oral rehydration (solutions containing glucose, sodium bicarbonate, potassium, magnesium, and phosphorus); in severe cases, intravenous hydration may be required
  - Antidiarrheal agents: atropine/diphenoxylate (Lomotil), loperamide (Imodium), tincture of opium (Paregoric)
  - Antispasmodics
  - Antiemetics
  - Topical treatment for the anorectal area, as needed (Tucks pads, sitz baths)
- No antiparasitic therapy has been proven to cure or prevent cryptosporidiosis. Most patients experience symptom improvement or resolution with immune reconstitution achieved by effective antiretroviral therapy (ART), especially if the CD4 count increases to >100 cells/μL. All patients with cryptosporidiosis should be treated with ART, unless it is contraindicated, as early in the course of cryptosporidiosis therapy as possible (see chapter *Antiretroviral Therapy*).
- Antiparasitic agents have not been proven effective, but are sometimes used. These include:
  - Paromomycin (Humatin), which may result in initial response, although its efficacy remains unclear. The usual adult dosage is 500 mg orally 4 times daily or 1,000 mg twice daily, with meals.
  - Paromomycin in combination with azithromycin. One study found substantial short-term benefit from this combination, although cure rates were low.
  - Nitazoxanide (Cryptaz), 500 mg orally twice daily. This agent is approved for use in children with diarrhea caused by *C parvum*. Its usefulness in adults and those with immunodeficiency has not been demonstrated consistently.
- For patients with weight loss, nutritional supplementation is usually an important aspect of treatment. In some cases, partial or total parenteral nutrition may be necessary while patients are awaiting clinical improvement in response to ART or other therapies. Consult or refer to a dietitian or nutritionist, if available. If not, assess food intake and counsel the patient about increasing caloric and nutritional intake.

Cryptosporidiosis in Resource-Limited Settings

Cryptosporidium infection in HIV-uninfected populations is more common in countries with overcrowding and poor sanitary conditions. The disease is also associated with rainy seasons and is frequent in children <2 years of age.

The prognosis for HIV-infected patients with cryptosporidiosis and without access to ART is poor. In one study, the mean survival time of coinfected patients was 25 weeks.

Patient Education

- Recommend scrupulous handwashing for the patient and all contacts, especially household members and sexual partners.
- Explain that effective ART is the best treatment for alleviating symptoms and helping the immune system eradicate the parasite.
- Advise the patient to increase fluid intake (not alcohol), and avoid foods that aggravate diarrhea.
- Educate the patient about healthful food choices that increase calories and nutrition.
- Provide supportive counseling; discuss how to manage symptoms and the isolation that may accompany chronic diarrhea.

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Cytomegalovirus Disease

Background

Chronic infection with cytomegalovirus (CMV), a member of the human herpesvirus family, is common among sexually active adults. CMV is spread by sexual or other types of close personal contact, blood-to-blood contact (via transfusion or needle sharing), organ transplantation, and perinatal transmission. The estimated prevalence of CMV infection among adults ranges from 40% to 60% in resource-rich countries and from 80% to 100% in resource-poor countries. As with other herpesviruses, CMV is not cleared from the body, but is kept in a state of latency by an intact immune system. Chronic CMV infection rarely causes disease among immunocompetent persons, but it is a major cause of morbidity and mortality in HIV-infected patients with CD4 counts of <50 cells/μL. CMV can cause several clinical illnesses in immunocompromised patients, including chorioretinitis, pneumonia, esophagitis, colitis, encephalitis, polyradiculopathy, adrenalitis, and hepatitis. Symptomatic disease represents either primary infection or reactivation of latent infection that has escaped immunologic control. Effective antiretroviral therapy (ART) greatly reduces the risk of CMV reactivation and disease.

S: Subjective

The patient may report symptoms including the following:

- Floaters, scotomata (blind spots), "flashing lights," loss of peripheral or field vision (chorioretinitis)
- Headache, difficulty concentrating, sleepiness, personality changes (encephalitis, dementia)
- Mouth ulcerations
- Dysphagia or odynophagia (esophagitis)
- Abdominal pain and bloody diarrhea, weight loss, rectal ulcers, fever (colitis)
- Persistent fever, fatigue, weight loss (adrenalitis)
- Shortness of breath, dyspnea on exertion, dry cough (pneumonia; rare in patients with advanced HIV infection)
- Bilateral lower extremity weakness, urinary retention, incontinence, spasticity (polyradiculopathy)
- Low back pain, especially radiating to the perianal area (polyradiculopathy, myelitis)

Family members or caregivers may report confusion, apathy, lethargy, somnolence, withdrawal, or personality changes in the patient (CMV encephalitis, dementia).

The history should include questions about the presence and characteristics of the symptoms listed above, as well as the following:

- Duration of symptoms
- Associated symptoms
- Recent CD4 count; nadir CD4 count (risk is highest at <50 cells/μL)
- Whether the patient is taking ART; if so, date initiated, specific medications, and CD4 and HIV RNA responses

O: Objective

Perform a thorough physical examination, with particular attention to the following:

- Vital signs: Document fever.
- Weight: Compare with previous values; document weight loss.
- Eyes: Funduscopic examination in patients with CMV retinitis may show pathognomonic "cottage cheese in ketchup" yellow-white lesions, representing vascular hemorrhages and exudates.
- Nervous system: Evaluate mental status and perform a complete neurologic examination, including cranial nerves, sensation (sensory deficits may occur with preserved vibratory sense and proprioception), motor, deep tendon reflexes, coordination, and gait.

A: Assessment

For HIV-infected patients with advanced immunosuppression, the differential diagnosis includes the following:

- For suspected CMV retinitis, consider cotton-wool spots and progressive outer or acute retinal necrosis.
- For suspected CMV enteritis, consider

gastrointestinal pathogens such as *Mycobacterium avium* complex, *Cryptosporidium*, other parasites, and lymphoma.

- For suspected CMV pneumonitis, consider *Pneumocystis jiroveci* pneumonia (PCP).
- For suspected CMV encephalitis, consider causes of neurologic deterioration such as progressive multifocal leukoencephalopathy, toxoplasmosis, central nervous system lymphoma, and other mass lesions.

P: Plan

Diagnostic Evaluation

CMV can be detected by serology, culture, antigen testing, nucleic acid amplification, or examination of tissue samples. However, serologic tests are not reliable for diagnosing CMV disease because most adults are seropositive and because patients with advanced AIDS may serorevert while remaining infected. Furthermore, for HIV-infected patients, demonstration of CMV in the blood, urine, semen, cervical secretions, or bronchoalveolar lavage (BAL) fluid does not necessarily indicate active disease, although patients with end-organ disease are usually viremic.

Diagnosis of end-organ disease generally requires demonstration of tissue invasion. The recommended evaluation is as follows.

CMV retinitis

Dilated retinal examination should be performed emergently by an ophthalmologist experienced in the diagnosis of CMV retinitis. The diagnosis is usually based on the identification of typical lesions.

Gastrointestinal CMV disease (esophagitis or colitis)

Perform endoscopy with visualization of ulcers, and conduct tissue biopsy showing viral inclusions to demonstrate viral invasion.

Pulmonary CMV disease

Perform chest radiography showing interstitial pneumonia, and conduct lung tissue biopsy showing inclusion bodies.

Neurologic CMV disease

- Encephalitis: Magnetic resonance imaging (MRI) of the brain should be done to rule out mass lesions. Periventricular or meningeal enhancement may be detected with CMV disease. Lumbar puncture should be performed; cerebrospinal fluid (CSF) should be analyzed for CMV (by polymerase chain reaction, which is sensitive and specific), cell count (may show lymphocytic or mixed lymphocytic or polymorphonuclear pleocytosis), glucose (may be low), and protein (may be high). A brain biopsy may be performed if the diagnosis is uncertain after imaging and CSF evaluation.
- Polyradiculopathy: Spinal MRI should be done to rule out mass lesions. In CMV disease, nerve root thickening may be present. Lumbar puncture with CSF analysis should be performed, as described above.
- Myelitis: Spinal MRI should be done to rule out mass lesions. Cord enhancement may be present. Lumbar puncture with CSF analysis should be performed, as described above.

Other sites

Detection of CMV at other sites requires BAL, visualization with endoscopy, or tissue biopsy. Viral inclusions ("owl's eye cells") in biopsied tissue demonstrate invasive disease (as opposed to colonization). Because retinitis is the most common manifestation of CMV disease, patients with gastrointestinal, central nervous system, or pulmonary disease should undergo ophthalmologic evaluation to detect subclinical retinal disease.

Treatment

Ganciclovir, valganciclovir, foscarnet, and cidofovir may be effective for treating CMV end-organ disease. The choice of therapy depends on the site and severity of the infection, the level of underlying immunosuppression, the patient's ability to tolerate the medications and adhere to the treatment regimen, and the potential medication interactions.

Immune reconstitution through ART is also a key component of CMV treatment and relapse prevention. The optimal timing of ART initiation in relation to the treatment of CMV is not clear. CMV flares may occur if patients develop immune reconstitution inflammatory syndrome (see chapter *Immune Reconstitution Syndrome*), but in most cases of nonneurologic disease, ART probably should not be delayed.

CMV retinitis

Treatment consists of 2 phases: initial therapy and chronic maintenance therapy.

Initial therapy

Before the advent of valganciclovir, the preferred strategy for treating CMV retinitis involved ganciclovir intraocular implants and systemic therapy. Because implants deliver a higher dose of drug to the retina than any other modality (1.4 mcg/hour for up to 8 months), many experts still prefer them for patients with sight-threatening (zone 1) disease. About half of patients treated with implants develop disease in the contralateral eye, and a third experience systemic disease, within 3 months of implantation. Therefore, patients with implants should be treated systemically with valganciclovir (900 mg once daily; some experts increase this to 900 mg twice daily for patients with vision-threatening disease).

For patients with peripheral retinitis (beyond zone 1), oral valganciclovir (see below) is the preferred treatment because it is easy to administer and is not associated with the surgery- or catheter-related complications seen with intraocular treatments and intravenous therapies. This formulation quickly converts to ganciclovir in the body and has good bioavailability. Valganciclovir should be used only if the patient is thought to be capable of strict adherence. Other possible intravenous treatments include ganciclovir, ganciclovir followed by oral valganciclovir, foscarnet, and cidofovir. See below for dosing recommendations.

For sight-threatening disease, treat with ganciclovir intraocular implants plus valganciclovir 900 mg orally once daily or twice daily.

For peripheral disease, treat with valganciclovir 900 mg orally twice daily for 14-21 days.

Alternatives for initial therapy

- Intravenous ganciclovir 5 mg/kg every 12 hours for 14-21 days
- Intravenous foscarnet 60 mg/kg every 8 hours or 90 mg/kg every 12 hours for 14-21 days
- Intravenous cidofovir 5 mg/kg weekly for 2 weeks, then every other week (must be given with probenecid [2 g orally 3 hours before, 1 g orally 2 hours after, and 1 g orally 8 hours after the cidofovir infusion] and intravenous saline to decrease the risk of renal toxicity)

Note: Valganciclovir, ganciclovir, and foscarnet require dosage adjustment in patients with renal insufficiency. Cidofovir is contraindicated in patients with renal insufficiency or proteinuria.

Monitor patients closely to gauge the response to therapy. Repeat the dilated retinal examination after the completion of induction therapy, 1 month after initiation of therapy, and monthly during anti-CMV therapy. Consult with a specialist if the response to therapy is suboptimal.

Note: Retinal detachment may occur in up to 50-60% of patients in the first year after diagnosis. Regular follow-up with an ophthalmologist is required for all patients. Patients should report any vision loss immediately.

Chronic maintenance therapy

After initial CMV treatment, lifelong maintenance therapy with valganciclovir or intravenous foscarnet should be given to prevent recurrence, and the patient needs regular reevaluation by an ophthalmologist. Recommended dosages for maintenance therapy are as follows:

- Valganciclovir 900 mg orally once daily
- Intravenous foscarnet 90-120 mg/kg once daily

Discontinuation of maintenance therapy can be considered for patients with inactive CMV and sustained immune reconstitution during ART (CD4 count of >100-150 cells/μL for at least 6 months). However, the decision should be guided by factors such as the extent and location of the CMV lesions and the status of the patient's vision. An ophthalmologist who is experienced in caring for HIV-infected patients should be involved in making any decision to discontinue therapy, and patients should receive regular ophthalmologic follow-up. Maintenance therapy should be resumed if the CD4 count drops below 100-150 cells/μL or the patient develops other signs of HIV progression.

Gastrointestinal and pulmonary CMV disease

These infections are usually treated with intravenous ganciclovir or foscarnet for 21-28 days unless the patient is able to absorb oral medications, in which case oral valganciclovir is an option (refer to the dosing suggestions above). Some specialists recommend a follow-up endoscopy to verify regression of lesions before discontinuing therapy. Many experts do not recommend maintenance therapy for gastrointestinal CMV infections unless the disease recurs.

Neurologic CMV disease

The optimal treatment of neurologic disease has not been determined. Prompt initiation of dual therapy with intravenous ganciclovir and foscarnet may be effective in some patients.

Monitoring CMV therapies

The medications used to treat CMV have several important potential adverse effects, and monitoring for these is required. Valganciclovir and ganciclovir have been associated with bone marrow suppression, neutropenia, anemia, thrombocytopenia, and renal dysfunction. Foscarnet has been associated with cytopenia, renal insufficiency, electrolyte abnormalities, and seizures. For patients taking these medications, perform complete blood count with differential and check electrolytes and creatinine twice weekly during initial therapy and once weekly during maintenance therapy. Cidofovir has been associated with renal insufficiency and ocular hypotony. For patients taking cidofovir, check creatinine and blood urea nitrogen and perform urinalysis (for proteinuria) before each dose. Intraocular pressure must be checked at least every 6 months.

Patient Education

- Educate patients about the importance of ART in treating CMV. Urge patients to start ART if they have not done so already.
- Patients with CMV retinitis may have to remain on suppressive therapy for life to prevent blindness. Patients with CMV esophagitis or enteritis usually see improvements within 2-4 weeks of therapy.
- Treatment of CMV retinitis halts progression of the infection but does not reverse the damage already done to the retina. Warn patients that vision will not return to pre-CMV status.
- Advise patients to report any visual deterioration immediately. Retinal detachment or progression of CMV must be treated immediately to avoid further vision loss.
- With gastrointestinal disease, recurrence of symptoms warrants repeat endoscopy. Advise patients to report any recurrence of symptoms.
- Adverse reactions to current therapies are common. Educate patients about these and advise them to promptly report any adverse reactions.
- Help patients cope with the possibility of therapeutic failure, and, in the case of CMV retinitis, permanent loss of vision.
- Teach patients how to maintain indwelling venous access lines, if used. Have patients demonstrate these techniques before discharge.

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Dermatologic Staphylococcal Infections

Background

Staphylococcus aureus is the most common cause of community-acquired (CA) or hospital-acquired (HA) bacterial skin and soft-tissue infections (SSTIs) among patients with HIV infection. Staphylococcal infection may present as cellulitis, folliculitis, furuncles, abscesses, ecthyma, bullous impetigo, or plaques resembling hidradenitis suppurativa. Staphylococcal SSTIs can occur in isolation or as a complication of other skin pathology. HIV-positive patients are at risk of superinfection, bacteremia, and metastatic infection from SSTIs that might be considered trivial in other patients.

Most CA staphylococcal infections involve methicillin-susceptible *S aureus* (MSSA). However, a strain of CA methicillin-resistant *S aureus* (MRSA) is increasingly common; MRSA is now found in up to 50% of CA SSTIs in many localities. This strain carries an SSTI virulence gene (the Panton-Valentine leucocidin gene), is more aggressive in causing SSTIs, and appears more likely to result in serious pneumonia than was previous CA *S aureus*. Resistance is conferred by the mec IV gene (different from mec III of HA MRSA). CA MRSA is commonly sensitive to tetracyclines, rifampin, trimethoprim-sulfamethoxazole (TMP-SMX), quinolones, and clindamycin.

The treatment of SSTIs is determined by the extent, depth, and speed of progression of the infection. Hospital admission for intravenous antibiotic therapy is indicated when systemic toxicity accompanies a staphylococcal skin infection, the infection is rapidly advancing, or there is concern about compartment syndrome, necrotizing fasciitis, or other complications.

S: Subjective

The patient complains of inflammation (erythema and tenderness) of the skin and subcutaneous tissue, itchy rash (folliculitis), furuncles, pustules, or abscesses.

Inquire about the following:

- Risk factors, including other recent skin infections, trauma, hospitalization, close skin contact with other people (especially those with skin infections), injection drug use, diabetes mellitus, chronic venous insufficiency
- Constitutional symptoms, such as fever
- Localizing pain
- Symptoms distant from the index lesion, which may suggest systemic spread

Review medications, supplements, and herbal preparations.

O: Objective

Physical Examination

Note: SSTIs may be highly contagious. During examination of any skin lesions, the health care worker should wear gloves and wash hands thoroughly after glove removal.

Check vital signs. Perform a focused physical examination of the skin, lymph nodes, and other areas as indicated (eg, the heart for signs of endocarditis, the mucous membranes for lesions, or the joints for signs of septic arthritis).

Cellulitis

Findings include swelling, tenderness, erythema, and warmth of localized tissue, most commonly on the face and extremities. Cellulitis may be associated with other types of lesions.

Furuncles/abscesses

Palpation of the affected area reveals a firm nodule or a fluid collection in the subcutaneous tissue, often surrounded by cellulitis. Most abscesses or furuncles with more than a few mm^3 of pus should be drained.

Folliculitis

Follicular pustules are pruritic, often very painful lesions that may be present on the face, trunk, axillae, or groin. A tiny central pustule may be visible when the skin is stretched, although sometimes the lesions are almost urticarial. These may extend below the skin surface, forming abscesses or, in rare cases, large, violaceous hidradenitis-like plaques with pustules. Note that excoriations may obscure primary lesions.

Ecthyma

This appears as a superficially ulcerated "punched out" or eroded lesion with an extremely adherent crust. A purulent layer of material is usually found under the crust.

Bullous impetigo

Superficial blisters or erosions, often with yellow crusts, appear on the face, groin, or axillae.

A: Assessment

A partial differential diagnosis of cellulitis, abscess, eruptions, or ulcerations includes the following:

- Streptococcal or other bacterial SSTI
- *Candida albicans* or other fungal infection (particularly in the groin and perineal area and under pendulous breasts, or as a cause of folliculitis)
- Eosinophilic folliculitis
- Syphilis
- Herpes simplex, herpes zoster
- Cutaneous hypersensitivity reactions to drug therapy
- Deep vein thrombosis in the calf, causing swelling with apparent cellulitis
- Pyogenic granuloma
- Angiosarcoma
- Kaposi sarcoma, particularly if femoral or inguinal lymph node enlargement is present
- Bacillary angiomatosis
- Gout

P: Plan

Diagnostic Evaluation

Often, SSTIs can be diagnosed and treated on the basis of the history and physical examination, and diagnostic testing is not required.

For exudative or pustular lesions, obtain exudate for Gram stain, culture, and sensitivity, to identify the organism and to choose the optimal antibiotic therapy. Note that CA MRSA is common among HIV-infected patients in most urban and many rural areas.

If systemic illness is suspected, check complete blood count with differential, blood cultures, and a metabolic panel.

Order tests to rule out other causes of skin infection, as indicated (eg, syphilis, herpes). Consider biopsy if the diagnosis is unclear after initial workup or if the lesion does not respond to empiric treatment.

Treatment

If the patient has extensive, spreading cellulitis or systemic illness, or is suspected to have deep abscess, necrotizing infection, compartment syndrome, or other deep soft-tissue infection, hospitalize immediately for intravenous antibiotic therapy (consult an infectious disease specialist for antimicrobial therapy) and obtain urgent surgical consultation. Mild and moderate SSTIs can usually be treated on an outpatient basis.

Abscesses and fluctuant lesions should be incised and drained, if possible. Antibiotic therapy may not be necessary if the abscess is drained adequately.

For suspected *S aureus* infections, initiate empiric antibiotic treatment, if indicated; consider the local prevalence of MRSA when selecting antibiotics (see "Treatment note" below).

Impetigo

Treat impetigo for 7-14 days.

- Dicloxacillin 250 mg orally 4 times per day
- Cephalexin 250 mg orally 4 times per day
- Erythromycin 250 mg orally 4 times per day
- Clindamycin 300-450 mg orally 4 times per day
- Doxycycline 100 mg orally twice daily

Known or suspected MSSA SSTI

Treat known or suspected MSSA SSTIs for 7-14 days.

- Dicloxacillin 500 mg orally 4 times per day
- Cephalexin 500 mg orally 4 times per day
- Clindamycin 300-450 mg orally 4 times per day; if the patient has been taking azithromycin for *Mycobacterium avium* complex prophylaxis, staphylococcal infections may be resistant to clindamycin
- Doxycycline 100 mg twice daily orally
- TMP-SMX 2 double-strength tablets orally twice daily

Known or suspected MRSA SSTI

Treat according to the patient's culture and sensitivity results, or according to local trends in MRSA susceptibility (see "Treatment note" below). The following are often effective:

- Clindamycin 300-450 mg orally 4 times per day
- Doxycycline 100 mg orally twice daily
- TMP-SMX 2 double-strength tablets orally twice daily

For severe infections, use intravenous antibiotics selected according to *S aureus* susceptibility. For MRSA, consider vancomycin, clindamycin, linezolid, or daptomycin, if available.

Recurrent lesions may indicate MRSA carriage in the nose or elsewhere. Nasal carriage can be treated with topical mupirocin ointment to the anterior nares 3 times daily for 7 days. If nasal mupirocin fails and MRSA SSTI recurs frequently, consider the addition of a quinolone or TMP-SMX (2 double-strength tablets twice daily) plus rifampin (600 mg twice daily) to mupirocin nasal ointment for 14-21 days may be effective. With all treatments, staphylococcal eradication may be temporary.

Treatment note

To guide empiric antimicrobial therapy, monitor the percentage of staphylococcal isolates that are MRSA in the particular clinical setting, as well as local MRSA antibiotic sensitivities. (The laboratory must perform the "D-test" to rule out erythromycin induction of clindamycin resistance.)

Patient Education

- Patients should be informed that impetigo and some other staphylococcal infections are highly contagious. Patients should avoid hand contact with lesions, and should not allow other people to touch the affected areas.
- Antibiotics should be taken exactly as prescribed.
- Patients should call or return to the clinic if symptoms do not improve in 3-5 days or if symptoms worsen.
- Instruct patients to wash the affected area with antibacterial soap (such as Hibiclens, Betadine, or benzoyl peroxide wash). If living quarters are shared, patients should clean contaminated surfaces to protect others from MRSA colonization or infection.
- Instruct patients to use of warm soaks in aluminum acetate astringent solution (Domeboro solution) if needed for discomfort or irritation.

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Gonorrhea and Chlamydia

Background

Gonorrhea, caused by *Neisseria gonorrhoeae* (GC), and chlamydia, caused by *Chlamydia trachomatis* (CT), are sexually transmitted infections (STIs). These infections may be transmitted during oral, vaginal, or anal sex; they can also be transmitted from the mother to baby during delivery and cause significant illness in the infant.

Both organisms can infect the urethra, oropharynx, and rectum in women and men; the epididymis in men, and the cervix, uterus, and fallopian tubes in women. Untreated GC or CT in women may lead to pelvic inflammatory disease, which can cause scarring of the fallopian tubes and result in infertility or ectopic pregnancy (tubal pregnancy). The organisms can also affect other sites; *N gonorrhoeae* can cause disseminated infection involving the skin, joints, and other systems.

Certain strains of CT can cause lymphogranuloma venereum (LGV). This infection is common in parts of Africa, India, Southeast Asia, and the Caribbean. Outbreaks among men who have sex with men (MSM) have been reported over the past several years in Europe and the United States. LGV may cause genital ulcers followed by inguinal adenopathy; it can also (as in the recent cases in MSM) cause gastrointestinal symptoms, notably anorectal discharge and pain.

Patients with symptoms of gonorrhea or chlamydia should be evaluated and treated as indicated below. Although GC or CT urethritis in men typically causes symptoms, urethral infection in women and oral or rectal infections in both men and women often cause no symptoms. In fact, a substantial number of individuals with GC or CT infection have no symptoms. Thus, sexually active individuals at risk for GC and CT should receive regular screening for these infections as well as for syphilis and other STIs. Patients are frequently infected with both *N gonorrhoeae* and *C trachomatis*, so they should be tested and treated for both.

S: Subjective

Symptoms will depend on the site of infection (eg, oropharynx, urethra, cervix, rectum). Symptoms are not present in all patients.

If symptoms are present, **women** may notice:

- Vaginal discharge
- Urinary hesitancy
- Pain with sexual intercourse
- Pain or burning on urination
- Abdominal or pelvic pain
- Sore throat
- Mouth sores
- Rectal discharge
- Anal discomfort

If symptoms are present, **men** may notice:

- Increased urinary frequency or urgency
- Urethral discharge
- Red or swollen urethra
- Incontinence
- Pain on urination
- Testicular tenderness or pain
- Rectal discharge
- Anal discomfort

During the history, ask the patient about the following:

- Any of the symptoms listed above, and their duration
- Previous diagnosis of gonorrhea or chlamydia
- New sex partner(s)
- Unprotected sex (oral, vaginal, anal)
- Use of an intrauterine device
- Last menstrual period, and whether the patient could be pregnant

O: Objective

Physical Examination

During the physical examination, check for fever and document other vital signs.

In **women**, focus the physical examination on the mouth, abdomen, and pelvis. Inspect the oropharynx for discharge and lesions; check the abdomen for bowel sounds, distention, rebound, guarding, masses, and suprapubic or costovertebral angle tenderness; perform a complete pelvic examination for abnormal discharge or bleeding; check for uterine, adnexal, or cervical motion tenderness; and search for pelvic masses or adnexal enlargement. Check the anus for discharge and lesions; perform anoscopy if symptoms of proctitis are present. Check for inguinal lymphadenopathy.

In **men**, focus the physical examination on the mouth, genitals, and anus/rectum. Check the oropharynx for discharge and lesions, the urethra for discharge, the external genitalia for other lesions, and the anus for discharge and lesions; perform anoscopy if symptoms of proctitis are present. Check for inguinal lymphadenopathy.

A: Assessment

A partial differential diagnosis includes the following:

- Urinary tract infection
- Dysmenorrhea
- Appendicitis
- Cystitis
- Proctitis
- Pelvic inflammatory disease (PID)
- Irritable bowel syndrome
- Pyelonephritis

P: Plan

Diagnostic Evaluation

Test for oral, urethral, or anorectal infection, according to symptoms and possible exposures. Perform concurrent testing for both gonorrhea and chlamydia. The availability of the various testing methods depends on the clinical site. Consider the following:

- Gram stain (pharyngeal, cervical, or urethral discharge)
- Culture (oropharynx, endocervix, urethra, rectum)
- Nucleic acid amplification test (NAAT): urine specimens (first stream) and urethral, vaginal, and endocervical swab specimens; has also been used for pharyngeal and rectal swab specimens, although it is not currently approved for this use
- Nucleic acid hybridization assay (DNA probe): endocervical and male urethral swab specimens
- Serologic tests (microimmunofluorescence test or complement fixation test) for suspected LGV

Treatment

Treatments for gonorrhea and chlamydia are indicated below. High rates of fluoroquinolone-resistant *N gonorrhoeae* exist in California, Hawaii and the Pacific Islands, Asia, and Great Britain. Fluoroquinolone-resistant GC is also common among MSM in the United States. Thus, the U.S. Centers for Disease Control and Prevention (CDC) recommends that fluoroquinolones not be used for treatment of GC in MSM or in any patient infected in the areas listed above, unless antimicrobial susceptibility test results are used to guide therapy.

Because dual infection is common, patients diagnosed with either GC or CT should receive empiric treatment for both infections, unless the other infection has been ruled out. Reinfection is likely if reexposure occurs. Any sex partners within the last 60 days, or the most recent sex partner from >60 days before diagnosis, also should receive treatment. Patients should abstain from sexual activity for 7 days after a single-dose treatment or until a 7-day treatment course is completed.

Adherence is essential for treatment success. Single-dose treatments maximize the likeliness of adherence and are preferred. Other considerations in choosing the treatment include antibiotic resistance, cost, allergies, and pregnancy. For further information, see the CDC STD treatment guidelines and the revised recommendations (references below).

Treatment of Gonorrhea

Treatment options include the following. (See the full CDC STD treatment guidelines, referenced below.)

- Ceftriaxone 125 mg or 250 mg intramuscular (IM) injection in a single dose (some providers recommend 250 mg because of slightly higher cure rates)

- Cefixime 400 mg orally in a single dose (tablet formulation not currently available in the United States)
- Spectinomycin 2 g IM injection in a single dose (for urogenital or anorectal GC; not sufficiently effective to treat pharyngeal GC)
- Cefpodoxime 400 mg orally in a single dose (insufficient data to be recommended by the CDC)
- Ciprofloxacin 500 mg orally in a single dose (see "Note" below)
- Ofloxacin 400 mg orally in a single dose (see "Note" below)
- Levofloxacin 250 mg orally in a single dose (see "Note" below)
- Azithromycin 2 g orally in a single dose (not recommended by the CDC; high rate of gastrointestinal intolerance)

Note: Fluoroquinolones are not recommended for treatment of gonococcal infection in MSM or in any patient who acquired GC infection in California, Hawaii, Massachusetts, New York City, the Pacific Basin, Asia, or Great Britain, because of the high prevalence of fluoroquinolone resistance.

Treatment of Chlamydia

(See the full CDC STD treatment guidelines, referenced below.)

Recommended regimens

- Azithromycin 1 g orally in a single dose
- Doxycycline 100 mg orally twice daily for 7 days

Alternative regimens

- Erythromycin base 500 mg orally 4 times daily for 7 days
- Erythromycin ethylsuccinate 800 mg orally 4 times daily for 7 days
- Ofloxacin 300 mg orally twice daily for 7 days (see note above)
- Levofloxacin 500 mg orally once daily for 7 days (see note above)

Treatment of LGV

Recommended regimens

- Doxycycline 100 mg orally twice daily for 21 days

Alternative regimens

- Erythromycin base 500 mg orally 4 times daily for 21 days
- Azithromycin 1 g orally once a week for 3 weeks (limited data)

For recent sex partners (within 30 days of the onset of symptoms), treat with azithromycin 1 g orally in a single dose or doxycycline 100 mg orally twice daily for 7 days.

Treatment during Pregnancy

Fluoroquinolones and tetracyclines should be avoided during pregnancy. For the treatment of GC in pregnant women, the CDC advises using either a recommended cephalosporin or spectinomycin. For the treatment of CT in pregnant women, see the following.

Recommended CT regimens

- Erythromycin base 500 mg orally 4 times daily for 7 days
- Amoxicillin 500 mg orally 3 times daily for 7 days

Alternative CT regimens

- Erythromycin base 250 mg orally 4 times daily for 14 days
- Erythromycin ethylsuccinate 800 mg orally 4 times daily for 7 days
- Erythromycin ethylsuccinate 400 mg orally 4 times daily for 14 days
- Azithromycin 1 g orally in a single dose

Follow-up

- Evaluate sex partners and treat them if they had sexual contact with the patient during the 60 days preceding the patient's onset of symptoms.
- Most recurrent infections come from sex partners who were not treated.
- If symptoms persist, evaluate for the possibility of reinfection, treatment failure, or a different cause of symptoms. If treatment failure is suspected, perform culture and antimicrobial sensitivity testing.
- For pregnant women with chlamydia, retest (by culture) 3 weeks after completion of treatment.
- Screen for chlamydia, syphilis, and other STIs at regular intervals according to the patient's risk factors. The sites of sampling (eg, pharynx, urethra, endocervix, anus/rectum) will depend on the patient's sexual exposures.
- Evaluate each patient's sexual practices with regard to the risk of acquiring STIs and of transmitting HIV; work with the patient to reduce sexual risks.

Patient Education

- Instruct patients to take all of their medications. Advise patients to take medications with food if they are nauseated, and to call or return to clinic right away if they have vomiting or are unable to take their medications.
- Sex partners from the previous 60 days need to be tested for sexually transmitted pathogens, and treated as soon as possible with a regimen effective against gonorrhea and chlamydia, even if they have no symptoms. Advise patients to inform their partner(s) that they need to be tested and treated. Otherwise, patients may be reinfected.
- Advise patients to avoid sexual contact until the infection has been cured (at least 7 days).
- Provide education about sexual risk reduction. Instruct patients to use condoms with every sexual contact to prevent reinfection with gonorrhea or chlamydia, to prevent other STIs, and to prevent transmission of HIV to sexual partners.

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Hepatitis B Infection

Background

Hepatitis B virus (HBV) is the most common cause of chronic liver disease worldwide. HBV is a DNA virus that is transmitted primarily through blood exposure, sexual contact, and from mothers to their children. Because HIV and HBV share transmission routes, up to 90% of HIV-infected patients have evidence of previous or current HBV infection.

Most people who become infected with HBV are able to clear the virus without treatment, and they subsequently become immune to HBV. A small proportion of individuals infected with HBV (approximately 10% in the general population) develop chronic HBV infection. Over time, chronic HBV can cause hepatic fibrosis and eventually cirrhosis, end-stage liver disease (ESLD), and hepatocellular carcinoma (HCC). HIV infection appears to increase the risk of developing chronic HBV infection after HBV exposure. Patients coinfected with HBV and HIV also tend to have faster progression of liver disease, with associated morbidity and mortality.

To identify patients with HBV coinfection, and to identify and vaccinate susceptible individuals, all HIV-infected persons should be tested for HBV. Table 1 outlines routine baseline HBV serologic screening tests for HIV-infected individuals:

Table 1. Interpreting Hepatitis-B-Related Laboratory Tests

Name of Test	Interpretation of Positive Results	Interpretation of Negative Result
Hepatitis B surface antigen (HBsAg)	Active HBV	Usually indicates absence of HBV infection; may be falsely negative in some patients with active HBV
Hepatitis B surface antibody (HBsAb)	Immune to HBV (through past exposure or vaccination)	Not immune; if active HBV disease is not present, consider vaccination
Hepatitis B core antibody (HBcAb), IgG	Past exposure to HBV; does not indicate whether patient has active infection or has cleared infection (check HBsAg and HBsAb)	Probably has not been infected with HBV

A positive result for hepatitis B surface antigen (HBsAg) that persists longer than 6 months indicates chronic infection. In some cases of active HBV infection, a positive result for hepatitis B core antibody (HBcAb) may be the only detectable marker, because HBsAg may be negative. Ongoing viral replication and infectiousness is indicated by the presence of HBV DNA or a positive result for hepatitis B envelope antigen (HBeAg).

S: Subjective

Symptoms of acute HBV infection may include fatigue, nausea, vomiting, arthralgias, fever, right upper quadrant pain, jaundice, dark urine, and clay-colored stools. Some patients may have no symptoms.

Patients with chronic HBV are often asymptomatic until ESLD has developed. Progressive HBV can lead to decompensated liver disease, portal hypertension, cirrhosis, esophageal varices, coagulopathy, thrombocytopenia, hepatic encephalopathy, and HCC, or some combination of these conditions. Patients may experience fatigue, right upper quadrant pain, or complications of ESLD such as jaundice, increased abdominal girth, easy bruising, gastrointestinal bleeding, and altered mentation.

O: Objective

Perform a thorough physical examination, with special attention to the eyes and mouth (icterus, gum bleeding), skin (jaundice, palmar erythema, petechiae, ecchymoses), abdomen (caput medusa, distention, ascites, hepatomegaly, splenomegaly), heart and lungs (signs of congestive heart failure), extremities (edema), and the neurologic system.

A: Assessment

A partial differential diagnosis includes:

- Medication-induced hepatotoxicity
- Alcohol- or drug-related liver injury
- Fungal, bacterial, or other viral infection

P: Plan

Diagnostic Evaluation

- Assess the severity of liver disease at the time of diagnosis and at least every 6 months with alanine aminotransferase (ALT), albumin, bilirubin, prothrombin time, platelet count, and complete blood count.
- Consider checking the HBV DNA (viral load). DNA levels are usually high in persons with active HBV (in the absence of treatment) and can be used to confirm active disease (in those not taking effective treatment) and monitor the response to treatment (in patients taking HBV treatment). Note, however, that HBV DNA levels apparently do not predict the progression of liver disease.
- Check for HBeAg; this test indicates active infection and infectiousness, as does the HBV viral load.
- Persons with chronic HBV are at elevated risk for HCC. Consider screening for HCC every 6-12 months with the serum alpha-fetoprotein (AFP) level or imaging of the liver (ultrasound, computed tomography, or magnetic resonance imaging). Screening is especially important if the patient is in a high-risk group (eg, patients aged >45 years, those with cirrhosis, or those with a family history of HCC).
- Liver biopsy is the only definitive test to assess the grade (inflammation) and stage (degree of fibrosis) of liver disease. Many experts recommend liver biopsy to guide decisions about therapy, whereas others start therapy based on ALT and HBV DNA, without liver biopsy.

Treatment

The optimal treatment strategies for patients with HIV and HBV coinfection have not been defined, and individual patient characteristics should be used to guide therapy. The patient's need for HIV treatment (antiretroviral therapy [ART]) should be considered carefully because it will influence the selection of HBV therapy. When ART is indicated, agents that have activity against both HIV and HBV (eg, lamivudine, emtricitabine, tenofovir) can be considered for inclusion in the ART regimen. Patients who need HBV treatment but are not candidates for HIV treatment can be given agents that do not have activity against HIV at standard doses (eg, interferon, adefovir, entecavir).

For some therapies, data on efficacy and safety are limited, the proper duration of treatment is not yet clear, and the role of combination therapy has not been defined. Studies of treatment in HIV/HBV-coinfected populations are ongoing. Consider consulting with an HBV treatment expert to determine the best approach to HBV treatment for a particular patient.

Some experts treat all patients with proven chronic HBV, whereas others consider treatment for patients with both of the following:

- Positive HBeAg or HBV DNA >10,000 copies/mL
- ALT >2 times the upper limit of normal, or inflammation or fibrosis on liver biopsy

Table 2 describes the possible treatments for HBV.

Treatment considerations

- Adefovir, interferon, and entecavir are preferred for HIV/HBV coinfected patients who do not require ART.
- For HIV/HBV-coinfected patients who require ART, consider agents with both anti-HIV and anti-HBV activity.
- When lamivudine is used as a single agent, HBV resistance develops in many patients by 1-2 years. Although combination therapy has not been well studied, specialists recommend using 2 nucleoside/nucleotide combinations that have activity against HBV (lamivudine + tenofovir, or emtricitabine + tenofovir [Truvada]) as part of the antiretroviral regimen, to treat HBV and to prevent HBV resistance.
- For patients infected with hepatitis C virus (HCV) as well as HBV and HIV, evaluate the need for HIV therapy first. If ART is not required, consider treating HCV first, because interferon therapy is active against both HCV and HBV. If interferon-based therapy for HCV has failed, consider treating chronic HBV with an oral agent.
- Patients taking therapy should be monitored regularly for changes in ALT. If possible, HBeAg (if initially positive) and HBV DNA should also be monitored.
- Some patients treated with ART may experience worsening of HBV symptoms and laboratory markers in the weeks after ART initiation, because of immune reconstitution. Hepatic decompensation due to immune reconstitution must be distinguished

from other causes, such as medication toxicity, or other infection. Liver function tests should be monitored closely in patients starting ART.

- Some antiretroviral medications are hepatotoxic and should be avoided or used cautiously. These include nevirapine, tipranavir, and high-dose ritonavir.
- Numerous other medications (eg, fluconazole and issoniazid) are known to be hepatotoxic and can pose problems for people with impaired liver function.
- For patients with treatment failure, consult an HBV specialist.
- *Caution:* Discontinuation of HBV medications in patients with HIV/HBV coinfection may cause a flare of liver disease. If this occurs, consider reinstating HBV therapy as soon as possible. Be very cautious when discontinuing HBV-active medications from an HIV ART regimen. In this scenario, consider continuing or substituting the HBV-active medications to avoid rebound liver inflammation and decompensation. For example, if it is decided to discontinue HIV treatment for an HIV/HBV-coinfected patient taking lamivudine + tenofovir + lopinavir/ritonavir, consider starting adefovir or entecavir to maintain activity against HPV.

Other care issues

Acute hepatitis A virus (HAV) or HCV in persons with chronic HBV infection can cause decompensated liver disease. All patients with HBV infection should be tested for immunity to HAV and HCV. Patients who are not immune to HAV should be vaccinated and patients who are not immune to HCV should be counseled about how to avoid the acquisition of HCV.

All HBV-infected individuals should be taught how to reduce the risk of HBV transmission to others. As appropriate, patients should be counseled to adopt "safer sex" approaches, avoid blood exposures (eg, from sharing razors or tattoo equipment), and practice safe drug injection techniques. Persons with HBV infection should be counseled to avoid exposure to hepatotoxins, including alcohol and hepatotoxic medications (eg, acetaminophen in large doses, fluconazole, and isoniazid).

Table 2. Hepatitis B Treatment Regimens

Medication	Treatment Regimen	Comments
Interferon-alfa 2a or 2b	5 million units (MU) daily or 10 MU 3 times weekly for 4-6 months*	• Interferon is contraindicated in patients with decompensated cirrhosis. • Expect the CD4 count to drop by 100-150 cells/µL or more during treatment with interferon or pegylated interferon. (The CD4 percentage usually remains stable.
Pegylated interferon-alfa 2a (Pegasys)	180 micrograms per week for 4-6 months*	
Lamivudine (Epivir, 3TC)#	150 mg twice daily or 300 mg daily (dosage as part of ART regimen) for 1 year or more*	• Use only as part of an effective HIV ART regimen. • High rate of HBV resistance occurs after 1-2 years of treatment. Lamivudine-resistant HBV is also resistant to emtricitabine. • Most specialists recommend combination with a second agent (eg, tenofovir or emtricitabine)
Tenofovir (Viread)#	300 mg daily: treatment duration unknown*	• Use only as part of an effective HIV ART regimen. • Active against lamivudine-resistant strains of HBV. • Most specialists recommend combination with a second agent (eg, lamivudine or emtricitabine)
Emtricitabine (Emtriva)#	200 mg daily: treatment duration unknown*	• Use only as part of an effective HIV ART regimen. • Emtricitabine-resistant HBV also is resistant to lamivudine. • Most specialists recommend combination with a second agent (eg, tenofovir or lamivudine)
Adefovir (Hepsera)	10 mg daily: treatment duration unknown*	• Active against lamivudine-resistant strains of HBV.
Entecavir (Baraclude)	0.5-1.0 mg daily: treatment duration unknown*	• Active against lamivudine-resistant strains of HBV.

Agents are active against both HIV and HBV.
* The duration and expected efficacy of treatment vary according to the treatment strategy and the individual patient characteristics.

Patient Education

- Most patients with HBV will remain asymptomatic for several years. However, ongoing injury to the liver occurs during this time, and can culminate in liver failure. Patients can slow the damage by avoiding alcohol and any medications (including over-the-counter drugs and recreational drugs) that may damage the liver. Instruct patients to call their pharmacist or health care provider if they have questions about a specific medication or supplement.
- As with HIV, patients must avoid passing HBV to others. Instruct patients not to share toothbrushes, dental appliances, razors, sex toys, tattoo equipment, injection equipment, or personal care items that may have blood on them. Emphasize the importance of safer sex to protect themselves and their partner(s).
- Tell patients to discuss HBV with their sex partner(s), and suggest that partner(s) get tested for HBV.
- Certain antiretroviral drugs are more likely to cause problems with the liver because of HBV. Advise patients that if they start an ART regimen, their liver function tests should be watched carefully to determine whether the body is able to process the medicines.
- Patients who have not been vaccinated against HAV, will need to receive 2 vaccinations 6 months apart. HAV can cause severe illness, liver damage, or even death, in people with HBV.
- Patients who have not been tested for HCV should be tested for this virus.
- HCV can worsen liver function greatly if it is acquired in addition to HBV. Patients with HCV should use safe sex practices (latex barriers) to avoid exposure. Patients who use injection drugs should not share needles or injection equipment.
- If children were born after women were infected with HBV, consider having them tested. Even though their risk is low, they should be screened for HBV.
- HBV treatments may cause adverse effects. Most of these are treatable with medications. Patients should contact their health care provider know right away if they experience adverse effects or new symptoms.

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Hepatitis C Infection

Background

Hepatitis C virus (HCV) is a single-stranded RNA virus that is transmitted primarily through blood exposure. The virus can also be transmitted perinatally and through sexual contact, although the latter appears to occur rarely. In some populations of HIV-infected injection drug users (IDUs) and hemophiliacs in the United States, up to 90% may be coinfected with HCV. Rates of HCV are approximately 15% among HIV-infected men who have sex with men and 2-3% among monogamous heterosexual partners of HCV-infected individuals. HIV infection appears to increase the rate of progression of chronic HCV, and increases the risk of developing end-stage liver disease. It is not yet clear whether HCV affects the progression of HIV disease.

Impact of Coinfection on Vertical Transmission of HIV and HCV

Women coinfected with HIV and HCV have a higher risk of transmitting HIV to their infants; some studies have shown a 10% (or greater) rate above that of women infected with HIV alone. Coinfected women are also more likely to pass HCV to their infants. Approximately 20% of babies born to HIV/HCV-coinfected mothers acquire HCV, compared with 5-6% of infants born to HCV-infected women without HIV. Breast-feeding is not known to transmit HCV, although HIV-infected women are advised against breast-feeding because of the risk of transmitting HIV.

O: Objective

Acute HCV Infection

Acute HCV infection is usually not recognized. In most cases, patients with acute HCV infection are asymptomatic or have nonspecific symptoms such as fatigue and, occasionally, jaundice and scleral icterus. Acute HCV infection is sometimes discovered on the basis of elevations in aspartate aminotransferase (AST) or alanine aminotransferase (ALT) in asymptomatic patients who receive regular monitoring of hepatic transaminases. Most patients with acute HCV will not resolve the infection and will progress to chronic infection, but symptomatic patients generally have a higher likelihood of clearing the virus than do asymptomatic patients (see "Treatment for Acute HCV," below).

Chronic HCV Infection

About 60-85% of people who become infected with HCV are unable to clear the virus and become chronically infected. Major manifestations are usually not seen in immunocompetent people for 15-20 years, although ALT may be transiently elevated during earlier stages of disease. The virus can cause gradual hepatic fibrosis and eventual cirrhosis, end-stage liver disease, and hepatocellular carcinoma (HCC). Death can occur from decompensated liver disease; the consequences of portal hypertension, esophageal varices, coagulopathy, and thrombocytopenia; HCC; or some combination of these conditions. HIV-infected patients who are not treated with antiretroviral (ARV) medications tend to have faster progression of liver disease than those who are treated.

P: Plan

Diagnostic Evaluation

Enzyme immunoassay

According to the 2002 guidelines of the United States Public Health Service and the Infectious Diseases Society of America, all HIV-infected patients should be tested for anti-HCV antibodies using the enzyme immunoassay (EIA) test. HCV EIA tests are sometimes falsely negative in HIV-infected patients, although the third version of the test is highly sensitive and specific; it is also the least expensive screening test currently available. HIV-infected people who test positive on the EIA should be tested to determine whether they have circulating virus (ie, detectable HCV RNA). Falsely negative HCV viral load testing is are uncommon.

Genotyping

Genotyping of HCV is helpful in assessing the likelihood of response to therapy. Patients with genotype 1 have much lower rates of response to treatment than do patients with genotype 2 or 3. Some specialists use the genotype to determine the type and duration of treatment, whereas others treat all HIV/HCV-coinfected patients similarly.

Alanine aminotransferase

Monitoring of ALT is used to assess liver inflammation, although levels may be low in patients with advanced liver disease.

Imaging

Ultrasonography can be performed to screen for cirrhosis or mass lesions. Computed tomography (CT), magnetic resonance imaging (MRI), and single-photon emission computed tomography (SPECT) are more expensive and are generally reserved for evaluation of liver masses. Some specialists recommend screening for HCC every 6 months.

Liver biopsy

Liver biopsy is used to stage the degree of inflammation and fibrosis to determine the need for HCV treatment. Biopsy should be considered in patients who are candidates for HCV treatment, after education about HCV therapy (including the expected success rates given the genotype, potential adverse effects, and the duration and logistics of treatment). Recently, blood tests have been used as noninvasive markers of hepatic fibrosis and have shown reasonable ability to identify patients with either mild or advanced liver fibrosis (currently about 40% of patients with HCV), allowing them to avoid liver biopsies.

Treatment

Treatment of chronic HCV

The recommendations of the National Institutes of Health (NIH) from June 2002 suggest that current alcohol users, pregnant women, patients with untreated depression, patients with renal disease, and patients with advanced cirrhosis are not candidates for HCV treatment. However, more recent data suggest that patients in several of these "special groups" can be treated on a case-by-case basis. Although pregnant women and persons with active alcohol use should not receive HCV treatment, certain individuals with renal disease, depression, injection drug use, and lower degrees of hepatic fibrosis (ie, Child-Pugh class A) should be considered for HCV treatment. These comorbid conditions should, of course, be treated to the degree possible.

HIV-infected patients with low CD4 counts should not be excluded from HCV treatment on the basis of CD4 count alone. Some studies do not support an association between absolute CD4 cell counts and treatment response.

Patients with a high risk of progression to cirrhosis should receive higher priority for treatment. Risk is indicated by portal or bridging cirrhosis, moderate inflammation and necrosis, measurable HCV RNA levels, or persistently elevated ALT levels. However, because ALT levels do not correlate with liver damage and some patients with normal ALT levels have abnormal liver biopsies, many experts treat patients who have normal ALT levels. For patients with minimal findings on liver biopsy and minimal ALT elevations, therapy should be deferred and the patients should be monitored. Patients with decompensated liver disease generally should not receive HCV treatment; appropriate candidates can be considered for clinical studies of liver transplantation in HIV/HCV-coinfected patients.

The most effective treatment for HCV in patients with or without HIV is combination therapy with pegylated interferon-alfa (PEG-IFN) plus ribavirin. Among HIV-uninfected patients, approximately 50% with genotype 1 achieve HCV viral clearance using this combination. HCV/HIV-coinfected patients with genotype 1 have a 22% rate of sustained virologic response to PEG-IFN plus ribavirin if treated for 48 weeks, whereas patients with other genotypes have approximately a 55% rate of sustained virologic response. Data suggest that early virologic response (EVR), defined as a $\geq 2 \log_{10}$ decrease in HCV viral load 12 weeks into treatment, predicts sustained virologic response to treatment; treatment may be stopped if patients do not demonstrate EVR. The recommended duration of treatment in patients with genotype 1 HCV and EVR is 48 weeks. For genotype 2 or 3, the optimal duration of treatment is not clear; some specialists treat for 24 weeks, whereas others treat for 48 weeks.

Adverse effects of treatment

HCV therapy may cause significant adverse effects. IFN reduces total white blood cell counts, and can cause neutropenia. It also decreases CD4 cell counts, although the CD4 percentage usually does not change. IFN can reduce HIV RNA somewhat (approximately a 0.5 $\log_{10}$ decrease). IFN may also produce flulike symptoms, depression, peripheral neuropathy, and other symptoms. Ribavirin can cause anemia and other adverse effects. Zidovudine and didanosine should be avoided, if possible, in patients taking HCV treatment.

HCV treatment should not be given during pregnancy, and women receiving HCV treatment should avoid

pregnancy. Ribavirin is teratogenic, and both women and men must use contraception consistently during treatment with ribavirin and for 6 months after treatment. IFN may cause fetal growth abnormalities, and is abortifacient in animals.

Treatment of acute HCV

Treatment of acute HCV is associated with a much higher response rate than treatment during the chronic phase. However, delaying therapy for 12 weeks to ascertain whether spontaneous clearance will occur does not affect treatment response rates. Treatment with PEG-IFN monotherapy has been associated with viral eradication in >90% of patients. Treatment for 24 weeks appears to be sufficient to clear HCV.

Timing of HCV treatment and HIV treatment

The decision of whether and when to treat HCV among people infected with HIV must be determined individually. When coinfected patients require treatment for both infections, some experts begin with HIV treatment in hope that by improving CD4 counts, they may enhance the response to HCV therapy, even though CD4 cell counts by themselves are not firmly associated with an increased likelihood of a sustained virologic response. Other experts choose to treat HCV before initiating ARV therapy (ART) in those with high CD4 counts and low HIV viral loads to simplify treatment and improve the tolerability of ART. Consult with an HCV treatment expert to determine the appropriateness and timing of HCV treatment.

Some patients with HCV will experience worsening of hepatic function during ART, and liver function tests should be monitored closely. Some ARV medications are hepatotoxic and should be avoided or used cautiously; these include nevirapine, tipranavir, and high-dose ritonavir. Numerous other medications (eg, fluconazole and isoniazid) are hepatotoxic and can pose problems for people with impaired liver function.

Other Care Issues

Acute hepatitis A or hepatitis B infection in persons with chronic HCV can cause fulminant liver disease. All patients with HCV infection should be tested for immunity to hepatitis A and hepatitis B; patients who are not immune should be vaccinated.

Persons with HCV infection should be counseled to avoid exposure to hepatotoxins, including alcohol and hepatotoxic medications (eg, acetaminophen in large doses, fluconazole, and isoniazid). All patients should be counseled to reduce the risk of transmitting HCV to others. As appropriate, patients should be advised to adopt "safer sex" approaches, avoid blood exposures (eg, from sharing razors or tattoo equipment), practice safe drug injection techniques, and avoid pregnancy.

Patient Education

- Most patients with HCV will remain asymptomatic for several years. However, ongoing injury to the liver occurs during this time and can culminate in liver failure. Patients can slow the damage by avoiding alcohol and any medications (including over-the-counter drugs and recreational drugs) that may damage the liver. Patients should contact their pharmacist or health care provider if they have questions about a specific medication or supplement.
- As with HIV, patients must avoid passing HCV to others. Instruct patients not to share toothbrushes, dental appliances, razors, sex toys, tattoo equipment, injection equipment, or personal care items that may have blood on them. Emphasize the importance of safer sex to protect themselves and their partner(s).
- Tell patients to discuss HCV with their sex partner(s), and suggest that partner(s) get tested for HCV.
- Pregnant women have a high risk of transmitting HIV or HCV infection to the baby because each virus makes it easier to transmit the other. Women who are pregnant or considering pregnancy should talk with a specialist in HIV and HCV to discuss ways to decrease the infection risk for the baby.
- HCV medications (ribavirin and interferon) should not be given during pregnancy. Both men and women who are taking ribavirin should use contraception consistently during ribavirin therapy and for 6 months after completion of treatment.
- If children were born after women were infected with HCV, consider having them tested as well. Even though their risk is low, they should be screened for HCV.
- Certain ARV drugs are more likely to cause problems with the liver because of HCV. Advise patients that if they start an ARV regimen, their liver function tests should be watched carefully to be sure that the body is able to process the medicines.
- Patients who not been vaccinated against hepatitis A need to receive 2 vaccinations 6 months apart.

Hepatitis A can cause severe illness damage, or even death, in people with HCV.

- Patients who have not been vaccinated against hepatitis B should complete the vaccine series, which requires 3 shots. If patients have been vaccinated in the past, they should have the anti-HBV titer checked to make sure that they are still protected.
- Hepatitis B can worsen liver function greatly if it is acquired in addition to HCV. Patients who are not immune to hepatitis B should use safer sex (latex barriers) to avoid exposure. Patients who use injection drugs should not share needles or injection equipment.
- Patients who use injection drugs should consider entering a treatment program. Quitting drug use will reduce the strain on the liver, protect patients from other blood-borne illnesses that can affect the liver, and help prevent transmission of HCV to others. Patients who are not ready to stop injection drug use should let their providers know so that they can try to help find a source for clean, single-use needles.
- Hepatitis C is not spread by coughing, sneezing, hugging, sharing food and water, or other casual contact.
- The HCV treatments interferon alfa and ribavirin can cause flulike symptoms, body aches, fevers, anemia, neuropathy, and depression. Most of these adverse effects are treatable with medications. Patients should contact their medical provider right away if they experience depression. Antidepressant medications that can help relieve depression, but the medications take a couple of weeks to become effective.

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Herpes Simplex, Mucocutaneous

Background

Herpes simplex virus (HSV) types 1 and 2 cause both primary and recurrent oral and genital disease. HSV usually appears as a vesicular eruption of the mucous membranes of the oral or perioral area, vulva, perianal skin, rectum, and occasionally the inguinal or buttock areas. The eruption develops into tender or painful ulcerated lesions that are frequently covered with a clear yellow crust. In some patients, however, the typical painful vesicular or ulcerative lesions may be absent. Persons with HIV disease and low CD4 counts have more frequent recurrences of HSV and more extensive ulcerations than HIV-uninfected people. Persistent HSV eruption (>1 month) is an AIDS-indicator diagnosis.

S: Subjective

The patient may complain of eruption of red, painful vesicles or ulcers ("fever blisters") with or without an exudate in the mouth, on the genitals, or in the perianal area. The patient may complain of burning, tingling, or itching before eruption of the lesions.

The vesicles will rupture and ulcerate, generally crusting over and healing in approximately 7-14 days. The lesions may be pruritic and are often painful. As immunosuppression progresses, the lesions may recur more frequently, grow larger or coalesce, and become chronic and nonhealing.

Perform a history, asking the patient about the symptoms above, duration, associated symptoms, and history of HSV or similar symptoms.

O: Objective

Look for punctate, grouped vesicular or ulcerative lesions on an erythematous base on the mouth, anus, or external genitals, or are visible on speculum or anoscopic examination. When immunosuppression is severe, lesions may coalesce into large painful ulcerations that spread to the skin of the thighs, lips, face, or perirectal region. Recurrent lesions may start atypically, first appearing as a fissure, pustule, or abrasion.

A: Assessment

A partial differential diagnosis includes:

- Oral aphthous ulcers
- Chancroid
- Syphilis
- Cytomegalovirus
- Candidiasis
- Drug-related eruption

P: Plan

Diagnostic Evaluation

The diagnosis of HSV is usually based on the clinical appearance and symptoms, without laboratory testing.

If the diagnosis is uncertain, obtain a specimen from a freshly opened vesicle or the base of an ulcer for culture confirmation. Note that lesions that are >72 hours old or are beginning to resolve may not show HSV in culture.

Polymerase chain reaction (PCR) is also a sensitive diagnostic test for detection of herpes DNA in ulcerative lesions, but is more expensive and less widely available than viral culture.

If culture is not available, perform a Tzanck smear by staining scrapings from the base of the lesion with Giemsa or methylene blue to reveal multinucleated giant cells. Note that this test is fairly insensitive.

If cultures are negative and there is a high suspicion of HSV infection, skin may be taken from the edge of the ulcer for biopsy. Biopsy material may also be cultured.

Single serologic tests that detect HSV-1 or HSV-2 antibodies can determine whether a patient has ever been infected with herpes, and a 4-fold or greater rise in antibody titer between acute and convalescent serum specimens may diagnose primary HSV. However, only about 5% of persons with recurrences will develop a 4-fold rise in titer.

Strongly consider checking for syphilis with a rapid plasma reagin (RPR) or Venereal Disease Research Laboratory (VDRL) test in any patient who presents with genital, anal, or oral ulceration.

Treatment

Empiric treatment for suspicious lesions is often initiated in the absence of laboratory confirmation. In some instances, treatment can be started empirically and, if no response is seen within 7-10 days, laboratory studies could be undertaken.

Episodic outbreak

- Acyclovir (Zovirax) can be given 400 mg orally 3 times daily or 200 mg orally 5 times daily until ulcers heal, usually within 7-14 days. This treatment helps the healing of lesions but does not prevent recurrences. Large, extensive ulcers may need to be treated for a longer period of time.
- Famciclovir (Famvir) 500 mg orally for 7-14 days is another option but is more expensive than acyclovir.
- Valacyclovir (Valtrex) 1,000 mg orally twice daily for 7-14 days is also more expensive than acyclovir.

Adjust the dosage for renal impairment.

Severe disease

- Treat initially with intravenous acyclovir.

Acyclovir-resistant HSV

- The diagnosis of acyclovir-resistant HSV should be confirmed with culture and sensitivities. Cross-resistance to famciclovir, valacyclovir, and ganciclovir will be present as well. The usual alternative is foscarnet (40 mg/kg every 8 hours intravenously); other possibilities include topical trifluridine and topical cidofovir.

Chronic suppressive therapy

- Consider suppressive therapy with acyclovir (200-400 mg orally twice daily), famciclovir (250 mg orally twice daily), or valacyclovir (500 mg orally twice daily) for patients with frequent or severe recurrences. Treatment should be continued indefinitely. Note that suppressive therapy also reduces the risk of transmission of HSV.

Patient Education

- Patients should be told that HSV has no cure, and outbreaks may occur at intervals for the rest of their lives.
- HSV is easily spread through kissing (if mouth or lips are infected) and sexual contact (oral, anal, or vaginal). HSV is often is transmitted when no lesions are present, so it is important that patients inform their sex partners of their herpes infection before sex. Patients must avoid all sexual contact while lesions are visible, because a lot of virus is present at those times. Condom use at each sexual encounter offers the best chance of preventing HSV transmission. If HSV is transmitted, sexual partners also will have it for life.
- Instruct patients to avoid use of occlusive dressings or ointments, which can prevent healing of sores.
- Acyclovir is most effective when taken early in the outbreak, so patients not taking suppressive therapy should keep medication on hand and start treatment at the first signs of eruption.
- HSV in a pregnant woman can cause severe illness in the newborn, so women must inform their obstetricians and pediatricians if they are exposed to or infected with HSV during pregnancy. Pregnant women should avoid having sex with partners who have HSV. Men who have HSV should avoid having sex with pregnant women who do not have HSV, because new HSV infection during pregnancy is much riskier to the baby than HSV infection acquired before the pregnancy.

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Herpes Zoster/Shingles

Background

Shingles is a skin or mucosal infection caused by the varicella-zoster virus (VZV) that occurs along a dermatome and represents a reactivation of varicella (chickenpox). Zoster is common in patients with HIV infection, including apparently healthy individuals before the onset of other HIV-related symptoms. The incidence may be higher at low CD4 cell counts and also within 4 months of initiating effective antiretroviral therapy.

Zoster may be particularly painful or necrotic in HIV-infected individuals. Disseminated infection, defined as outbreaks with >20 vesicles outside the primary and immediately adjacent dermatomes, usually involves the skin and the visceral organs. Neurologic complications of zoster include encephalitis, transverse myelitis, and vasculitic stroke.

S: Subjective

The patient complains of painful skin blisters or ulcerations along 1 side of the face or body. Loss of vision may accompany the appearance of facial lesions. Pain in a dermatomal distribution may precede the appearance of lesions by many days (prodrome).

Assess the following during the history:

- Duration of pain or blisters (average of 2-3 weeks if untreated)
- Location of pain or blisters; severity of pain
- History of chickenpox (usually in childhood)

O: Objective

Perform a skin and neurologic examination to include the following:

- Vesicular lesions with erythematous bases in a dermatomal distribution; may be bullous or hemorrhagic
- Necrotic lesions; may persist for as long as 6 weeks
- Dermatomal scarring (particularly in dark-skinned individuals)
- Lesions in the eye area or tip of nose, along the trigeminal nerve represent ophthalmic nerve involvement, which requires immediate evaluation and intravenous treatment (see below)

A: Assessment

- Rule out other causes of vesicular skin eruptions (eg, herpes simplex virus, severe drug reactions).
- Assess contact exposures (see below).

P: Plan

Diagnostic Evaluation

The diagnosis is usually clinical and is based on the characteristic appearance and distribution of lesions. If the diagnosis is uncertain, perform viral cultures or antigen detection by direct fluorescent antibody from a freshly opened vesicle or biopsy from the border of a lesion.

Treatment

- Treatment ideally should begin within 72 hours of an outbreak or while new lesions are appearing. Famciclovir (Famvir) 500 mg orally 3 times per day for 7-10 days or valacyclovir (Valtrex) 1 g orally every 8 hours for 7 days is the preferred regimen and may attenuate a herpes/VZV attack if started early.
- An alternative treatment is acyclovir 800 mg orally 5 times per day.
- Dosage reductions of these drugs are required for patients with renal impairment.
- If new blisters are still appearing at the end of treatment, repeat course of oral therapy or consider intravenous treatment. Adjunctive corticosteroids aimed at preventing postherpetic neuralgia are not recommended.
- Consult an ophthalmologist immediately if lesions appear in the eye area or on the tip of the nose, or if patient complains of visual disturbances, because VZV-related retinal necrosis can cause blindness. Because of the rapid progression associated with this diagnosis, hospitalization for intravenous acyclovir and possibly foscarnet is recommended.

- VZV from zoster lesions is contagious, and contact or airborne spread from vesicle fluid may cause chickenpox in nonimmune people. If a zoster patient's household includes a pregnant woman (HIV infected or uninfected) or an HIV-infected child, consult with a specialist immediately for advice on management of exposed household members. (See "Postcontact Chickenpox Prevention" below.)
- Give analgesics for pain; narcotics may be required.
- Antiviral therapy may reduce the risk of postherpetic neuralgia, but if it does occur, special pain control techniques will be required:
  - Nortriptyline 10-20 mg should be taken every night at bedtime and increased until pain is controlled and adverse effects remain tolerable. Other tricyclics may be used.
  - Lidocaine 5% patches provide good local relief with minimal systemic absorption. Up to 3 patches may be applied simultaneously to the affected area for up to 12 hours in a 24-hour period.
  - Gabapentin is given at 100-300 mg orally 3 times per day; this may be increased until reaching 3,600-mg total daily dosage.
  - Sustained-release opiates may be required.

(See chapter *Pain Syndrome and Peripheral Neuropathy* for more options and specific recommendations.)

Severe or unresponsive cases

- Intravenous acyclovir may be indicated if:
  - The patient is severely immunocompromised
  - The ophthalmic branch of the trigeminal nerve is affected (as noted above)
  - Dissemination has occurred
  - Lesions are not responsive to oral therapy
  - Pain is intractable
- The usual adult dosage is 10-12 mg/kg every 8 hours for 7-14 days; dosage reduction is required for patients with renal impairment. Refer to an infectious disease specialist.
- Acyclovir resistance may occur in patients previously treated with acyclovir or related drugs, and foscarnet may be required for effective treatment. Resistance should be suspected if lesions are not resolving after 10 days of therapy or if they develop a verrucous appearance. Such lesions should be cultured and drug sensitivities should be obtained.

Postcontact Chickenpox Prevention

All persons, including pregnant women, who have close contact with a patient who has chickenpox or shingles must be treated to prevent chickenpox. Those who have no history of chickenpox or shingles or no detectable antibody against VZV should be administered varicella zoster immune globulin as soon as possible, but at least within 96 hours after contact. Even immunocompetent adults with primary VZV (chickenpox) can develop viral dissemination to the visceral organs. HIV-infected patients may develop encephalitis, pneumonia, or polyradiculopathy during primary zoster (chickenpox) or reactivated zoster (shingles).

Patient Education

- Patients should bathe the skin lesions in mild soap and water. For necrotic lesions, patients should use warm, moist compresses 2-3 times a day to remove debris.
- Antibiotic ointments may help prevent secondary infection and keep dressings from sticking.
- Advise patients to take their medications as directed, and to call the clinic if symptoms worsen.

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Histoplasmosis

Background

Histoplasmosis is caused by *Histoplasma capsulatum*, a fungus that thrives in soil contaminated by certain bird and bat droppings. In the United States, *H capsulatum* is found most often along the Ohio and Mississippi river valleys, and in the central, mid-Atlantic and south-central states, from Alabama to southwest Texas. In highly prevalent areas, such as Indianapolis and Kansas City, more than 80% of the population has been exposed to *Histoplasma* through inhalation of airborne infectious elements. Histoplasmosis is also found in the Canadian provinces of Quebec and Ontario, Mexico, Central and South America, Africa, East Asia, and Australia.

The initial infection usually causes no symptoms or only in mild flulike illness. However, immunosuppressed individuals may develop disseminated disease. Progressive disseminated histoplasmosis often represents a reactivation of latent infection, occurs late in the course of HIV disease (the CD4 count usually is <150 cells/μL), and is an AIDS-defining illness. Pulmonary histoplasmosis (without dissemination) may occur in people with higher CD4 counts. Within endemic areas, histoplasmosis accounts for 5% of opportunistic infections among AIDS patients. In hyperendemic areas, the prevalence of histoplasmosis may reach 25% among patients with AIDS. The incidence of histoplasmosis in the United States has declined with the use of effective antiretroviral therapy (ART).

Table 1 describes common clinical features that may be associated with histoplasmosis.

S: Subjective

Histoplasmosis may be difficult to diagnose because the symptoms are nonspecific. In addition, clinicians may not suspect this diagnosis in low-prevalence areas.

The patient complains of fever, weight loss, fatigue, cough, and shortness of breath. He or she may also note skin lesions, adenopathy, central nervous system (CNS) changes, oropharyngeal ulcers, nausea, diarrhea, or abdominal pain. Symptoms usually begin several weeks before presentation. On occasion, histoplasmosis presents abruptly as a sepsis-like syndrome.

The following activities are associated with significant risk of exposure (note that absence of reported exposures does not rule out histoplasmosis):

- Residence or travel in endemic areas (or coastal AIDS centers of New York, Los Angeles, San Francisco, and Miami)
- Occupational history of farming or construction/remodeling
- Hobbies that involve contact with caves, bird roosts or nests, or farm areas
- Contact with soil with a high organic content and undisturbed bird droppings, such as around old chicken coops and bird roosts

Table 1. Common Clinical Manifestations of Histoplasmosis

Symptom Group	% Cases	Examples
Constitutional	95%	• Weight loss • Fever
Gastrointestinal	>10%	• Splenomegaly • Hepatomegaly • Diarrhea • Abdominal pain
Respiratory	50-60%	• Pneumonia • Pneumonitis
Hematologic	>50%	• Anemia • Leukopenia • Thrombocytopenia
Neurologic	15-20%	• Meningitis, cerebritis • Encephalopathy • Focal parenchymal lesions
Septic	10-20%	• Hypotension • Respiratory insufficiency • Renal or hepatic failure • Disseminated intravascular coagulopathy • High fever
Dermatologic	<10%	• Follicular, pustular, maculopapular, or erythematous lesions

O: Objective

Measure vital signs and document fever. Perform a complete physical examination, with special attention to the lymph nodes, lungs, abdomen, skin, and neurologic system. Common findings include enlargement of the liver, spleen, and lymph nodes. Skin lesions and oropharyngeal ulcers may be seen.

A: Assessment

A partial differential diagnosis includes:

- Other deep-seated fungal infections, such as cryptococcosis and coccidioidomycosis
- Mycobacterial disease (*Mycobacterium tuberculosis* or *Mycobacterium avium* complex
- Pneumocystic pneumonia
- Lymphoma

P: Plan

Diagnostic Evaluation

- The *H capsulatum* polysaccharide antigen test is sensitive and specific. The test is most sensitive for urine samples, but can be used on serum, bronchial fluids, or cerebrospinal fluid specimens. Results may be obtained in a few days. Urine antigen levels can be used to monitor the response to therapy. The antigen test is available from a private laboratory, MiraVista Diagnostics (http://www.miravistalabs.com).
- Cultures of blood, bone marrow, and specimens from other sources have reasonable sensitivity but may take several weeks. Wright stain of buffy coat of blood may reveal intracellular organisms.
- Biopsies of lymph nodes, liver, cutaneous lesions, and lungs may be diagnostic in up to 50% of cases; bone marrow can be stained with methenamine silver to show the organism within macrophages.
- Lactate dehydrogenase (LDH) and ferritin, although not specific, may be markedly elevated in disseminated disease.
- Complete blood count and chemistry panels may show pancytopenia, elevated creatinine, or abnormal liver function tests.

Treatment

Treatment consists of 2 phases: induction and chronic maintenance.

Induction therapy

Mild to moderate disseminated histoplasmosis without CNS involvement

Administer itraconazole 200 mg orally 3 times daily or 300 mg orally twice daily for 3 days, followed by itraconazole 200 mg twice daily for 12 weeks. (See "Treatment note" below regarding itraconazole.) Induction therapy must be followed by maintenance therapy (see below).

Severe disseminated histoplasmosis

Severe infection requires intravenous induction therapy with amphotericin B 0.7-1.0 mg/kg/d (or a lipid formulation 3-5 mg/kg/d). After 3-10 days of therapy and stabilization of the patient's clinical status, therapy may be switched to itraconazole 200 mg twice daily to complete 12 weeks of therapy. If itraconazole is not available or is not tolerated, fluconazole 800 mg orally once daily can be used as an alternative. (See "Treatment note" below regarding itraconazole and fluconazole.) CNS infection must be treated with a full course of amphotericin B, because of poor penetration of itraconazole into the CNS. Induction therapy must be followed by maintenance therapy (see below).

Maintenance/suppressive therapy

Lifelong maintenance therapy must be given to prevent relapse after the 12-week course of induction therapy and typically includes itraconazole 200 mg orally once daily or twice daily. Amphotericin B 50 mg once weekly or fluconazole 400-800 mg daily are alternatives for those who cannot tolerate or cannot obtain itraconazole. (See "Treatment note" below regarding itraconazole and fluconazole.)

It is not known whether maintenance therapy can be discontinued safely in patients who achieve immune reconstitution during antiretroviral therapy.

Treatment note

Itraconazole and fluconazole may cause fetal abnormalities if taken during the first trimester of pregnancy. Check pregnancy status in women of childbearing potential before starting these medications, and ensure that women are using appropriate birth control. Note the possibility of drug interactions involving itraconazole, especially with rifamycins.

Patient Education

- Histoplasmosis is not transmitted from person to person, so isolation is not necessary.
- Patients should take all of their medications exactly as prescribed by their health care providers.
- Even with maintenance therapy, relapses can occur. Patients should call their providers immediately if symptoms worsen.
- Itraconazole and fluconazole may cause birth defects. Women who are taking either of these medicines should avoid pregnancy. In addition, itraconazole interacts with some other medications; patients should tell their providers if they begin any other new medicines while taking itraconazole.

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Kaposi Sarcoma

Background

Kaposi sarcoma (KS) is an endothelial neoplasm that usually occurs as skin or oral lesions but may involve the internal organs. It is the most common AIDS-associated neoplasm and is an AIDS-defining disease. AIDS-associated KS is 1 of 4 types of KS, along with classic, endemic, and organ transplant-associated KS. Although the types vary in epidemiology and clinical presentation, all are associated with human herpesvirus type 8 (HHV-8), also known as KS-associated herpesvirus. The clinical manifestations of AIDS-associated KS (sometimes called epidemic KS) range in severity from mild to life threatening. The progression of disease may be rapid or slow, but the overall prognosis is poor in the absence of treatment. The skin lesions of KS, even when they do not cause medical morbidity, may cause significant disfigurement and emotional distress.

AIDS-associated KS usually occurs in HIV-infected persons with advanced immunosuppression (CD4 count <200 cells/μL), but may occur at any CD4 count. In the United States and Europe, KS occurs in all HIV risk groups, but most frequently in men who have sex with men (MSM). Risk factors in MSM include multiple sexual partners and a history of sexually transmitted infections (STIs); risk factors in other groups have not been clearly identified. The transmission of HHV-8 is not well understood. Although experts believe HHV-8 is transmitted sexually, it apparently also passes from person to person by other routes.

The incidence of KS in resource-abundant countries has declined markedly since the early 1990s, in part because of the widespread availability of effective combination antiretroviral therapy (ART). In parts of sub-Saharan Africa, where endemic KS has long existed in people with normal immune function, the incidence of KS has risen sharply in people with HIV/AIDS. ART appears to be effective in reducing the risk of AIDS-associated KS, particularly when initiated before the development of advanced immunosuppression.

S: Subjective

The cutaneous presentation of KS is the most common, occurring in 95% of cases. The patient may complain of a new painless pigmented (often purplish) lesion or lesions on the skin (usually of the extremities, face, or torso), or in the mouth. Lesions on the lower extremities, genitals, or face may be accompanied by swelling and pain. The patient may complain only of swelling or edema, without skin lesions, or may note enlarged lymph nodes. Oral lesions, if extensive, may cause tooth loss, pain, and ulceration.

Pulmonary KS may cause intractable cough, bronchospasm, hemoptysis, chest pain, and dyspnea.

Gastrointestinal KS may cause no symptoms, or the patient may have bleeding, pain, and symptoms of bowel obstruction.

During the history, ask about the symptoms noted above and associated characteristics, including the following:

- Duration of lesion(s)
- Pain
- Frequency of new lesions
- Respiratory or gastrointestinal symptoms
- Edema or swelling
- Recent CD4 cell counts.

O: Objective

Physical Examination

Perform a careful physical examination, with particular attention to the following:

- Vital signs
- Skin (examine the entire skin surface)
- Oropharynx
- Extremities and external genitals (look for lesions, edema)
- Lymph nodes

Examine the lungs, abdomen, rectum, and other systems as indicated.

Common Manifestations

Skin lesions

Skin lesions may occur anywhere on the skin. Common sites include the face (under the eyes and on the tip of the nose), behind the ears, and on the extremities and torso. Lesions may be macules, papules, plaques, or nodules. At first, the lesions are small and may be flat. Their color may vary from pink or red to purple or brown-black (the latter particularly in dark-skinned individuals), and they are nonblanching, nonpruritic, and painless. Over time, the lesions often increase in size and number, darken, and rise from the surface; they may progress to tumor plaques (eg, on the thighs or soles of the feet), or to exophytic tumor masses, which can cause bleeding, necrosis, or extreme pain.

Oral lesions

Oral lesions may be flat or nodular and are red or purplish. They usually appear on the hard palate, but may develop on the soft palate, gums, tongue, or elsewhere.

Lymphedema

Lymphedema associated with KS usually appears in patients with visible cutaneous lesions, and edema may be out of proportion to the extent of visible lesions. Lymphedema may also occur in patients with no visible skin lesions. Common sites include the face, neck, external genitals, and lower extremities. Usually, a contiguous area of skin is also involved. Lymph nodes may be enlarged.

Pulmonary KS

Pulmonary KS usually causes severe, pneumonia-like symptoms and is rapidly progressive. The patient may exhibit difficulty breathing, bronchospasm, cough (sometimes with hemoptysis), and hypoxemia. The chest x-ray typically shows diffuse interstitial infiltrates, often accompanied by nodules or pleural effusion.

Gastrointestinal KS

Gastrointestinal KS may arise anywhere in the gastrointestinal tract. Patients are usually asymptomatic except in cases of intestinal obstruction or bleeding. KS may also cause protein-losing enteropathy. Visceral disease is uncommon in the absence of extensive cutaneous disease.

A: Assessment

The partial differential diagnosis depends on the type of symptoms present.

For cutaneous, oral, and lymph node presentations, consider the following:

- Bacillary angiomatosis
- Lymphoma
- Dermatofibromas
- Bacterial or fungal skin infections
- Stasis

For pulmonary symptoms, consider:

- *Pneumocystis jiroveci* pneumonia (PCP)
- Cytomegalovirus (CMV) pneumonia
- Pulmonary lymphoma (rare)

P: Plan

Diagnostic Evaluation

For cutaneous or oral KS, a presumptive diagnosis can often be made by the appearance of skin or mucous membrane lesions. Biopsy of a lesion (or a suspect lymph node) is recommended to verify the diagnosis and rule out infectious or other neoplastic causes. Biopsy is particularly important if the lesions are unusual in appearance or if the patient has systemic or atypical symptoms.

If respiratory symptoms are present, obtain chest x-rays or computed tomography (CT) studies. Radiographic findings may be suggestive of KS, but cannot provide a definitive diagnosis. Bronchoscopy with visualization of characteristic endobronchial lesions is usually adequate for diagnosis.

For patients with gastrointestinal symptoms and suspected KS, perform endoscopy.

Review recent CD4 cell counts. The CD4 count is typically low (<200 cells/μL) but KS can occur with any CD4 count.

If the patient has fever or respiratory, gastrointestinal, or constitutional symptoms, evaluate for other infectious and malignant causes (eg, by culture or biopsy) as suggested by the history and physical examination.

Treatment

Treatment of KS is not considered curative, and no single therapy is completely efficacious. ART is a key component of the treatment of KS and should be initiated (or maximized) in all persons with KS, unless contraindicated (for further information, see chapter *Antiretroviral Therapy*). KS often regresses and sometimes resolves in patients treated with effective ART. Other treatment modalities may be used concurrently, depending on the severity of KS and the speed of progression. Consult with a KS-experienced oncologist or dermatologist.

Specific treatment of KS depends on various factors such as the number, extent, severity, and location of lesions; cosmetic considerations; and presence of visceral involvement. The goals of therapy may also vary according to the clinical presentation and may include controlling symptoms, improving cosmetic appearance, reducing edema, eliminating pain, and clearing lesions.

Local treatment (preferably in conjunction with ART) is usually given to patients who have a few small lesions causing only minor symptoms. Systemic therapy (in conjunction with ART) is needed for more extensive or more severe disease, including symptomatic visceral disease, widespread skin involvement, significant edema, and rapidly progressive KS.

Local treatment of limited disease

Options for local treatment of limited disease include the following:

- ART followed by observation for response (limited, stable cutaneous disease may require no specific treatment)
- Topical treatment with alitretinoin gel (Panretin) 0.1%
- Intralesional chemotherapy (eg, vinblastine)
- Radiation therapy, for localized or facial lesions (may cause mucositis when used for oropharyngeal lesions)
- Cryotherapy
- Laser therapy

Treatment of extensive or rapidly progressing disease

Extensive or rapidly progressing disease may include lymphedema, intraoral or pharyngeal disease that interferes with eating, pulmonary KS, and painful or bulky lesions. Options for treatment include:

- Intralesional chemotherapy (eg, vinblastine)
- Systemic chemotherapy (eg, liposomal formulations of doxorubicin or daunorubicin, vincristine, paclitaxel [Taxol], etoposide [VP16], or bleomycin; these agents can be used alone or in combination for visceral or extensive cutaneous disease)
- Interferon-alfa

Patient Education

- KS often responds to treatment. Educate patients that ART is a cornerstone of treatment; encourage them to start and adhere to ART.
- Swollen or edematous lesions increase the risk of cellulitis, whereupon lesions can become infected and progress rapidly. Advise patients to avoid injuring swollen or edematous lesions, to keep them clean, and to call their health care provider if lesions appear to be spreading or if swelling worsens.
- Advise patients to return to the clinic if respiratory or gastrointestinal symptoms develop.
- Patients may use cosmetic preparations to cover facial lesions. Refer patients to support groups or counseling services if they are having difficulty coping with their physical appearance.

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Molluscum Contagiosum

Background

Molluscum contagiosum is a benign viral infection of the skin, caused by a double-stranded DNA virus of the Poxviridae family. Transmission occurs by direct bodily contact (eg, through sexual activity), fomites (eg, underwear), or self-inoculation. The incubation period is 14-50 days. The infection is most common in children, sexually active adults, and immunocompromised persons and occurs in 5-18% of HIV-infected patients. In immunocompetent persons, the infection usually lasts 6 to 12 months, although genital lesions in HIV uninfected adults may persist longer. Persons with HIV infection may have extensive lesions and a strong correlation exists between the degree of immunosuppression and the risk of molluscum, the number of lesions, and their resistance to treatment.

S: Subjective

The patient complains of new or increased papular lesions on the face, upper trunk, or genitals. Papules of molluscum contagiosum may cause no symptoms or can be pruritic or tender to the touch. Genital lesions are transmitted sexually; the patient may recall seeing such lesions on the genitals of a previous partner. Ask about fever or other systemic symptoms.

O: Objective

Perform a thorough evaluation of the skin, the genitals, and the mouth. Molluscum lesions are white, pink, or flesh-colored; smooth-surfaced, firm, pearly, and spherical (dome-shaped) papules (2-5 mm) or nodules (6-10 mm), with umbilicated centers. Lesions are usually found on the head or neck and the genital area, but may affect every part of the body except the palms and soles of the feet. Molluscum may occur intraorally. Molluscum commonly presents as multiple lesions. Patients with HIV infection may develop giant lesions (>1 cm) or clusters of hundreds of small lesions.

A: Assessment

A partial differential diagnosis includes the following:

- Disseminated cryptococcosis
- Other fungal infection
- Folliculitis
- Syphilis, condyloma acuminata, vulvar syringoma for multiple small molluscum genital lesions
- Squamous or basal cell carcinoma for large, solitary genital lesions

P: Plan

Diagnostic Evaluation

The diagnosis of molluscum is usually based on the characteristic appearance of the lesions. Perform laboratory testing, if indicated, to exclude other infections or malignancies.

Treatment

Because molluscum does not cause illness and rarely causes symptoms, the goal of treatment is primarily cosmetic. Molluscum is difficult to eradicate in HIV-infected patients, and lesions often recur, particularly if immune suppression persists. Effective antiretroviral therapy may achieve resolution of lesions or significant improvement in the extent or appearance of molluscum. Refer complex cases to a dermatologist. Other therapeutic options include:

- Local excision may be done by electrocautery, evisceration, curettage, or cryotherapy. Adverse effects include pain, irritation, soreness, and mild scarring. Repeated treatments are necessary.
- Imiquimod 5% (Aldara), an immune response modifier, stimulates production of interferon-alpha and other proinflammatory cytokines, inducing a tissue reaction known to be associated with viral clearance from the skin. Apply 3 times per week for up to 16 weeks or nightly for 4 weeks. Clearing can take up to 3 months.
- Tretinoin (Retin-A) 0.1% cream can be applied to lesions twice daily. Adverse effects include drying, peeling, irritation, and soreness.

- Podophyllum resin (podophyllin) is administered by a health care provider and washed off after 1-4 hours. This treatment is caustic and may cause significant irritation, is contraindicated in pregnancy, and has limited effectiveness.
- Patient-administered podophyllotoxin (Podofilox) may be a safer alternative to podophyllum. Adverse effects include burning, pain, inflammation, erosion, and itching.
- Trichloroacetic acid is administered by a health care provider. Controlling the depth of acid penetration is difficult. Adverse effects include pain, irritation, and mild scarring are common.
- Laser therapy may be used to remove lesions.
- Cidofovir 1% to 3% topical cream, combined with a vehicle, is applied twice daily for 2 weeks, followed by a 30-day rest period and then 2 additional cycles. This treatment was effective in several small studies and case reports, but it is expensive and difficult to compound. No systemic adverse effects are noted.
- Investigational treatments include 5-aminolevulinic acid with subsequent photodynamic therapy and intravenous cidofovir.

Patient Education

- Molluscum infection is benign but may be distressing.
- Patients should avoid shaving in areas with lesions because shaving could spread the lesions to other areas.
- Molluscum infection may be transmitted both sexually and nonsexually, through direct contact with lesions. Patients should avoid close contact between their molluscum lesions and the skin, mouth, and genitals of other people. Latex condoms may not prevent transmission.

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Mycobacterium avium Complex

Background

Mycobacterium avium complex (MAC) is an opportunistic infection caused by species of *Mycobacterium* that can cause severe illness in people with advanced AIDS but rarely affects others. The risk of disseminated MAC (DMAC) is directly related to the severity of immunosuppression. DMAC typically occurs in persons with CD4 counts of <50 cells/μL, and its frequency increases as the CD4 count declines. In the absence of antibiotic prophylaxis, DMAC occurs in up to 40% of AIDS patients with CD4 counts of <50 cells/μL. Antimicrobial therapy, especially if given in conjunction with antiretroviral therapy (ART) that achieves immune reconstitution, can be successful in treating MAC disease. Specific antimicrobial prophylaxis and effective ART may also be used to prevent MAC in patients with advanced AIDS (see chapter *Preventing Exposure to Opportunistic and Other Infections*).

Mycobacterium organisms are common in the environment. They are found worldwide and have been isolated from soil, water, animals, birds, and foods. They usually enter the body through the respiratory or gastrointestinal tract and disseminate to cause multisystem infection, typically manifested by nonspecific symptoms and signs such as fever, sweats, weight loss, abdominal pain, fatigue, chronic diarrhea, and anemia and other cytopenias. MAC can also cause local disease such as central nervous system infection, soft-tissue or bone infections, or endocarditis. In patients with subclinical or incompletely treated MAC who have recently started ART, an immune reconstitution inflammatory syndrome may occur with localized lymphadenitis or paradoxically worsening symptoms may (see chapter *Immune Reconstitution Syndrome*).

S: Subjective

The patient complains of 1 or more of the following symptoms:

- Persistent or cyclic fever
- Night sweats
- Unintentional weight loss
- Anorexia
- Chronic diarrhea
- Weakness
- Fatigue
- Abdominal pain

During the history, ask about the following:

- Any symptoms as above, including duration and intensity. Ask about other symptoms of infection.
- Whether the patient is taking MAC prophylaxis or ART

O: Objective

Perform a full physical examination with particular attention to the following:

- Vital signs (temperature, heart rate, blood pressure, respiratory rate)
- Weight (compare with previous measurements)
- General appearance (cachexia, wasting, signs of chronic illness, jaundice, pallor)
- Lymph nodes (lymphadenopathy)
- Abdomen (hepatosplenomegaly, tenderness)

Review previous laboratory values, particularly the CD4 cell count (usually <50 cells/μL).

A: Assessment

Rule out other infectious or neoplastic causes of constitutional symptoms, anemia, or organomegaly. A partial differential diagnosis would include the following:

- *Mycobacterium tuberculosis*
- Cytomegalovirus
- Lymphoma
- *Bartonella*
- Disseminated fungal infection
- Pyogenic abscess
- Other septicemia

P: Plan

Diagnostic Evaluation

A definitive diagnosis requires isolation of MAC from the blood or other normally sterile body fluids or tissues (*M avium* cultured from sputum, bronchial washing, or stool may represent colonization rather than infection). Send blood for acid-fast bacilli (AFB) culture (2-3 samples drawn at different times will increase sensitivity).

Because MAC may take weeks to grow in culture, ancillary studies should be performed. These are not specific, but may be helpful in reaching a presumptive diagnosis:

- Complete blood count (CBC) for anemia, lymphopenia, thrombocytopenia
- Serum alkaline phosphatase (often elevated in DMAC)
- Computed tomography (CT) scan of the chest and abdomen (intra-abdominal and mediastinal lymphadenopathy or hepatosplenomegaly are often present)

If blood cultures are negative and MAC is suspected, consider biopsy of the lymph nodes, bone marrow, liver, or bowel (via endoscopy) to detect DMAC by microscopic examination for AFB and culture. If the evidence suggests pulmonary MAC, consider bronchoscopy and bronchoalveolar lavage.

Perform additional studies as indicated to rule out other causes of the patient's symptoms, including bacterial blood cultures, sputum for *M tuberculosis, Bartonella* studies, lymph node cytology for lymphoma, and stool cultures.

Treatment

Because antimicrobial resistance develops quickly with single-drug therapy, multidrug regimens must be administered for DMAC.

The U.S. Centers for Disease Control and prevention recommends the following 2-drug regimens:

- Clarithromycin 500 mg twice daily + ethambutol 15 mg/kg once daily,
- Azithromycin 500-600 mg once daily + ethambutol 15 mg/kg once daily

Some experts recommend including a third agent for more advanced disease or for patients not taking effective ART. The addition of rifabutin (300 mg daily) has been associated with increased mycobacterial clearance, but no survival benefit. A fluoroquinolone (eg, ciprofloxacin, levofloxacin) or amikacin may be used instead of rifabutin as a third agent, or in addition to rifabutin as a fourth agent; however, studies have not confirmed the clinical benefit of these medications.

Because immune reconstitution is essential for controlling MAC, all patients not already taking ART should begin ART, if possible. Patients taking suboptimal ART should be evaluated for enhancement of their regimen. The optimal timing of ART initiation in relation to MAC treatment is unclear. Because immune reconstitution from effective ART may cause a paradoxical inflammatory response if started during active DMAC infection, some experts recommend treating DMAC for about a month before adding antiretroviral (ARV) medications (see chapter *Immune Reconstitution Syndrome*). This strategy also helps to avoid or forestall interactions between DMAC and ARV drugs and the additive toxicities of these medications.

Clarithromycin is often considered the macrolide of choice for use in combination therapy for MAC, but azithromycin is equally efficacious and may cause fewer gastrointestinal adverse effects and drug interactions. In particular, clarithromycin should not be combined with efavirenz because the interaction will result in decreased efavirenz drug concentrations.

Rifabutin has significant interactions with many drugs, including ARV medications and therefore dosage adjustments or alternative agents may be needed (Table 1).

Table 1. Interactions between Rifabutin and Antiretroviral Medications: Contraindicated Combinations and Dosage Adjustments

Antiretroviral Agent	Management When Used with Rifabutin
Nonnucleoside Reverse Transcriptase Inhibitors	
Efavirenz	Use standard efavirenz dosage; increase rifabutin to 450-600 mg daily.
Nevirapine	Use standard dosage of nevirapine; give rifabutin at 300 mg daily or 3 times weekly.
Delavirdine	Do not combine.
Ritonavir-Boosted Protease Inhibitors	
Lopinavir/Ritonavir (Kaletra)	Give standard dosage of lopinavir/ritonavir; decrease rifabutin to 150 mg alternate days or 3 times weekly.
All Other Ritonavir-Boosted PIs	Give standard dosage of PI/ritonavir; decrease rifabutin to 150 mg on alternate days or 3 times weekly.
Unboosted Protease Inhibitors	
Ritonavir	Use ritonavir at standard dosage; give rifabutin at 150 mg on alternate days or 3 times weekly.
Amprenavir, Fosamprenavir	Use PIs at standard dosages; give rifabutin at 150 mg/day or 300 mg 3 times weekly.
Atazanavir	Give atazanavir at standard dosage; give rifabutin at 150 mg on alternate days or 3 times weekly.
Indinavir	Increase indinavir to 1,000 mg every 8 hours; give rifabutin at 150 mg/day or 300 mg 3 times weekly.
Nelfinavir	Increase nelfinavir to 1,000 mg every 8 hours; give rifabutin at 150 mg/day or 300 mg 3 times weekly.
Ritonavir	Give ritonavir at standard dosage; give rifabutin at 150 mg on alternate days or 3 times weekly.

Source: HIV InSite. Database of Antiretroviral Drug Interactions. San Francisco: UCSF Center for HIV Information. Available online at http://hivinsite.ucsf.edu/arvdb?page=ar-00-02. Accessed April 26, 2006.

The patient should show clinical improvement within the first weeks of treatment. If the patient is not responding to treatment after 2-4 weeks of therapy, assess adherence, consider adding 1 or more drugs, and consider evaluation for other or additional causes of the patient's symptoms. Consider repeating a blood culture with antimicrobial sensitivities in patients whose clinical status has not improved after 4-8 weeks of treatment. If immune reconstitution inflammatory reactions are suspected, consider adding anti-inflammatory medications (see chapter *Immune Reconstitution Syndrome*).

Treatment of MAC is generally required for the remainder of the patient's life, although it may be reasonable to discontinue MAC therapy if patients complete at least 12 months of MAC treatment, have no further symptoms, and demonstrate immune restoration in response to ART (an increase in CD4 counts to >100 cells/μL for at least 6 months). If MAC treatment is discontinued, the patient must be monitored carefully for any decrease in CD4 cell count or recurrence of MAC symptoms. Some clinicians verify negative AFB cultures before discontinuing therapy. Treatment should be resumed if the CD4 count drops to <100 cells/μL or if symptoms recur.

Patient Education

- Advise patients that antimycobacterial therapy alone will not eradicate MAC infection, but should decrease symptoms and improve quality of life. A response to treatment may take up to 4 weeks. If medications are discontinued, the disease almost always recurs, unless the CD4 count has increased to >50-100 cells/μL in response to ART.
- Patients must take all medicines exactly as prescribed. If doses are missed, or if the medication is stopped and restarted, *Mycobacterium* can develop resistance to the medications. If patients are having trouble taking the medications on schedule, they should contact their health care providers immediately.
- Educate patients about the benefits of ART in strengthening the immune system and preventing opportunistic infections such as DMAC.
- Urge patients to contact the clinic immediately if they notice worsening symptoms, or new symptoms.
- DMAC is an opportunistic infection of late-stage HIV and indicates profound immune suppression. Some patients may not respond to MAC treatment or to ART. Because this is a life-threatening disease, clinicians should discuss advance directives and durable power of attorney with patients. Referral to a social worker, mental health clinician, or chaplain experienced in such issues may facilitate this discussion.

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Mycobacterium tuberculosis: Treatment in the United States and Other High-Income Nations

Background

Tuberculosis (TB) is an infection caused by organisms in the family *Mycobacteria*. These organisms grow slowly and can be identified only with special staining techniques, a trait that led to the name "acid-fast bacteria." Organisms in the *Mycobacterium tuberculosis* (MTB) group cause human disease, usually a chronic pneumonia. The destruction of MTB may produce holes or cavities in the lung containing huge numbers of organisms. MTB can also cause disease in other individual organs (eg, lymph nodes, meninges, bone, pericardium, peritoneum, intestines, urogenital tract) and can disseminate to multiple organs, often including the lungs, blood, liver, and spleen.

TB is almost always transmitted by persons with active pulmonary TB who release large numbers of organisms in their sputum. The organisms remain suspended in the air for hours or days, making TB one of the most easily transmitted respiratory pathogens. Most immunologically healthy persons who are infected with MTB do not develop active TB but remain infected with inactive organisms (latent TB infection); only about 10% of infected persons develop active disease during their lifetimes. Persons with HIV infection have much higher rates of active TB and develop active disease at a rate approximating 10% per year.

Before the development of effective treatment, half of all persons with TB disease died within about 5 years; others recovered but were prone to relapse. Appropriate application of modern chemotherapy to drug-susceptible MTB disease cured at least 95% of persons in the pre-HIV era.

HIV and TB cause more deaths than any other infectious diseases worldwide, each claiming millions of lives annually. A biologic synergy exists between these infections: HIV-induced immunosuppression increases susceptibility to TB infection, and active TB infection enhances HIV replication through immunologic stimulation. The populations infected by these 2 pathogens overlap in many respects, creating epidemiologic synergy. Poverty, crowded living conditions, and inadequate efforts to reduce transmission combine to enhance the transmission of both organisms.

In the United States, most cases of TB occur among immigrants, and TB is a relatively infrequent AIDS-defining illness. Nevertheless, TB remains important to HIV clinicians in the United States because it is highly infectious yet curable with proper treatment and because improper treatment leads to drug resistance both in the original patient and in those to whom that patient transmits. Although other conditions (eg, malnutrition, diabetes, end-stage renal disease, pulmonary silicosis, iatrogenic immunosuppression) increase the risk of TB disease, HIV is by far the most important risk factor.

Classic pulmonary TB, with upper-lobe infiltrates and cavitary lesions, may occur in HIV-infected persons with relatively intact immunity. As the CD4 cell count decreases, TB is more likely to manifest atypically in the chest (without cavitary disease, or with lower-lobe disease, adenopathy, pleural effusions, or interstitial or miliary infiltrates), as extrapulmonary disease (particularly in lymph nodes, as meningitis, and as disseminated infection), or both. Bone, joint, and urogenital sites of TB are less commonly associated with HIV-induced immunosuppression. Symptoms and signs of TB in HIV-infected person therefore can vary widely.

Improper or erratic treatment may cause resistance to TB medications. MTB resistance to a single drug may complicate treatment, but usually does not prevent successful treatment. Resistance to several drugs (polydrug resistance) requires a longer course of therapy using medications that are less potent and cause more adverse effects, and markedly reduces the chance of cure. Resistance to both isoniazid and rifampin is called multidrug resistance (MDR) and makes treatment especially difficult. It is extremely important to try to avoid the development of drug resistance, especially MDR. Treatment of drug-resistant TB should be managed by experts or in consultation with experts.

S: Subjective

Persons with TB generally describe an illness lasting several weeks to months, associated with systemic features such as high fever, night sweats, loss of appetite, and weight loss. These symptoms may be nonspecific, but should raise the possibility of TB.

- Pulmonary TB causes a chronic productive cough, sometimes with hemoptysis; shortness of breath occurs late in the disease.
- TB adenitis causes enlargement of the lymph nodes (usually asymmetric involvement in 1 region) which may suppurate and drain but usually are not painful, hot, or erythematous.
- TB meningitis causes headache, gradual change in mental status, and sometimes cranial nerve abnormalities such as double vision or decreased hearing.
- Disseminated TB may occur with only systemic manifestations such as fever, sweats, and weight loss, with no localizing features.

Risks for TB include known previous contact with an active case, previous positive result of a tuberculin skin test (TST, also known as a purified protein derivative test [PPD]), exposure in congregate settings (such as homeless shelters and prisons, but also health care facilities), or travel or residence in countries with high rates of endemic TB. In the United States, persons with active or past substance use disorders and persons of color are more likely than others to have had TB exposure.

O: Objective

- Measure vital signs, including oxygen saturation.
- Measure weight; compare with previous values.
- Perform thorough physical examination with particular attention to the lungs, heart, abdomen, lymph nodes, and neurologic system.

Systemic signs of chronic disease and inflammation are common, including fever, night sweats (which may occur without awareness of the high fever that precedes them), and weight loss.

In patients with pulmonary TB, the breath sounds may be normal or focally abnormal; tachypnea and hypoxia occur only with extensive lung damage.

Extrapulmonary TB may present with focal adenopathy without local signs of inflammation, but perhaps with a draining sinus.

TB meningitis causes subacute or chronic symptoms, with neck stiffness and changes in mental status, with or without cranial nerve palsies caused by inflammation at the base of the brain or increased intracranial pressure.

Pericardial disease can be associated with the pain and friction rub of pericarditis or signs of pericardial tamponade.

Patients with disseminated TB may have diffuse adenopathy and hepatic or splenic enlargement.

A: Assessment

The differential diagnosis of TB is extensive and depends in part on the degree of immunosuppression (as indicated by the CD4 cell count) of the individual. It includes a broad range of bacterial, mycobacterial, viral, and fungal infections in addition to noninfections causes. A partial differential diagnosis of pulmonary TB includes:

- Bacterial pneumonia
- Pulmonary *Mycobacterium* pneumonia (nontuberculous)
- *Pneumocystis jiroveci* pneumonia (PCP)
- *Cryptococcus neoformans* pneumonia/pneumonitis
- Pulmonary Kaposi sarcoma
- *Toxoplasma* pneumonitis
- Disseminated histoplasmosis
- Disseminated coccidioidomycosis
- Cytomegalovirus pneumonia
- Bronchogenic carcinoma
- Non-Hodgkin lymphoma
- Influenza
- Pulmonary embolus
- Chronic obstructive pulmonary disease
- Reactive airway disease
- Congestive heart failure
- Lactic acidosis

P: Plan

Diagnostic Evaluation

During the initial evaluation, check complete blood count (CBC) and differential, sputum gram stain, sputum AFB stain and culture (see below) blood cultures, and chest x-ray. For patients with lymphadenopathy, consider fine needle aspiration biopsy for bacterial and AFB stains and culture, and cytologic evaluation. For patients with meningitis or central nervous system abnormalities, perform lumbar puncture (LP) and cerebral spinal fluid (CSF) analysis including cell count, protein, glucose, AFB smear, AFB, bacterial and fungal cultures. If focal neurologic abnormalities are present, obtain computed tomography (CT) scan of the head to rule out mass lesion before doing the LP. Perform other diagnostic tests as suggested by the clinical presentation.

Pulmonary TB can be associated with any chest x-ray appearance, including a normal x-ray. However, the chest x-ray classically demonstrates upper-lobe infiltrates with or without cavities. Patients with HIV-associated immunosuppression are more likely to have atypical chest x-rays, including absence of cavities, lower-lobe disease, hilar or mediastinal adenopathy, and pleural effusions. In disseminated TB, the chest x-ray may show a miliary pattern with small nodules ("millet seeds") scattered throughout both lungs.

Suspected TB should be evaluated aggressively. Diagnosis of TB should include identification of the organism in stained sputum smears or stains of biopsied tissue and confirmed by culture or nucleic acid amplification (such as polymerase chain reaction). All positive cultures should be tested for drug susceptibility. Proof of the diagnosis is important because other opportunistic diseases can mimic TB, and other mycobacterial infections requiring different treatment can occur in HIV-infected persons. Drug susceptibility testing is necessary because improper treatment of drug-resistant TB will lead to treatment failure, more severe drug resistance within the patient, and increased risk of transmission of drug-resistant TB.

A presumptive diagnosis of TB is made on acid-fast stains of expectorated sputum; 3 specimens should be sent for acid-fast staining and mycobacterial culture on 3 successive days (preferably first morning specimens). Sputum induction with nebulized saline can be used for patients who do not have spontaneous sputum production. Patients with suspected pulmonary TB and negative sputum smears should undergo bronchoscopy and transbronchial biopsy (which is more sensitive than bronchoalveolar lavage for TB). Young children cannot not produce sputum, so gastric lavage on 3 successive mornings can be performed to obtain swallowed sputum for smear (although false-positive smears occur) and culture.

The diagnosis of extrapulmonary TB generally requires microscopic examination of tissue and culture. An aspirate of a suspect lymph node will often be positive on smear, on histopathologic examination, and on culture. Specimens of organs with suspected TB can be obtained by CT-guided aspiration and biopsy, liver biopsy, bone marrow biopsy, "blind" needle biopsies of pleura or peritoneum, or thoracoscopy or laparoscopy-guided biopsies of pleura or peritoneum. At times an open surgical procedure is required to obtain appropriate specimens. Blood cultures for *mycobacteria* (using appropriate mycobacterial media rather than standard blood culture media) may be positive in disseminated TB; the technique is the same as in culturing blood for *M avium* complex organisms. Urine culture is used to diagnose renal TB, which is rare among HIV-infected persons.

Some laboratories will perform a nucleic acid detection test on positive sputum smears and can confirm MTB in positive smears within 1 or a few days. The test is not sufficiently sensitive to use on negative smears, and drug sensitivity testing requires growth in culture. Initial growth may occur within 3-8 weeks. A nucleic acid probe can confirm a positive culture as MTB within a few days of culture growth; otherwise speciation may take several weeks. Susceptibility testing generally takes 3-4 weeks after the initial culture growth, depending on the laboratory procedures used.

Note that a positive TST result indicates TB infection but does not prove active disease (see chapter *Latent Tuberculosis*). Similarly, a negative test can occur in HIV-infected persons with active TB and this was common among persons with disseminated TB prior to the HIV epidemic. A positive TST provides supporting evidence of TB disease; a negative test is not as informative in HIV-infected persons.

Respiratory Precautions

Respiratory infection control precautions should be implemented for HIV-infected patients with an undiagnosed chronic cough or undiagnosed inflammatory infiltrate on chest x-ray. Individual institutions have specific guidelines that should be followed; usually patients are housed in single negative-pressure rooms and persons entering the rooms are required to wear individual protective respirators. If 3 sputum smears are negative on acid-fast staining, or if a single deep specimen (bronchial lavage or tracheal aspirate) is smear negative, infectious TB is unlikely and respiratory precautions can be discontinued. Patients who are highly suspect for MTB and lack an alternative diagnosis should be kept on precautions and empiric treatment may be started. Persons who have responded to treatment for an alternative diagnosis (eg, bacterial pneumonia) and who cannot produce the requisite 3 sputum samples, may be released from the TB precautions.

The impact of TB transmission is severe in a health care setting, where immunosuppressed persons may be exposed. Children aged <5 years and immunosuppressed persons in the home are at increased risk.

Treatment

Treatment should be instituted when TB is considered likely and the proper specimens to determine the diagnosis have been obtained. It is ideal to have a positive smear and confirmation by nucleic acid amplification before to initiating treatment, but empiric treatment can be started after the specimens have been collected if the suspicion of TB is high, the patient is severely ill, or a positive smear is unlikely (eg, cerebrospinal fluid smears).

Once the decision to treat is made and an appropriate regimen is selected, adherence becomes the most important issue. The treating clinician must ensure that the patient completes a full course of therapy. Therefore, it is strongly recommended that patients be referred to public health departments for TB treatment. Health departments usually provide free TB treatment and have specific resources and systems to promote adherence. All patients should receive directly observed therapy (DOT), whereby the taking of every dose of anti-TB medication is observed and documented. The intermittent TB therapies in Table 1 (regimens 1b, 2, and 3) were designed to simplify DOT. Clinical trials have documented that DOT with enhancements to maximize adherence improves the rate of completion of therapy and reduces mortality in HIV-infected TB patients. If the health department manages the TB treatment, the HIV clinician must coordinate with the health department to do the following: 1) avoid drug interactions; 2) provide antiretroviral therapy (ART), if indicated, that does not conflict with the TB treatment; 3) ensure that immune reconstitution inflammatory syndrome (IRS) or incident opportunistic diseases are not misinterpreted as progression of TB; and 4) maximize adherence with the TB medications, ART, and any other medications.

The U.S. guidelines for TB treatment in HIV-infected persons are shown in Table 1; dosages are given in Table 2. Four anti-TB drugs are administered for the first 2 months, and then 2 drugs are administered for an additional 4 months (if the organism is susceptible to standard medications). The initial phase of TB treatment usually consists of isoniazid, rifampin, pyrazinamide, and ethambutol; the continuation phase typically is simplified to isoniazid and rifampin. If drug resistance or MDR is suspected, more drugs can be used initially, and treatment should be directed by, or in consultation with, experts. Resistance may be suspected among persons who were exposed to TB in countries with high rates of endemic resistance, those who failed previous treatment, those who have used treatment erratically, those who may have had a specific exposure to drug-resistant TB, or those who were diagnosed during an MDR outbreak. Treatment is extended in certain circumstances. Cavitary TB or TB in an HIV-infected person who remains sputum-culture positive after 2 months of treatment should be treated for a total of 9 months; bone and joint TB are treated for 6-9 months; and meningeal TB is treated for 9-12 months. If cultures obtained before treatment demonstrate drug resistance, the regimen and the duration of therapy may need to be changed. In patients with TB meningitis or pericarditis, and for persons with adrenal insufficiency, a course of corticosteroids is given in addition to specific anti-TB therapy.

Considerations in pregnancy

Pyrazinamide has not been formally proven safe during pregnancy although no problems have been reported with its use during pregnancy. Some health departments in the United States avoid pyrazinamide in pregnant women and extend the continuation phase to 7 months. Others. prescribe the standard regimens in Table 1 during pregnancy. Streptomycin and certain second-line

Table 1. Regimens for Treatment of Tuberculosis among HIV-Infected Persons in the United States

Initial Phase		Continuation Phase			Complete Therapy
Drugs	Interval and Doses (minimum duration)	Regimen	Drugs	Interval and Doses (minimum duration)	Range of Total Doses (minimum duration)
1. Preferred Regimen					
Isoniazid Rifampin* Pyrazinamide Ethambutol	• 7 days/week for 56 doses or 5 days/week for 40 doses (8 weeks)	1a.	Isoniazid Rifampin*	7 days/week for 126 doses or 5 days/week for 90 doses (18 weeks)#	182-130 doses (28 weeks)
		1b. if CD4 count >100 cells/µL	Isoniazid Rifampin*	Twice weekly for 36 doses (18 weeks)** #	92-76 doses (28 weeks)
2. Acceptable Alternative if CD4 >100 cells/µL					
Isoniazid Rifampin* Pyrazinamide Ethambutol	• 7 days/week for 14 doses (2 weeks) followed by twice weekly for 12 doses (6 weeks) *OR* • 5 days/week for 10 doses (2 weeks) followed by twice weekly for 12 doses (6 weeks)	2. if CD4 count >100 cells/µL	Isoniazid Rifampin*	Twice weekly for 36 doses (18 weeks)** #	62-58 doses (28 weeks)
3. Acceptable Alternative					
Isoniazid Rifampin* Pyrazinamide Ethambutol	3 times weekly for 24 doses (8 weeks)	3.	Isoniazid Rifampin*	3 times weekly for 54 doses (18 weeks)#	72 doses (28 weeks)

Source: American Thoracic Society, CDC, and Infectious Disease Society of America. *Treatment of Tuberculosis.* Morb Mort Weekly Rpts Recommendations and Reports. June 20, 2003, 52(RR11);1-77.

* See Table 2 for dosages. See Table 3 for contraindications, substitutions, and dosage adjustments of rifampin. Rifampin should not be used with nevirapine or with HIV protease inhibitors other than ritonavir; rifabutin may be substituted with appropriate dosage adjustments.

** Twice-weekly regimens (1b and 2) should not be used in persons with HIV and a CD4 lymphocyte count ≤100 cells/µL.

\# For patients who are slow to respond, or in whom sputum cultures are still positive after the initial 2 months of treatment, the continuation phase may be extended to 7 months, for a total of 9 months of treatment. Pediatric patients should be treated for a 7 months in the continuation phase, for a total of 9 months of treatment. TB meningitis caused by susceptible organisms should be treated for 9-12 months. Bone and joint TB should be treated for 6-9 months; the longer time may be prudent when multiple bones and joints are involved or when it is difficult to document a response to treatment.

Table 2. Dosages of First-Line Antituberculous Drugs Used in the United States

	Regimen 1 or 2: Daily or 5 times/week Dosage (maximum)		Regimen 1b or 2: 2 times/week Dosage (maximum)		Regimen 3: 3 times/week Dosage (maximum)	
Agent	**Adults**	**Children**	**Adults**	**Children**	**Adults**	**Children**
Isoniazid* (tabs: 100 and 300 mg)	5 mg/kg (300 mg max)	10-15 mg/kg (300 mg max)	15 mg/kg (900 mg max)	20-30 mg/kg (900 mg max)	15 mg/kg (900 mg max)	NA
Rifampin** (caps 300 mg)	10 mg/kg (600 mg max)	10-20 mg/kg (600 mg max)	10 mg/kg (600 mg max)	10-20 mg/kg (600 mg max)	10 mg/kg (600 mg max)	NA
Pyrazinamide (tabs 500 mg)	20-25 mg/kg (2 g max)	10-30 mg/kg (2 g max)	35-50 mg/kg (3 g max)	10-30 mg/kg (2 g max)	35-55 mg/kg (4 g max)	NA
Ethambutol (tabs 100 and 400 mg)	15-20 mg/kg (1,600 mg max)	10-20 mg/kg (1 g max)	20-30 mg/kg (2,400 mg max)	10-20 mg/kg (1 g max)	35-50 mg/kg (4,000 mg max)	NA
Rifamate# (caps isoniazid 150 mg, rifampin 300 mg)	2 caps daily	NA	NA	NA	NA	NA
Rifater## (tabs isoniazid 50 mg, rifampin 120 mg, pyrazinamide 300 mg)	≤44 kg: 4 tabs 45-54 kg: 5 tabs 55-90 kg: 6 tabs	NA	NA	NA	NA	NA

Source: American Thoracic Society, CDC, and Infectious Disease Society of America. *Treatment of Tuberculosis.* Morb Mort Weekly Rpts Recommendations and Reports. June 20, 2003, 52(RR11);1-77.
Typical daily dosage for a 60 kg patient: isoniazid 300 mg (2 tabs), rifampin 600 mg (2 caps), pyrazinamide 1,500 mg (3 tabs), ethambutol 1,200 mg (3 tabs)

* Add pyridoxine 10-25 mg per dose of isoniazid.

** See Table 3 for dosage adjustments or rifabutin substitution when combined with ART.

\# Suitable for daily dosing during the continuation phase.

May be part of daily initial phase combined with ethambutol tablets.

drugs should be avoided during pregnancy. HIV-infected women in the United States are instructed not to breast-feed, so there are usually no issues regarding TB treatment of HIV-infected women during breast-feeding.

Treatment of pediatric patients

Children are often treated with a 7-month continuation phase for a total treatment time of 9 months, although there are no data on this issue. Some experts avoid ethambutol in young children who cannot be tested for the adverse event of color blindness; others consider the risk so small with current ethambutol dosages that the drug can be included safely. Treatment of children for TB should be done in consultation with an expert.

Coordinating with Antiretroviral Therapy

ART and TB treatment must be coordinated for both to be successful. Rifampin is a potent inducer of cytochrome p450 enzymes and has clinically important interactions with many medications, including certain antiretrovirals and oral contraceptives. Rifampin reduces the blood concentrations of nonnucleoside reverse transcriptase inhibitors (NNRTIs) and protease inhibitors (PIs), but does not affect nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs) or the entry inhibitor enfuvirtide. Some NNRTIs and PIs cannot be used with rifampin while other require dose adjustment when coadministered (Table 3). Triple-nucleoside regimens can be administered safely during rifampin treatment but are less potent than other first-line antiretroviral (ARV) combinations. The safest ARV

Table 3. Interactions of Antiretroviral Medications with Rifampin or Rifabutin: Contraindicated Combinations and Dosage Adjustments

	Rifampin	Rifabutin*
Nonnucleoside Reverse Transcriptase Inhibitors		
Efavirenz**	Rifampin dosage is unchanged; give efavirenz dosage of 600-800 mg daily	No change in efavirenz dosage; increase rifabutin to 450-600 mg 3 times daily
Nevirapine	Generally not recommended; despite 25-50% reduction in nevirapine levels, 2 small studies claim standard dosages are effective	Use standard dosage of nevirapine; rifabutin 300 mg daily or 3 times weekly
Delavirdine	Never combine	Never combine
Unboosted Protease Inhibitors		
Ritonavir	May be used at standard dosages; limited clinical experience	Ritonavir at standard dosage; rifabutin 150 mg alternate days or 3 times weekly
Amprenavir, fosamprenavir	Never combine	PIs at standard dosage; rifabutin 150 mg/day or 300 mg 3 times weekly
Atazanavir	Never combine	Atazanavir at standard dosage; rifabutin 150 mg alternate days or 3 times weekly
Indinavir	Never combine	Increase indinavir to 1,000 mg every 8 hours; rifabutin 150 mg/day or 300 mg 3 times weekly
Nelfinavir	Never combine	Increase nelfinavir to 1,000 mg every 8 hours; rifabutin 150 mg/day or 300 mg 3 times weekly
Ritonavir-Boosted Protease Inhibitors		
Lopinavir/ritonavir (Kaletra)	Lopinavir/ritonavir (3 caps twice daily) must be supplemented with additional ritonavir 300 mg twice daily; limited experience, not well tolerated	Standard dosage of lopinavir/ritonavir; decrease rifabutin to 150 mg alternate days or 3 times weekly
Saquinavir/ritonavir	Should not be used because of high rates of hepatotoxicity	Standard dosage of lopinavir/ritonavir; decrease rifabutin to 150 mg alternate days or 3 times weekly
All other ritonavir-boosted PIs	Should not be used (adequate dosing regimens not defined)	Standard dosage of PI/ritonavir; decrease rifabutin to 150 mg alternate days or 3 times weekly

Adapted from *Updated Guidelines for the Use of Rifamycins for the Treatment of Tuberculosis Among HIV-Infected Patients Taking Protease Inhibitors or Nonnucleoside Reverse Transcriptase Inhibitors*. Updated January 20, 2004. Nucleoside and nucleotide analogues are given in standard dosages with either rifampin or rifabutin.

* If available, rifabutin may be substituted for rifampin when TB treatment and antiretroviral therapy is combined.

** Avoid efavirenz during pregnancy or in women who may become pregnant on therapy. Both rifampin and rifabutin significantly reduce estrogen and progestin levels for women on hormonal contraceptives; efavirenz raises estrogen levels moderately. Two forms of birth control including one barrier method and either a mid-high dose hormonal contraceptive or intrauterine device are most often recommended. Barrier methods are also recommended for women who are infertile to reduce HIV transmission.

combination to use with rifampin is a 2-drug nucleoside backbone with efavirenz. Some clinicians increase the efavirenz dosage to 800 mg/day because efavirenz blood concentrations may be reduced 25% by concomitant rifampin. Note that efavirenz is teratogenic; women who take efavirenz should avoid pregnancy by using birth control methods that use are not affected by rifampin (preferably condoms plus injectable progestins or condoms plus an intrauterine device).

Rifabutin may be substituted for rifampin to avoid rifampin-ARV interactions. Rifabutin has less marked effects on the pharmacokinetics of other drugs compared to rifampin, although its own blood concentrations can be affected by certain ARVs. See Table 3 for dosing recommendations for coadministration of rifabutin with ARVs. Rifabutin is expensive; some public health systems do not provide rifabutin as part of TB treatment and it generally is not available in resource-limited countries. The U.S. Food and Drug Administration characterizes rifabutin in pregnancy category B: it has been safe in animal studies of pregnancy but has not been proven safe in humans. For pregnant women who require both TB and ARV therapy, the use of rifabutin rather than rifampin allows the use of non-efavirenz-based ARV regimens.

Persons who are already taking ART when TB treatment is begun should have their ARV regimens reassessed. The appropriate dosages of rifampin or rifabutin must be chosen and the ARV regimen may need to be modified, at least until the completion of TB treatment.

In HIV/TB coinfected patients the optimal timing of ART initiation in relation to TB therapy is not known. For patients who are not taking ART at the time they start TB therapy, many specialists recommend postponing ART for the first 4-8 weeks of TB therapy. This strategy decreases the pills burden, adherence problems, the risk of drug adverse effects, and the risk of IRS (see below). Some experts recommend that persons with very low CD4 cell counts (<50-100 cells/μL) start ART 2 weeks after initiating TB treatment, although others believe that an increased risk of complications remains. International studies are under way, and others are planned, to inform this decision.

Persons who do not require immediate ARV treatment (eg, those with CD4 counts >350 cells/μL) may be best served by completing TB treatment first and then reassessing the need for ARVs.

Monitoring for efficacy

Ideally, every dosing of anti-TB therapy is observed and documented by a health care agent or responsible individual. A member of the health care team should evaluate patients' adherence at least weekly during the initial phase or monthly during the continuation phase. If gaps in medication use occur, the cause must be evaluated and a plan to improve adherence must be implemented.

During the treatment of pulmonary TB, monthly sputum specimens should be obtained for smear and culture until 2 sequential specimens are sterile on culture. Patients with extrapulmonary and disseminated TB are usually monitored clinically and with imaging studies. Biopsies are not repeated but other specimens (cerebrospinal and other body fluids) may be obtained for repeat laboratory study including acid-fast bacilli smear and culture, cell counts, and protein levels. Monitoring of patients with extrapulmonary and disseminated TB should be done in consultation with an expert.

Managing immune reconstitution syndrome

Patients in the initial months of treatment for active TB who begin ART may experience a paradoxical increase in signs and symptoms of TB (fever, dyspnea, increased cough, enlarging lymph nodes, worsening chest x-ray findings, increased inflammation at other involved sites, or enlargement of central nervous system tuberculomas). In many cases, this phenomena is caused by an enhanced immune response against remaining MTB organisms because of immunologic improvement from ART. IRS often occurs within 2 weeks up to several months after ARVs are begun and is usually accompanied by a sharp decline in the HIV viral load and at least a 2-fold increase in the CD4 cell count. TB treatment failure (potentially due to an inappropriate treatment regimen, inadequate adherence, or drug resistance) must be ruled out and the possibility of drug toxicity should be considered. If IRS is diagnosed, TB and ARV treatment should be continued and symptoms should be managed with nonsteroidal anti-inflammatory drugs, or in severe cases, with a short course of corticosteroids. See chapter *Immune Reconstitution Syndrome*.)

Monitoring for toxicity

Antituberculous medications may have significant adverse effects. Table 4 lists the most important adverse reactions reported for the commonly used anti-TB medications. Before initiating TB treatment, check complete blood count with platelet count, serum creatinine, liver function tests (aspartate aminotransferase [AST], alanine aminotransferase [ALT], bilirubin, alkaline phosphatase), and hepatitis B and C serology. Newly diagnosed TB patients with unknown HIV status should be encouraged to undergo testing for HIV infection. Thereafter, all patients taking TB therapy should be monitored monthly with a symptom review to assess possible toxicity.

Although HIV-uninfected persons without risks for liver disease do not require routine laboratory monitoring, HIV/TB coinfected patients have a higher risk of drug toxicity. Laboratory monitoring may be repeated after 1 month of treatment and every 3 months thereafter, unless symptoms or laboratory abnormalities warrant more frequent testing. Persons with symptoms and AST or ALT elevations ≥3 times the upper limit of normal, and asymptomatic persons with aminotransferase elevations ≥5 times the upper limit of normal, should have therapy interrupted and should be managed thereafter in consultation with an expert. Patients should be monitored for isoniazid-induced peripheral neuropathy; this adverse effect is rare if pyridoxine is administered with isoniazid, as recommended (Table 2). Testing of visual acuity and red-green color discrimination is recommended at the start of therapy with ethambutol. Persons taking standard ethambutol doses who have normal baseline examinationss should be asked monthly about visual disturbances. Those taking higher ethambutol dosages or prolonged ethambutol treatment (>2 months) should have periodic eye examinations for acuity and color discrimination.

Table 4. Adverse Events Associated with Common Antituberculous Medications

Drug	Frequent (≥5 per 100 patients)	Common (≥1-5 per 100 patients)	Infrequent (≥1 per 1,000 patients and <1 per 100 patients)
Isoniazid	• Liver enzyme elevations		• Hepatitis • Peripheral neuropathy • Drug fever
Rifampin	• Bilirubin elevations in the beginning of treatment • Orange discoloration of urine and tears • Liver enzyme elevations		• Hepatitis • Pruritus • Flu syndrome • Drug fever
Pyrazinamide	• Arthralgias	• Nausea	• Hepatitis • Rash • Nausea
Ethambutol			• Retrobulbar neuritis • Periaxial ocular toxicity
Streptomycin	• Vestibular toxicity	• Cochlear toxicity • Hypersensitivity reactions	• Renal damage

Adapted from IUATLD slide sets and Reider H.L. *Interventions for Tuberculosis Control and Elimination*. 2002. International Union Against Tuberculosis and Lung Disease. Available at: www.tbrieder.org. Accessed July 4, 2005.
Note: Rare adverse events (≤1 per 1,000 patients) are not included in this table.

Patient Education

- All patients with TB-positive sputum or bronchoscopy specimens can infect others with TB. All close contacts, especially children, should be screened for TB as soon as possible and given medication to prevent (or treat) active disease.
- The health department will be notified of each TB case and will provide the required follow-up care.
- Patients must take all medicines exactly as prescribed. If doses are missed, or if the medication is stopped and restarted, the TB bacteria can develop resistance to even the best medications and become even more dangerous. If patients are having trouble taking the medication on schedule, they should contact their health care providers immediately.
- If patients become ill, if their skin or eyes turn yellow, or if their urine darkens to a cola color, they should see their health care providers immediately.
- Patients must keep all follow-up appointments. Blood tests will be done regularly to be sure the liver is working well, and patients will be checked for medication adverse effects. They should show their health care providers all medications, vitamins, and supplements that they are taking so that the providers can check for drug interactions.
- Rifampin will make urine, sweat, and tears turn orange; this is not harmful. It will also stain plastic contact lens; patients should avoid wearing these if they are taking rifampin.
- Rifampin will cause birth control pills to fail. An alternate method of contraception should be used when the patient is under treatment.
- Alcohol should be avoided during treatment with TB drugs to avoid liver damage.

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Tuberculosis Treatment in Resource-Limited Settings

Background

Tuberculosis (TB) is the most common severe opportunistic infection associated with HIV in many resource-limited areas such as sub-Saharan Africa. The enormous and increasing number of cases of TB associated with HIV infection has greatly increased the demands on TB treatment programs. TB treatment in HIV-infected patients is different in resource-limited settings than in resource-abundant settings, and treatment details may differ by country. In general, the emphasis of TB treatment and control in resource-limited areas has been on diagnosing sputum smear-positive patients (ie, those with infectious pulmonary TB) to minimize the need for expensive technology and to maximize the public health impact of treatment. The target for many national TB control programs is to diagnose 70% of new cases, and for 85% of newly diagnosed patients to complete a course of therapy. The following recommendations for diagnosis and treatment are derived from guidelines by the World Health Organization (WHO) and the International Union Against Tuberculosis and Lung Disease.

See the *Treatment of Latent Tuberculosis in Resource-Limited Settings* chapter for a discussion of isoniazid preventive treatment (IPT) for HIV-infected persons.

For more information on tuberculosis, including diagnosis and treatment, see chapter *Mycobacterium tuberculosis: Treatment in the United States and Other High-Income Nations.*

Diagnosis

HIV counseling and voluntary testing should be encouraged for every person diagnosed with TB. In addition, screening for TB symptoms should occur at every health care interaction with HIV-infected persons. Patients with both conditions should be referred between the TB and HIV treatment facilities in order to access both treatments appropriately. Coordination between TB and HIV treatment is crucial because of potential drug interactions, increased risk of toxicity, risk of immune reconstitution inflammatory syndrome (IRS), and increased adherence challenges. In many countries, an effort to coordinate HIV and TB care is just beginning.

Three sputum smears should be examined for acid-fast bacilli (AFB) in all patients with chronic cough. The presence of other respiratory symptoms (eg, breathlessness, chest pain, hemoptysis) or systemic symptoms (eg, fever, night sweats, weight loss, loss of appetite) increase the likelihood of pulmonary TB. For outpatients, an initial (spot) sputum specimen should be obtained on the day a patient presents for evaluation. The patient then is sent home with a sputum cup to collect a sample immediately after awakening the next morning. The patient brings the morning specimen back to the health facility the day it is collected. On that day, the patient provides a second spot specimen in the health facility, so that 3 specimens are collected in 2 days. All 3 are stained and examined microscopically for AFB.

HIV-infected patients with TB, especially those with advanced immunosuppression, often have either smear-negative pulmonary disease or extrapulmonary disease. In such cases, diagnosis relies on clinical judgment and radiographic imaging, and sometimes on aspirates and biopsies. In some locations, x-rays may be unavailable, so TB treatment may be instituted in smear-negative patients in whom pulmonary TB is suspected (eg, in patients in whom at least 1 trial of standard antibiotics has been ineffective and a medical doctor or an appropriately trained clinician has not made an alternative diagnosis). In some cases, diagnostic testing may not be available, and AIDS patients with a wasting febrile disease may be treated empirically for TB.

TB lymphadenitis often can be diagnosed on an AFB smear of a needle aspirate of a suspicious lymph node, or on the gross appearance of caseous necrosis in a biopsied lymph node. AFB smears are usually negative in pleural, pericardial, peritoneal, joint, and cerebrospinal fluids of patients with TB in those compartments. Diagnosis is based on clinical presentation and on cell counts and chemistry tests of the fluids. (Where chemistry tests are not available, the fluid may be observed for formation of protein clots over the course of several hours, indicating elevated fluid protein levels.) Liver and bone marrow biopsy may be helpful in diagnosing disseminated TB, revealing granulomas if not acid-fast organisms. If possible,

these fluids and biopsied tissues should be cultured for *Mycobacterium tuberculosis*.

Young children do not produce sputum, and usually are treated on the basis of clinical presentation and chest x-ray findings. A point system has been used to assist in selecting children for treatment, especially where x-ray facilities are not available. However, this point system may not be very specific in HIV-infected children, who may have other illnesses unrelated to TB. Children exposed to TB in the home need to be assessed for symptoms and signs of active disease, and should receive either IPT (see the *Treatment of Latent Tuberculosis in Resource-Limited Settings* chapter) or empiric treatment for active TB.

Treatment Adherence

Directly observed therapy—short course (DOTS) is recommended. The DOTS framework includes systems for

- Standardized short-course (6-month) chemotherapy promoting adherence and observing each dose of medication;
- Access to quality-assured sputum microscopy;
- Uninterrupted access to appropriate drugs;
- A quality-assured data and monitoring system; and
- The political will and resources to implement a national TB control program.

Therapy may be directly observed by health care workers, family members, lay community volunteers or activists, or coworkers. The treatment supporter documents the observation of doses using forms and procedures analogous to those used for this purpose by health care workers. The treatment supporter accompanies the patient to the TB treatment visits, bringing remaining medications and treatment documentation paperwork each time.

Treatment Regimens

The TB treatment regimens recommended by the WHO for HIV-infected persons are shown in Table 1. Where DOTS can be assured, regimens for new patients are the same as those used in industrialized countries. Fixed-dose combination (FDC) tablets are available in some countries for both initial and continuation phases of treatment, for both adults and children, and may be available in blister packs. Use of the FDCs reduces the time demands on health care workers, ensures more accurate weight-based dosing, simplifies assessment of adherence, and eliminates the option for patients to avoid individual medications in their regimen.

Patients who are smear positive after completing TB treatment ("relapse") or return after a 2-month gap in treatment having had at least 1 month of prior exposure to TB medications ("return from default") are considered retreatment cases (Category II; see Table 1) and receive an expanded and extended regimen. If possible, sputum for culture and sensitivity is obtained at the beginning of a retreatment regimen. In some countries with high rates of multidrug resistance, these patients may be referred directly to second-line treatment (Category IV).

Ethambutol is included in regimens for HIV-infected persons. However, it may be omitted in HIV-uninfected persons with smear-negative pulmonary TB without cavities and without suspicion of drug resistance. Some countries do not include ethambutol in the treatment of young children with TB.

TB meningitis is treated with streptomycin instead of ethambutol during the initial phase of therapy.

Corticosteroids are recommended for patients with TB meningitis, pericarditis, severe or bilateral pleural effusions, TB laryngitis threatening the airway, massive TB adenopathy with dangerous pressure effects, severe IRS, and severe drug toxicity (prednisone 1 mg/kg with tapering over the course of weeks to months). For patients with adrenal insufficiency due to TB, stress-doses of corticosteroids will need to be followed by chronic replacement doses.

Thiacetazone was previously widely used in Africa as part of TB treatment. Its use is discouraged now because of a high rate of severe skin reactions including fatalities from Stevens-Johnson syndrome and toxic epidermal necrolysis, especially in HIV-infected persons.

Table 1. World Health Organization's Recommended First-Line Regimens for Tuberculosis Treatment

TB Category	TB Patients	TB Treatment Regimens	
		Initial Phase (daily or 3 times weekly)	Continuation Phase (daily or 3 times weekly)
I	New smear positive; new smear negative with extensive chest x-ray abnormalities, severe HIV disease, or severe extrapulmonary TB	Isoniazid,* rifampin,** pyrazinamide, ethambutol*** for 2 months	Isoniazid* and rifampin** for 4 months Isoniazid and ethambutol† daily for 6 months
II	Previously treated smear-positive pulmonary TB# • relapse • return after default • treatment failure	Isoniazid,* rifampin,** pyrazinamide, ethambutol and streptomycin for 2 months, followed by isoniazid,* rifampin,** pyrazinamide and ethambutol for 1 month	Isoniazid,* rifampin,** and ethambutol for 5 months
III	Smear-negative TB and extrapulmonary TB less severe than category 1##	Isoniazid,* rifampin,** pyrazinamide, ethambutol for 2 months	Isoniazid* and rifampin** for 2 months Isoniazid* and ethambutol† daily for 6 months
IV	Chronic and multidrug-resistant TB (smear positive after supervised retreatment)	Multidrug-resistant or individualized regimen per country protocol	

Source: Harries A, Maher D, Graham S. *TB/HIV: A Clinical Manual*, second edition. 2004. WHO, Geneva.

* Pyridoxine 10 mg daily is added to each dose of isoniazid.

** Rifampin is called rifampicin in other countries. It is recommended that every rifampin dose be supervised (directly observed therapy). Rifampin should not be used with nevirapine or protease inhibitors; rifabutin may be substituted with appropriate dosage adjustments.

*** In TB meningitis, the World Health Organization recommends substituting streptomycin for ethambutol.

† Isoniazid and ethambutol is expected to have a higher failure rate than isoniazid and rifampin; however, it is included for treatment when continuation-phase therapy cannot be directly supervised, to avoid the risk of promoting resistance to rifampin.

Culture and susceptibility testing (if available) should be performed at the beginning of Category II treatment.

HIV-infected patients in Category III will take the same treatment as persons in Category I.

Pregnancy

The WHO considers all Category I medications to be safe in pregnancy. Avoid streptomycin (Category II treatment) if possible, as it can cause 8th cranial nerve damage to the fetus.

Breastfeeding

The WHO considers all anti-TB medications to be safe during breast-feeding.

Hepatic Disease

Pyrazinamide should be avoided in patients with preexisting liver disease. For mild-to-moderate liver disease, an initial 2-month regimen of isoniazid, rifampin, ethambutol, and streptomycin can be followed by a 6-month course of isoniazid and rifampin. For severe liver disease, 2 months of isoniazid, ethambutol, and streptomycin is followed by 10 months of isoniazid and ethambutol. If these regimens are not tolerated, or if drug resistance is suspected, consult an expert.

Renal Disease

Ethambutol should be dose-adjusted or avoided altogether in severe renal insufficiency. Streptomycin doses must be adjusted in patients with abnormal renal function.

Polydrug or Multidrug Resistance

Patients with polydrug or multidrug resistance may be treated with standardized Category IV regimens or individualized regimens, depending on the country protocol. Category IV patients should be treated according to expert advice or in specialized centers.

Monitoring for Treatment Effectiveness

Patients who are smear positive initially should be monitored by repeat sputum smears (Table 2). Young children, smear-negative pulmonary TB patients, and extrapulmonary TB patients can be followed clinically. Repeat chest x-ray is not recommended for routine follow-up and is considered a poor use of resources. Chest x-ray should be repeated only for a patient with new or progressive symptoms.

Table 2. Timing of Sputum Smears

When to Monitor	Category I (6-month regimen)	Category II (8-month regimen)
At diagnosis	3 specimens	3 specimens
End of initial phase	1 spot specimen	1 spot specimen
End of additional month of initial phase, if needed*	1 spot specimen	1 spot specimen
In continuation phase	1 spot specimen at end of month 5	1 spot specimen at end of month 5
During last month of treatment	1 spot specimen during month 6	1 spot specimen during month 8

Source: Harries A, Maher D, Graham S. TB/HIV: A Clinical Manual, second edition. 2004. World Health Organization, Geneva. *See text.

Patients who were previously sputum smear-positive with 2 subsequent negative sputum smears and completion of 6-8 months of treatment are considered cured. Previously sputum smear-negative patients, or patients who cannot produce sputum, who respond clinically (cessation of cough and fever, weight gain) and complete 6-8 months of treatment are considered "completers." Successful treatment includes all cured patients and "completers."

Patients who are smear positive at the end of the initial phase (2 months of Category I treatment or 3 months of Category II treatment) should continue on the initial phase for 1 additional month. Patients who are smear positive after the additional month need 2 sputum samples sent for culture and sensitivity (if available) and progress to the continuation phase for the usual 4 months (Category I) or 6 months (Category II).

Patients who are smear positive at 5 months are considered treatment failures; sputum is sent for culture and sensitivity and they progress to the retreatment regimen.

Those who have a gap in treatment are called "interrupters," and efforts must be made to get them back into treatment. Those who have at least a 2-month gap in treatment are "defaulters," and must be reassessed with new sputum smears.

Monitoring for Toxicity

(See Table 4 in chapter *Mycobacterium tuberculosis:* Treatment in the United States and Other High-Income Nations for information on adverse effects of TB therapy.)

Standard guidelines for anti-TB therapy in resource-limited settings do not require baseline or follow-up laboratory tests as a matter of routine. Rather, clinical assessment should be performed at least monthly and should include evaluation of symptoms or signs such as gastrointestinal intolerance, minor and major cutaneous drug reactions, joint pain, hepatitis (nausea, vomiting, abdominal pain, jaundice), peripheral neuropathy, changes in visual acuity, or development of blind spots (Table 3). Where laboratory facilities and financial resources allow, many clinicians prefer to check baseline and periodic complete blood counts with differential, alanine/aspartate aminotransferase (ALT/AST) or bilirubin, and baseline creatinine. Laboratory monitoring is more important in persons with preexisting liver disease or those on concomitant ART although TB treatment should not be withheld for lack of access to hematology or chemistry laboratory testing.

Management of severe rash includes discontinuation of TB therapy, supportive care, administration of corticosteroids for severe or life-threatening desquamation, and gradual reintroduction of escalating dosages of medications after resolution. Drugs are reintroduced in the reverse order of their likelihood of causing severe rash: isoniazid, rifampin, pyrazinamide, ethambutol, streptomycin. Avoid thiacetazone because of high risk of severe cutaneous reactions. Seek expert advice.

Management of liver toxicity includes cessation of therapy until bilirubin and ALT return to normal levels. If laboratory testing is not available, wait until 2 weeks after the resolution of jaundice. Treat with ethambutol, streptomycin, rifampin (if tolerated), and isoniazid (if tolerated). See the discussion of hepatic disease, above, for 2 possible treatment regimens. If the TB is severe, treatment may have to be resumed early without hepatotoxic drugs (ethambutol and streptomycin), until additional drugs can be reintroduced to the regimen. Seek expert advice.

Table 3. Monitoring for Toxicity

Side Effects	Drugs Likely Responsible	Management
Minor Side Effects		
Anorexia, nausea, abdominal pain	Rifampin	Give dose last thing at night
Joint pain	Pyrazinamide	Aspirin or nonsteroidal anti-inflammatory drugs
Burning in feet, neuropathy	Isoniazid	Pyridoxine 50-75 mg daily
Orange/red urine	Rifampin	Reassurance
Major Side Effects		
Severe rash or skin itching	Thiacetazone, streptomycin	Stop TB therapy for severe reactions; give supportive care; after resolution of symptoms, reinstitute therapy (see text)
Decreased hearing, deafness (rule out wax in ears)	Streptomycin	Substitute ethambutol or other
Dizziness, vertigo, nystagmus	Streptomycin	Substitute ethambutol or other
Jaundice	Pyrazinamide, isoniazid, rifampin	Stop TB treatment until jaundice resolves (see text)
Vomiting and confusion	Pyrazinamide, isoniazid, rifampin	Stop TB treatment and perform liver function tests
Visual impairment	Ethambutol	Stop ethambutol
Generalized hypersensitivity reaction with shock and purpura	Rifampin	Stop rifampin

Source: Harries A, Maher D, Graham S. *TB/HIV: A Clinical Manual*, second edition. 2004. World Health Organization, Geneva.

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Non-Hodgkin Lymphoma

Background

Non-Hodgkin lymphoma (NHL) is a diverse group of more than 20 malignant diseases originating in the cells of the immune system. The incidence of NHL is up to 60 times higher in HIV-infected patients than in HIV-noninfected persons, and the risk of NHL increases with declining immune function. In the United States, rates of NHL among HIV-infected persons increased dramatically in the early years of the HIV epidemic, but the rate has stabilized since the advent of antiretroviral therapy (ART).

Ninety percent of HIV-related NHL cases are of B-cell origin and they are frequently high-grade in nature. Although B-cell lymphomas may occur at any stage of HIV disease, they are seen more frequently in patients with lower CD4 cell counts (particularly CD4 counts of <100 cells/μL). Central nervous system (CNS) lymphoma typically is seen only in patients with advanced AIDS (the CD4 count usually is <50 cells/μL). NHL is an AIDS-defining condition. A viral factor, the Epstein-Barr virus (EBV), is linked to CNS and some types of systemic NHL in people with AIDS.

The majority of patients with NHL present with unexplained fever, sweats, or weight loss ("B symptoms"), and lymphadenopathy. Extranodal disease often is present at the time of diagnosis. Common sites of extranodal disease include the CNS, gastrointestinal (GI) tract, lungs, and bone marrow.

S: Subjective

Patients may complain of enlarged lymph nodes and often report B symptoms such as fever, weight loss, and night sweats. B symptoms are present in 80% of patients with systemic AIDS-related NHL. In patients with these complaints, it is important to exclude opportunistic infections (OIs) when evaluating for lymphoma.

Headaches, seizures, and altered mental status often are present in patients with CNS lymphoma.

Other symptoms may include changes in bowel habits, GI bleeding, abdominal pain, and early satiety, shortness of breath, and cough.

Take a careful history, asking about the symptoms described above, their duration, severity, progression, and any associated symptoms.

Inquire about current or recent CD4 cell counts and the CD4 nadir. Ask whether the patient is taking ART or OI prophylaxis.

O: Objective

Measure vital signs and weight; compare with previous values.

Perform a complete physical examination with special attention to:

- General appearance and nutritional status (appearance of illness, cachexia)
- Skin (pallor, jaundice)
- Lungs (effusion, abnormal sounds)
- Abdomen (hepatosplenomegaly)
- Lymph nodes (note size, consistency, mobility, and degree of tenderness)
- Nervous system, including mental status

A: Assessment

The differential diagnosis is broad and is determined in part by the patient's CD4 count. It includes both infectious and noninfectious etiologies, such as:

- Other malignancies, including Hodgkin disease
- HIV infection; persistent generalized lymphadenopathy
- Immune reconstitution syndrome
- Mononucleosis; Epstein-Barr virus infection
- *Mycobacterium avium* complex (MAC)
- Tuberculosis
- Histoplasmosis, other fungal diseases
- Toxoplasmosis (for CNS disease)
- Progressive multifocal leukoencephalopathy (PML) (for CNS disease)

- *Bartonella*
- Lymphogranuloma venereum
- Castleman disease

P: Plan

Diagnostic Evaluation

Definitive diagnosis of lymphoma requires identification of lymphomatous cells, usually obtained by excisional biopsy.

Biopsy of lymph node or other site

Rapidly expanding or otherwise abnormal lymph nodes or masses should be biopsied. Fine needle aspiration (FNA) biopsy may determine the diagnosis, but excisional biopsy should be obtained if the FNA is unrevealing. (Also, FNA may not yield enough cells for definitive diagnosis). See chapter *Lymphadenopathy* for more information.

Other that studies help to determine the extent of involvement, rule out other diseases, and determine the patient's clinical status include complete blood count (CBC) with differential, liver function tests, electrolyte and lactate dehydrogenase (LDH) measurements, and peripheral blood smear. (Otherwise-unexplained cytopenias and peripheral blood smear abnormalities may suggest bone marrow involvement. Elevated LDH is nonspecific but may be seen in patients with lymphoma.)

Perform blood cultures, MAC culture, tuberculosis studies, serum cryptococcal antigen, or other laboratory work as indicated by the patient's symptoms.

Radiographic studies

Patients with unexplained CNS symptoms or signs should receive brain imaging by computed tomography (CT) scan with contrast or magnetic resonance imaging (MRI); MRI is the more sensitive study. See chapter *Neurologic Symptoms* for more information.

Perform chest x-ray and CT scans of other areas as indicated by the patient's presentation. Positron emission tomography or gallium scanning also may be used to assess the extent of the disease.

Cerebrospinal fluid studies

Lumbar puncture (LP) should be performed in all persons diagnosed with NHL and in those suspected of having CNS lymphoma (brain imaging should be obtained first to rule out the presence of mass lesions that might cause herniation upon LP). Studies should include cytology, cell count, protein and glucose measurements, and any studies needed to rule out infections or other causes of the patient's symptoms (eg, bacterial, mycobacterial, and fungal cultures).

Bone marrow biopsy

This procedure may yield the diagnosis if other studies are negative. It also should be performed for patients with known NHL to assess for bone marrow involvement.

Treatment

If possible, patients should be evaluated and treated by an oncologist experienced in the treatment of HIV-related malignancies. Systemic chemotherapy is the only curative treatment, but the optimal treatment for AIDS-related NHL has not been defined. The standard regimen for advanced disease is R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone), though the specific treatment will depend on the specific type of lymphoma and on patient characteristics. In patients with very low CD4 cell counts, rituximab may be withheld because of the risks of further immunosuppression. Patients with meningeal involvement should receive concomitant intrathecal chemotherapy (medication given directly into the CNS via a lumbar puncture or Ommaya reservoir) using methotrexate and cytarabine.

Patients treated with ART in addition to chemotherapy appear to have better survival rates than do those treated with chemotherapy alone. Therefore, all patients should receive ART, if possible, in addition to chemotherapy.

Prognosis is dependent on the type and stage of the lymphoma and on the stage of HIV disease. A CD4 count of <200 cells/μL, extranodal disease including bone marrow, and a poor performance status are indicative of a poor prognosis. Patients with Stage IV NHL and very low CD4 counts usually have a life expectancy of <6 months. However, 50% of those patients may die from an OI rather than from the lymphoma. Patients who achieve a complete response with chemotherapy have a survival benefit that may range from 6 to 20 months or longer. In general, outcomes are better in patients taking ART for their HIV infection.

Patient Education

- Successful treatment of NHL requires meticulous adherence to the treatment plan. Patients who sporadically receive treatment put themselves at risk for the adverse effects of treatment but may receive little of the benefit. Advise patients to take all of their medications exactly as prescribed and to attend all of their scheduled chemotherapy and follow-up clinic appointments.
- Different chemotherapy regimens have different side effect profiles. Not all patients who receive chemotherapy will be nauseous or lose their hair. Educate patients about the possible side effects of chemotherapy and other medications and advise them to call their health care providers if they develop these.
- Encourage patients who are not taking ART to agree to start; emphasize the importance of close adherence.
- Emphasize to patients the importance of medications in preventing OIs, if these are indicated.

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Pelvic Inflammatory Disease

Background

Pelvic inflammatory disease (PID) is the syndrome resulting from the ascent of microorganisms from the vagina and cervix to the uterine endometrium, fallopian tubes, ovaries, or contiguous abdominal structures. Many episodes of PID go unrecognized, because of lack of symptoms or mild, nonspecific symptoms (eg, dyspareunia, abnormal bleeding, and vaginal discharge). Infecting organisms may include *Neisseria gonorrhoeae* and *Chlamydia trachomatis*, which are sexually transmitted, and anaerobic bacteria *(Gardnerella vaginalis* or *Haemophilus influenzae)*, gram-negative rods *(Escherichia coli)*, *Streptococcus agalactiae*, gastrointestinal flora, and mycoplasmas *(Mycoplasma hominis)*, which may not be sexually transmitted. PID is coepidemic with HIV among some urban populations of reproductive age. Data on PID outcomes in HIV-infected women are limited. Many studies have documented no difference in length or severity of lower abdominal pain, vaginal discharge, fever, abnormal vaginal bleeding, or low back pain between HIV-positive and HIV-negative women with PID. However, there is a higher rate of tubo-ovarian abscesses and severe salpingitis and pyosalpinx in HIV-positive women.

Clinical presentation may include salpingitis, endometritis, tubal and/or ovarian abscess, and pelvic peritonitis, although PID may present with subtle or mild symptoms even in HIV-infected women. Long-term complications of PID may include infertility, ectopic pregnancy, pelvic adhesions, and chronic pain.

S: Subjective

The patient may complain of mild-to-moderate lower abdominal pain and tenderness, pain with intercourse, vaginal discharge, fever, chills, heavy menstrual bleeding, or other abnormal vaginal bleeding.

Inquire about the following during the history:

- Symptoms listed above, and duration
- New sex partner(s), unprotected sex
- Use of intrauterine device
- Last menstrual period
- Previous diagnosis of gonorrhea or chlamydia
- Previous abdominal or gynecologic surgery

O: Objective

Perform a focused physical examination, documenting fever (temperature may be elevated or normal) and other vital signs. Check abdomen for bowel sounds, distention, rebound, guarding, masses, suprapubic and costovertebral angle (CVA) tenderness; perform complete pelvic examination looking for abnormal bleeding or discharge; uterine, adnexal, or cervical motion tenderness; pelvic masses or adnexal enlargement.

A: Assessment

A partial differential diagnosis includes the following:

- Pregnancy, uterine or ectopic
- Ruptured or hemorrhagic ovarian cyst
- Dysmenorrhea
- Appendicitis
- Pyelonephritis
- Diverticulitis
- Irritable bowel syndrome
- Cystitis
- Uterine fibroids/leiomyomas
- Ovarian torsion
- Mittelschmerz
- Kidney stones
- Pyelonephritis

P: Plan

Diagnostic Evaluation

- Gram stain of endocervical discharge
- Microscopic examination of saline preparation of vaginal secretions
- Endocervical and rectal cultures, urine for *N gonorrhoeae*
- Endocervical and rectal culture, or nucleic acid amplification test, for endocervical swab or first void urine
- Pregnancy test (if menses is late or pregnancy is possible)

Treatment

Because clinical diagnostic criteria for PID are not always conclusive, presumptive diagnosis and early treatment is common. The positive predictive value of a clinical diagnosis is 65-90%. The absence of infection from the lower genital tract, where samples are usually taken, does not exclude PID and should not influence the decision to treat.

Empiric treatment for PID should be initiated in sexually active women at risk for sexually transmitted infection if the following minimum criteria are met:

- Uterine or adnexal tenderness
- Cervical motion tenderness
- Additional criteria that support the diagnosis of PID include:
  - Oral temperature >101° F
  - Abnormal cervical or vaginal mucopurulent discharge
  - Presence of white blood cells in vaginal secretions
  - Elevated erythrocyte sedimentation rate
  - Elevated C-reactive protein
  - Laboratory documentation of infection with *N gonorrhoeae* or *C trachomatis*
- Definitive criteria:
  - Endometrial biopsy with histopathologic evidence of endometritis
  - Transvaginal sonogram showing thickened, fluid-filled tubes with or without free pelvic fluid or tubo-ovarian complex
  - Laparoscopic abnormalities consistent with PID

Treatment considerations

Antimicrobial regimens must provide broad-spectrum coverage of likely pathogens (Table 1). HIV-infected women respond equally well to standard antibiotic regimens as HIV-negative women. Whether the management HIV-infected women with advanced immunocompromise requires more aggressive interventions (eg, hospitalization or parenteral antimicrobial regimens) has not been determined. Decisions about whether to use oral or parenteral therapy must be individualized.

In moderate to severe cases of PID, intrauterine devices (IUDs) should be removed, if present.

The goals of treatment are to:

- Alleviate the pain and systemic malaise associated with infection
- Achieve microbiological cure
- Prevent development of permanent tubal damage with associated problems, such as chronic pelvic pain, ectopic pregnancy, and infertility
- Prevent the transmission of infection to others

Indications for hospitalization of patients with PID include:

- Unsure diagnosis; surgical emergency cannot be excluded
- Tubo-ovarian abscess
- Severe illness with nausea and vomiting or high fever
- Pregnancy
- Inability to follow outpatient regimen
- Immunosuppression (low CD4 count or significant comorbidity)

Pregnancy

If the patient is pregnant, aggressive treatment is essential to prevent preterm delivery, fetal loss, and maternal morbidity. Certain medications should be avoided to reduce the risk of fetal toxicity; these include doxycycline, fluoroquinolones, and gentamicin. Hospitalization for parenteral antibiotic therapy is recommended.

Table 1. Treatment Regimens for Pelvic Inflammatory Disease

Antibiotic Regimens	
Oral / Outpatient Treatment (see CDC STD Treatment Guidelines, referenced below)	
Regimen 1	• Ofloxacin* 400 mg orally twice daily for 14 days *or* • Levofloxacin* 500 mg orally once daily for 14 days *with or without* • Metronidazole 500 mg orally twice daily for 14 days (provides activity against anaerobes)
Regimen 2	• Ceftriaxone 250 mg intramuscular (IM) injection in a single dose *or* • Cefoxitin 2 g IM injection in a single dose, administered concurrently with probenecid 1 g orally in a single dose *or* • Other parenteral third generation cephalosporin (eg, ceftizoxime or cefotaxime) *plus* • Doxycycline 100 mg orally twice daily for 14 days *with or without* • Metronidazole 500 mg orally twice daily for 14 days
Parenteral / Inpatient Treatment	
Regimen 1	• Cefotetan 2 g intravenously (IV) every 12 hours *or* • Cefoxitin 2 g IV every 6 hours *plus* • Doxycycline 100 mg orally or IV every 12 hours (oral form is preferable because of the irritant qualities of the IV solution)
Regimen 2	• Clindamycin 900 mg IV every 8 hours *plus* • Gentamicin loading dose IV or IM injection (2 mg/kg of body weight) followed by maintenance dose (1.5 mg/kg) IV every 8 hours or 5-7 mg/kg IV daily
Alternative Parenteral Regimens	
Regimen 1	• Ofloxacin* 400 mg IV every 12 hours *or* • Levofloxacin* 500 mg IV daily *with or without* • Metronidazole 500 mg IV every 8 hours (provides anaerobic activity)
Regimen 2	• Ampicillin/Sulbactam 3 g IV every 6 hours *plus* • Doxycycline 100 mg orally or IV every 12 hours (oral form is preferable due to the irritant qualities of IV solution)

* Fluoroquinolones should not be used to treat PID in California, Hawaii, Massachusetts, New York City, the Pacific Basin, or Asia, because of high rates of fluoroquinolone-resistant gonorrhea in these areas.

Follow-Up

- Patients should show significant clinical improvement within 3 days of initiation of therapy (eg, improvement in fever, abdominal tenderness, and uterine, adnexal, and cervical motion tenderness). If the patient has not improved, consider hospitalization, additional diagnostic testing, or surgical intervention. Patients who are initially hospitalized for treatment may be switched to an oral regimen and discharged on oral therapy after they have improved clinically.
- Evaluate sexual partners and offer them treatment if they had sexual contact with the patient during the 60 days preceding the patient's onset of symptoms. Treat empirically for both chlamydia and gonorrhea.
- Some specialists recommend rescreening for *C trachomatis* and *N gonorrhoeae* after therapy is completed in women with documented infection with these pathogens.
- Provide education about sexual risk reduction. Instruct patients to use condoms with every sexual contact to prevent becoming reinfected with chlamydia or gonorrhea, to prevent other sexually transmitted infections, and to prevent passing HIV to sexual partners.

Patient Education

- Instruct patients to take all of their medications. Advise patients to take medications with food if they are nauseated, and to call or return to clinic right away if they have vomiting or are unable to take their medications.
- Sexual partners from the previous 60 days need to be tested for sexually transmitted pathogens, and treated as soon as possible with a regimen effective against gonorrhea and chlamydia, even if they have no symptoms. Advise patients to inform their partner(s) that they need to be tested and treated. Otherwise, they may be reinfected.
- Advise patients to avoid sexual contact until the infection has been cured.
- Provide education about sexual risk reduction. Instruct patients to use condoms with every sexual contact to prevent becoming reinfected, to prevent other sexually transmitted infections, and to prevent passing HIV to sexual partners.
- Advise patients that PID can recur, and that they should call or return to the clinic if symptoms such as pain or fever develop.
- Patients must not drink beer, wine, or any other alcoholic beverage during treatment while taking metronidazole, and for at least 24-48 hours after the last dose. Metronidazole may cause a disulfiram reaction, resulting in severe nausea and vomiting. Note that patients taking ritonavir may experience symptoms due to the small amount of alcohol in the capsules; advise patients to call if nausea and vomiting occur.

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Pneumocystis Pneumonia

Background

Pneumocystis jiroveci pneumonia (previously called *Pneumocystis carinii* pneumonia, and still abbreviated PCP), is caused by an unusual fungus, *Pneumocystis jiroveci*. Many humans appear to be infected in childhood, but clinical illness occurs only in people with advanced immunosuppression, either through new infection or reactivation of latent infection. Cases of PCP in otherwise healthy young homosexual men were among the first recognized manifestations of AIDS, in 1981. The organism can affect many organ sites, but pneumonia is far and away the most common form of disease. In the United States, the incidence of PCP has declined sharply since the use of prophylaxis and effective antiretroviral therapy (ART), but PCP is still many patients' initial presenting opportunistic infection and a significant cause of morbidity and mortality in HIV-infected patients.

S: Subjective

The patient complains of fever, shortness of breath, particularly with exertion, nonproductive cough, night sweats, weight loss, or fatigue. Typically, the symptoms worsen over days to weeks. Pleuritic pain and retrosternal pain or burning also may be present. There may be minimal symptoms if early in the course of PCP.

Note: Given the possibility of HIV-associated tuberculosis (TB), patients with cough should be kept in respiratory isolation until TB is ruled out.

Ask patient about fever, fatigue, and weight loss, which may be present for weeks, with gradual worsening of shortness of breath. PCP may present less commonly with acute onset symptoms of fevers, chills, sweats, dyspnea, and cough.

O: Objective

Perform a full physical examination with particular attention to the following:

- Vital signs including temperature, heart rate, blood pressure, respiratory rate, oxygen saturation at rest and after exertion (there is often a sharp drop in oxygen saturation with exertion)
- Appearance
- Lung examination

Patients may appear relatively well, or acutely ill. Tachypnea may be pronounced, and patients may exhibit such a high respiratory rate (>30 breaths per minute) that they are unable to speak without stopping frequently to breathe. Chest examination may be normal, or reveal only minimal rales, although coughing is common on deep inspiration. Cyanosis may be present around the mouth, in the nail beds, and on mucous membranes. Cough is either unproductive, or productive of a thin clear or whitish mucus.

A: Assessment

A partial differential diagnosis includes the following:

- Pneumococcal pneumonia
- Other bacterial pneumonias
- Tuberculosis
- *Mycobacterium avium* complex
- Lymphocytic interstitial pneumonitis
- Bronchitis
- CMV pneumonitis
- Histoplasmosis
- Other fungal pneumonia, especially *cryptococcus*
- Pulmonary Kaposi sarcoma
- Asthma, chronic obstructive pulmonary disease
- Congestive heart failure
- Pulmonary hypertension

P: Plan

Diagnostic Evaluation

- CD4 count is usually <200 cells/μL (>90% of PCP cases occur in patients with CD4 counts <200 cells/μL).
- Arterial blood gas (ABG): hypoxemia is common, as is elevation in alveolar-arterial O_2 gradient (A-a gradient). Generally, PO_2 levels and A-a gradient are associated with disease severity. Poorer outcomes are seen with PO_2 <70 mm Hg and A-a gradient >35 mm Hg.
- Elevated serum lactate dehydrogenase (LDH) (>300-500 IU is common.)
- Thin-section chest computed tomography (CT) scan may show ground glass opacities; in a patient with clinical signs or symptoms of PCP, these are suggestive but not diagnostic of PCP.
- Chest x-ray typically shows bilateral interstitial infiltrates, but atypical patterns with cavitation, lobar infiltrates, nodules, or pneumothorax may occur, and chest x-ray may be normal in some cases. Upper lobe predominance is common if the patient is receiving aerosolized pentamidine for PCP prophylaxis.
- Sputum induction: The patient inhales saline mist to mobilize sputum from the lungs. The respiratory therapist collects expectorated sputum, which is stained with Giemsa and examined for *P jiroveci* organisms. This technique is useful because of its noninvasive approach, but requires an experienced technician, and may not be available at all centers. Sensitivity varies widely (10-95%) depending on the expertise of the center. If there is any chance that the patient has TB, sputum induction should be done in a confined space in a negative pressure area or near an exhaust fan vented safely outside.
- Bronchoscopy with bronchoalveolar lavage (BAL): If induced sputum is negative for PCP organisms, definitive diagnosis is made through detection of organisms in BAL fluid obtained during bronchoscopy. Sensitivity is >95% in experienced centers. BAL fluid can be evaluated for bacteria, *mycobacteria*, and fungi, as well as for *P jiroveci*.
- Transbronchial biopsy may be done if lung disease is progressive despite treatment, to look for diagnoses other than PCP. Open lung biopsy is rarely done.

Treatment

Presumptive treatment is often initiated based on clinical presentation, chest x-ray findings, and ABG results, while definitive diagnostic tests are pending. Table 1 shows the standard and alternative treatment regimens.

Standard Therapy

Trimethoprim-sulfamethoxazole

Trimethoprim-sulfamethoxazole (TMP-SMX, Bactrim, Septra, cotrimoxazole) is the drug of choice: 15-20 mg/kg of theTMP component and 75-100 mg/kg of the SMX component, divided into 3 or 4 doses daily intravenously or orally for 21 days (a typical oral dose is 2 double-strength tablets 3 times daily). Adverse effects of TMP-SMX are common (eg, rash, fever, leukopenia, anemia, gastrointestinal intolerance), mostly mild, and can usually be "treated through." Patients who have had previous reactions to sulfa drugs also may be successfully desensitized (see chapter *Sulfa Desensitization*). TMP-SMX requires dose adjustment in cases of renal insufficiency.

Adjunctive corticosteroids

Adjunctive corticosteroids should be given if the room air PO2 is <70 mm Hg or the A-a gradient is >35 mm Hg. Corticosteroids should be given as early as possible (preferably before or with the first dose of antibiotic therapy) and within 36-72 hours of the start of antipneumocystis therapy:

- Prednisone 40 mg twice daily days 1-5; 40 mg once daily on days 6-10; 20 mg once daily on days 11-21. Intravenous methylprednisolone can be given, as 75% of the prednisone dose.

Table 1. Standard and Alternative PCP Therapy

Drugs	Dosages	Notes
Standard Therapy		
Trimethoprim + sulfamethoxazole (TMP-SMX)	TMP: 15-20 mg/kg plus SMX: 75-100 mg/kg divided into 3 or 4 doses daily intravenously (IV) or orally for 21 days	Patients who have had previous reactions to sulfa drugs may be successfully desensitized. Adjust dose in renal insufficiency.
Alternative Therapies		
Pentamidine	4 mg/kg IV daily for 21 days	Similar efficacy to TMP-SMX but greater toxicity (nephrotoxicity, pancreatitis, glucose dysregulation, cardiac arrhythmias). Usually reserved for patients with severe disease who require intravenous therapy.
Dapsone + trimethoprim	Dapsone* 100 mg orally daily plus trimethoprim 15 mg/kg orally daily for 21 days	Appropriate for mild-to-moderate disease
Clindamycin + primaquine	Clindamycin 600-900 mg IV every 6-8 hours (or 300-450 mg orally every 6-8 hours) plus Primaquine* base 15-30 mg orally once daily for 21 days	Appropriate for mild-to-moderate disease.
Atovaquone	750 mg orally twice daily for 21 days	For mild-to-moderate PCP only; not as potent as TMP-SMX
Trimetrexate (+ leucovorin)	Trimetrexate 45 mg/m^2 (or 1.2 mg/kg) IV daily plus Leucovorin 25 mg orally every 6 hours for 21 days	Not as potent as TMP-SMX. Leucovorin must be continued for 3 days beyond completion of trimetrexate

* Screen for G6PD deficiency (most common in patients of African or Mediterranean descent).

Other therapy notes

- Patients started on intravenous therapy can be switched to an oral treatment regimen to complete the 3-week course when they are afebrile, have improved oxygenation, and are able to take oral medications.
- Paradoxical worsening of PCP due to presumed immune reconstitution inflammatory syndrome (see chapter) has been reported in patients who initiated ART close to the time of diagnosis and treatment for PCP. At present, there is no consensus on whether initiation of ART during an acute episode of PCP is preferable to delaying ART, and clinical trials are under way to explore this question.
- Many providers prefer to wait until completion of PCP therapy and clinical stabilization of the patient before initiating ART. Consultation with HIV experts is advisable when considering starting ART in the setting of PCP.

Treatment failures

The average time to clinical improvement in hospitalized patients is 4-8 days, so avoid premature change in therapy. In patients who fail to improve on appropriate therapy, it is important to exclude other diagnoses, rule out fluid overload, and consult an infectious disease specialist. Some patients do not respond to any therapy, and the mortality rate of hospitalized patients is about 15%.

Secondary Prophylaxis

Anti-PCP prophylaxis (chronic maintenance therapy) should be given to all patients who have had an episode of PCP. Prophylaxis should be continued for life, unless immune reconstitution occurs as a result of ART, and the CD4 count has been >200 cells/μL for at least 3 months.

Standard prophylactic therapy

TMP-SMX, 1 double-strength tablet orally daily, or 1 single-strength tablet orally daily

Alternative prophylactic therapy

- Dapsone* 100 mg orally once daily, or 50 mg orally twice daily
- Dapsone* 50 mg orally once daily + pyrimethamine 50 mg orally once per week + leucovorin 25 mg orally once per week
- Dapsone* 200 mg orally + pyrimethamine 75 mg + leucovorin 25 mg, all once per week
  * *Warning:* Screen for G6PD deficiency before starting dapsone.
- Aerosolized pentamidine 300 mg once per month, via Respirgard II nebulizer (note: does not prevent toxoplasmosis)
  Warning: May increase the risk of extrapulmonary pneumocystosis, pneumothorax, and bronchospasm.
- Atovaquone suspension 1,500 mg orally once daily
- TMP-SMX: 1 double-strength tablet orally 3 times per week (eg, Monday, Wednesday, Friday)

Primary Prophylaxis

Primary prophylaxis against PCP should be given to all HIV-infected patients with CD4 counts <200 cells/μL or CD4 percentages <14%, or a history of oral candidiasis. See chapter *Opportunistic Infection Prophylaxis*.

Patient Education

- Instruct patients to take all medications exactly as prescribed.
- Patients should call their health care providers if symptoms worsen.
- Patients being treated with TMP-SMX who develop rash, fever, or other new symptoms, should call their providers to be evaluated for a drug reaction.
- Explain to patients that taking anti-PCP prophylaxis is extremely important to prevent repeat episodes of illness. Patients should not stop taking these medicines without talking with their health care providers, and should not let their prescriptions run out.

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Seborrheic Dermatitis

Background

Seborrheic dermatitis is one of the most common skin manifestations of HIV disease. It occurs in <5% of the general HIV-uninfected population, but in 34-83% of those with advanced HIV disease. It may flare and subside over time, and tends to worsen after severe illness. Seborrheic dermatitis is characterized by reddish or pink patches of skin, accompanied by greasy flakes or scales. It most commonly occurs in the scalp and on the face, especially at the nasolabial folds, eyebrows, and forehead, but also may develop on the ears, chest, upper back, axillae, or groin. Occasionally, seborrheic dermatitis may be severe and may involve large areas of the body.

The etiology of seborrheic dermatitis is not entirely clear. Malassezia yeast (formerly called Pityrosporum ovale) may play a causative role, as may high sebum levels.

S: Subjective

The patient complains of a new rash, sometimes itchy, or of "dry skin" that will not go away despite the application of topical moisturizers.

O: Objective

Perform a thorough evaluation of the skin with special attention to the scalp, nasolabial folds, ears, eyebrows, eyelashes, central chest, back, axillae, and groin. Seborrheic dermatitis appears as greasy or waxy flakes of skin over red or pink patches of skin. The distribution often is symmetrical.

A: Assessment

The diagnosis of seborrheic dermatitis usually is based on the characteristic appearance. A partial differential diagnosis includes psoriasis and rosacea.

P: Plan

Treatment

- Antiretroviral therapy, if otherwise indicated.
- Topical antifungal medications: various preparations are available; selection can be based on cost and availability. Antifungals may be used in combination with topical corticosteroid therapy (see below). Effective antifungals are not limited to this list.
  - Ketoconazole (Nizoral) 2% cream or shampoo. Studies suggest this is as effective as 1% hydrocortisone cream. Ketoconazole is one of the most widely studied of all topical treatments.
  - Bifonazole ointment, miconazole cream (Monistat), terbinafine (Lamisil) 1% solution, or clotrimazole (Lotrimin) 1% cream, lotion, or solution.
  - Ciclopiroxolamine (Loprox) 1% shampoo, gel, or cream.
  - Zinc pyrithione (keratolytic/antifungal) shampoo or cream.
- Topical corticosteroids are generally effective and may be used in combination with topical antifungal therapy (see above). Low-potency agents (eg, hydrocortisone 1%) rather than high-potency corticosteroids (eg, betamethasone dipropionate, triamcinolone), are recommended, especially for the face, to reduce the adverse effects associated with all corticosteroids (eg, atrophy, telangiectasias, and perioral dermatitis).
- Selenium sulfide/sulfur preparations (the most common is selenium sulfide shampoo).
- Whole coal tar and crude coal tar extract.
- Lithium succinate ointment, available in some countries as a combination of 8% lithium succinate and 0.05% zinc sulfate (may have antifungal or anti-inflammatory effects).
- Antibiotic agents:
  - Metronidazole 1% gel
- Honey, 90% diluted with warm water, may be useful to treat seborrheic dermatitis and dandruff.

- Noncorticosteroid topical immunomodulators (eg, tacrolimus, pimecrolimus) are helpful in atopic dermatitis and may be useful for seborrheic dermatitis.
- Oral therapy may be used for patients refractory to topical treatment (check for possible drug-drug interactions with antiretroviral and other medications before prescribing).
  - Itraconazole 200 mg once daily for 7 days (safest and best option)
  - Ketoconazole 200 mg once daily for no more than 4 weeks (prolonged use may cause hepatotoxicity)
  - Terbinafine 250 mg once daily for 4 weeks

Patient Education

- Although topical and oral medicines can relieve symptoms, recurrence of symptoms is common. Effective antiretroviral therapy also should be considered to control the effects of HIV on the immune system and thereby treat the underlying cause of seborrheic dermatitis.

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Sinusitis

Background

Sinusitis is defined as an inflammation involving the membrane lining of any sinus, and is a frequent finding in people with HIV disease. It occurs very commonly as part of a viral upper respiratory infection (URI), and usually is self-limited. Bacterial sinusitis usually occurs as a secondary complication of a viral URI, which causes decreased patency of the nasal ostia, decreased nasal ciliary action, and increased mucus production. Acute sinusitis is defined as lasting up to 4 weeks, whereas chronic sinusitis persists for at least 12 weeks.

HIV-infected patients are susceptible to sinusitis for a number of reasons related to their immunosuppression. Pathophysiologic mechanisms for this susceptibility may include proliferation of lymphatic tissue contributing to nasal obstruction, defects in B-cell and T-cell immunity due to HIV, and defects in production of immunoglobulins, specifically IgE, resulting in an exaggerated allergic response in the nasal mucosa. As in the general population, the most common pathogens causing acute bacterial sinusitis are *Streptococcus pneumoniae, Moraxella catarrhalis,* and *Haemophilus influenzae.* However, HIV-infected patients have a greater incidence of sinusitis caused by *Staphylococcus aureus* and *Pseudomonas aeruginosa.* The bacterial causes of chronic sinusitis are not well understood, but may involve more polymicrobial and anaerobic infections. In patients with severe immunosuppression, particularly those with CD4 counts ≤50 cells/μL, sinusitis may be caused by *Aspergillus* and other fungal pathogens.

S: Subjective

The patient may complain of facial pain, frontal or maxillary headache, postnasal drip, or fever.

Ask the patient about specific symptoms, the duration and progression of symptoms, and treatments attempted.

- Fever
- Facial pain or pressure, headache; positional pain (worse when patient bends forward)
- Purulent or bloody nasal discharge
- Postnasal drip
- Nasal congestion
- Recent URI
- Malaise
- Chronic cough
- Maxillary tooth pain
- Ear pressure
- History of chronic sinusitis, seasonal allergies, antibiotic allergies, atopy
- Tobacco use, inhaled recreational drugs

O: Objective

- Document vital signs.
- Perform a careful physical examination focusing on the head and face, neck, and lungs. Examine the nose, mouth, ears, and sinuses; look for nares inflammation, drainage from sinus ostia; examine the tympanic membranes and external auditory canals, evaluate the oropharynx for mucous drainage, lesions, exudates; check the teeth and gums for tenderness and erythema; palpate for tenderness over frontal and maxillary sinus cavities; examine the face and orbits for swelling or erythema.
- Perform cranial nerves examination.
- Auscultate the chest for abnormal lung sounds.

A: Assessment

Partial differential diagnosis includes:

- Allergic rhinitis
- Sinus blockage by other lesions such as Kaposi sarcoma or lymphoma (particularly if the CD4 count is <200 cells/μL) or fungal infections (if CD4 count is <50 cells/μL)
- Dental abscess, caries
- Meningitis
- Trauma

P: Plan

Diagnostic Evaluation

Uncomplicated acute sinusitis is usually a clinical diagnosis. There are no symptoms, physical findings, or tests that reliably distinguish bacterial from viral sinusitis. Patients can generally be assumed to have bacterial sinusitis if symptoms do not resolve, or if they worsen, over the course of 7-10 days. Any patient with high fever or severe or unusual symptoms should be evaluated urgently for other causes of illness.

Imaging studies usually are not indicated for uncomplicated acute sinusitis. In patients with a poor response to empiric antibiotic therapy and/or worsening symptoms, and those with suspected chronic sinusitis, computed tomography (CT) scans of the paranasal sinuses are the best initial radiologic study. Standard x-rays (sinus series) can detect cloudiness or air-fluid levels and will show mucosal thickening (a nonspecific finding in HIV-infected individuals).

Cultures of nasal aspirates are not useful for diagnosis, because nasal fluids do not accurately represent pathogens in the paranasal sinuses. Sinus aspirate cultures will give definitive diagnosis of a specific organism in the majority of cases; this may be considered in complicated cases. Definitive diagnosis of invasive fungal sinusitis requires tissue for culture.

Treatment

Treatment is multimodal. For viral sinusitis, treatment is based on symptom suppression; for bacterial sinusitis, an antibiotic is added to other therapies:

- Antihistamine: chlorpheniramine or other
- Decongestant: pseudoephedrine
- Nonsteroidal anti-inflammatory drugs (NSAIDs): ibuprofen or other
- Cough suppressant as needed
- Mucolytic agent: guaifenesin
- Inhaled steam and saline nasal irrigation to promote sinus drainage

If acute bacterial sinusitis is suspected, treat as above and add an antibiotic for a 10-14 day course of therapy:

- Amoxicillin 500-1,000 mg 3 times daily
- Amoxicillin/clavulanate (Augmentin) 825/125 mg twice daily
- Cefpodoxime 200-400 mg twice daily
- Doxycycline 100 mg twice daily
- Levofloxacin 500 mg once daily or moxifloxacin 400 mg once daily

For chronic sinusitis, administer multimodal treatments and an antibiotic as listed above for 3-4 weeks; add a nasal steroid such as budesonide, fluticasone, mometasone, or triamcinolone.

Note: Avoid fluticasone (Flonase) and budesonide (Rhinocort Aqua) nasal spray in patients taking ritonavir (including ritonavir-boosted protease inhibitors such as Kaletra), because significant increases in serum levels of these glucocorticoids may occur.

If symptoms persist or worsen, refer patients to an otolaryngologist for further evaluation and treatment.

Patient Education

- Instruct patients in the correct use of medications used to treat sinusitis, including proper technique for nasal irrigation or steam inhalation, as required.
- Instruct patients to take antibiotics on schedule until the entire prescription is gone in order to prevent recurrence of the infection.
- Advise patients that drinking 8 glasses (8-12 oz each) of fluid daily helps to keep the mucus thin enough to drain the sinus passages.
- Advise patients to call or return to clinic for swelling of the face or swelling around the eyes, increased facial tenderness, new or worsening fever, or other concerning symptoms.

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Syphilis

Background

Syphilis is a sexually transmitted infection (STI) caused by the spirochete Treponema pallidum. It is a complex disease with protean variations that can mimic many common infections or illnesses. HIV infection may alter the natural history and management of syphilis, causing a more rapid course of illness, higher risk of neurologic complications, and greater risk of treatment failure with standard regimens. Because many individuals with syphilis have no symptoms, or have symptoms that subside without treatment, sexually active individuals at risk for syphilis should receive regular screening for syphilis as well as for other STIs. Many clinicians strongly recommend routine syphilis testing every 3-6 months in patients at risk for syphilis.

In recent years, increasing numbers of syphilis cases have been reported in HIV-infected men who have sex with men (MSM), predominantly in major metropolitan areas. This trend reflects reduced use of safer sex practices, and is concerning both because syphilis can have major health consequences if it is undetected and untreated, and because it is associated with increased risk of new HIV infections. Risk assessment should be conducted at each patient visit for unprotected sex (including oral sex), multiple sexual partners, and use of recreational drugs (methamphetamine and cocaine, in particular, are associated with high-risk sexual practices in MSM). Asymptomatic persons at risk of acquiring syphilis should be screened at regular intervals (with rapid plasma reagin [RPR] or Venereal Diseases Research Laboratory [VDRL] testing, as below), depending on their risk factors. MSM with multiple partners should be tested every 3-6 months.

The natural history of untreated syphilis infection is divided into several different stages based on length of infection.

Primary Syphilis

Primary syphilis usually manifests after an incubation period of 1-3 weeks from exposure and is characterized by a painless self-limiting ulcer (chancre) at the site of sexual contact. HIV-infected individuals may have multiple or atypical chancres that might be misidentified. Some patients have no primary lesion, or have a primary lesion that is not visible. Associated regional lymphadenopathy can occur. HIV-infected individuals sometimes have a chancre concurrently with rash typical of secondary syphilis.

Secondary Syphilis

Secondary syphilis usually develops 2-8 weeks after initial infection and is caused by ongoing replication of the spirochete, with disseminated infection that may involve multiple systems. Rash is the most common presenting symptom; skin lesions may be macular, maculopapular, papular, or pustular, or may appear as condyloma lata. The rash often appears on the trunk and extremities and may involve the palms and soles of feet. Constitutional symptoms, lymphadenopathy, arthralgias, and myalgias are common and neurologic or other symptoms may occur. In the absence of treatment, the manifestations of secondary syphilis last days to weeks, then usually resolve to the latent stages.

Latent Syphilis

Latent syphilis follows resolution of secondary syphilis. As in HIV-uninfected individuals, latent syphilis is asymptomatic and the diagnosis is determined by positive serologic tests. Latent syphilis is further classified as "early latent" if the infection is known to be less than 1 year in duration, "late latent" if the infection is known to be greater than 1 year in duration, or "latent syphilis of unknown duration" if the duration of infection is not known.

Late or Tertiary Syphilis

Late or tertiary syphilis is due to chronic infection with progressive disease in any system causing serious illness and death in untreated patients. The most common manifestations include neurosyphilis, cardiovascular syphilis, and gummatous syphilis.

Neurosyphilis

Neurosyphilis can occur at any time after initial infection, due to spread of the spirochete to the central nervous system (CNS). In HIV-infected individuals, neurosyphilis may occur more commonly early in the course of infection, during secondary or latent syphilis. It is associated with neurologic symptoms, including cranial nerve abnormalities (particularly extraocular

or facial muscle palsies, tinnitus or hearing loss) or symptoms of meningitis. Uveitis or other eye disease may occur in conjunction with neurosyphilis.

S: Subjective

Symptoms will depend on the site of initial infection, the stage of disease, and whether neurosyphilis is present. Symptoms are not present in all patients.

If symptoms are present, the patient may complain of:

- Painless sore(s) or ulcer(s) in the genital area, vagina, anus, or oral cavity
- New rash, usually on the trunk, soles, and/or palms; patchy hair loss
- Fever, malaise, swollen glands, arthralgias, myalgias
- Altered mental status, weakness, paralysis
- Neurosyphilis: vision changes, eye pain, hearing loss, headaches, dizziness, generalized weakness, seizures, confusion, changes in personality or affect

Conduct a targeted history, asking the patient about symptoms listed above, including duration; inquire about other or associated symptoms Ascertain the following:

- Previous diagnosis of syphilis
- New sex partner(s) in past 90 days (for primary or secondary syphilis)
- Unprotected sex (oral, vaginal, anal)
- Date of last syphilis test
- Possible pregnancy

O: Objective

Check for fever, document other vital signs

Perform a complete examination including:

- Skin and mucosal areas (including the genitals, palm, and soles): rash, gummas, granulomas, patchy hair loss
- Oropharynx: chancres, mucous patches, condyloma lata
- Lymph nodes
- Heart: murmurs
- Ophthalmic examination
- Neurologic examination (mental status, cranial nerves [including visual acuity], sensory, motor, reflexes, coordination, gait): abnormal mental status, visual acuity changes, extraocular movement abnormalities, neurosensory hearing loss, facial palsy, paraesthesias, paralysis, hemiplegia, hyperactive reflexes, ataxia

A: Assessment

Because syphilis has a wide range of manifestations, the differential diagnosis is broad. It is important to consider syphilis as a possible cause of many presenting illnesses. A partial differential diagnosis includes:

- Other causes of maculopapular rashes: pityriasis, drug eruption, condyloma, folliculitis, psoriasis, acute HIV infection
- Other causes of genital ulcerative disease: herpes simplex virus (HSV), chancroid
- Other causes of ocular disease; glaucoma, cytomegalovirus (CMV) retinitis, CMV immune reconstitution uveitis, HSV keratitis
- Other causes of neurologic disease: stroke, Bell's palsy, CNS lymphoma, toxoplasmosis, meningitis
- Other causes of cardiac murmurs: bacterial endocarditis, congenital abnormalities
- Other causes of systemic symptoms (eg, fever, malaise, adenopathy): acute HIV infection, acute hepatitis, other infections or malignancies

P: Plan

Diagnostic Evaluation

Darkfield examination and direct fluorescent antibody

Darkfield examination and direct fluorescent antibody (DFA) testing of a sample from suspicious genital or anal chancres or moist dermatologic lesions (not oral lesions) are definitive tests for syphilis.

Serologic tests

Nontreponemal tests (RPR or VDRL) are most sensitive in primary and secondary syphilis when titers are high, though the response may be delayed in HIV-infected patients (typically nontreponemal tests are positive within 3 months after infection). Because false-positive results may occur, positive nontreponemal test results must be confirmed with a treponemal test. Titers may be used to follow response to treatment; a fourfold change in titer is considered a significant change. Note

that the same nontreponemal test should be used consistently for a single patient; RPR titers cannot be compared with VDRL titers.

Treponemal antibody tests (TP-PA [T pallidum particle agglutination] or FTA-ABS [fluorescent treponemal antibody absorption]) confirm a positive nontreponemal test.

A false-negative RPR or VDRL test may occur, usually when the test is performed in early infection, before a sufficient antibody response has developed. Another possible cause of a false-negative nontreponemal test is the prozone phenomenon, seen when antibody concentrations are very high (usually in secondary syphilis) and the specimen is not diluted sufficiently. If serologic tests are negative and suspicion of syphilis is high, perform other diagnostic tests (biopsy, etc) and/or request that the laboratory perform additional dilutions on nontreponemal test specimens.

Cerebrospinal fluid (CSF) evaluation

HIV-infected patients with clinical evidence of neurologic or ocular syphilis, late latent syphilis, syphilis of unknown duration, or tertiary syphilis should receive lumbar puncture (LP) and CSF analysis. LP also is indicated for patients in whom treatment for early syphilis fails (see below). Some specialists recommend CSF evaluation for all HIV-infected patients with syphilis of any stage. CSF analysis should include:

- CSF-VDRL: this test is specific but is not very sensitive.
- Leukocytes: elevated white blood cell count (>10 cells/μL) is suggestive but is not specific. Note that mononuclear pleocytosis (up to 5-20 cells/μL) is not uncommon in patients with HIV infection, particularly those with higher CD4 cell counts.

Other testing

All patients who test positive for syphilis should be tested for gonorrhea and chlamydia, with sampling sites based on sexual practices and exposures (oropharyngeal, urethral, vaginal, or anorectal testing). Patients not known to be HIV-infected also should be tested for HIV.

Treatment

Treatment of syphilis in HIV-infected individuals essentially is the same as in HIV-uninfected individuals, and depends on stage and the presence or absence of neurosyphilis. It is important to follow patients closely to assure the success of treatment. For further information, see the Centers for Disease Control and Prevention (CDC) Sexually Transmitted Diseases Treatment Guidelines (reference below).

Early syphilis

Less than 1 year duration, ie, primary, secondary, and early latent; nonneurologic

- *Preferred:* benzathine penicillin G, 2.4 million units intramuscularly (IM) (single dose).
- *Alternatives:* In penicillin-allergic, nonpregnant patients, consider the following. Note that these therapies are not as well proven in HIV-infected individuals; close monitoring for treatment response is recommended.
  - Doxycycline, 100 mg orally twice daily for 14 days
  - Tetracycline, 500 mg orally 4 times daily for 14 days
  - Ceftriaxone, 1 gm IM or intravenously (IV) daily for 8-10 days
  - High rates of treatment failure have been reported in patients treated with azithromycin (2 grams, single dose); this regimen should be used only if other options are contraindicated and close follow-up is possible

Late latent syphilis

More than 1 year duration or of unknown duration; nonneurologic

- CSF examination to rule out neurosyphilis should be done on all patients with a history of syphilis of more than 1 year or of unknown duration.
- If CSF examination is negative, treat with benzathine penicillin G, 2.4 million units IM weekly for 3 consecutive weeks (7.2 million units total).
- In penicillin-allergic clients, refer for desensitization to penicillin. As an alternative, some consider doxycycline 100 mg orally twice daily for 28 days. Referral to infectious disease specialist and close clinical monitoring are required, as treatment is not proven in HIV-infected individuals.

Tertiary syphilis

Consult with specialists.

Neurosyphilis

Syphilis at any stage with neurologic or ocular symptoms or CSF findings of neurosyphilis

Ideally, patients should be hospitalized and given 2 weeks of penicillin IV under close observation. Penicillin-allergic patients should be referred for desensitization, if possible.

- *Preferred:* aqueous crystalline penicillin G, 18-24 million units IV per day (3-4 million units every 4 hours [or continuous infusion] for 10-14 days).
- *Alternatives* (require strict adherence with therapy):
  - Procaine penicillin 2.4 million units IM per day, plus probenecid 500 mg orally 4 times daily, both for 10-14 days.
  - Some consider use of ceftriaxone, 2 gm IM or IV once daily for 10-14 days with close clinical monitoring.
- Some specialists recommend administration of benzathine penicillin, 2.4 million units IM weekly for 3 weeks, after completion of the standard 10- to 14-day course of therapy for neurosyphilis.
- Recheck CSF leukocyte count every 6 months until the cell count normalizes (if CSF pleocytosis was present at initial evaluation). If the leukocyte count is not lower at 6 months, consider retreatment (consult with a specialist).

Note that a Jarisch-Herxheimer reaction may occur after initial syphilis treatment, especially in primary, secondary, or even latent syphilis. This self-limited treatment effect should not be confused with an allergic reaction to penicillin. It usually begins 2-8 hours after the first dose of penicillin and consists of fever, chills, arthralgias, malaise, tender lymphadenopathy, and intensification of rash. It resolves within 24 hours and is best treated with rest and acetaminophen. Patients should be warned about the possibility of Jarisch-Herxheimer reaction.

Pregnancy

Pregnant women should be treated with penicillin, if possible, using a regimen appropriate to the stage of infection (see above). Penicillin-allergic pregnant women should be referred for desensitization to penicillin. Doxycycline and tetracycline may cause fetal toxicity and should not be used during pregnancy; erythromycin is not sufficiently effective in treating syphilis in the fetus. The efficacy of azithromycin and ceftriaxone in pregnancy is uncertain.

Women treated during the second half of pregnancy are at risk of contractions, early labor, and fetal distress if they develop a Jarisch-Herxheimer reaction; thus, they should be monitored carefully.

Sex partners

Syphilis is transmitted sexually only when mucocutaneous lesions of syphilis are present; this is uncommon after the first year of infection. Nevertheless, sex partners of a patient who has syphilis in any stage should be evaluated.

- Persons exposed within 90 days preceding the diagnosis of primary, secondary, or early latent syphilis should be treated presumptively, as they might be infected with syphilis even if they are seronegative.
- Persons exposed more than 90 days before the diagnosis of primary, secondary, or early latent syphilis should be treated presumptively if serologic test results are not available immediately and the patient's follow-up is in doubt. Otherwise, they should receive serologic testing and be treated appropriately if the test result is positive. Note that some experts recommend presumptive treatment of all persons potentially exposed to syphilis. For patients with primary syphilis, this means partners within the previous 3 months; for secondary, within 6 months; for early latent, within 1 year.

Follow-up

All HIV-infected patients treated for syphilis should be evaluated clinically and serologically at 3, 6, 9, 12, and 24 months (at 6, 12, 18, and 24 months for late syphilis) to rule out treatment failure. Treatment success is determined by a fourfold decrease in RPR or VDRL titer by 6-12 months (for early syphilis) or 12-24 months (for late syphilis) after treatment. Patients whose titers do not decrease appropriately probably either experienced treatment failure or were reinfected. Any patient with apparent treatment failure should undergo an LP for CSF analysis and be re-treated as appropriate. If, at any time, symptoms develop or nontreponemal test titers increase fourfold, CSF examination should be performed and appropriate treatment should be given.

Some patients retain reactive (low-titer) nontreponemal

test results after successful treatment for syphilis. In these "serofast" individuals, reinfection with syphilis is indicated by a rise in test titer of at least 4-fold.

Risk-reduction counseling

All patients with syphilis should receive risk evaluation and risk-reduction counseling. Evaluate each patient's sexual practices with regard to risk of acquiring STIs and of transmitting HIV. Work with the patient to reduce sexual risks.

Patient Education

- Instruct patients to go to clinic for treatment at the intervals recommended. If patients are given oral antibiotics (penicillin-allergic individuals), instruct them to take their medications exactly as prescribed.
- Warn patients about the possibility of Jarisch-Herxheimer reaction and advise them about self-management of associated symptoms (eg, acetaminophen or aspirin at usual doses, fluids, and rest).
- Instruct patients about the required follow-up laboratory and clinical evaluations necessary to document adequate treatment. Emphasize the need for regular evaluation of treatment efficacy.
- Sexual partners from the previous 3-6 months (sometimes longer, depending on the stage of syphilis) need to be evaluated and treated as soon as possible, even if they have no symptoms. Advise patients to inform their partner(s) that they need to be tested and treated.
- Syphilis is a reportable communicable disease in the United States. Patients will be contacted to assist with partner tracing and to ensure appropriate treatment.
- Provide education about sexual risk reduction. Review sexual practices and support patients in using condoms with every sexual contact to prevent becoming reinfected with syphilis or infected with other STIs, and to prevent passing HIV to sexual partners.

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Toxoplasmosis

Background

Toxoplasma gondii is a common intracellular protozoan that preferentially infects the central nervous system (CNS) of immunodeficient patients, causing severe neurologic disease. *T gondii* also can cause local disease such as chorioretinitis or pneumonia. *Toxoplasma* has an infectious reservoir in almost all animals; humans acquire infection either through ingestion of tissue cysts contained in undercooked meat (usually pork or lamb) or oocysts on contaminated vegetables or through exposure to cat feces containing oocysts. There is no transmission by person-to-person contact.

Clinical disease usually occurs through reactivation of latent infection in patients who have CD4 counts of <100 cells/μL. Seroprevalence varies widely, from 15% in the United States to 75% in some European countries, and even higher in certain resource-limited countries. In the absence of prophylaxis, toxoplasmic encephalitis occurs in more than 30% of patients with advanced HIV disease who are seropositive for *T gondii*.

CNS toxoplasmosis is an AIDS-defining condition that can be progressive and fatal. However, antimicrobial therapy, especially if given in conjunction with antiretroviral therapy (ART) that results in immune reconstitution, can be successful in treating toxoplasmosis. Specific prophylaxis and effective ART also may be used to prevent toxoplasmosis in patients with advanced AIDS who have latent *T gondii* infection (as demonstrated by the presence of anti-Toxoplasma immunoglobulin G [IgG] antibodies; see chapter *Preventing Exposure to Opportunistic and Other Infections*).

S: Subjective

The patient may complain of subacute onset of dull, constant headache, fever, visual changes or other focal neurologic symptoms, confusion, or disorientation. Seizures may occur. Caregivers may report subtle alterations in mental status or mood.

Take a careful history from the patient and caregivers about the symptoms listed above and their duration, progression, and severity. Inquire about other related symptoms. Ask whether the patient is taking *Toxoplasma* prophylaxis or ART.

O: Objective

- Measure vital signs (temperature, heart rate, blood pressure, respiratory rate).
- Perform a full physical examination including a thorough neurologic examination, looking for focal or nonfocal neurologic deficits, particularly weakness, cranial nerve abnormalities, visual field defects, gait disturbances, and abnormalities in speech, cognitive, or affective functions.
- Review previous laboratory values, particularly:
  - CD4 count (which usually is <50-100 cells/μL in patients with toxoplasmosis)
  - Toxoplasma IgG (>95% of patients with *toxoplasmosis* have positive IgG)

A: Assessment

Rule out other infectious or neoplastic causes of headache, fever, and neurologic changes. A partial differential diagnosis includes:

- CNS lymphoma
- Cryptococcal meningitis
- Progressive multifocal leukoencephalopathy (PML)
- Tuberculous meningitis
- Brain abscesses of bacterial, fungal, or mycobacterial etiologies
- Herpes simplex virus or cytomegalovirus (CMV) encephalitis
- Primary HIV encephalopathy
- AIDS dementia complex
- Cerebrovascular accident secondary to hemorrhage, hypoxia, or emboli from vegetative endocarditis
- Neurosyphilis
- Other causes of chorioretinitis such as CMV, HIV, and cryptosporidiosis

P: Plan

Diagnostic Evaluation

Definitive diagnosis requires identification of *T gondii* in tissue biopsy or body fluid samples. Brain biopsy usually is not performed if toxoplasmosis is strongly suspected; instead, presumptive diagnosis is made on the basis of clinical presentation, laboratory and imaging tests, and response to therapy. Brain biopsy should be considered in patients who do not respond to therapy or in whom the diagnosis is unclear.

- Serum *Toxoplasma* IgG antibody test results are positive in nearly all patients with toxoplasmic encephalitis. A negative IgG test result makes the diagnosis very unlikely but does not rule it out. (Antibody titer changes are uncommon in reactivation disease and are not useful in making a diagnosis.)
- CNS imaging with computed tomography (CT) typically shows multiple contrast-enhancing mass lesions, but may show a single lesion or no lesions. Magnetic resonance imaging (MRI) is more sensitive than CT for CNS toxoplasmosis. Other imaging studies, such as single photon emission CT (SPECT), may be useful in distinguishing toxoplasmic lesions from CNS lymphoma.
- Polymerase chain reaction (PCR) tests for *T gondii* in the cerebrospinal fluid have poor sensitivity.
- Other diagnostic tests should be performed as indicated to rule out other potential causes of the patient's symptoms.
- Patients with toxoplasmic encephalitis typically respond quickly to treatment. If clinical improvement is not seen after 10-14 days of appropriate treatment, or if clinical worsening is seen in the first week, consider brain biopsy for alternative diagnoses.

Treatment

Treatment consists of 2 phases: acute therapy and chronic maintenance therapy.

Presumptive treatment often is begun on the basis of clinical presentation, positive *Toxoplasma* IgG, and results of brain imaging studies. If patients do not respond quickly to treatment, other diagnoses should be considered. The following recommendations are based on treatment guidelines published by the Centers for Disease Control and Prevention, National Institutes of Health, and HIV Medicine Association/Infectious Diseases Society of America (see References below).

Acute Therapy

Preferred

- Pyrimethamine 200 mg orally as a single loading dose, then 50 mg (<60 kg body weight) to 75 mg (>60 kg body weight) daily + sulfadiazine 1,000 mg (<60 kg body weight) to 1,500 mg orally every 6 hours (>60 kg body weight) + folinic acid (leucovorin) 10-20 mg daily.

Dosage adjustments to the lower end of therapeutic range of pyrimethamine and sulfadiazine may be considered for patients who have significant bone marrow suppression despite folinic acid supplementation. Monitor patients carefully for cytopenias, especially if they are on other agents that cause bone marrow suppression, such as zidovudine, valganciclovir, and ganciclovir.

Note: Patients at risk for G6PD deficiency should be checked for G6PD deficiency before starting pyrimethamine.

Alternatives

- Pyrimethamine + folinic acid (administered as described above) + 1 of the following:
  - Clindamycin 600 mg orally or intravenously every 6 hours; recommended for patients with significant allergic reactions to sulfa medications
  - Atovaquone 1500 mg orally every 12 hours
  - Azithromycin 900-1,200 mg orally once daily
- Trimethoprim-sulfamethoxazole (TMP-SMX) 5 mg/kg TMP and 25 mg/kg SMX orally or intravenously every 12 hours. This can be considered when the availability of other regimens is limited or when patients need intravenous therapy.

- Atovaquone 1,500 mg orally twice daily + sulfadiazine 1,000-1,500 mg orally every 6 hours.

Note: The regimens that contain sulfadiazine, TMP-SMX, or atovaquone also are effective in preventing *Pneumocystis jiroveci* pneumonia (PCP), so patients on these regimens do not need additional PCP prophylaxis.

Adjunctive corticosteroids (eg, dexamethasone 4 mg orally or intravenously every 6 hours) may be indicated for patients with significant CNS edema or mass effect. Use is based on clinical judgment and should be discontinued as soon as clinically feasible.

Anticonvulsant therapy should be given to patients with seizures.

Ventilatory support may be necessary if severe CNS symptomatology is present.

Chronic Maintenance Therapy

After at least 6 weeks of initial therapy, and significant clinical and radiologic improvement, chronic maintenance therapy can be considered.

Preferred

- Pyrimethamine 25-50 mg orally once daily + sulfadiazine 500-1,000 mg orally every 6 hours + folinic acid 10 mg orally once daily (also effective as PCP prophylaxis).

Alternatives

- Pyrimethamine 25-50 mg orally once daily + clindamycin 300-450 mg orally every 6-8 hours + folinic acid 10 mg orally once daily.
- Pyrimethamine 25-50 mg orally once daily + atovaquone 1,500 mg orally once daily + folinic acid 10 mg orally once daily (also effective as PCP prophylaxis).

Chronic maintenance therapy generally should be continued for life. For patients who complete acute therapy successfully, have resolution of signs and symptoms of toxoplasmosis, and have immune reconstitution (with CD4 counts >200 cells/μL) for more than 6 months on ART, it is reasonable to consider discontinuing maintenance therapy. Some specialists would require resolution of CNS lesions on radiologic studies before discontinuation of therapy. Patients must be observed for recurrence of symptoms, and treatment should be restarted if the CD4 count decreases to <200 cells/μL.

Considerations in Pregnancy

All pregnant women should be tested for *T gondii*. If the result is positive, evaluate the mother for toxoplasmosis and the neonate for evidence of congenital infection. Perinatal transmission usually occurs only with acute maternal infection, but in advanced HIV, it may occur with reactivation of chronic infection. If *T gondii* infection occurs during pregnancy, consult with a maternal-fetal specialist. Treatment for pregnant women is the same as for nonpregnant adults (see above). Note that sulfadiazine taken at the time of delivery may increase the risk of neonatal hyperbilirubinemia and kernicterus.

Patient Education

- Advise patients that antimicrobial therapy alone will not eradicate toxoplasmosis, but should decrease symptoms and improve quality of life. If medications are discontinued, the disease is likely to recur, unless the CD4 count increases to >100-200 cells/μL in response to ART.
- Inform patients that suppressive therapy must be continued to prevent recurrence. This therapy may be lifelong.
- It is essential for patients to take all medicines exactly as prescribed. If doses are missed, or if the medications are stopped and restarted, *Toxoplasma* can develop resistance to the medications. If patients are having trouble taking the medication on schedule, they should contact their health care providers immediately.
- Educate patients about the benefits of ART in strengthening the immune system and preventing opportunistic infections such as toxoplasmosis.
- Advise patients to return to clinic promptly if symptoms worsen or new symptoms develop.
- Toxoplasmosis is a late-stage HIV opportunistic infection and indicates profound immune suppression. Some patients may not respond to treatment or to ART. As with any patient who is at risk for a life-threatening HIV-related disease, clinicians should discuss advance directives and durable power of attorney with patients. Referral to a social worker, mental health clinician, or chaplain experienced in such issues may facilitate this discussion.

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Linear Gingival Erythema

Background

Linear gingival erythema is inflammation of the margins of the gingiva. It is characterized by a 2-3 mm band of intense erythema around the necks of the teeth that does not resolve with routine oral hygiene. The erythematous changes usually are generalized, but may be confined to a few teeth. This condition is one of the most common oral manifestations of advanced HIV/AIDS. It also may be referred to as HIV gingivitis or red-band gingivitis.

S: Subjective

The patient may complain of bleeding, tender gums, and a bad taste in the mouth.

O: Objective

Examine the oral cavity carefully for inflamed gingival tissues, which bleed easily upon manipulation (including brushing). This condition is seen most commonly in the buccal area of lower anterior teeth, as a continuous red band around the necks of teeth.

A: Assessment

The differential diagnosis includes necrotizing gingivitis, periodontitis, and Kaposi sarcoma. (See chapters on *Necrotizing Ulcerative Periodontitis and Gingivitis* and *Kaposi Sarcoma* for more information.)

P: Plan

The diagnosis is based on clinical features; perform additional testing to rule out other causes, as indicated. Recommend patient education and counseling, meticulous home care, frequent dental visits during treatment phase, and regular recall visits. Refer for nutrition counseling as needed.

Treatment

Linear gingival erythema should be treated aggressively to prevent progression to necrotizing periodontal disease; referral should be made for prompt dental care and the patient should be educated in oral hygiene techniques.

A chlorhexidine gluconate (0.12%) rinse twice daily for 2 weeks will relieve some of the symptoms. Refer to a dentist or dental hygienist for a thorough dental prophylaxis (cleaning). If this combination is not successful, it may be appropriate to add an antibiotic such as:

- Metronidazole 250 mg orally 4 times daily for 7 days
- Amoxicillin-clavulanate (Augmentin) 875 mg orally twice daily for 7 days
- Clindamycin 150-300 mg orally 4 times daily for 7 days

Patient Education

- Good oral hygiene is essential to management, especially with concomitant periodontitis. Advise patients to brush and floss after every meal. Any rinses prescribed by care providers should be used after brushing.
- Advise patients not to eat or drink for 30 minutes after rinsing with chlorhexidine gluconate.
- Urge regular dental checkups and cleaning at least every 3-6 months.
- Patients should not drink alcohol while taking metronidazole, and for at least 48 hours after the last dose.

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Necrotizing Ulcerative Periodontitis and Gingivitis

Background

Necrotizing ulcerating periodontitis (NUP) is a marker of severe immunosuppression that affects the gums and extends to the underlying bone or periodontium. It may or may not be distinct from necrotizing ulcerative gingivitis (NUG), which is considered to be confined to the gums. This discussion will focus primarily on NUP, but the microbial profiles and treatment recommendations for these two periodontal diseases are similar.

NUP in HIV-infected individuals is believed to be an endogenous infection that progresses to necrosis of the gingiva. Pathogens may include anaerobic bacteria and fungi. NUP usually presents as "blunting" at interdental papillae, but rapidly progresses to destruction of underlying alveolar bone. It usually is associated with severe pain and spontaneous bleeding. Several case reports have described extensive destruction leading to exfoliation of teeth within 3-6 months of onset, with sequestration of necrotic alveolar bone and necrotic involvement of the adjacent mandible and maxilla. Patients may present with concomitant malnutrition due to inability to take food by mouth. The prevalence of NUP in the HIV-infected population has been reported as 0-5%. NUP is the most serious form of periodontal disease associated with HIV.

S: Subjective

The patient complains of painful, spontaneously bleeding gums, diminished or metallic taste, bad breath, or loose teeth (with a prevalence toward anterior teeth and first molars). "Deep jaw pain" is a common complaint and may reflect extension to adjacent mucosa.

O: Objective

Examine the oral cavity carefully. NUP and NUG present with fiery red, ulcerated gingival tissues, and grayish exudate. Teeth may be very loose or missing and there will be a fetid odor from the mouth. The ulcerated tissues can extend past the attached gingiva to the adjacent mucosa. Necrosis of adjacent bone also is common.

A: Assessment

The differential diagnosis includes other causes of gingival ulceration, such as herpes simplex virus, herpes zoster, cytomegalovirus, and Kaposi sarcoma. (See relevant chapters on these conditions.)

P: Plan

Treatment

Treatment usually is divided into the acute phase and the maintenance phase. The primary concern in the acute phase is pain control. For the maintenance phase, treatment is directed toward reducing the burden of potential pathogens, preventing further tissue destruction, and promoting healing.

- For uncomplicated NUP or NUG, perform local debridement with irrigation and periodontal curettage (extending below the marginal gingiva).
- Chlorhexidine gluconate rinse (0.12%) twice daily after brushing and flossing (the alcohol-free preparation is preferred).
- Antibiotic therapy (preferably narrow spectrum, to leave gram-positive aerobic flora unperturbed).
  - Metronidazole or penicillin is the drug of choice, 250 mg orally 3 times daily for 10-14 days.
  - Coadminister with amoxicillin-clavulanate (Augmentin) 875 mg orally twice daily for 10-14 days, if no hypersensitivity or allergy to either drug exists.
- Refer to a dentist for the following:
  - Removal of plaque and debris from the site of infection and inflammation
  - Debridement of necrotic hard and soft tissues, with a 0.12% chlorhexidine gluconate lavage

Patient Education

- Advise the patient of the following: Good oral hygiene is critical to arresting gum, periodontium, and tooth loss. Avoid smoking and try to eliminate emotional stress. When primary stabilization is achieved, resume daily brushing and flossing after every meal. This may be difficult during the acute phase, but it is very important to keep the mouth as clean as possible. Nutrition supplements (liquid diet, plus vitamins/minerals) are recommended.
- Frequent professional cleaning (every 2-3 months) may be needed during the maintenance phase.
- Patients taking metronidazole should not drink alcohol during treatment with metronidazole, and for at least 24-48 hours after last dose, in order to avoid severe nausea and vomiting from a disulfiram reaction.
- Instruct patients not to drink, eat, or rinse their mouths with water for 30 minutes after rinsing with chlorhexidine.
- Bleeding gums may transmit HIV (or hepatitis C) during "deep kissing" or other activities (oral-genital contact). Advise patients/clients to avoid exposing partners to HIV by taking all necessary precautions, including abstaining from risky activities until this condition is healed and stable (no oozing of oral fluids).

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Oral Health

Background

Examination of the oral cavity should be included in both the initial and interim physical examination of all HIV-infected patients. Patients with lesions suspected to be oral manifestations of HIV disease should be referred to a dental health expert with experience in treating oral lesions associated with HIV/AIDS. Other oral lesions may be a sign of a systemic disease, a side effect of medications, or a result of poor oral hygiene.

The following is an overview of conditions commonly seen in patients with HIV infection. See chapters *Oral and Esophageal Candidiasis*, *Oral Hairy Leukoplakia*, *Oral Warts*, *Oral Ulceration*, *Linear Gingival Erythema*, and *Necrotizing Ulcerative Periodontitis and Gingivitis* for more information about those conditions.

Xerostomia (Dry Mouth)

S: Subjective

The chief complaint may be a dry, "sticky," or burning sensation in mouth, or an inability to "taste" food. The patient may present with difficulty swallowing.

O: Objective

The oral mucosal tissues appear dry and sometimes "shiny" in appearance. The lips may be dry and cracked, and the tongue is dry. Dental decay may be present on the cervical portion of the teeth. Oral candidiasis (thrush) may or may not be present.

A: Assessment

The differential diagnosis includes medication side effects (eg, from anticholinergics), systemic diseases (eg, Sjögren's syndrome), and adverse effects of radiation therapy.

P: Plan

Identify the cause of xerostomia and modify, if possible. Treat with artificial saliva products or oral lubricant products (eg, Salivart, Biotene Oral Balance Dry Mouth Relief Moisturizing Gel, or TheraSpray). Discourage sucking on hard candies, as that can promote dental caries. Promote good oral hygiene with flossing and brushing with a fluoride toothpaste, and encourage regular (every 3-4 months) dental recall visits. Severe cases of xerostomia may be treated by prescribing cholinergic stimulants such as pilocarpine (Salagen).

Burning Mouth Syndrome; Atrophic Glossitis

S: Subjective

The patient may complain of a constant burning sensation in the mouth or a numbness or tingling feeling of the tongue. Eating certain foods or spices may trigger the burning sensation. The patient also may complain of dry mouth or a metallic taste in the mouth.

O: Objective

The tongue and oral mucosal tissues may be normal in appearance or there may be a slight redness on the tip and lateral margins of the tongue. In other cases, the tongue may appear "bald" due to the loss of papillae on the dorsal surface, and it may be "beef red" in color.

A: Assessment

Possible systemic etiologies include nutritional and vitamin deficiencies (atrophic glossitis), chronic alcoholism, medication adverse effects, diabetes mellitus, and gastric reflux. Local etiologies include denture irritation, oral habits such as tongue or cheek biting, and excessive use of certain toothpastes or mouthwashes. Psychological factors and nerve damage also may cause burning mouth. Erythematous candidiasis also can present as a burning sensation.

P: Plan

Identify the cause of the burning sensation, if possible, by review of the medical history and by performing diagnostic tests as indicated (eg, complete blood count, biopsy, or oral cytological smears). Once the underlying cause is identified, treatment may be as simple as changing a dentifrice or eliminating the identified irritant, or the condition may require systemic treatment.

Aphthous Ulceration

S: Subjective

The patient complains of a painful ulcer or ulcers in the mouth.

O: Objective

The typical appearance of an aphthous ulcer is a "red raised border with a depressed, necrotic (white to yellow psuedomembrane) center." Aphthous ulcers may be small or large, solitary or in clusters, and can resemble intraoral herpetic lesions.

A: Assessment

The differential diagnosis includes traumatic ulcers and herpes simplex virus ulcers.

P: Plan

The diagnosis usually is based on appearance. For further information, see the chapter on *Oral Ulceration*.

Recurrent Herpes Simplex

S: Subjective

The patient complains of a locally painful ulcer(s) on the lips or intraoral areas.

O: Objective

Herpes lesions are located on the lips and around the mouth, the gums, or gingival or hard palate. They may appear as small vesicular lesions that rupture, forming small ulcers. They may rupture and coalesce into larger lesions.

A: Assessment

The differential diagnosis includes aphthous ulcer and traumatic ulcer.

P: Plan

The diagnosis usually is based on appearance. For further information, see chapters *Oral Ulceration* and *Herpes Simplex, Mucocutaneous*.

Periodontal Disease

The medical evaluation of patients with HIV infection should include assessment of periodontal health. Whereas the same type of plaque-induced periodontal diseases can be seen in both immunocompetent and immunosuppressed individuals, periodontal disease in HIV-infected patients can be a marker of HIV disease progression. In the HIV-infected patient with periodontal disease, it is important to distinguish whether or not the periodontitis represents an aggressive and/or chronic presentation unique to those with HIV disease. In addition, it is important to determine whether the patient has an inflammatory oral disease process that may further compromise his or her health.

Various illnesses and systemic factors (eg, diabetes mellitus, hormonal abnormalities, medications, and malnutrition) can complicate the clinical presentation of periodontal disease. If significant periodontal disease is suspected, refer to an experienced dentist for diagnosis and treatment. Gingivitis, a milder form of periodontal disease, usually is reversible with proper professional and home oral health care. For further information on linear gingival erythema, necrotizing ulcerative gingivitis, or necrotizing ulcerative periodontitis, see chapters *Linear Gingival Erythema* and *Necrotizing Ulcerative Gingivitis or Periodontitis*.

S: Subjective

The patient may complain of red, swollen, or painful gums, which may bleed spontaneously or with brushing; chronic bad breath or bad taste in the mouth; loose teeth or teeth that are separating; or a "bite" that feels abnormal.

O: Objective

Examine the gums. Periodontitis appears as localized or generalized gingival inflammation. The gingivae appear bright red or reddish-purple, ulcerated, and/or necrotic. Spontaneous gingival hemorrhage and purulent discharge may be evident around the teeth, especially if pressure is applied to the gingivae. Fetor oris may be present.

A: Assessment

The differential diagnosis includes gingivitis, periodontitis, trench mouth, and oral abscesses. Diagnosis usually is based on appearance. Patients with severe or recalcitrant disease should be referred to a dental care provider for definitive diagnosis and treatment.

P: Plan

Treatment may include:

- Warm saline rinses
- Daily brushing and flossing
- Antimicrobial mouth rinse (eg, Listerine, chlorhexidine)
- Antibiotic therapy

For further information, see chapters *Linear Gingival Erythema* and *Necrotizing Ulcerative Periodontitis or Gingivitis*.

Dental Caries due to "Meth Mouth"

Meth mouth refers to dental decay seen in individuals who smoke methamphetamine or use cocaine orally.

S: Subjective

The chief complaint may be pain in 1 or more teeth. However, if the condition is chronic, the patient may not complain of pain.

O: Objective

In meth mouth, the enamel on all teeth or multiple teeth is grayish-brown to black in color (due to decay), and appears "soft" (this has been described as a "texture less like that of hard enamel and more like that of a piece of ripened fruit"). Oral mucosal tissues appear dry due to decreased salivary flow. The gingiva appears red or inflamed, and there may be spontaneous bleeding of the gingiva around the teeth.

Another pattern of dental decay can be seen in cocaine users who rub the drug along the gingiva in order to test its strength or purity. This can lead to localized dryness of the gingival tissues. Consequently, plaque sticks to the cervical portion of the teeth in the area where the cocaine is rubbed, resulting in dental caries along the cervical portion of the teeth.

A: Assessment

The differential diagnosis includes other causes of caries and dental decay.

P: Plan

Refer to a dentist for restorative or endodontic therapy. In severe cases, extraction of the involved teeth and replacement with a partial or complete denture may be necessary. Encourage proper oral hygiene; evaluate sucrose intake.

Oral Cancer

S: Subjective

Oral malignancies may be symptomatic or asymptomatic. They are more common in users of tobacco products than in nonusers of tobacco. The patient may complain of a mouth sore that fails to heal or that bleeds easily, or a persistent white or red (or mixed) patch. The patient may note a lump, thickening or soreness in the mouth, throat, or tongue; difficulty chewing or swallowing food; difficulty moving the jaw or tongue; chronic hoarseness; numbness of the tongue or other areas of the mouth; or a swelling of the jaw causing dentures to fit poorly or become uncomfortable.

O: Objective

Perform a thorough evaluation of the oropharynx, as well as lymph nodes in the head and neck. Suspicious lesions may occur on the lips, tongue, floor of the mouth, palate, gingiva, or oral mucosa, and may appear as an ulcer or a soft-tissue mass or masses that can be pink, reddish, purple, white, or mixed red and white. The lesion typically is indurated and may be painful. It may enlarge rapidly between examinations.

A: Assessment

The differential diagnosis includes oral cancer, traumatic ulcer, hyperplasia or hyperkeratosis, and Kaposi sarcoma.

P: Plan

An ulcerated lesion or symptom described above that is present for 2 weeks or more should be evaluated promptly by a dentist or physician. If cancer is suspected, a biopsy should be obtained to make a definitive diagnosis. Treatment will be based on the specific diagnosis.

Bruxism

S: Subjective

The patient may complain of chronic facial or jaw pain, sensitive teeth, earache, or waking up with a headache or facial pain. Often, the patient is not aware that he or she is clenching or grinding the teeth. Bruxism very often is a result of increased stress or anxiety, causing the patient consciously or unconsciously to clench or grind the teeth. However, some people may be "nighttime bruxers" and grind their teeth while sleeping, often loudly enough to wake others sleeping in the same room.

O: Objective

Perform a focused evaluation of the oropharynx, jaw, and facial muscles. The teeth may appear shortened, flattened, or worn down as a result of chronic grinding or clenching of the teeth. There may be hyperkeratotic lesions on the inside of cheeks due to chronic grinding or biting. There may be tenderness with palpation of facial muscles.

A: Assessment

The differential diagnosis includes other causes of facial or jaw pain, including caries, dental abscesses, and trauma.

P: Plan

Refer the patient to a dentist for treatment. Treatment may include wearing a bite guard and/or psychological or behavioral management therapy.

Oral Piercing

S: Subjective/Objective/Assessment

Jewelry worn in piercings in the tongue, lips, or cheeks can chip or fracture the teeth. Chronic rubbing of jewelry against the gingiva can cause the gingiva to recede, leading to periodontal problems. (These complications occur apart from procedure- or technique-associated complications associated with body piercing, such as inflammation and infection, bleeding, or transmission of bloodborne pathogens.)

P: Plan

Refer the patient to a dentist for treatment. Removal of the jewelry may be warranted.

Maxillary Tori; Mandibular Tori

S: Subjective

The patient may complain of a "lump" in the roof of the mouth or floor of mouth, behind the lower front teeth.

O: Objective

Exostosis of normal bone (covered by oral mucosal tissue) can appear as a nodular or lobulated protuberance centrally located on the hard palate (maxillary tori) or unilaterally or bilaterally located behind the mandibular incisors (mandibular tori). This develops slowly and the patient may become aware of exophytic growth only if the area is inadvertently traumatized.

A: Assessment

Differential includes other benign or malignant lesions including oral cancer and Kaposi sarcoma.

P: Plan

No treatment is indicated unless the exostosis interferes with speech or swallowing, or removal is needed for fabrication of dentures or a partial denture.

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Oral Hairy Leukoplakia

Background

Oral hairy leukoplakia (OHL) is an oral infection caused by Epstein-Barr virus (EBV). It appears as white corrugated lesions (sometimes "hairy" in appearance) on the lateral aspects of the tongue. This infection may spread across the entire dorsal surface, onto the ventral surface of the tongue, and occasionally may be found on buccal mucosa. It is common in people with HIV infection, particularly in those with advanced immunosuppression (CD4 count <200 cells/μL).

S: Subjective

The patient notices new, white lesions on the tongue that cannot be wiped off or removed by scraping or brushing. The OHL lesions usually are asymptomatic, but occasionally may cause alteration in taste, discomfort, or other symptoms.

O: Objective

Perform a focused examination of the oropharynx. OHL appears as unilateral or bilateral white plaques or papillary lesions on the lateral, dorsal, or ventral surfaces of the tongue or on buccal mucosa. The lesions may vary in appearance from smooth, flat, small lesions to irregular, "hairy" or "verrucous" lesions with prominent vertical folds or projections.

A: Assessment

A partial differential diagnosis for OHL includes:

- Oral candidiasis
- Squamous cell carcinoma
- Geographic tongue
- Lichen planus
- Smoker's leukoplakia
- Epithelial dysplasia
- White sponge nevus

P: Plan

Diagnostic Evaluation

A presumptive diagnosis of OHL usually is made on the basis of the clinical appearance of the lesions. Because OHL is often confused with candidiasis, the diagnosis of OHL should be considered for lesions that resemble oral candidiasis but do not respond to treatment for candidiasis (see chapter *Candidiasis, Oral and Esophageal*). Definitive diagnosis of OHL requires biopsy and demonstration of EBV.

- Biopsy lesions if they are ulcerated or unusual in appearance, to distinguish OHL from cancer or other causes.

Treatment

- Because OHL usually is asymptomatic, specific treatment generally is not necessary.
- Consider initiation of HIV treatment (antiretroviral therapy [ART]), if otherwise indicated, for immune system reconstitution. OHL may respond to ART.
- If specific treatment is required, the following may be considered. Relapse is common after discontinuation of treatment.
  - Acyclovir 800 mg orally 5 times per day for 2 weeks; famciclovir and valacyclovir may be considered.
  - Topical tretinoin (Retin-A) 0.025-0.05% solution, podophyllin 25% in tincture of benzoin, and other treatments also have been used.
  - For relapse of severe OHL, consider maintenance therapy with high-dose acyclovir, famciclovir, or valacyclovir.
- For severe symptomatic cases, surgical treatment (cryosurgery, excision, etc) may provide temporary resolution.
- Candidiasis may be present concurrently; treat candidiasis if it is present (see chapter *Candidiasis, Oral and Esophageal*).

Patient Education

- Advise the patient that OHL rarely is a problem in itself, but may be a marker of HIV progression.
- If treatment is given, review possible drug side effects and interactions, and advise the patient to call if new symptoms develop.
- Instruct the patient to comply with regular dental and medical care regimens.

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Oral Ulceration

Background

Oral ulcerations appear as necrotic or eroded areas on the oral mucosa, including the tongue. Most such lesions are idiopathic (aphthous) or of viral etiology (eg, herpes simplex virus [HSV]; rarely herpes zoster [VZV]). Oral ulcerations also may be caused by fungal, parasitic, or bacteriologic pathogens; by malignancy; or by other systemic processes. This chapter will focus on herpetic and aphthous ulcers.

Herpetic ulcerations tend to appear on keratinized tissues such as the hard palate or gingiva. Aphthous ulcerations tend to manifest on nonkeratinized tissues such as buccal mucosa, soft palate, and lingual (bottom) surface of the tongue.

S: Subjective

The patient complains of painful ulcerated areas in mouth. He or she may have difficulty eating, drinking, swallowing, or opening the mouth, and also may complain of sore throat.

History

Inquire about previous occurrences of oral ulcerative disease as well as ulcerative gastrointestinal diseases, including HSV, cytomegalovirus (CMV), or histoplasmosis. Ask about recent sexual exposures. Inquire about recent trauma or burns. Note current medications and any recent changes in medications; obtain history of tobacco (smoked and chewed) and alcohol use.

O: Objective

Look for red or white-bordered erosions or ulcerations varying in size from 1 mm to 2 cm on the buccal mucosa, oropharynx, tongue, lips, gingiva, and hard or soft palate. Lesions due to HSV tend to be shallow and occur on keratinized tissues. HSV lesions may appear as clusters of vesicles that may coalesce into ulcerations with scalloped borders. Aphthous ulcers present with a white or grey pseudomembrane surrounded by a halo of inflammation.

A: Assessment

Rule out recurrence of previous gastrointestinal or oral lesions, such as HSV and aphthous ulcers. Rule out syphilis and other suspected pathogens.

P: Plan

Diagnostic Evaluation

The diagnosis of HSV and aphthous ulcers usually is made on the basis of characteristic lesions. If diagnosis is uncertain, it is possible to perform HSV culture or HSV antigen detection using direct florescent antibody (DFA) testing on oral ulcerations that appear on keratinized tissues or the dorsal and lateral surfaces of the tongue, scraping near the margin of the lesion or unroofing a fresh vesicle, if available, and scraping the base. The sensitivity of HSV testing decreases when collections are taken from older, resolving herpetic areas; herpetic lesions >72 hours old usually will not yield a positive culture.

If other diagnoses are suspected, perform culture or biopsy as indicated.

Note that syphilis is very common in some HIV-infected populations. For patients in whom primary syphilis (manifested by an oral chancre) is suspected, perform (or refer for) darkfield examination; check Venereal Disease Research Laboratory (VDRL) or rapid plasma reagin (RPR) results (note that VDRL or RPR may be negative in primary syphilis); see *Syphilis* chapter for further information

Treatment

If HSV culture is positive, or if HSV is strongly suspected due to the appearance of the lesions or the patient's history, treat with HSV antiviral medication (eg, acyclovir, famciclovir, or valacyclovir) while awaiting results of culture. Do not use topical steroids without a concomitant oral HSV antiviral if the lesion is of possible herpetic etiology. Refer to *Herpes Simplex, Mucocutaneous* chapter for more complete information regarding management and treatment of HSV lesions.

Recalcitrant aphthous ulcerations should be treated with topical corticosteroids (eg, fluocinonide 0.05% or clobetasol 0.05% ointments mixed 1:1 with Orabase).

For multiple small lesions or lesions in areas where topical ointments are difficult to apply, consider dexamethasone elixir (0.5 mg/5 mL). Rinse 3 times daily with 5 mL for 1 minute, then expectorate. As with all oral topical steroids, advise the patient not to drink or eat for 30 minutes after rinsing. Continue treatment for 1 week or until lesions resolve.

Some aphthous ulcers may respond to one of the various "magic mouthwashes" that contain combinations of antibiotic, antifungal, corticosteroid, antihistamine, and anesthetic medication. The inclusion of an antihistamine (eg, diphenhydramine) and/or anesthetic (eg, lidocaine) may be helpful in treating pain associated with these ulcers.

For large or extensive aphthous ulcers, systemic corticosteroids may be needed: prednisone 40-60 mg orally daily for 1 week followed by a taper should prove beneficial. If this is ineffective, refer for biopsy to rule out CMV, other infection, or neoplastic disease.

For patients with major oral aphthous ulcers that are recalcitrant to other therapies, thalidomide 200 mg daily for 2 weeks may be considered. Thalidomide should not be used in women of childbearing potential due to its teratogenicity. It must be used very carefully with thorough patient education and 2 concomitant methods of birth control.

Pain control may be needed in order for the patient to maintain food intake and prevent weight loss. Most of the topical treatments noted above will ease pain as well as treat the ulcer. Additional considerations for pain control include:

- For small accessible ulcerations, topically apply Orabase Soothe-N-Seal (2-octyl cyanoacrylate) directly to the lesion every 4-6 hours. (This is an over-the-counter product.)
- Oral anesthetics: Various products are available such as gels, viscous liquids, or sprays (eg, benzocaine, lidocaine). These may be applied topically or swished and expectorated. They will provide temporary relief, but also may lead to a temporary loss of taste sensation.
- Systemic: If topical treatments are inadequate, consider systemic analgesics, eg, nonsteroidal anti-inflammatory drugs or opiates. Refer to the Pain Syndrome and Peripheral Neuropathy chapter.

Assess nutritional status and consider adding liquid food supplements. Suggest soft, nonspicy, or salty foods if the ulcer is interfering with food intake. Refer to a registered dietician if client is having pain, problems eating, or weight loss.

Refer to an oral health specialist or an HIV-experienced dentist as needed.

Patient Education

- Advise patients to report any oral pain or difficulty swallowing to their health care provider.
- Instruct patients in the application of topical ointments, and that they may require assistance if the lesion is difficult for the patient to see on his or her own.
- It is important for patients to maintain good nutrition and food intake while their oral ulcers heal. Advise them to eat soft, bland foods, and refer to a nutritionist if they have difficulty.

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Oral Warts

Background

Oral warts are caused by human papillomavirus (HPV) and may appear anywhere within the oral cavity or on the lips. They occur more frequently and more extensively in people with HIV infection than in those with normal immune function, especially in patients with advancing immune suppression (CD4 count <200-300 cells/μL). Oral warts in patients with CD4 counts <100 cells/μL may be refractory to therapy. The frequency of oral warts may increase, at least temporarily, in patients treated with antiretroviral therapy.

S: Subjective

The patient notices new raised lesions in the mouth or on the lips. Warts are not painful unless they have been traumatized.

O: Objective

Examine the oral cavity carefully for abnormalities. Wart lesions may vary in appearance from smooth, small, and slightly raised lesions to cauliflowerlike or spiked masses with prominent folds or projections. They may be single or multiple.

Review recent CD4 counts. In patients with oral warts, the CD4 count usually is <300 cells/μL.

A: Assessment

Partial differential diagnosis: squamous cell carcinoma, lichen planus, traumatic hyperkeratinized areas due to cheek biting or tongue thrusting.

P: Plan

Diagnostic Evaluation

- The diagnosis of oral warts usually is based on the appearance of the lesions. If lesions are unusual in appearance, are ulcerated, or have grown rapidly, perform biopsy to rule out cancer. If there is suspicion of other causes, perform other diagnostic evaluations as indicated.
- HPV may be demonstrated with electron micropsy or in situ hybridization; this testing is not required routinely.
- Observation of these lesions is important due to the potential, however minimal, for development of squamous cell carcinoma.

Treatment

- Treatment is difficult, as these lesions tend to recur. Treatment options include cryosurgery and surgical or laser excision. Care must be taken when using laser excision, as HPV can survive in an aerosol. Extraoral lesions (lip or corner of mouth) may be treated with topical agents such as podofilox topical solution (Condylox) or fluorouracil 5% topical (Efudex). Imiquimod 5% cream (Aldara) may help to prevent recurrence once the lesions have resolved.
- Refer to an oral health specialist or dentist for treatment.

Patient Education

- Instruct patients to comply with regular dental and medical care regimens.
- Instruct patients to use medications exactly as prescribed.

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Pain Syndrome and Peripheral Neuropathy

Background

The International Association for the Study of Pain defines pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage." Pain is subjective, it is whatever patient says it is, and it exists whenever the patient says it does. Pain is a common symptom in people with HIV infection, especially in those with advanced HIV disease. It occurs in 30-60% of HIV/AIDS patients and can diminish their quality of life significantly. Like cancer patients, HIV patients experience, on average, 2.5 to 3 types of pain at once. Pain in HIV-infected patients may have many causes (as discussed below).

Peripheral Neuropathy

Pain from HIV-associated peripheral neuropathy is particularly common, and may be debilitating. Peripheral neuropathy is clinically present in approximately 30% of HIV-infected individuals and typically presents as distal sensory polyneuropathy (DSP). It may be related to HIV itself (especially at CD4 counts <200 cells/μL), to medication toxicity (eg, from certain nucleoside analogues such as didanosine or stavudine), or to the effects of chronic illnesses (eg, diabetes mellitus). Patients with peripheral neuropathy may complain of numbness or burning, a pins-and-needles sensation, shooting or lancinating pain, and a sensation that their shoes are too tight or their feet are swollen. These symptoms typically begin in the feet and progress upward; the hands may be affected. Patients may develop difficulty walking because of discomfort. Factors associated with increased risk of peripheral neuropathy include the following:

- Previous peripheral neuropathy
- Low CD4 count (≤100 cells/μL)
- Prior AIDS-defining opportunistic infection or neoplasm
- Vitamin B12 deficiency
- Concomitant use of other drugs associated with peripheral neuropathy (eg, isoniazid)
- Use of neurotoxic agents (eg, alcohol)

Patients should be assessed carefully before the introduction of a potentially neurotoxic nucleoside analogue (eg, didanosine, stavudine) to avoid the use of these medications in patients at greatest risk of developing peripheral neuropathy.

Pain is significantly undertreated, especially in HIV-infected women, because of factors ranging from providers' lack of knowledge about the diagnosis and treatment of pain to patients' fear of addiction to analgesic medications. Pain, as the so-called fifth vital sign, should be assessed at every patient visit.

S: Subjective

The patient complains of pain. The site and character of the pain will vary with the underlying cause. Ascertain the following from the patient:

History

- Duration, onset, progression
- Distribution, symmetry
- Character or quality (eg, burning, sharp, dull)
- Intensity
- Severity (see below)
- Neurologic symptoms (eg, weakness, cranial nerve abnormalities, bowel or bladder abnormalities)
- Exacerbating or relieving factors
- Response to current or past treatments
- Past medical history (eg, AIDS, diabetes mellitus)
- Alcohol intake (amount, duration)
- Medications, current and recent (particularly zalcitabine, didanosine, stavudine, and isoniazid)
- Nutrition (vitamin deficiencies)
- Meaning of the pain to the patient

O: Objective

Measure vital signs (an increase in blood pressure,

respiratory rate, and heart rate can correlate with pain). Perform a symptom-directed physical examination, including a thorough neurologic examination. Look for masses, lesions, and localizing signs. Pay special attention to sensory deficits (check for focality, symmetry, and distribution [such as "stocking-glove"]), muscular weakness, reflexes, and gait. Patients with significant motor weakness or paralysis, especially if progressive over days to weeks, should be evaluated emergently.

A: Assessment

Pain assessment includes determining the type of pain: nociceptive or neuropathic. Nociceptive pain occurs as a result of tissue injury (somatic) or activation of nociceptors resulting from stretching, distention, or inflammation of the internal organs of the body. Nociceptive pain usually is well localized; may be described as sharp, dull, aching, throbbing, or gnawing in nature; and typically involves bones, joints, and soft tissue. Neuropathic pain occurs from injury to peripheral nerves or central nervous system structures. Neuropathic pain may be described as burning, shooting, tingling, stabbing or like a vise or electric shock; it involves the brain, central nervous system, nerve plexuses, nerve roots, or peripheral nerves.

Assess the severity of the pain. Have the patient rate the pain severity on a numeric scale of 0-10 (0 = no pain and 10 = worst imaginable pain), a verbal scale (none, small, mild, moderate, or severe), or a pediatric faces pain scale (when verbal or language abilities are absent). Note that pain ratings >3 usually indicate pain that interferes with daily activities. Use the same scale for evaluation of treatment response.

Although pain in HIV-infected patients is often due to opportunistic infections, neoplasms, or medication-related neuropathy, it is important to include non-HIV-related causes of pain in a differential diagnosis. Some of these other causes may be more frequent in HIV-infected individuals. A partial list for the differential diagnosis includes:

- Anorectal carcinoma
- Aphthous ulcers
- Appendicitis
- Arthritis, myalgias
- Candidiasis, oral or esophageal
- Cholecystitis
- Cryptococcal disease
- Cytomegalovirus colitis
- Dental abscesses
- Gastroesophageal reflux disease (GERD)
- Ectopic pregnancy
- Herpes simplex
- Herpes zoster
- Kaposi sarcoma
- Lymphoma
- Medication-induced pain syndromes (eg, due to growth hormone, granulocyte colony-stimulating factor)
- Medication-induced peripheral neuropathy (eg, due to didanosine, stavudine, isoniazid, vincristine)
- *Mycobacterium avium* complex
- Myopathy
- Other neuropathy
- Pancreatitis
- Pelvic inflammatory disease
- Toxoplasmosis

P: Plan

Perform a diagnostic evaluation based on the suspected causes of pain.

Treatment

Treatment should be aimed at eliminating the source of pain, if possible. If symptomatic treatment of pain is needed, begin treatment based on the patient's pain rating scale, using the least invasive route. The goal is to achieve optimal patient comfort and functioning with minimal medication adverse effects. Use the 3-step pain analgesic ladder originally devised by the World Health Organization (WHO).

Nonpharmacologic Interventions

Interventions such as relaxation techniques, guided imagery, massage, reflexology, acupuncture, thermal modalities, prayer, deep breathing, and meditation can be used as adjunctive therapy at any step in the treatment plan.

Pharmacologic interventions

The following 3 steps are adapted from the WHO analgesic ladder.

Step 1: Nonopiates for mild pain (scale 1-3)

- The most common agents in this step include acetaminophen and nonsteroidal antiinflammatory drugs (NSAIDs), and cyclooxygenase-2 (COX-2) inhibitors.
- Acetaminophen has no effect on platelets and no antiinflammatory properties; avoid use in patients with hepatic insufficiency.
- Note that COX-2 inhibitors have been associated with an increased risk of cardiovascular events and should be used with caution.
- Tramadol (Ultram) is a centrally acting nonopiate that can be combined with NSAIDs. Avoid coadministration with selective serotonin reuptake inhibitors (SSRIs) and monoamine oxidase inhibitors (MAOIs) because of serotonin syndrome; also avoid in patients with a seizure history.

Step 2: Mild opiates with or without non-opiates for moderate pain (scale 4-6)

- Most agents used to treat moderate pain are combinations of opioids and Step 1 agents.
- The most common agents are acetaminophen combined with codeine, oxycodone, or hydrocodone.
- Meperidine (Demerol) should be avoided because its active metabolite, normeperidine, has activating properties that may cause delirium and seizures.
- Chronic pain is more likely to be controlled when analgesics are dosed on a continuous schedule rather than "as needed." Sustained-release formulations of opioids should be used whenever possible.
- For breakthrough pain, use "as needed" medications in addition to scheduled-dosage analgesics.

Step 3: Opioid agonist drugs for severe pain (scale 7-10)

- Morphine is the drug of choice in this step. Others used are oxycodone, hydromorphone, fentanyl, levorphanol, methadone, codeine, hydrocodone, oxymorphone, and buprenorphine.
- Avoid meperidine because of the increased risk of delirium and seizures.
- Around-the-clock, oral, sustained-release dosing will achieve optimum pain relief. Patients unable to take oral therapy may use transdermal fentanyl patches or rectal administration of sustained-release tablets.
- Anticipate and treat complications and adverse effects of opioid therapy, such as nausea, vomiting, and constipation.

Adjunctive Treatments

The addition of antidepressant medications can improve pain management, especially for chronic pain syndromes. These agents, and anticonvulsants, are usually used to treat neuropathic pain (discussed in more detail below), but should be considered for other chronic pain syndromes as well.

Treatment of Neuropathic Pain

Assess the underlying etiology, as discussed above, and treat the cause as appropriate. Review the patient's medication list for medications that can cause neuropathic pain. Discontinue the offending agents, if possible. Consider dosage reductions of stavudine to reduce peripheral neuropathy (consult with an HIV expert). For isoniazid regimens, ensure that patients are taking vitamin B6 (pyridoxine) regularly to avoid isoniazid-related neuropathy.

Nonpharmacologic interventions for neuropathic pain

The nonpharmacologic interventions described above also can be useful in treating neuropathic pain.

Pharmacologic interventions for neuropathic pain

Follow the WHO ladder of pain management described above. If Step 1 medications are ineffective, consider adding antidepressants, anticonvulsants, or both before moving on to opioid treatments.

Antidepressants

Antidepressant medications often exert analgesic effects at dosages that are lower than those required for antidepressant effects. However, as with antidepressant effects, optimum analgesic effects may not be achieved until several weeks of therapy.

- Tricyclic antidepressants (TCAs): Doses may be titrated upward every 3-5 days, as tolerated.
- Amitriptyline (Elavil): Starting dose is 10-25 mg at bedtime. Usual maintenance dosage is 25-150 mg at bedtime.
- Desipramine (Norpramin): Starting dose is 25 mg at bedtime. Usual maintenance dosage is 25-250 mg at bedtime.

- Nortriptyline (Pamelor): Starting dose is 10 mg at bedtime. Usual maintenance dosage is 20-150 mg at bedtime.
  - Adverse effects include sedation, anticholinergic effects (eg, dry mouth, urinary retention), and orthostatic hypotension. There is a risk of overdose if taken in excess.
- SSRIs: See chapter *Depression* for dosing, side effects, and drug interactions associated with this class of agents. SSRIs are less effective than TCAs in treating chronic pain.
- Venlafaxine (Effexor): Starting dosage is 37.5 mg daily. Usual maintenance dosage is 75-300 mg daily in divided doses or by extended-release formulation (Effexor XR).

Anticonvulsants

The following may be effective for neuropathic pain.

- Gabapentin (Neurontin): Starting dosage is 100-300 mg 2 or 3 times daily. Usual maintenance dosage is 1,200-3,600 mg/day in divided doses. Monitor response and increase the dosage every 1-2 weeks by 300-600 mg/day.
  Adverse effects include somnolence, dizziness, fatigue, and nausea.
- Lamotrigine (Lamictal): Starting dosage is 25 mg twice daily. Usual maintenance dosage is 50-300 mg/day in divided doses.
  Adverse effects include sedation, dizziness, ataxia, confusion, nausea, blurred vision, and rash.
- Valproic acid (Depakote): Starting dosage is 500 mg twice daily. Usual maintenance dosage is 500-1,500 mg 2 or 3 times daily. Monitor valproic acid serum levels.
  Adverse effects include weight gain, sedation, ataxia, nausea, and diarrhea.
- Although phenytoin and carbamazepine have some effectiveness in treating neuropathy, they have significant drug interactions with protease inhibitors and nonnucleoside reverse transcriptase inhibitors, and their use in HIV-infected patients is limited.

Substance Abuse, HIV, and Pain

Some health care providers hesitate to treat pain in patients with current or past substance abuse because of concern about worsening these patients' dependence on opioids or suspicion that such patients are seeking pain medications for illicit purposes. However, the following points should be considered:

- Many patients with current or past substance abuse do experience pain, and this pain should be evaluated by care providers and treated appropriately.
- Failure to distinguish among addiction, tolerance, and dependence can lead to undertreatment of chronic pain by health care providers.
  - Addiction (substance abuse) is a complex behavioral syndrome characterized by compulsive drug use for the secondary gain of euphoria.
  - Pharmacologic tolerance refers to the reduction of effectiveness, over time, of a given dosage of medication.
  - Physical dependence is the consequence of neurophysiologic changes that take place in the presence of exogenous opioids.
- Aberrant use of pain medications, if it develops, is best managed by an interdisciplinary team of providers from HIV clinical care, psychiatry, psychology, pharmacy, social services, and drug addition management.
- Drug-drug interactions between certain antiretroviral medications and methadone can decrease methadone serum concentrations (see chapter *Drug-Drug Interactions with HIV-Related Medications*). If this occurs, methadone dosages may need to be increased to prevent opiate withdrawal.
- As part of chronic pain management in patients with substance abuse, consider establishing a written pain-management contract to be signed by the clinician and the patient. The contract should:
  - Clearly state limits and expectations for both the patient and provider
  - Identify a single clinician responsible for managing the pain regimen
  - Tell the patient what to do if the pain regimen is not working
  - Describe the procedure for providing prescriptions (eg, 1 prescription given to the patient, in person, for a limited period of time, such as 1 month).
  - List the rules for dealing with lost medications or prescriptions

Patient Education

- Pain management is part of HIV treatment and patients should give feedback to allow the best treatment decisions. If pain persists for more than 24 hours at a level that interferes with daily life, patients should call so that their health care provider can change the plan and try additional measures if needed.
- Patients should not expect full pain relief in most cases, but enough relief that they can perform their daily activities.
- "Mild" pain medications (eg, NSAIDs, aspirin, acetaminophen) usually are continued even after "stronger" medications are started because their mechanism of action is different from that of opiates. This combination of pain medication has additive effects, so that pain may be controllable with a lower narcotic dosage.
- Patients taking "around the clock" medications, should take them on schedule. Those taking "as needed" medications should take them between doses if they have breakthrough pain.
- Opiates are noted for causing severe constipation. Patients must remain hydrated and may need stool softeners, laxatives, or other measures. They should call their health care provider quickly if constipation occurs.
- Patients should avoid recreational drugs or alcohol when taking opiates because opiates can interact with them or cause additive adverse effects, possibly resulting in central nervous system depression, coma, or death.
- Patients taking opiates should avoid driving and operating machinery.

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Palliative Care and HIV

Background

Palliative care is not curative care, but is supportive, symptom-oriented care. It is usually needed throughout the course of disease progression to relieve patients' suffering and promote quality of life. Palliative care is important for patients with any medical condition. It may be used in conjunction with disease-specific care or as the sole approach to care. Palliative care includes the following:

- Management of symptoms (eg, fatigue, pain)
- Treatment of adverse effects (eg, nausea, vomiting)
- Psychosocial support (eg, depression, advance care planning)
- End-of-life care

Following is the widely used definition of palliative care according to the World Health Organization:

> Palliative medicine is the study and management of patients with active, progressive, far advanced disease for whom the prognosis is limited and the focus of care is the quality of life. [It is] the active total care of patients whose disease is not responsive to curative treatment. Control of pain, of other symptoms, and of psychological, social, and spiritual problems, is paramount. The goal of palliative care is achievement of the best quality of life for patients and their families.

Palliative care in AIDS patients comprises a continuum of treatment consisting of therapy directed at AIDS-related illnesses (eg, infection or malignancy) and treatments focused on providing comfort and symptom control throughout the life span. This care may involve multidimensional and multidisciplinary services, including HIV medicine, nursing, pharmacy, social work, complementary/alternative medicine, and physical therapy.

Palliative Care in the Era of Antiretroviral Therapy

With advances in HIV-specific therapy and care, HIV infection is no longer a rapidly fatal illness. Instead, those patients who are able to tolerate antiretroviral therapy (ART) often experience a manageable, chronic illness.

The death rate from AIDS, however, continues to be significant: approximately 15,000-16,000 per year in the United States. In many parts of the world, patients are not able to obtain specific treatments for HIV or for opportunistic illnesses, and supportive or palliative care may be the primary mode of care available to patients with advanced AIDS. Regardless of access to disease-specific treatment, people living with HIV continue to experience symptoms from HIV disease and its comorbid conditions, and those taking ART may experience adverse effects. Integrating palliative care with disease-specific care is important in the treatment of patients with HIV to promote quality of life and to relieve suffering.

S: Subjective

The patient with advanced HIV disease complains of 1 or more of the following:

- Agitation
- Anorexia
- Chronic pain
- Constipation
- Cough
- Decubitus ulcers or pressure sores
- Delirium
- Dementia
- Depression
- Diarrhea
- Dry skin
- Dyspnea
- Fatigue
- Fever
- Increased secretions *("death rattle")*
- Nausea
- Pruritus
- Sweats
- Vomiting
- Weakness
- Weight loss

O: Objective

Conduct a complete symptom-directed physical examination.

A: Assessment and P: Plan

Treatment

Table 1 lists common symptoms of AIDS and their possible causes. Also included are disease-specific treatments and palliative interventions. Depending on the situation, either or both of these treatments may be appropriate. Consider the patient's disease stage and symptom burden, the risks and benefits of therapies, and the patient's wishes. Practitioners should note that some of the palliative treatments may have substantial long-term adverse effects and should be used to alleviate symptoms only in late-stage or dying patients.

Table 1. Common Symptoms in Patients with AIDS and Possible Disease-Specific and Palliative Interventions

Symptom	Possible Causes	Disease-Specific or Curative Treatment	Palliative Treatment*
CONSTITUTIONAL			
Fatigue, weakness	• AIDS • Opportunistic infections (OIs) • Anemia	• ART • Treat specific infections • Erythropoietin, transfusion	• Psychostimulants (methylphenidate, pemoline, dextroamphetamine, modafinil) • Testosterone/androgens • Corticosteroids (prednisone, dexamethasone)
Weight loss/ anorexia	• HIV • Malignancy	• ART • Chemotherapy • Nutritional support/enteral feedings	• Testosterone/androgens • Oxandrolone • Megestrol acetate • Dronabinol • Recombinant growth hormone • Corticosteroids
Fevers, sweats	• Disseminated MAC and other infections • HIV lymphoma, and other malignancies	• Specific treatment of OIs or malignancy • ART	• Nonsteroidal anti-inflammatory drugs (NSAIDs, ibuprofen, naproxen, indomethacin) • Anticholinergics (hyoscine, thioridazine) • H2-antagonists (cimetidine)
PAIN			
Nociceptive, somatic, visceral	• Opportunistic infections • HIV-related malignancies, nonspecific	• Specific treatment of disease entities	• NSAIDS • Opioids • Corticosteroids

Neuropathic	• HIV-related peripheral neuropathy
	• Cytomegalovirus (CMV)
	• Varicella zoster virus (VZV)
	• Medications (eg, dideoxynucleosides: didanosine, zalcitabine, stavudine), isoniazid, vincristine
		• ART
		• Discontinue offending medication;
		• Change antiretroviral or other regimen
			• NSAIDS
			• Neuropathic pain medications:
			  ◦ tricyclics (amitriptyline, imipramine)
			  ◦ benzodiazepines (clonazepam)
			  ◦ anticonvulsants (gabapentin, lamotrigine)
			• Opioids (eg, methadone) and adjuvants
			• Corticosteroids
			• Acupuncture

GASTROINTESTINAL			
Nausea, vomiting	• Antiretroviral medications • Esophageal candidiasis • CMV	• Specific treatment of disease entities • Change antiretroviral regimen	• Dopamine antagonists (prochlorperazine, haloperidol) • Prokinetic agents (metoclopramide) • Antihistamines (diphenhydramine, promethazine) • Anticholinergics (hyoscine, scopolamine) • Serotonin antagonists (granisetron, ondansetron, dolasetron) • H2 blockers (cimetidine) • Proton pump inhibitors (omeprazole) • Somatostatin analogues (octreotide) • Benzodiazepines (lorazepam) • Marijuana, dronabinol
Diarrhea	• MAC • Cryptosporidiosis • CMV microsporidiosis • Other intestinal infections • Malabsorption • Medications (eg, protease inhibitors)	• Specific treatment of disease entities • Discontinue offending medication	• Bismuth, methylcellulose • Psyllium • Kaolin • Diphenoxylate + atropine • Loperamide • Calcium carbonate • Ferrous sulfate • Octreotide • Tincture of opium

Constipation	• Dehydration
	• Malignancy
	• Anticholinergic medications
	• Opioids
		• Hydration
		• Radiation and chemotherapy
		• Medication adjustment
			• Activity/diet
			• Prophylaxis for patients taking opioids
			• Peristalsis-stimulating agents:
			  ◦ anthracenes (senna)
			  ◦ polyphenolics (bisacodyl)
			  ◦ Softening agents:
			  –surfactant laxatives (docusate)
			  –bulk-forming agents (bran, methylcellulose)
			  –osmotic laxatives (lactulose, sorbitol)
			  –saline laxatives (magnesium hydroxide)

RESPIRATORY			
Dyspnea	• PCP • Bacterial pneumonia • Anemia • Pleural effusion, mass, or obstruction • Decreased respiratory muscle function	• Specific treatment of disease entities • Erythropoietin, transfusion • Drainage, radiation, or surgery	• Use of fan, open windows, oxygen • Opioids • Bronchodilators • Methylxanthines • Benzodiazepines (eg, lorazepam)
Cough	• PCP, bacterial pneumonia • TB • Acid reflux • Postnasal drip	• Specific treatment of disease entities	• Cough suppressants (dextromethorphan, codeine, other opioids) • Decongestants, expectorants (various)
Increased secretions ("death rattle")	• Fluid shifts • Ineffective cough • Sepsis • Pneumonia	• Antibiotics as indicated	• Atropine, hyoscine, transdermal scopolamine, glycopyrrolate • Fluid restriction, discontinue intravenous fluids

DERMATOLOGIC			
Dry skin	• Dehydration • End-stage renal disease • End-stage liver disease • Malnutrition medications (eg, indinavir)	• Hydration • Dialysis • Nutritional support • Discontinue offending medication	• Emollients with or without salicylates • Lubricating ointments or creams (eg, petrolatum, Eucerin)
Pruritus	• Fungal infection • End-stage renal disease • End-stage liver disease • Dehydration • Eosinophilic folliculitis	• Antifungal agents (itraconazole for eosinophilic folliculitis) • Dialysis • Hydration • Topical corticosteroids	• Topical agents (menthol, phenol, calamine, doxepin, capsaicin) • Antihistamines (doxepin - oral, diphenhydramine) • Corticosteroids (topical or systemic) • Serotonin antagonists (ondansetron) • Opioid antagonists (naloxone, naltrexone) • Antidepressants • Anxiolytics • Neuroleptics • Thalidomide
Decubitus ulcers, Pressure sores	• Poor nutrition • Decreased mobility, prolonged bed rest	• Increase mobility • Enhance nutrition	• Prevention (nutrition, mobility, skin integrity) • Wound protection (semipermeable film, hydrocolloid dressing) • Debridement (normal saline, enzymatic agents, alginates)
NEUROPSYCHIATRIC			
Delirium/agitation	• Electrolyte imbalances, glucose abnormalities • Dehydration • Toxoplasmosis • Cryptococcal meningitis • Sepsis • Medication adverse effects (eg, benzodiazepines, opioids, efavirenz) • Intoxication	• Correct imbalances • Hydration • Specific treatment of disease entities • Discontinue offending medications	• Neuroleptics (haloperidol, risperidone, chlorpromazine) • Benzodiazepines (eg, lorazepam, midazolam) (Note: in some patients, these may have adverse effects.)
Dementia	• AIDS-related dementia • Other dementia	• ART	• Psychostimulants (methylphenidate) • Low-dose neuroleptics (haloperidol)
Depression	• Chronic illness • Reactive depression, major depression	• Antidepressants (SSRIs, tricyclics, other)	• Psychostimulants (methylphenidate, pemoline, dextroamphetamine, modafinil) • Corticosteroids (prednisone, dexamethasone)

Key to abbreviations: ART = antiretroviral therapy; MAC = *Mycobacterium avium* complex; NSAIDs = nonsteroidal antiinflammatory drugs; CMV = cytomegalovirus; PCP = *Pneumocystis jiroveci* pneumonia; TB = tuberculosis; SSRI = selective serotonin reuptake inhibitor.

* Some of the palliative treatments may have substantial long-term adverse effects and should be used to alleviate symptoms only in late-stage or dying patients.

Adapted with permission from Selwyn PA, Rivard M. Palliative care for AIDS: Challenges and opportunities in the era of highly active anti-retroviral therapy. Innovations in End-of-Life Care. 2002;4(3), Available at http://www.edc.org/lastacts.

Advance Care Planning

Advance care planning involves planning for future medical care. Two main documents are produced:

- Advance directive (living will)
- Health care proxy (a person to speak for the patient or make decisions if the patient is too sick to do so)

The clinician should initiate these conversations and make referrals to helpful resources.

Patient Education

- Discuss advance care planning with patients, and the option of hospice care, if appropriate.
- Provide the patient and his or her family with detailed information so that they understand the illness and associated treatments.
- Instruct patients to discuss their pain or other bothersome symptoms with their health care providers.
- Encourage patients to talk with their health care providers if they are feeling anxious, depressed, or fearful.
- Discuss with patients what their death might be like. Some patients may feel relieved to be able to talk openly about their last days. Assure them that their pain will be controlled and that their health care providers will be there to help them.

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Anxiety Disorders

Background

Anxiety symptoms can develop because of a patient's uncertainty about HIV infection and treatment or because of issues unrelated to HIV. Symptoms can include mild distress, full-blown panic attacks, generalized anxiety disorder, or other disorders. The criteria for a diagnosis of generalized anxiety disorder include unrealistic or excessive worry about 2 or more life circumstances for more than 6 months, and at least 6 of the subjective complaints listed below.

It is important to differentiate between anxiety with and without panic attacks. Symptoms of anxiety can mimic symptoms of physical illness, and an appropriate workup should be performed to rule out other illnesses. (For more information about panic disorders, see chapter *Panic Disorder*.)

S: Subjective

The patient complains of the following:

- Difficulty concentrating
- Dizziness or lightheadedness
- Dry mouth
- Easy fatigability
- Exaggerated startle response
- Feeling anxious or on edge
- Flushes or chills
- Frequent urination
- Irritability
- Muscle tension, aches, or soreness
- Nausea, diarrhea, or other abdominal distress
- Palpitations or accelerated heart rate
- Restlessness
- Shortness of breath or smothering sensations
- Skin rashes
- Sweating or cold, clammy hands
- Trembling, twitching, or feeling shaky
- Trouble falling or staying asleep
- Trouble swallowing or "lump in the throat"

History

Obtain the following information during the history:

- Anxiety patterns (eg, constant or intermittent; timing)
- Caffeine intake
- Concomitant illnesses
- Family history of similar problems
- Medications, supplements, and herbal preparations
- New or recurrence of previous episodes
- Onset: sudden or gradual
- Recent stressors
- Recreational drugs or alcohol use (current or recent)
- Sleep disturbances
- Other physical symptoms

O: Objective

Perform a physical examination, including mental status and neurologic examination. Note heart rate, respiratory rate (shortness of breath, hyperventilation), tremor, rashes.

A: Assessment

A partial differential diagnosis includes the following:

- Allergic reactions
- Anemia
- Central nervous system (CNS) or opportunistic infections or malignancies
- Electrolyte imbalances
- Excessive caffeine intake
- Heart disease, arrhythmias
- Hyperthyroidism
- Hypoglycemia
- Immune disorders
- Medications such as efavirenz, isoniazid, steroids, theophylline
- Respiratory disease
- Sleep disturbances or sleep deprivation
- Substance use (eg, amphetamines, cocaine)
- Substance withdrawal (eg, alcohol, benzodiazepines)
- Systemic or other infections
- Vitamin B12 deficiency

P: Plan

Laboratory and Diagnostic Evaluation

Perform the following tests:

- Electrocardiogram (EKG)
- Thyroid studies
- Blood glucose
- Arterial blood gases (if frank difficulty breathing is not self-limited)
- Other tests as indicated based on symptoms and physical examination

Treatment

Once other diagnoses have been ruled out and the diagnosis of anxiety disorder is established, several options are available:

Cognitive-behavioral interventions

Options include individual cognitive-behavioral therapy, a stress-management group, relaxation therapy, visualization, and guided imagery. Refer the patient to available community-based support.

Psychotherapy

Psychotherapy may be indicated if experienced professionals are available and the patient is capable of forming an ongoing relationship. If possible, refer to an HIV-experienced therapist.

Pharmacotherapy

Patients with advanced HIV disease, like geriatric patients, may become more vulnerable to the CNS effects of certain medications. Medications that affect the CNS should be started at low dosage and titrated slowly. Similar precautions should apply to patients with liver dysfunction.

Interactions may occur between selective serotonin reuptake inhibitors (SSRIs), benzodiazepines, and HIV medications. Consult with an HIV expert or pharmacist before prescribing.

- SSRI-type antidepressants, including fluoxetine (Prozac), paroxetine (Paxil), sertraline (Zoloft), citalopram (Celexa), and escitalopram (Lexapro) may be effective. Venlafaxine timed-release formulation (Effexor XR), at dosages of 75-225 mg/d, has been approved for the treatment of generalized anxiety disorder. Note: There is a risk of hypertension at the higher dosages of venlafaxine; monitor blood pressure.
- Buspirone (BuSpar) is a nonaddictive anxiolytic. Start at 5 mg orally 3 times per day. If symptoms persist, the dosage can be increased by 5 mg per dose each week to a maximum of 10-15 mg orally 3 times per day (for a total daily dosage of 30-45 mg). It will take several weeks for patients to notice a decrease in anxiety; low-dose benzodiazepines may be used during this interval. The major potential adverse effects of buspirone are dizziness and lightheadedness.
- Treatment may include intermediate half-life benzodiazepines such as oxazepam (Serax) 10 mg orally every 6 hours or lorazepam (Ativan) 0.5 mg orally every 8 hours, if buspirone is not tolerated or to alleviate anxiety symptoms until buspirone takes effect. Longer-acting benzodiazepines such as clonazepam (Klonopin) also may be useful at dosages of 0.25-0.5 mg orally twice a day.
  - Benzodiazepines should be used only for acute, short-term management because of the risk of tolerance and physiologic dependence. These risks are even more problematic in patients with a history of addiction.
  - Note that protease inhibitors and nonnucleoside reverse transcriptase inhibitors may raise blood concentrations of many benzodiazepines. If benzodiazepines are used, they should be started at low dosages, and other CNS depressants should be avoided. Consult with a clinical pharmacist before prescribing.
  - Midazolam (Versed) and triazolam (Halcion) are contraindicated with all protease inhibitors and with delavirdine and efavirenz.
- Some sedating antidepressants are effective, nonaddictive anxiolytic agents. These include trazodone (Desyrel) 25-100 mg at bedtime or imipramine (Tofranil) 25 mg at bedtime. Note that imipramine is contraindicated with ritonavir or in advanced HIV disease. Neurontin 200-400 mg 2 times daily or 4 times daily can also be used.

Patient Education

- Behavioral interventions can help to reduce anxiety, but may take practice. Patients should seek help from a therapist, an experienced source, or a friend.
- Some patients develop problems with sexual function because of antianxiety medications. Patients should report any problems to their prescribers.

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Depression

Background

Major depression is a cause of significant morbidity among people with HIV disease. Management of this condition may be complicated by its multifactorial etiology. A diagnosis of HIV may not only cause psychological crisis, but may also complicate underlying psychological or psychiatric problems (eg, preexisting depression, anxiety, or substance abuse). In addition, direct viral infection of the central nervous system (CNS) can cause several neuropsychiatric syndromes. Finally, both constitutional disease and medications can impair neurologic function and mood.

The clinician's task is 4-fold:

- Maintain a high index of suspicion for depression and screen frequently for mood disorders.
- Elicit any history of psychiatric diagnoses or treatment.
- Rule out organic causes of mood or functional alterations.
- Refer for appropriate psychiatric evaluation and psychosocial support, including substance abuse counselors and domestic violence service providers.

Patients with untreated depression experience substantial morbidity and may become self-destructive or suicidal. They are also at continuing risk for unsafe behaviors that may lead to HIV transmission.

Major depression in persons with comorbid medical illness, including HIV infection, has been associated with numerous adverse events, such as the following:

- Decreased survival
- Impaired quality of life
- Decreased treatment adherence
- Longer hospital stays
- Increased risk behaviors
- Suicide

Although depression occurs independently of physical symptoms, recent research has concluded that it is associated with higher mortality rates in HIV-infected individuals. Stress and depressive symptoms, especially when they occur jointly, are associated with diminished immune defenses in HIV-infected individuals.

S: Subjective

The patient may complain of the following:

- Appetite changes with weight changes (increase or decrease)
- Decreased ability to concentrate
- Depressed mood, sadness, hopelessness
- Diminished interest or pleasure in activities
- Fatigue or loss of energy
- Feelings of worthlessness or guilt
- Insomnia or hypersomnia
- Psychomotor agitation or retardation
- Recurrent thoughts of death or suicide

History

Inquire about the symptoms listed above, and about associated symptoms. If 5 of these symptoms occur on most days for at least 2 weeks, a clinically significant major affective disorder is present and requires intervention. Depressed mood or diminished interest or pleasure must be 1 of the 5 symptoms present.

Take a careful history of the timing of symptoms, their relationship to life events (eg, HIV testing, loss of a friend) and any other physical changes noted along with the mood changes. Elicit personal and family histories of depression or suicidal behavior. Probe for suicidal thoughts, plans, and materials to execute the plans. Inquire about hallucinations, paranoia, and other symptoms. Take a thorough history of medication use and substance abuse.

O: Objective

Perform mental status examination, including affect, mood, orientation, appearance, agitation, or psychomotor slowing; perform neurologic examination if appropriate.

A: Assessment

Partial Nonpsychiatric Differential Diagnosis

Rule out nonpsychiatric causes of symptoms, which may include the following:

- Vitamin B12, folate (B6), zinc, or vitamin A deficiency
- Hypothyroidism or hyperthyroidism
- Endocrine disorders such as Addison disease or hypotestosteronism (hypogonadism)
- HIV dementia or minor cognitive motor disorder
- HIV encephalopathy
- Neurosyphilis
- Opportunistic illnesses affecting CNS (eg, toxoplasmosis, cryptococcal disease, CNS cytomegalovirus, progressive multifocal leukoencephalopathy)
- Medication adverse effects (eg, from steroids, efavirenz, isoniazid, interferon-alfa)
- Substance-induced mood disorder (intoxication or withdrawal)

Partial Psychiatric Differential Diagnosis

- Adjustment disorder (eg, acute reaction to a life crisis, such as HIV diagnosis, bereavement, job loss)
- Anxiety disorders
- Bereavement
- Dysthymia (depressed mood of long duration with less intensive symptoms)
- Psychotic depression

P: Plan

Laboratory Tests

Check thyroid function tests and vitamin B12, folate, and testosterone levels.

Treatment

Make sure that the patient has been referred to available community organizations for support.

Refer immediately for psychiatric evaluation or treatment if the patient is:

- Suicidal (see chapter *Suicidal Ideation*)
- Displaying psychotic symptoms
- Debilitated or functionally impaired by severe symptoms
- Not responding to treatment

Psychotherapy

Individual psychotherapy with a skilled, HIV-experienced mental health professional can be very effective in treating depression. The combination of psychotherapy and antidepressant medication is more effective than either treatment modality alone.

Pharmacotherapy

When selecting antidepressant medications, consider their side effect profiles as a means to treat other symptoms. For example, activating medications can be taken in the morning if the patient complains of low energy; medications that increase appetite may be useful for patients with wasting syndrome; sedating medications may be taken at bedtime if the patient complains of sleep problems.

Monitor patients closely after starting antidepressant medications. Some patients may be at risk of worsening depression, including suicidality, after initiation of therapy.

Because of the potent inhibition of the microsomal cytochrome P450 isoenzymes by protease inhibitors (especially ritonavir), antidepressants used concomitantly with protease inhibitors should be started at low dosages and titrated cautiously to prevent antidepressant adverse effects and toxicity. Interactions between selective serotonin reuptake inhibitors (SSRIs) and HIV medications are fairly common. For patients who are starting antiretroviral medications (particularly protease inhibitors) and are on a stable antidepressant regimen, an empiric dosage reduction of antidepressant therapy should be considered, especially if the antidepressant dosage is at the high end of the range or the patient is having adverse effects of the antidepressant before starting antiretroviral therapy. Consultation with an HIV expert, psychiatrist, and clinical pharmacist can assist in developing an effective antidepressant and HIV therapy combination.

A therapeutic trial consists of treatment for 4-6 weeks at a therapeutic dosage. Medications should be continued for 6-9 months beyond the resolution of symptoms to reduce the risk of recurrence. After this time, treatment may be gradually tapered if the patient wishes, with careful monitoring for recurrence

of symptoms. The risk of recurrence is higher if the first depressive episode is inadequately treated or if the patient has had multiple depressive episodes.

Table 1 lists the available antidepressant medications (SSRIs and serotonin/norepinephrine reuptake inhibitors [SNRIs]), including therapeutic dosages and possible positive and negative effects.

Table 1. SSRI and SNRI Antidepressant Medications and Possible Positive and Negative Effects

Medication: Usual Dosage	Possible Positive Effects	Possible Negative Effects
Fluoxetine (Prozac): 10-40 mg once daily	Rarely sedating, often energizing, no cardiovascular adverse effects, no anticholinergic effects, nonfatal in overdose	Insomnia, agitation, nausea, headache, sexual dysfunction in men and women, long half-life
Paroxetine* (Paxil): 10-40 mg once daily	May be sedating (for patients experiencing sedation with paroxetine, dose at bedtime; can be useful with depression-associated insomnia)	Insomnia, agitation (for patients experiencing these effects, administer dose in mornings), nausea, headache, sexual dysfunction in men and women
Sertraline (Zoloft): 50-100 mg once daily	May have lower incidence of significant drug-drug interactions compared with fluoxetine and paroxetine; nevertheless, start with lower dosages when this medication is used with protease inhibitors	Insomnia, agitation, nausea, headache, sexual dysfunction in men and women, long half-life
Venlafaxine XR** (Effexor XR): 75-375 mg once daily	May have lower risk of significant drug-drug interactions compared with SSRIs	Nausea, headache, nervousness, sexual dysfunction
Citalopram (Celexa): 10-60 mg once daily or escitalopram (Lexapro): 10-20 mg once daily	May have lower risk of significant drug-drug interactions than other SSRIs	Mild nausea, possible sedation

* When discontinuing paroxetine therapy, carefully titrate the dosage reduction to avoid serious adverse effects associated with abrupt discontinuation. Such effects include confusion, agitation, irritability, sensory disturbances, and insomnia.
** Note: Monitor blood pressure at higher dosages of venlafaxine.

Other Agents

Newer antidepressants such as mirtazapine may be particularly useful in patients who have significant insomnia and in those who have experienced sexual dysfunction with other antidepressant agents such as SSRIs.

- Mirtazapine (Remeron) should be administered at bedtime because of its sedating effects. Sedation is commonly noted with the starting dosage of 15 mg once daily, but may be lessened by increasing the dosage to 30 mg at bedtime. Individuals may also experience an increase in appetite, weight gain, and dry mouth. Mirtazapine has minimal drug-drug interactions. The therapeutic dosage range is 15-45 mg once daily. Consider starting with 15 mg at bedtime for 7 days, then increasing to 30 mg if sedation is problematic.
- Bupropion (Wellbutrin) sustained-release (SR) or extended-release (XL) formulation may be used in individuals with depression who experience sexual dysfunction with other antidepressant agents. Bupropion SR or XL dosing should not exceed 400 mg per day (the SR formulation should be administered twice daily in divided doses) because of an increased risk of seizures at higher bupropion dosages, particularly in individuals who have other risk factors for seizures. For patients taking protease inhibitors, caution should be used as the dosage approaches 300-400 mg per day because of possible increases in levels of bupropion. Bupropion may have an activating effect, which some patients may experience as agitation, insomnia, or both, and also may have an appetite suppressant effect.
- Nefazodone (Serzone) may cause liver toxicity and generally is not recommended as an antidepressant for patients with HIV/AIDS because of the high rates of preexisting liver abnormalities in HIV-infected patients. This medication has recently received a black box warning regarding severe liver toxicity from the U.S. Food and Drug Administration. If the patient has ever had liver toxicity from the drug, restarting is contraindicated.

- Tricyclic antidepressants may be effective, but in general have a higher risk of adverse effects than SSRIs and are dangerous if overdosed.
- Treatment may involve antidepressant combinations, including psychostimulants.
- Patients with prominent insomnia may benefit from the addition of trazodone 25-50 mg, given 1-2 hours before bedtime.
- St. John's wort is an herbal antidepressant that is contraindicated for use with protease inhibitors and nonnucleoside reverse transcriptase inhibitors. St. John's wort can significantly decrease serum concentrations of these HIV medications.

Patient Education

- Providers should explain to patients that illness (physical or emotional) is not a character flaw or a moral or spiritual weakness. It is an expected aspect of HIV infection. Sadness is a normal part of life, but major depression is always abnormal and often can be alleviated with medication, therapy, or both.
- Antidepressants typically are given for a long time, usually for a year or longer, to help patients with the chemical imbalances associated with depression.
- When starting an antidepressant medication, patients should expect that it will take 2-4 weeks for them to notice any improvement. Their symptoms should continue to decrease over the following weeks. If they do not have much improvement in symptoms, their providers may choose to adjust the dosage of the medication or to change medications. Patients must continue taking their medications so that the symptoms of depression do not return.
- Some patients develop problems with sexual function while they are taking antidepressants. They should report any problems to their prescribers.
- Patients should note the major symptoms of depression and be aware of what factors led them to seek treatment. They will need to monitor themselves for recurrences and get help if the symptoms come back. Providers should explain to patients that if they notice changes in their sleep, appetite, mood, activity level, or concentration, or if they notice fatigue, isolation, sadness or helplessness, it is time to get help.

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Panic Disorder

Background

Panic disorder is persistent fear that interferes with the ability to conduct activities of daily living. A patient is diagnosed as having panic disorder when he or she has experienced 4 panic attacks within a 4-week period, or at least 1 panic attack followed by a month of persistent fear. Panic attacks are discrete, sudden-onset episodes of intense fear or apprehension accompanied by specific somatic or psychiatric symptoms (eg, palpitations, shortness of breath, or fear of losing control).

Patients may associate panic attacks with various activities, such as leaving home, driving, and even visiting health care providers for medical appointments. The symptoms of panic disorder usually begin in late adolescence to the mid-30s and may coincide with the presentation of major depressive disorder, social phobia, or generalized anxiety disorder. Symptoms may mimic physical illness. Patients with panic disorder have an increased incidence of suicide.

S: Subjective

The patient complains of panic attacks, or describes episodes of:

- Chest pain or discomfort
- Depersonalization or derealization
- Dizziness, lightheadedness, faintness, or feeling of unsteadiness
- Fear of dying
- Fear of going crazy or losing control
- Hot flashes or chills
- Nausea or abdominal distress
- Numbness or tingling sensations
- Palpitations or accelerated heart rate
- Sensation of choking
- Shortness of breath or smothering sensation
- Sweating
- Trembling or shaking

In the absence of physical causes, 4 or more of the above symptoms accompanying multiple panic attacks are diagnostic of panic disorder. Panic attacks are, by definition, self-limited and they peak quickly, usually within 10 minutes. Symptoms that persist continuously for longer periods suggest other causes.

History

Inquire about the following:

- Any associated or concurrent symptoms, such as rash, cough, or fever
- Current medications, herbal products, and supplements
- Family history of mood and psychiatric illnesses, particularly anxiety and panic
- Frequency, duration, and onset of panic episodes
- Any relationship to food or hunger
- Settings in which attacks occur to determine whether there are triggers, such as being outdoors (agoraphobia)
- Intake of caffeine, recreational drugs, and alcohol (current and recent)
- New onset versus previous incidents
- Sleep disturbances
- Concomitant illnesses

O: Objective

Perform a complete physical examination, including vital signs and thyroid, cardiac, pulmonary, and neurologic evaluation.

During actual panic attacks, patients may have an increased heart rate or respiratory rate.

A: Assessment

A partial differential diagnosis includes the following conditions:

- Allergic reactions
- Cardiac insufficiency, congestive heart failure, myocardial ischemia
- Hyperthyroidism
- Hypoglycemia
- Major depression with superimposed panic attack
- Medication effect
- Pheochromocytoma medication effect
- Phobia (phobia is a specific response to a specific stimulus, whereas a patient with panic attacks is unsure when they will recur and what will trigger them)
- Respiratory infection
- Pheochromocytoma
- Withdrawal from or intoxication with psychoactive substances (eg, caffeine, amphetamines, cocaine, hallucinogens, or medications)

P: Plan

Diagnostic Evaluation

Perform the following tests:

- Blood glucose; gamma-glutamyl transpeptidase (GGT) if symptoms are related to hunger or are consistent with rebound hypoglycemia
- Thyroid studies
- Arterial blood gases if the patient has persistent shortness of breath
- Electrocardiogram if chest pain is present

Treatment

Once other diagnoses have been ruled out, consider the following treatments:

Cognitive-behavioral therapy

Options include individual cognitive-behavioral therapy (CBT) interventions (refer to community-based support), a stress management group, relaxation therapy, visualization, and guided imagery. Emergency referrals may be needed.

Psychotherapy

Psychotherapy may be indicated if the patient is capable of forming an ongoing relationship with a therapist. If possible, refer to an HIV-experienced professional.

Pharmacotherapy

Patients with advanced HIV disease, like geriatric patients, may become more vulnerable to the central nervous system (CNS) effects of certain medications. Medications that affect the CNS should be started at low doses and should be titrated slowly. Similar precautions should apply to patients with liver dysfunction.

Some interactions occur between selective serotonin reuptake inhibitors (SSRIs), benzodiazepines, and HIV medications. Consult with an HIV expert or pharmacist before prescribing.

Treatment should be continued for at least 6 months beyond the resolution of symptoms.

Options

- SSRI-type antidepressants, including fluoxetine (Prozac), paroxetine (Paxil), sertraline (Zoloft), citalopram (Celexa), and escitalopram (Lexapro) may be effective. Venlafaxine timed-release formulation (Effexor XR), at a dosage of 75-225 mg/d, has been approved for the treatment of generalized anxiety disorder. There is a risk of hypertension at the higher dosages of venlafaxine; monitor blood pressure.
- Tricyclic antidepressants may be used at low doses, including nortriptyline (Pamelor), 10-75 mg at bedtime; desipramine (Norpramin), 10-50 mg daily; amitriptyline (Elavil), 25-75 mg at bedtime; and imipramine (Tofranil), 25-75 mg at bedtime. Doses should be titrated slowly. Tricyclic antidepressants may reach higher blood concentrations when coadministered with certain protease inhibitors, including ritonavir (contained in Kaletra); consult with an HIV expert or pharmacist.
- Many patients will require initial short-term treatment with benzodiazepines, which are titrated downward as the antidepressant is titrated upward. Benzodiazepines should be used only for acute, short-term management, because of the risks of tolerance and physiologic dependence. These risks are more problematic in patients with a history of addiction. Note that protease inhibitors and nonnucleoside reverse transcriptase inhibitors may raise blood concentrations of many benzodiazepines.

If benzodiazepines are used, they should be started at low doses, and other CNS depressants should be avoided. Consult with a clinical pharmacist before prescribing.

- Note that midazolam (Versed) and triazolam (Halcion) are contraindicated with all protease inhibitors and with delavirdine and efavirenz.

Patient Education

- Behavioral interventions can help to reduce the frequency and severity of panic attacks. Patients should seek help from a therapist, an experienced source, or a friend.
- Some patients develop problems with sexual function because of the medications. Patients should report any problems to their prescribers.

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Insomnia

Background

Insomnia is a common accompaniment to HIV infection, especially as the disease progresses and complications worsen. Once present, insomnia tends to be chronic, unlike the transient disturbances of sleep that are a normal part of life. Most insomnia related to HIV can be characterized by the amount, quality, or timing of sleep. Insomnia may cause progressive fatigue and diminished functioning.

S: Subjective

The patient may complain of the following:

- Difficulty initiating sleep
- Early-morning waking
- Mind-racing thoughts (eg, "I can't turn off my thoughts.")
- Difficulty maintaining sleep
- Nonrestorative sleep (ie, although the amount of sleep is adequate, the patient does not feel rested upon awakening)
- Nighttime restlessness

Take a history to include:

- Determine the patient's bedtime sleep habits; if possible, request additional history from a sleep partner.
- Try to quantify how long the patient actually sleeps each night.
- Ask about alcohol and recreational drug use, caffeine intake, and concurrent medications that may cause insomnia as an adverse effect (eg, efavirenz, corticosteroids, pseudoephedrine, and decongestants).
- Screen for depression and anxiety.
- Ask about nightmares, life stressors, and any over-the-counter medications or supplements used to promote sleep.
- Ask about shift work, exercise, nighttime reflux or heartburn, snoring, and periods of apnea (not breathing).
- Ask about collar size (size >16 or 16 1/2 is more often associated with sleep apnea).

O: Objective

Perform a general symptom-directed physical examination, including evaluation of body habitus, neurologic status, and mental status.

Polysomnography may be indicated when a physiologic cause is suspected or insomnia is severe.

A: Assessment

A partial differential diagnosis includes the following:

- Alcohol intake (interferes with sleep 2-4 hours after ingestion)
- Anxiety disorder
- Caffeine intake
- Cognitive impairment
- Disturbance of the sleep/wake cycle because of excessive time in bed
- Major depression (insomnia is a primary symptom)
- Medication adverse effects (eg, from steroids, efavirenz)
- Other identifiable sleep disorders (eg, obstructive sleep apnea, periodic leg movements)
- Pain
- Recreational drug use
- Transient insomnia related to acute stress

P: Plan

Treatment

The following options are available for treatment:

Behavioral strategies

- To correct deleterious sleep habits, patients should do the following:
  - Establish a bedtime routine.
  - Avoid stimuli before bedtime.
  - Avoid vigorous exercise within 3-4 hours of bedtime.
  - Reduce or eliminate daytime napping.
  - Avoid eating, reading, watching TV, or working in bed.

  - Wake up at the same time each day regardless of total hours of sleep.
  - Have a dark, quiet, comfortable environment conducive to sleep.
- If unable to fall sleep after 15-20 minutes, the patient should get up, go into another room for nonstimulating activity in dim light (such as reading), and not go back to bed until sleepy.
- The patient should discontinue use of caffeine, central nervous system stimulants, alcohol, and tobacco, with tapering if necessary to avoid withdrawal symptoms.
- Teach or refer the patient for relaxation techniques.

Pharmacotherapy

The following options are available:

- Antihistamines, such as diphenhydramine or hydroxyzine 25-50 mg at bedtime (be aware of anticholinergic adverse effects).
- Sedating antidepressants such as trazodone 25-50 mg at bedtime, or amitriptyline 10-50 mg at bedtime. Check for drug interactions with antiretroviral agents and other medications. Mirtazapine (Remeron) is a newer antidepressant with fewer drug interactions that may be used at low dosages (7.5-15 mg) for insomnia.
- Sedative hypnotics, such as triazolam (Halcion) 0.125-0.25 mg at bedtime as needed; temazepam (Restoril), 15 mg at bedtime; and newer agents such as zolpidem (Ambien), eszopiclone (Lunesta), zaleplon (Sonata). Because of addictive potential and problems such as amnesia and confusion, these should be used only for short-term management (5-7 days).
- Note that protease inhibitors and nonnucleoside reverse transcriptase inhibitors may raise blood concentrations of many benzodiazepines. If benzodiazepines are used, they should be started at low dosages, and other central nervous system depressants should be avoided. Consult with a clinical pharmacist before prescribing.
- Midazolam (Versed) and triazolam (Halcion) are contraindicated with all protease inhibitors and delavirdine and efavirenz.
- Consult with a skilled mental health clinician if problems persist or depression is suspected.

Patient Education

- Behavioral interventions can help to reduce insomnia.
- Patients should report new or worsening symptoms to their health care provider.

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Suicidal Ideation

Background

Transient suicidal thoughts are common in some people throughout the course of HIV disease and do not usually indicate significant risk of suicide. However, persistent suicidal thoughts with associated feelings of hopelessness and intent to die are very serious and must be assessed promptly and carefully. The risk of suicide is especially high for patients who are depressed and for those at pivotal points in the course of HIV infection.

Many events may trigger suicidal thoughts among persons with HIV. Such events may include learning about their positive HIV status, disclosing to family and friends, starting antiretroviral therapy, noticing the first symptoms, having a decrease in CD4 counts, undergoing a major illness or hospitalization, receiving an AIDS diagnosis, losing a job, experiencing major changes in lifestyle, requiring evaluation for dementia, and losing of a significant relationship. A suicide assessment must always be included in the psychiatric evaluation.

Risk factors for suicide attempts include the following:

- Abandonment by, or isolation from family, friends, or significant others
- Age, especially teen years or >45 years of age
- Recent or current illness
- Any acute change in health status
- Fear of HIV-associated dementia
- Financial difficulty
- Hopelessness
- Multiple losses or recent stressors
- Pain
- Perception of poor prognosis
- Perception of poor social support
- Previous suicide attempts
- Substance abuse, especially alcohol
- Relapse into drug use after significant recovery
- Severe anxiety, depression, or other mental health disorder
- Social isolation (eg, being single, divorced, or alone, or experiencing the death of a spouse)
- Stigmatization due to illness, sexual orientation, substance use history, or other factors

S: Subjective

The patient expresses or exhibits, or a personal care giver discloses the following:

- Active suicidal ideation with intent and plan, such as giving away significant personal belongings, saying goodbye, gathering the means (eg, gun, pills), writing a suicide note
- Passive withdrawal from therapy or medical care or decreased adherence (eg, stopping medications, missing appointments)
- A desire for HIV disease to progress more rapidly

History

Inquire about the following during the history:

- Previous suicide attempt(s)
- Friend or family member who has committed suicide
- Personal or family history of depression
- Previous episode of psychosis
- Presence of risk factors described above

Probe for other depressive symptoms and the immediacy of potential suicidal intent. Sample questions may include the following:

- "It sounds as if you're in great pain. Have you ever thought life is not worth living?"
- "Do you often think of death?"
- "Do you think about hurting yourself?"
- "How might you do that?"
- "Is this something you feel you might do?"

O: Objective

- Perform a mental status examination and suicide assessment.
- Look for signs of self-inflicted injuries such as wrist lacerations or neck burns.

A: Assessment

See chapter *Depression* for differential diagnosis of possible causes of depression and suicidality.

P: Plan

Evaluation

Evaluate the patient for depression, risk factors for suicide, and contributing psychiatric illnesses or situational stressors. Determine the immediacy of potential suicidal intent. If a mental health professional is available on site or can be summoned, an urgent consultation is often helpful in making these determinations.

Take the following actions as appropriate:

- If the patient exhibits active suicidal ideation with a plan, hospitalize the patient immediately, preferably in a psychiatric facility.
- If suicidal behavior is passive, refer for psychotherapy with an HIV-experienced mental health provider.
- Establish a contract with the patient not to inflict self-harm, to contact you or another specified clinician for help, or to go to hospital if suicidal ideations become active.
- Contact the patient between appointments. Enlist the help of significant others (if the patient agrees); invite them to accompany the patient on the next visit and see all of them together. Consider a support group or peer referral if available.
- Consider dispensing medications on a weekly basis for the purposes of:
  - Monitoring emotional status and treatment adherence
  - Preventing the availability of lethal doses of medications
- Perform appropriate follow-up. In consultation with a skilled mental health provider, be sure that the patient is receiving appropriate ongoing treatment for underlying or persisting psychiatric illness. Assess at each visit for adherence to mental health care and for reoccurrence of symptoms.

Patient Education

- Suicidal ideation and severe depression are not normal aspects of HIV infection, and usually can be treated effectively.
- Patients should report suicidal thoughts to their health care providers.
- Providers should inform patients about local suicide prevention resources, including suicide hotlines, emergency response (eg, 911), and local emergency departments.

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HIV-Associated Dementia and Minor Cognitive Motor Disorder

Background

The HIV virus is neurotropic and directly invades brain tissue shortly after infection. Accordingly, HIV may cause cognitive difficulties, including HIV-associated dementia (HAD), also called AIDS dementia complex (ADC). In the United States in past years, HAD was the most common neurologic complication of AIDS, affecting 40-60% of all AIDS patients. In recent years, the incidence of HAD has declined, probably because of the use of potent combination antiretroviral therapy (ART). Other HIV-related opportunistic infections of the central nervous system (CNS) (eg, toxoplasmosis, cytomegalovirus encephalitis) and malignancies (eg, lymphoma) have declined in frequency even more sharply than HAD. The fact that HAD has not declined as much as other HIV-related CNS disease suggests that the CNS may be an important reservoir for HIV and that current antiretroviral medications do not protect the CNS as well as they protect the rest of the body. The HIV viral load in the CNS is correlated with cognitive decline; however, it is not correlated with plasma viral load and cannot be estimated from plasma viral load.

The American Psychiatric Association describes dementia as "an organic mental disorder defined as a loss of intellectual abilities of sufficient severity to interfere with social or occupational functioning." The clinical presentation of dementia varies. Patients may develop ambulation or gait problems, mania, panic, psychosis, social isolation, or anxiety. Dementia is progressive but with a variable course; some patients have a rapid progression, whereas others have a slow decline in function. Many patients with HIV-related neurocognitive impairments are acutely aware of their deterioration and may develop an adjustment disorder characterized by profound fear, anxiety, or depression.

Some HIV-infected patients may develop a milder form of cognitive disorder, called minor cognitive motor disorder (MCMD), which is not necessarily an early stage of dementia. The distinction between MCMD and dementia is important and may have a major psychological impact on the patient.

Manifestations of Dementia

Early manifestations of dementia may include the following:

- Decreased attention or concentration
- Reduced speed of information processing
- Psychomotor slowing
- Impaired executive functioning (eg, abstraction, divided attention, shifting cognitive sets)

Late manifestations may include:

- Visuospatial difficulties
- Language problems
- Apraxias

S: Subjective

The patient complains of, or a care giver reports, the following:

- Impairment in memory (short-term and long-term), abstract thinking, judgment, and higher cortical functioning
- Personality changes that interfere with relationships
- Inability to carry out normal social or occupational functions
- Some patients experience only minor forgetfulness and diminished visual or motor skills

History

Take a thorough history, including the following:

- Medications
- Approximate onset of symptoms
- Drug and alcohol use
- Symptoms of opportunistic infections
- Pain
- HIV history, including duration, opportunistic illnesses, and CD4 levels
- Common manifestations (see above)

O: Objective

Perform the following tests:

- Check temperature and other vital signs, and perform a thorough physical examination to determine potentially reversible causes such as opportunistic infections.
- Perform a thorough neurologic examination, including funduscopic exam. Check symmetry of brow wrinkling, eyelid closure, and pupil size. Perform Romberg and other tests to rule out focal neurologic deficits.
- Check gait by asking the patient to walk rapidly, turn, and stop. Ask the patient to walk on heels and tiptoes. Test steadiness of gait with eyes open and closed. Ask the patient to stand from a squatting position without assistance.
- Perform a complete minimental status examination. As a quick screen, ask the patient to write his or her name, date, and location; to spell "world" backwards; to perform memory-object recall of 3 objects after 5 minutes; and to make change from a dollar.

A: Assessment

Partial Differential Diagnosis

- Other CNS conditions, such as toxoplasmosis, fungal infection, *Mycobacterium avium* complex (MAC), lymphoma, cytomegalovirus ventriculitis or encephalitis, normal-pressure hydrocephalus, neurosyphilis, tuberculosis, or *Cryptococcus neoformans*. Many of these are treatable.
- Depression, which can present as cognitive impairment.
- Other medical causes, such as nutritional deficiencies (eg, vitamin B12), metabolic disorders (eg, hypothyroidism), toxins (eg, chronic alcohol use), or infections (eg, tertiary syphilis)
- Delirium, which is an acute manifestation of cognitive impairment with inability to maintain attention. Delirium can be due to many medical conditions, but is also commonly caused by medications, including those with anticholinergic adverse effects, such as amitriptyline (Elavil), promethazine (Phenergan), prochlorperazine (Compazine), and diphenhydramine (Benadryl). An anticholinergic delirium is characterized by visual or tactile hallucinations, confusion, and sometimes agitation. Other medications that may cause delirium include prednisone, meperidine (Demerol), lithium (at toxic levels, which may occur in a stable patient with a serious opportunistic infection or dehydration), agonist-antagonist analgesics such as pentazocine (Talwin), and short-acting benzodiazepines such as midazolam (Versed) and triazolam (Halcion).
- Intoxication or withdrawal.

Mild Manifestations: HIV-Associated Minor Cognitive Motor Disorder

At least 2 of the following symptom should be present:

- Impaired attention, concentration, or memory
- Mental and psychomotor slowing
- Personality changes

Rule out other causes.

Severe Manifestations: HIV-Associated Dementia

Signs will include the following:

- Acquired cognitive abnormality in 2 or more domains, causing functional impairment
- Acquired abnormality in motor performance or behavior
- No clouding of consciousness or other confounding cause (eg, CNS infections, psychopathology, drug abuse)

Table 1 describes the states of HAD.

Table 1. Stages and Characteristics of HIV-Associated Dementia

Stage	Characteristics
Stage 0 (normal)	Normal mental and motor function
Stage 0.5 (subclinical)	Equivocal symptoms of cognitive or motor dysfunction; no impairment of work or activities of daily living (ADL)
Stage 1 (mild)	Evidence of intellectual or motor impairment, but able to perform most ADL
Stage 2 (moderate)	Unable to work, but can manage self-care
Stage 3 (severe)	Major intellectual incapacity or motor disability
Stage 4 (end-stage)	Nearly vegetative

Source: Bartlett JG, Gallant JE. *2005-2006 Medical Management of HIV Infection.* Baltimore: Johns Hopkins University Division of Infectious Diseases; 2005. Available online at http://hopkins-aids.edu/mmhiv/order.html.

P: Plan

- Check thyroid function, vitamin B12, folate, rapid plasma reagin (RPR), blood chemistries and electrolytes, liver function tests (LFTs), complete blood count (CBC), and testosterone level.
- Order computed tomography (CT) scan or magnetic resonance imaging (MRI). (Cortical atrophy, similar to that seen in Alzheimer dementia, may be visible in very late stages of HAD.) Rule out masses and space-occupying lesions.
- Check cerebrospinal fluid (CSF): In patients with HAD, the CSF will show increased protein and mononuclear pleocytosis. It may be valuable to check the HIV viral load in the CSF, because sometimes the CSF viral load is high regardless of the plasma viral load; this may explain the patient's central deficits.
- Perform an electroencephalogram (may show mild, nonspecific slowing).
- Refer the patient to a psychiatrist and neurologist for further evaluation and neuropsychological testing.

Treatment

Pharmacotherapy

ART may be helpful in treating MCMD and HAD and should be recommended for all patients, unless there are contraindications. The ability of particular antiretroviral drugs to penetrate the blood-brain barrier may be less important to treatment success than the overall potency of the regimen and the ability of the patient to adhere to it.

Studies from the 1980s showed that zidovudine monotherapy was beneficial in patients with HAD, so some clinicians include it in the ART regimen for anyone with neurocognitive impairment. Others suggest using at least 2 drugs that cross the blood-brain barrier (eg, zidovudine, stavudine, abacavir, lamivudine, and nevirapine). Efavirenz, didanosine, and lamivudine cross to a lesser degree. As a class, protease inhibitors (PIs) have poor blood-brain barrier penetration. Nevertheless, patients have shown neurocognitive improvement while taking PI-containing regimens, perhaps because of indirect effects on HIV activity in the CNS.

Treat depressive symptoms with low dosages of selective serotonin reuptake inhibitors (SSRIs) (see chapter *Depression* for details).

Antipsychotic medications may be useful in treating agitation and hallucinations, but patients with these conditions are often extremely sensitive to anticholinergic adverse effects and extrapyramidal symptoms. Newer neuroleptic or antipsychotic agents, such as olanzapine and risperidone, have lower rates of significant side effects compared with older drugs. The starting dosage of olanzapine is 2.5 mg orally at bedtime; that for risperidone is 0.5-1 mg orally at bedtime. Note that these drugs may interact with antiretroviral medications, especially ritonavir, and can cause weight gain and other metabolic adverse effects. Avoid benzodiazepines, which tend to increase confusion and decrease concentration. Consult with a knowledgeable psychiatrist or pharmacist.

Psychostimulants such as methylphenidate (Ritalin) and dextroamphetamine (Dexedrine) have been used to improve attention, concentration, and psychomotor function. Dosages of methylphenidate start at 5 mg for a test dose, then 2.5-5.0 mg twice daily, increasing by doses of 5 mg every other day until the desired effect is achieved. Usual dosages are in the range of 20-30 mg per day. Monitor blood pressure, heart rate, and symptoms of restlessness, agitation, nausea, and psychosis. No data are available regarding the use of atomoxetine (Strattera) to improve attention and concentration in patients with HAD.

Psychosocial interventions

For a patient who is knowledgeable about HIV, a dementia workup or diagnosis often precipitates a crisis, with an increased risk of suicide. Carefully screen for depression and suicidality, and treat these if they develop.

Behavioral management strategies may assist the patient with early manifestations of dementia to continue living with some degree of independence and safety in the home. Memory aids such as posted notes, calendars, alarmed pill-boxes, and other environmental cues may help.

It is critical to enlist the support of family members and significant others at an early stage of the illness. Because the disease is frightening and may be progressive, the patient and members of the support system need assistance in anticipating and planning for the future. Plans for assisted living or other in-home custodial care should be made early. Severe or late dementia causes fear, misunderstanding, and frustration for both the patient and care givers. All involved will require

help from visiting nurses, social workers, hospice workers, and physicians. Recommend the preparation of an advance directive for the patient with early manifestations of dementia.

Patient Education

- Patients should maintain their support system as much as possible.
- Refer patients to a support group or an HIV-experienced counselor who can respond to their fears and concerns.
- ART has helped some people with HAD. Patients who are candidates for ART, should find someone to help with their antiretroviral medications, if at all possible. Enlist family members or roommates to help the patient take the medications as scheduled. Educate them about adverse effects, and whom to call with problems and questions.
- Teach patients to use cues (eg, notes, calendars, alarms) to help themselves keep track of medicines, appointments, social events, and other important activities. Help them identify ways to make the house safer and to maintain as much functionality and dignity as possible.

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Correctional Settings

Background

Caring for the HIV-infected incarcerated patient is complex and challenging. For many of these patients, the prison health service provides their first opportunity for access to health care. HIV seroprevalence rates among inmates in the United States are 5 times higher than in the nonincarcerated population (CDC, 2001). Within the prison system in the United States, mortality due to AIDS has dropped dramatically since the advent of effective combination antiretroviral therapy (ART), with the number of AIDS-related deaths decreasing by 72% in state prisons between 1995 and 2002 (Maruschak, 2001).

Often, behaviors that lead to incarceration also put inmates at high risk for becoming infected with HIV, hepatitis C virus (HCV), and other infectious diseases. These risk factors may include unsafe substance use behaviors, such as sharing syringes and other injection equipment, and high-risk sexual practices, such as having multiple sex partners or unprotected sex. Many inmates also may have conditions that increase the risk of HIV transmission or acquisition, such as untreated sexually transmitted diseases (STDs).

Of the approximately 1.8 million inmates in the United States, 30-40% are infected with HCV. The incidence is 10 times higher among inmates than among noninmates and is 33% higher in women than in men (Nerenberg et al, 2002). Chronic hepatitis B virus (HBV) infection and tuberculosis are substantially more common in the incarcerated population than in the general public. The presence of any of these conditions should prompt HIV testing (Nicodemus and Paris, 2002).

Incarcerated Women

Women represent 5-10% of the prison population in the United States. The HIV epidemic in the United States increasingly affects women of color, and this trend is reflected in HIV rates among the incarcerated. Incarcerated women have higher HIV seroprevalence rates than incarcerated men (3% vs 1.9%). Several risk factors for HIV are present in abundance among female inmates, including the following:

- History of childhood sexual abuse and neglect
- History of sex work, with increased frequency of forced, unprotected sex
- High rates of STDs
- High rates of mental illness
- History of injection drug use (IDU) and/or sex partners with IDU history
- Poverty

Among all women entering a correctional facility, 10% are pregnant (De Groot and Cu Uvin, 2005). These women should be offered HIV testing, and HIV-infected pregnant women should be offered ART immediately to prevent perinatal HIV transmission. Many incarcerated women will receive their first gynecologic care in prison. Because the incidence of cervical cancer is higher in women with HIV, referrals for colposcopy should be made for any HIV-infected woman with an abnormal Papanicolaou test.

Testing and Prevention

The correctional facility is an ideal location for identifying those already infected with HIV, HCV, and/or HBV, and for preventing infection among those at highest risk for these diseases. The corrections setting is often the first site at which an HIV-infected person interacts with the health care system, making it an important avenue for HIV testing. HIV testing policies in correctional facilities vary from state to state and among local, state, and federal penal institutions. Depending on the setting, policies may require testing of inmates upon entry, upon release, or both. Testing may be based on clinical indication or risk exposure during incarceration, and may be voluntary or mandatory (Bartlett et al, 2000). The U.S. Centers for Disease Control and Prevention (CDC) recommends routine counseling and testing in settings with an HIV prevalence of 1% or higher. In high-risk settings such as correctional facilities, routine, voluntary HIV testing has been shown to be cost-effective and clinically advantageous (Paltiel, 2005).

Testing and treatment of HIV-infected inmates prior to release is critical. Given the high HIV seroprevalence rates among inmates, the reentry of inmates into the community presents the danger of spreading HIV and other infectious diseases, and thus is a public health

concern. Inmates need adequate HIV prevention counseling before release both to protect themselves and to decrease transmission of HIV to others in their communities (Gaiter, 1996).

Health care providers in correctional settings are in a key position to evaluate inmates for HIV risk factors, to offer HIV testing, and to educate and counsel this high-risk group about HIV. Inmates often are hesitant to be tested for HIV because of fear of a positive diagnosis and because of the potential stigma involved. Often, they lack accurate information about HIV, including awareness of behaviors that may have put them at risk and knowledge of means for protecting themselves from becoming infected.

The World Health Organization (WHO) has stated: "All inmates and correctional staff and officers should be provided with education concerning transmission, prevention, treatment, and management of HIV infection. For inmates, this information should be provided at intake and updated regularly thereafter" (see: http://www.who.int/en/). Risk reduction counseling addresses specific ways the inmate can reduce the risk of becoming infected with HIV. If already HIV infected, the goal of counseling is to reduce the risk of infecting others or becoming infected with a drug-resistant strain of HIV. Education should focus on the use of latex barriers with all sexual activity. Although condoms and dental dams are not available in most prisons and jails, the inmate should receive education regarding their proper use.

Inmates with a history of IDU should be educated that needle sharing conveys a high risk of transmitting HIV, HCV, and HBV. Substance abuse treatment should be provided when appropriate.

Recovery from addiction often is a chronic process and relapses are common. In addition to treatment, risk reduction strategies should include planning for support after release. For example, prior to release, inmates should be provided with information about needle exchange or clean needle access programs in their communities. These programs have proved to be quite effective in decreasing the rate of parenteral HIV transmission (CDC, 1999).

Antiretroviral Therapy in Correctional Facilities

In correctional facilities, as in any setting, a consideration of HIV treatment must begin with educating the patient about the risks and benefits of treatment and the need to fully adhere to the entire regimen, as well as with an assessment of the patient's motivation to take ART.

Correctional facilities have two medical policies for dispensing medications. Each has advantages and disadvantages that can impact treatment adherence.

Directly Observed Therapy

Directly Observed Therapy (DOT) is the system in which the inmate goes directly to the medical unit or pharmacy for all medication doses. This system offers the advantage of more frequent interaction between the patient and the health care team, allowing for earlier identification of side effects and other issues. In general, patients have better medication adherence in this system, resulting in better control of HIV. For some inmates, however, the need for frequent visits to the medical unit or pharmacy may be a barrier to treatment, particularly if they are housed at a distance from the unit. Another disadvantage of DOT is the potential loss of confidentiality, as many inmates feel that the frequency of treatment and the large number of pills they must take will reveal clues that they are HIV infected. In addition, this system puts the inmate in a passive role in terms of medication treatment and does not foster self-sufficiency.

Keep on Person

Keep on Person (KOP) is the system that allows the inmates to keep their medications in their cells and take them independently. Monthly supplies are obtained at the medical unit or pharmacy. This system offers greater privacy and confidentiality regarding HIV status. It also allows the inmate to develop self-sufficiency in managing medications, which may facilitate improved adherence upon release. However, as the KOP system involves less interaction with medical staff, problems with adherence can be more difficult to identify (Ruby, 2000).

In a study comparing DOT in HIV-infected inmates with KOP in nonincarcerated HIV-infected patients receiving ART as part of a clinical trial, a higher percentage of DOT patients achieved undetectable viral loads compared with the KOP patients (85% vs 50%) over a 48-week period (Fischl, 2001).

Adherence

Adherence is one of the most important factors in determining success of ART. For the HIV-infected inmate starting ART, a number of issues can affect medication adherence. These include patient-related factors, factors related to systems of care (including the medication dispensing systems described above), and medication-related factors. The following are suggestions for supporting adherence to ART.

Patient-Related Factors

- Provide alcohol and substance abuse treatment prior to initiating ART. Without appropriate treatment during incarceration, linkages to supports, and follow-up treatment upon discharge, the inmate is at risk for returning to high-risk behaviors that may interfere with adherence to ART.
- Utilize mental health consultation to identify inmates with psychiatric needs. Treatment for underlying mental health disorders should precede or occur simultaneously with the initiation of ART to ensure successful adherence. Depression and other psychiatric illnesses are more prevalent among inmates than among the general population (Maruschak, 2001).
- Correct misconceptions about HIV and ART that are common among inmates and could affect adherence adversely. The inmate should be educated about the disease process and the role of the medications, along with the potential risks and benefits of taking ART.
- Encourage participation in peer support groups. These can be effective ways to foster self-esteem, empower inmates to come to terms with a positive diagnosis, allay fears and correct misconceptions about HIV disease, and aid adherence. Upon release, telephone hotlines may be available to provide follow-up support and linkages to community services. To the extent possible, family and friends should be included in the education process.
- Use teaching tools that are appropriate in terms of language and reading level. Illiteracy and low-level reading ability are common among inmates. Diagrams and videos may be more effective than reading-intensive material in some cases. Basic HIV education prior to initiation of ART should include:
  - How the medications work
  - Consequences of nonadherence
  - Names and dosages of all medications
  - Potential side effects with strategies to manage them

Factors Related to Systems of Care

- Educate security staff about the importance of timely medication dosing, and communicate with other facilities in advance of a transfer; this can eliminate or limit missed doses.
- Schedule frequent follow-up medical visits in the early weeks after ART is initiated; these can make the difference in whether or not patients "stay the course."
- Consult with an HIV specialist, if possible. If a facility's medical provider lacks experience in treating patients with HIV, the results may be undertreatment of side effects, or ART prescribing errors. Because caring for HIV patients is complicated, HIV specialists can provide assurance that patients are receiving proper care. Of particular concern are patients whose current ART regimens are failing, those who are declining clinically, and those who are coinfected with other infectious diseases such as tuberculosis, HCV, and HBV.

Medication-Related Factors

Any consideration of HIV treatment must begin with educating the patient about the risks and benefits of treatment and the need to fully adhere to the entire regimen, as well as with assessing the patient's motivation to take ART.

- *Aggressively monitor and treat side effects.* The most common barrier to adherence to ART is side effects from the medications. The inmate should be educated in advance about potential adverse events to observe and report. In the first weeks after starting a new ART regimen, patients should be assessed frequently for side effects. For treating gastrointestinal toxicities, antiemetics and antidiarrheals should be available on an as-needed basis. As with all patients on ART, inmates should have appropriate laboratory monitoring.
- *Be aware of food requirements.* Various food requirements must be considered carefully when administering ART. This can be especially challenging in the correctional environment,

particularly if the facility does not allow inmates to self-administer medications. Make arrangements with prison authorities to provide food when inmates are taking medications that require administration with food.

- *Avoid complex regimens and regimens with large pill burdens, if possible.* Simple regimens with few pills appear to help improve adherence.
- *Avoid drug-drug interactions.* Some antiretroviral medications have clinically significant interactions with other drugs (eg, methadone, oral contraceptives, cardiac medications, antacids). These interactions may cause failure of either the antiretroviral drug or the other medication, or may cause additional toxicity. Consult an HIV specialist or pharmacologist for information on drug interactions.
- The patient should be questioned about medication adherence at each appointment.
- ART regimens need to fit into each patient's schedule and lifestyle. This becomes a bigger issue when the inmate is close to release. Education about HIV management, including ART adherence, should begin well before the inmate is discharged back to the community.At the time of discharge from the correctional facility, all HIV-infected inmates should have a discharge plan that addresses:
  - Housing
  - Health insurance
  - 30-day supply of HIV medications
  - Follow-up appointments for medical care and, if necessary, psychiatric and substance abuse care

A number of HIV education resources for inmates and correctional health care providers are cited on Albany Medical College's Web site at http://www.amc.edu/Patient/Services/HIV/HIVMedicine/index.html (go to the section on correctional education).

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Karnofsky Performance Scale

Background

The Karnofsky Performance Scale is an assessment tool used to assist clinicians and caretakers in measuring a patient's ability to carry out activities of daily living. It is important to assess a patient's performance on a regular basis, especially as the effects of HIV progress.

Documentation of Karnofsky scores may be very helpful if a patient applies for disability benefits, and may be useful for some research applications.

Table 1. The Karnofsky Performance Scale

Description	Percent (%)
Normal; no complaints; no evidence of disease	100
Able to carry on normal activity; minor signs and symptoms of disease	90
Normal activity with effort; some signs and symptoms of disease	80
Cares for self; unable to carry on normal activity or do work	70
Requires occasional assistance, but is able to care for most personal needs	60
Requires considerable assistance and frequent medical care	50
Disabled; requires special care and assistance	40
Severely disabled; hospitalization indicated although death not imminent	30
Very sick; hospitalization necessary; requires active support treatment	20
Moribund; fatal processes progressing rapidly	10
Dead	0

Sulfa Desensitization

Background

Trimethoprim-sulfamethoxazole (TMP-SMX), also known as Septra, Bactrim, and cotrimoxazole, is a key antibiotic for prophylaxis and treatment of several HIV-related illnesses. It is the most effective prophylaxis and the first-line treatment for *Pneumocystis jiroveci pneumonia* (PCP). In addition, it is effective in preventing toxoplasmosis encephalitis in severely immunocompromised patients who have evidence of previous infection, and it is effective against certain bacterial infections. TMP-SMX also is quite inexpensive, which is a rarity in the world of HIV treatment. Because of its effectiveness and availability, it is used widely throughout the world. However, adverse reactions to TMP-SMX and other sulfa drugs occur in a high proportion of HIV-infected patients (roughly 25%), and such reactions may limit treatment.

Desensitization to TMP-SMX should be considered when there are no reasonable or available alternatives and the patient has not experienced severe reactions (eg, Stevens-Johnson syndrome) to sulfa drugs. Several methods of desensitizing patients with previous reactions to TMP-SMX have been tried. These methods vary in starting dosage and length of dosage escalation, but success rates are around 80% in most cases and may be higher in those patients with <200 CD4 cells/μL.

S: Subjective

The patient reports a previous adverse reaction to sulfa drugs, such as erythema, pruritus, or rash. The patient has no history of anaphylaxis, Stevens-Johnson syndrome, or toxic epidermal necrolysis, and no reaction involving vesiculation, desquamation, ulceration, exfoliative dermatitis, etc.

O: Objective

CD4 count <200 cells/μL, or other important indication for TMP-SMX.

A: Assessment

Reaction to sulfa, possibly reversible with desensitization protocol.

P: Plan

Begin 9- to 13-day desensitization protocol, starting with pediatric oral suspension, which contains 40 mg of TMP and 200 mg of SMX per 5 mL (1 teaspoon). Gradually increase the dosage according to the protocol.

If there is any question about the severity of a previous reaction, have the patient take the initial morning dose in the clinic so that the patient may be monitored for 3-4 hours before going home. (This assumes that emergency treatment, including IV access materials and IV fluids, antihistamines, and steroids, are readily available.)

Treat with an antihistamine medication 1 day before starting the desensitization regimen and continue daily until the dose escalation is completed.

More rapid desensitization protocols are available (see References below) for patients urgently needing treatment with TMP-SMX.

Desensitization Regimen

Use commercially available pediatric suspension (containing TMP 8 mg and SMX 40 mg per mL), followed by double-strength tablets, as follows:

Table 1. Sulfa Desensitization Regimen

Days	Dosage (TMP/SMX)	Volume or Tablet
1-3	8 mg/40 mg	1 mL
3-6	16 mg/80 mg	2 mL
5-9	40 mg/200 mg	5 mL
7-12	80 mg/400 mg	1/2 double-strength tablet (or 1 single-strength tablet)
9-10 and thereafter	160 mg/800 mg	1 double-strength tablet

In the event of mild reaction: If the patient experiences a mild reaction or itching, the same dosage should be given for an additional day. If the reaction diminishes, the patient may advance to the next dosage; if the reaction worsens, the TMP-SMX should be discontinued. Antihistamines or antipyretics may be used to treat symptoms of mild reactions.

In case of severe reaction: the desensitization regimen should be discontinued.

Patient Education

For home desensitization regimen

Explain the benefits of using TMP-SMX. Be sure the patient understands and is able to follow instructions.

- Measure your dose carefully and take it each morning, followed by a glass (6-8 oz) of water. (The patient should do a demonstration, if possible, using the syringe that will be used for the actual measuring at home.)
- TMP-SMX can make you very ill unless you pay attention to any problems you have. It is extremely important that you check your temperature each afternoon. If your temperature is more than 100.5° F by mouth, stop taking the drug and contact your clinician. Note: If you have shaking chills, check your temperature as soon as the shaking stops, and contact the clinic. If you continue the medication despite a red rash and/or fever, serious illness or a life-threatening reaction may occur. Report any adverse event immediately.
- Stop the regimen and return to the clinic or emergency room immediately if you develop a red rash, blisters on your skin or in your mouth, or vomiting. Check your skin each evening, and any time you notice itching.

If you have mild itching or a faint rash, you can take diphenhydramine (Benadryl) 25-50 mg. every 4 hours as needed. If this persists, stay with the same dosage for an additional day; and call or go to the clinic if you have questions or concerns.

- Call or go to the clinic for alternate dosage instructions in the event of persistent itching without rash.

For all desensitized patients

- After desensitization is complete, continue to take the daily dosage. If the drug is stopped, the entire regimen may have to be repeated.

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Patient Education

Background

It has long been acknowledged that informed and empowered patients are better able to achieve healthy outcomes due to improved communication and development of trust with their care providers. HIV patient education provides patients with knowledge about HIV infection and tools to enable them to participate more actively in decisions regarding their medical care. Given the complexity and the rapid evolution of HIV information, patients should be given ample and multiple opportunities to receive this information and to learn of updates in our understanding of HIV care. Similarly, the clinical management of HIV patients should include educating the patient on the various aspects of living with HIV infection. This chapter will review the areas that should be addressed in patient education and discuss some strategies for integrating patient education into HIV care.

S: Subjective

A newly diagnosed patient presents to clinic after being referred from a testing center in the community. He received his positive HIV results more than a year ago, but it took him this long to seek care. He wasn't ready to hear that he was "going to die." Now, he is ready to consider facing his "terminal" illness. He received some information about HIV infection at the testing center, but that was several months ago.

O: Objective

See *Initial History, Initial Physical Examination*, and *Initial and Interim Laboratory* and *Other Tests* chapters.

A: Assessment/Plan

This patient will need extensive information and education about HIV infection in general, his individual health status and prognosis, and the support and care systems available to him. Below are some suggestions about specific areas to review with a new patient.

What Should Be Included in Patient Education?

Patient education should cover the following topics:

- What is HIV?
- How HIV is transmitted
- Prognosis/progression of HIV
- Interpretation of lab results
- Treatment information
  - Indications for treatment, goals of treatment
  - General information regarding the benefits of treatment
  - General information regarding potential side effects of treatment
  - Access to medication
  - Insurance information
- Treatment options
- Prevention for positives
- Support services and support groups available to the patient

Who Should Provide Patient Education?

In most clinics, various personnel may take on the responsibilities of providing health education to patients. They may include primary care providers, nurses, social workers, case managers, and pharmacists. Some clinics have designated health educators whose role is to provide this type of support for patients. Even when a formal health educator is available, a collaborative, multidisciplinary approach to patient education serves both patients and providers optimally. However, it is important to ensure that patient education messages are coordinated and that patients are receiving consistent information.

Patient education must be provided in a language and at a literacy level appropriate for the patient. Patient education should be conducted in the patient's primary language, if possible; otherwise, skilled medical interpreters should be involved.

How Should Patient Education Be Provided?

Rarely are patients able to absorb all of the necessary information in a single session. Attention and comprehension levels are optimal during the first 15-20 minutes of a visit, after which an individual's ability to absorb and retain information declines. Therefore, clinics should consider strategies to integrate these patient education messages throughout the course of patient care and to engage patients in this process. Support groups, case managers, and peer educators can be invaluable in this process of engagement.

It is also important to keep the medical information specific to the patient. Although there are some areas of education that should be considered for all patients (see above), patients should not be required to have a high level of understanding in each area. Patients should be given the opportunity to learn as much about an area as they would like and to retain the volume of information necessary to keep them healthy and safe. For example, in the area of "What is HIV?" there may be some patients who want to know details about the basic science and immunologic impact of HIV. With this information, these patients might then want to take the lead in making treatment and care decisions for themselves, in consultation with their care providers. Other patients, however, would feel overwhelmed by this volume of information and involvement and may be best engaged in participating in their care by knowing how HIV is transmitted, how to keep themselves healthy, and how to access more information if they want it. Some patients would prefer for their care providers to "just tell them what to do" rather than take the lead in their own treatment decisions.

There are a number of Web sites that provide HIV information for patients (see *Web-Based Resources* chapter). Many patients may prefer this form of self-education. Encourage patients to bring any information they discover to clinic for further discussion. Reminding patients that they can be teachers as well as students can be a useful strategy for engaging patients in this process. In addition, patients may learn of novel tools and information sources that could be useful to others.

The following are some useful suggestions that providers can convey to their patients:

- Define your goals for each visit; please let your provider know your concerns and what you hope to learn in the course of the visit.
- Write down questions and concerns as they arise, and take that list with you to your appointments.
- Meet all the members of your care team and learn their areas of expertise and what they might be able to offer you.
- Ask about support groups and other peer groups that might be able to provide support/education.
- Review brochures and/or Web sites that provide additional information.
- Ask supportive friends or family members to accompany you to clinic visits. They may be able to obtain information that is helpful for their role in supporting your health or reminding you of information discussed at visits.

Web-Based Resources

Background

The care and management of HIV-infected patients is a rapidly evolving field. Keeping up to date with clinical information about HIV care has in the past required attendance at national and international conferences. With the increasing availability of the Internet, clinicians and patients are able to access the most current advances through Web coverage, without requiring travel or time away from work.

The challenge of using Internet resources is in determining which Web sites are accurate and current. Check for dates of authorship, the credentials of the site sponsors and authors, and how well supported any recommendations or analysis may be. Be aware of any possible commercial bias. Finally, it is important to remember that information on these sites does not replace clinical judgment or consultation with HIV experts.

Listed below are a selection of useful and accurate Internet sites. Many of these Web sites also link out to additional information resources, and many allow users to subscribe to receive updates via email. Many providers find it helpful to review sites geared toward patients, in order to maintain familiarity with patients' concerns and patient-based information resources.

Web-Based Resources for Providers

- **AIDS Education and Training Centers National Resource Center**
  http://www.aidsetc.org
  Clinical training resources, including curricula, self-study, and slide sets, including slides for all national guidelines. Online home for the Clinical Manual for Management of the HIV-Infected Adult.
- **AIDSInfo**
  http://aidsinfo.nih.gov
  Official repository for HIV/AIDS information from the U.S. Public Health Service. Content includes HIV/AIDS treatment guidelines, national clinical trial information, drug and vaccine overviews, and fact sheets for patients.
- **Aidsmap**
  http://www.aidsmap.org
  London-based HIV/AIDS news and treatment information site. Patient information written at both lower and higher literacy levels. International focus.
- **Clinical Care Options for HIV**
  http://clinicaloptions.com
  CME materials related to HIV/AIDS including conference reviews.
- **HIV InSite**
  http://hivinsite.ucsf.edu
  Major HIV/AIDS portal from the University of California San Francisco. Includes HIV InSite Knowledge Base, updated ARV information, including an interactions database, global country profiles, and links out to other useful sites.
- **HIV Resistance Web**
  http://hivresistanceweb.com
  Information on resistance mutations to antiretroviral medications.
- **HIV Web Study**
  http://hivwebstudy.org
  Northwest AETC, University of Washington. Dozens of online clinical cases featuring downloadable tables, charts, and images.

- **HIVandHepatits.com**
  http://www.hivandhepatitis.com/
  Clinical information on HIV and hepatitis B and hepatitis C viruses, including conferences reviews.
- **International Training and Education Center on HIV**
  http://go2itech.org
  The international AETC. Web site features extensive database of international HIV/AIDS training materials.
- **International AIDS Society-USA**
  http://iasusa.org
  ARV resistance mutations charts and "Cases on the Web" online CME courses.
- **Johns Hopkins AIDS Service**
  http://www.hopkins-aids.edu/
  Major clinical information site that includes expert Q&A, the popular Pocket Guide to Adult HIV/AIDS Treatment, and the online and PDA-based POC-IT HIV Guide.
- **Medscape HIV/AIDS Topic Area**
  http://www.medscape.com/hiv-home?src=pdown
  Continuing Medical Education (CME) materials related to HIV/AIDS, including conference coverage, news, and special features.
- **National HIV/AIDS Clinicians' Consultation Center**
  http://www.ucsf.edu/hivcntr
  An AIDS Education and Training Centers clinical resource for health care professionals, with contact information for the Warmline, PEPline, and Perinatal HIV Hotline.
- **VA National HIV/AIDS Program**
  http://www.hiv.va.gov/
  Comprehensive information portal for patients and providers.
- **Women, Children, and HIV**
  http://www.womenchildrenhiv.org/
  Expert-selected, evidence-based information on prevention of mother-to-child transmission of HIV, care of women and children with HIV, and related topics.

Web-Based Resources for Patients and the Community

- **AIDS.org**
  http://www.aids.org/
  Online home of AIDS Treatment News.
- **AIDS InfoNet**
  http://www.aidsinfonet.org/
  Comprehensive collection of fact sheets on clinical topics, available in English and Spanish, in print-friendly and downloadable formats. Regularly updated.
- **AIDSmeds**
  http://aidsmeds.com
  Information regarding HIV-related medications for patients, including drug interactions calculator.
- **AIDS Project Los Angeles**
  http://www.apla.org/
  Fact sheets, newsletters, and program information. Some information in Spanish.
- **The Body**
  http://thebody.com
  Major HIV information resource geared toward patients and the community.
- **Gay Men's Health Crisis**
  http://www.gmhc.org/
  Patient and program information from one of the oldest community organizations. Some information in Spanish.
- **Project Inform**
  http://projectinform.org
  Comprehensive information and advocacy information geared toward individuals infected and affected by HIV.
- **San Francisco AIDS Foundation**
  http://www.sfaf.org/
  AIDS 101, BETA treatment newsletter, and prevention and program information. Some information in Spanish.
- **Test Positive Aware Network (TPAN)**
  http://www.tpan.com/index.shtml
  Chicago-based community organization with newsletter, drug guide, and service information.
- **VA National HIV/AIDS Program**
  http://www.hiv.va.gov/
  Comprehensive information portal for patients and providers.