

Table 18. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations

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18a. Potentially Life-Threatening and Serious Adverse Events

Adverse effects	Causative ARVs	Onset/clinical manifestation	Estimated frequency	Risk Factors	Prevention/monitoring	Management
POTENTIALLY LIFE-THREATENING ADVERSE EFFECTS (In alphabetical order)						
Acute hepatic failure	NVP	<p><u>Onset:</u> Greatest risk within first few weeks of therapy; can occur through 18 weeks</p> <p><u>Symptoms:</u> Abrupt onset of flu-like symptoms (nausea, vomiting, myalgia, fatigue), abdominal pain, jaundice, or fever with or without skin rash; may progress to fulminant hepatic failure with encephalopathy</p> <p>Approximately 1/2 of the cases have accompanying skin rash</p> <p>Some may present as part of DRESS syndrome (drug rash with eosinophilia and systemic symptoms)</p>	<p><u>Symptomatic hepatic events:</u></p> <ul style="list-style-type: none"> • 4% overall (2.5%–11% from different trials) • In women - 11% in those w/ pre-NVP CD4 >250 cells/mm³ vs. 0.9% w/ CD4 <250 cells/mm³ • In men - 6.3% w/ pre-NVP CD4 >400 cells/mm³ vs. 2.3% w/ CD4 <400 cells/mm³ 	<ul style="list-style-type: none"> • Treatment-naïve patients with higher CD4 count at initiation (>250 cells/mm³ in women & >400 cells/mm³ in men) • Female gender (including pregnant women) • HIV (-) individuals when NVP is used for post-exposure prophylaxis • High NVP concentration 	<ul style="list-style-type: none"> • Avoid initiation of NVP in women w/ CD4 >250 cells/mm³ or men w/ CD4 >400 cells/mm³ unless the benefit clearly outweighs the risk • Counsel patients re: signs & symptoms of hepatitis; stop NVP & seek medical attention if signs & symptoms of hepatitis, severe skin rash, or hypersensitivity reactions appear • Monitoring of ALT & AST (every 2 weeks x first month, then monthly x 3 months, then every 3 months) • Obtain AST & ALT in patients with rash • 2-week dose escalation may reduce incidence of hepatic events 	<ul style="list-style-type: none"> • Discontinue ARV including nevirapine (caution should be taken in discontinuation of 3TC, FTC, or TDF in HBV-coinfected patients) • Discontinue all other hepatotoxic agents if possible • Rule out other causes of hepatitis • Aggressive supportive care as indicated <p>Note: Hepatic injury may progress despite treatment discontinuation. Careful monitoring should continue until symptom resolution.</p> <p>Do not rechallenge patient with NVP</p> <p>The safety of other NNRTIs (EFV, ETV, or DLV) in patients who experienced significant hepatic event from NVP is unknown – use with caution.</p>
Lactic acidosis/hepatic steatosis +/- pancreatitis (severe mitochondrial toxicities)	NRTIs, esp. d4T, ddI, ZDV	<p><u>Onset:</u> months after initiation of NRTIs</p> <p><u>Symptoms:</u></p> <ul style="list-style-type: none"> • Insidious onset with nonspecific gastrointestinal prodrome (nausea, anorexia, abdominal pain, vomiting), weight loss, and fatigue; • Subsequent symptoms may be rapidly progressive with tachycardia, tachypnea, hyperventilation, jaundice, muscular weakness, mental status changes, or respiratory distress • Some may present with multi-organ failure (hepatic failure, acute pancreatitis, encephalopathy, and respiratory failure) <p><u>Laboratory findings:</u></p> <ul style="list-style-type: none"> • Increased lactate (often >5 mmole) • Low arterial pH (some as low as <7.0) • Low serum bicarbonate • Increased anion gap • Elevated serum transaminases, prothrombin time, bilirubin • Low serum albumin • Increase serum amylase & lipase in patients with pancreatitis • Histologic findings of the liver – microvesicular or macrovesicular steatosis 	<p>Rare</p> <p>One estimate 0.85 cases per 1,000 patient-years</p> <p>Mortality up to 50% in some case series, (esp. in patients with serum lactate >10 mmole)</p>	<ul style="list-style-type: none"> • d4T + ddI • d4T, ZDV, ddI use (d4T most frequently implicated) • Long duration of NRTI use • Female gender • Obesity • Pregnancy (esp. with d4T+ddI) • ddI + hydroxyurea or ribavirin • High baseline body mass index 	<ul style="list-style-type: none"> • Routine monitoring of lactic acid is not recommended • Consider obtaining lactate levels in patients with low serum bicarbonate or high anion gap and with complaints consistent with lactic acidosis • Appropriate phlebotomy technique for obtaining lactate level should be employed 	<ul style="list-style-type: none"> • Discontinue all ARVs if this syndrome is highly suspected (diagnosis is established by clinical correlations, drug history, and lactate level) • Symptomatic support with fluid hydration • Some patients may require IV bicarbonate infusion, hemodialysis or hemofiltration, parenteral nutrition or mechanical ventilation • IV thiamine and/or riboflavin – resulted in rapid resolution of hyperlactatemia in some case reports <p>Note:</p> <ul style="list-style-type: none"> • Interpretation of high lactate level should be done in the context of clinical findings • The implication of asymptomatic hyperlactatemia is unknown at this point <p>ARV treatment options:</p> <ul style="list-style-type: none"> • Use NRTIs with less propensity of mitochondrial toxicities – (e.g., ABC, TDF, 3TC, FTC) – should not be introduced until lactate returns to normal • Recommend close monitoring of serum bicarbonate or lactate after restarting NRTIs • Consider NRTI-sparing regimens

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18a. Potentially Life-Threatening and Serious Adverse Events (continued)

Adverse effects	Causative ARVs	Onset/clinical manifestation	Estimated frequency	Risk Factors	Prevention/monitoring	Management
POTENTIALLY LIFE-THREATENING ADVERSE EFFECTS (In alphabetical order)						
Hypersensitivity reaction (HSR)	ABC	<p><u>Onset of 1st reaction:</u> median onset – 9 days; approximately 90% within 1st 6 weeks</p> <p><u>Onset of rechallenge reactions:</u> within hours of rechallenge dose</p> <p><u>Symptoms:</u> acute onset of symptoms (in descending frequency): high fever, diffuse skin rash, malaise, nausea, headache, myalgia, chills, diarrhea, vomiting, abdominal pain, dyspnea, arthralgia, respiratory symptoms (pharyngitis, dyspnea/tachypnea)</p> <p><i>With continuation of ABC, symptoms may worsen to include:</i> hypotension, respiratory distress, vascular collapse</p> <p><i>Rechallenge reactions:</i> generally greater intensity than 1st reaction, can mimic anaphylaxis</p>	Clinically suspected ≈ 8% in clinical trial (2%–9%); 5% in retrospective analysis; significantly reduced with pre-treatment HLA screening	<ul style="list-style-type: none"> •HLA-B*5701, HLA-DR7, HLA-DQ3 (from Australian data) •Higher incidence of grade 3 or 4 HSR with 600mg once-daily dose than 300mg twice-daily dose in one study (5% vs. 2%) 	<ul style="list-style-type: none"> •HLA B*5701 screening prior to initiation of ABC •Those patients tested (+) for HLA B*5701 should be labelled as allergic to abacavir in medical records •Educate patients about potential signs and symptoms of HSR and need for reporting of symptoms promptly •Wallet card with warning information for patients 	<ul style="list-style-type: none"> •Discontinue ABC and other ARVs •Rule out other causes of symptoms (e.g., intercurrent illnesses such as viral syndromes, and other causes of skin rash, etc.) •Most signs and symptoms resolve 48 hours after discontinuation of ABC <p><i>More severe cases:</i></p> <ul style="list-style-type: none"> •Symptomatic support – antipyretic, fluid resuscitation, pressure support (if necessary) <p>•Do not rechallenge patients with ABC after suspected HSR</p>
Lactic acidosis/ Rapidly progressive ascending neuromuscular weakness	Most frequently implicated ARV: d4T	<p><u>Onset:</u> months after initiation of ARV; then dramatic motor weakness occurring within days to weeks</p> <p><u>Symptoms:</u> very rapidly progressive ascending demyelinating polyneuropathy, may mimic Guillain-Barré syndrome; some patients may develop respiratory paralysis requiring mechanical ventilation; resulted in deaths in some patients</p> <p><u>Laboratory findings may include:</u></p> <ul style="list-style-type: none"> •Low arterial pH •Increased lactate •Low serum bicarbonate •Increased anion gap •Markedly increased creatine phosphokinase 	Rare	<ul style="list-style-type: none"> •Prolonged d4T use (found in 61 of 69 [88%] cases in one report) 	<ul style="list-style-type: none"> •Early recognition and discontinuation of ARVs may avoid further progression 	<ul style="list-style-type: none"> •Discontinuation of ARVs •Supportive care, including mechanical ventilation if needed (as in cases of lactic acidosis listed previously) •Other measures attempted with variable success: plasmapheresis, high-dose corticosteroid, intravenous immunoglobulin, carnitine, acetylcarnitine <p>•Recovery often takes months – ranging from complete recovery to substantial residual deficits</p> <p>•Symptoms may be irreversible in some patients</p> <p>Do not rechallenge patient with offending agent</p>
Stevens-Johnson syndrome (SJS)/ Toxic epidermal necrosis (TEN)	NVP > EFV, DLV, ETV Also reported with: APV, FPV, ABC, DRV, ZDV, ddI, IDV, LPV/r, ATV	<p><u>Onset:</u> first few days to weeks after initiation of therapy</p> <p><u>Symptoms:</u> <i>Cutaneous involvement:</i></p> <ul style="list-style-type: none"> •Skin eruption with mucosal ulcerations (may involve orolingival mucosa, conjunctiva, anogenital area) •Can rapidly evolve with blister or bullae formation •May eventually evolve to epidermal detachment and/or necrosis <p>•For NVP, may occur with hepatic toxicity</p> <p><i>Systemic Symptoms:</i> fever, tachycardia, malaise, myalgia, arthralgia</p> <p><i>Complications:</i> ↓ oral intake → fluid depletion; bacterial or fungal superinfection; multiorgan failure</p>	NVP: 0.3%–1% DLV & EFV: 0.1%, ETV <0.1% 1–2 case reports for ABC, FPV, ddI, ZDV, IDV, LPV/r, ATV, DRV	<ul style="list-style-type: none"> •NVP: Female, Black, Asian, Hispanic 	<ul style="list-style-type: none"> •For NVP: 2-week lead in period with 200mg once daily, then escalate to 200mg twice daily •Educate patients to report symptoms as soon as they appear •Avoid use of corticosteroid during NVP dose escalation – may increase incidence of rash 	<ul style="list-style-type: none"> •Discontinue all ARVs and any other possible agent(s) (e.g., cotrimoxazole) Aggressive symptomatic support may include: •Intensive care support •Aggressive local wound care (e.g., in a burn unit) •Intravenous hydration •Parenteral nutrition, if necessary •Pain management •Antipyretics •Empiric broad-spectrum antimicrobial therapy if superinfection is suspected <p><u>Controversial management strategies:</u></p> <ul style="list-style-type: none"> •Corticosteroid •Intravenous immunoglobulin <p>Do not rechallenge patient with offending agent</p> <ul style="list-style-type: none"> • It is unknown whether patients who experienced SJS while on one NNRTI are more susceptible to SJS from another NNRTI – most experts would suggest avoiding use of this class unless no other options are available

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18a. Potentially Life-Threatening and Serious Adverse Events (continued)

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POTENTIALLY SERIOUS ADVERSE EFFECTS (in alphabetical order)						
Bleeding events	TPV/r: reports of intracranial hemorrhage (ICH) PIs: ↑ bleeding in hemophiliac patients	<u>Median time to ICH event:</u> 525 days on TPV/r therapy <u>Hemophiliac patients:</u> ↑ spontaneous bleeding tendency – in joints, muscles, soft tissues, and hematuria	In 2006, 13 cases of ICH reported, w/ TPV/r use, including 8 fatalities <u>For hemophilia:</u> frequency unknown	<u>For ICH:</u> •Patients with CNS lesions, head trauma, recent neurosurgery, coagulopathy, hypertension, alcohol abuse, or receiving anticoagulant or anti-platelet agents <u>For hemophiliac patients:</u> •PI use	<u>For ICH:</u> •Avoid use of TPV/r in patients at risk for ICH <u>For hemophiliac patients:</u> •Consider using NNRTI-based regimen •Monitor for spontaneous bleeding	<u>For ICH:</u> •Discontinue TPV/r – manage ICH with supportive care <u>For hemophiliac patients:</u> •May require increased use of Factor VIII products
Bone marrow suppression	ZDV	<u>Onset:</u> few weeks to months <u>Laboratory abnormalities:</u> •Anemia •Neutropenia <u>Symptoms:</u> fatigue because of anemia; potential for increase of bacterial infections because of neutropenia	Severe Anemia (Hgb < 7 g/dL): 1.1%–4% Severe Neutropenia (ANC <500 cells/mm ³): 1.8%–8%	•Advanced HIV •High dose •Pre-existing anemia or neutropenia •Concomitant use of bone marrow suppressants (such as cotrimoxazole, ribavirin, ganciclovir, etc.)	•Avoid use in patients at risk •Avoid other bone marrow suppressants if possible •Monitor CBC with differential at least every three months (more frequently in patients at risk)	•Switch to another NRTI if there is an alternative option; •Discontinue concomitant bone marrow suppressant if there is an alternative option; otherwise: <u>For neutropenia:</u> •Identify and treat other causes •Consider treatment with filgrastim <u>For anemia:</u> •Identify and treat other causes of anemia (if present) •Blood transfusion if indicated •Consider erythropoietin therapy
Hepatotoxicity (clinical hepatitis or asymptomatic serum transaminase elevation)	All NNRTIs; All PIs; Most NRTIs; Maraviroc	<u>Onset:</u> NNRTI: for NVP – 2/3 within 1 st 12 weeks NRTI: over months to years PI: generally after weeks to months <u>Symptoms/Findings:</u> NNRTI: •Asymptomatic to non-specific symptoms such as anorexia, weight loss, or fatigue. Approximately ½ of patients with NVP-associated symptomatic hepatic events present with skin rash. NRTI: •ZDV, ddI, d4T: may cause hepatotoxicity associated with lactic acidosis with microvesicular or macrovesicular hepatic steatosis because of mitochondrial toxicity •3TC, FTC, or TDF: HBV-coinfected patients may develop severe hepatic flare when these drugs are withdrawn or when resistance develops. PI: •Clinical hepatitis & hepatic decompensation have been reported with TPV/RTV, but also other PIs to varying degrees. Underlying liver disease increases risk. •Generally asymptomatic, some with anorexia, weight loss, jaundice, etc.	Varies with the different agents	•Hepatitis B or C coinfection •Alcoholism •Concomitant hepatotoxic drugs •Elevated ALT &/or AST at baseline •For NVP-associated hepatic events – female w/ pre-NVP CD ₄ >250cells/mm ³ or male w/ pre-NVP CD ₄ >400cells/mm ³	•NVP: monitor liver-associated enzymes at baseline, 2 & 4 weeks, then monthly for 1 st 3 months; then every 3 months •TPV/RTV: contraindicated in patients with moderate to severe hepatic insufficiency; for other patients follow “frequently” during treatment •Other agents: monitor liver-associated enzymes at least every 3–4 months or more frequently in patients at risk	•Rule out other causes of hepatotoxicity – alcoholism, viral hepatitis, chronic HBV w/ 3TC, FTC, or TDF withdrawal, or HBV resistance, etc. <u>For symptomatic patients:</u> •Discontinue all ARVs (with caution in patients with chronic HBV infection treated w/ 3TC, FTC, and/or TDF) and other potential hepatotoxic agents •After symptoms subside & serum transaminases returned to normal, construct a new ARV regimen without the potential offending agent(s) <u>For asymptomatic patients:</u> •If ALT >5–10x ULN, some may consider discontinuing ARVs, others may continue therapy with close monitoring •After serum transaminases return to normal, construct a new ARV regimen without the potential offending agent(s) Note: Please refer to information regarding NVP-associated symptomatic hepatic events & NRTI-associated lactic acidosis with hepatic steatosis in this table

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POTENTIALLY SERIOUS ADVERSE EFFECTS (in alphabetical order)						
Nephrolithiasis/ urolithiasis/ crystalluria	IDV: most frequent; Reports with atazanavir	<u>Onset:</u> any time after beginning of therapy – especially at times of reduced fluid intake <u>Laboratory abnormalities:</u> pyuria, hematuria, crystalluria; rarely – rise in serum creatinine & acute renal failure <u>Symptoms:</u> flank pain and/or abdominal pain (can be severe), dysuria, frequency	12.4% of nephrolithiasis reported in clinical trials (4.7%–34.4% in different trials)	<ul style="list-style-type: none"> •History of nephrolithiasis •Patients unable to maintain adequate fluid intake •High peak IDV concentration •↑ duration of exposure 	<ul style="list-style-type: none"> •Drink at least 1.5–2 liters of non-caffeinated fluid (preferably water) per day •Increase fluid intake at first sign of darkened urine •Monitor urinalysis and serum creatinine every 3–6 months 	<ul style="list-style-type: none"> •Increase hydration •Pain control •May consider switching to alternative agent or therapeutic drug monitoring if treatment option is limited •Stent placement may be required
Nephrotoxicity	IDV, TDF	<u>Onset:</u> IDV: months after therapy TDF: weeks to months after therapy <u>Laboratory and other findings:</u> IDV: ↑ serum creatinine, pyuria; hydronephrosis or renal atrophy TDF: ↑ serum creatinine, proteinuria, hypophosphatemia, glycosuria, hypokalemia, non-anion gap metabolic acidosis <u>Symptoms:</u> IDV: asymptomatic; rarely develop to end stage renal disease TDF: asymptomatic to signs of nephrogenic diabetes insipidus, Fanconi syndrome	Severe toxicity is rare	<ul style="list-style-type: none"> •History of renal disease •Concomitant use of nephrotoxic drugs 	<ul style="list-style-type: none"> •Avoid use of other nephrotoxic drugs •Adequate hydration if on IDV therapy •Monitor serum creatinine, urinalysis, serum potassium and phosphorus in patients at risk 	<ul style="list-style-type: none"> •Stop offending agent, generally reversible •Supportive care •Electrolyte replacement as indicated
Pancreatitis	ddI alone; ddI + d4T; ddI + hydroxyurea (HU), ribavirin (RBV), or TDF	<u>Onset:</u> usually weeks to months <u>Laboratory abnormalities:</u> increased serum amylase and lipase <u>Symptoms:</u> postprandial abdominal pain, nausea, vomiting	ddI alone: 1%–7% ddI with HU: ↑ by 4–5 fold ddI with RBV, d4T, or TDF: ↑ frequency	<ul style="list-style-type: none"> •High intracellular and/or serum ddI concentrations •History of pancreatitis •Alcoholism •Hypertriglyceridemia •Concomitant use of ddI with d4T, HU, or RBV •Use of ddI + TDF without ddI dose reduction 	<ul style="list-style-type: none"> •ddI should not be used in patients with history of pancreatitis •Avoid concomitant use of ddI with d4T, TDF, HU, or RBV •Reduce ddI dose when used with TDF •Monitoring of amylase/lipase in asymptomatic patients is generally not recommended 	<ul style="list-style-type: none"> •Discontinue offending agent(s) •Symptomatic management of pancreatitis: bowel rest, IV hydration, pain control, then gradual resumption of oral intake •Parenteral nutrition may be necessary in patients with recurrent symptoms upon resumption of oral intake