

Please refer to the **Adverse Effects of Antiretroviral Agents** section of the Adult Guidelines for more detailed discussions.

Table 13. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations

Adverse Effects	Associated ARVs	Onset/Clinical Manifestation	Estimated Frequency	Risk Factors	Prevention/Monitoring	Management
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 [18] <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 including vitamin E <u>For hemophiliac patients:</u> • PI use	Avoid Vitamin E supplements, particularly with the oral solution formulation of tipranavir <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 (usually macrocytic) • neutropenia <u>Symptoms:</u> fatigue because of anemia; potential for increased 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 (e.g., cotrimoxazole, ganciclovir, valganciclovir, etc.) or drugs that cause hemolytic anemia (e.g., ribavirin)	• Avoid use in patients at risk • Avoid other bone marrow suppressants if possible • Monitor CBC with differential after the 1 st few weeks, then at least every 3 months (more frequently in patients at risk)	• Switch to another NNRTI 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
Cardiovascular effects [including myocardial infarction (MI)] and cerebrovascular accidents (CVA)	<u>MI & CVA:</u> associated with PI use <u>MI only:</u> Observational cohort found possible association of recent ABC & ddI use, and MI in pts with high risk for cardiovascular events [19]	<u>Onset:</u> months to years after beginning of therapy <u>Presentation:</u> premature coronary artery disease or CVA	3–6 per 1,000 patient-years CVA: ~ 1 per 1,000 patient-years	Other risk factors for cardiovascular disease, such as smoking, age, hyperlipidemia, hypertension, diabetes mellitus, family history of premature coronary artery disease, and personal history of coronary artery disease	• Assess cardiac disease risk factors • Monitor & identify patients with hyperlipidemia or hyperglycemia • Consider regimen with less adverse lipid effects • Life style modification: smoking cessation, diet, and exercise	• Early diagnosis, prevention, and pharmacologic management of other cardiovascular risk factors, such as hyperlipidemia, hypertension, and insulin resistance/diabetes mellitus • Lifestyle modifications: diet, exercise, and/or smoking cessation • Switch to agents with less propensity for increasing cardiovascular risk factors
Central nervous system effects	EFV	<u>Onset:</u> begin with first few doses <u>Symptoms:</u> may include one or more of the following: drowsiness, somnolence, insomnia, abnormal dreams, dizziness, impaired concentration & attention span, depression, hallucination, exacerbation of psychiatric disorders, psychosis, suicidal ideation Most symptoms subside or diminish after 2–4 weeks	>50% of patients may have some symptoms	• Pre-existing or unstable psychiatric illnesses • Use of concomitant drugs with CNS effects • Higher plasma EFV concentrations in people with G-->T polymorphism at position 516 (516G-->T) of CYP2B6 [20]	• Take at bedtime or 2–3 hours before bedtime • Take on an empty stomach to reduce drug concentration & CNS effects • Warn patients regarding restriction of risky activities, such as operating heavy machinery during the 1 st 2–4 weeks of therapy	• Symptoms usually diminish or disappear within 2–4 weeks • Consider switching to alternative agent if symptoms persist and cause significant impairment in daily function or exacerbation of psychiatric illness

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Gastrointestinal (GI) intolerance	All PIs, ZDV, ddI	<p><u>Onset:</u> within first doses</p> <p><u>Symptoms:</u></p> <ul style="list-style-type: none"> • nausea, vomiting, abdominal pain with all listed agents • Diarrhea, most commonly seen with NFV 	Varies with different agents	<ul style="list-style-type: none"> • All patients 	<ul style="list-style-type: none"> • Taking with food may reduce symptoms (not recommended for ddI or unboosted IDV) • Some patients may require antiemetics or antidiarrheals pre-emptively to reduce symptoms 	<p>May spontaneously resolve or become tolerable with time; if not: <u>For nausea & vomiting, consider:</u></p> <ul style="list-style-type: none"> • Antiemetic prior to dosing • Switch to less emetogenic ARV <p><u>For diarrhea, consider:</u></p> <ul style="list-style-type: none"> • Bulk-forming agents, such as psyllium products • Antimotility agents, such as loperamide, diphenoxylate/atropine • Calcium tablets • Pancreatic enzymes • L-glutamate: may ↓ diarrhea, esp. when assoc. w/ NFV or LPV/r <p><u>In case of severe GI loss:</u></p> <ul style="list-style-type: none"> • Rehydration & electrolyte replacement as indicated
Hepatic failure	NVP	<p><u>Onset:</u> Greatest risk within first 6 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 particularly in those with rash</p> <p>Approximately 1/2 of the cases have accompanying skin rash, some of which 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-naive patients with higher CD4 count at initiation (>250 cells/mm³ in women & >400 cells/mm³ in men) • Females 3-fold higher risk than males • HIV (-) individuals when NVP is used for post-exposure prophylaxis • Possibly, high NVP concentrations 	<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 • Do not use NVP in HIV(-) individuals for post-exposure prophylaxis • 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 ARVs, including NVP (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 (e.g., EFV, ETR, or DLV) in patients who experienced significant hepatic event from NVP is unknown; use with caution.</p>
Hepatotoxicity (clinical hepatitis or asymptomatic serum transaminase elevation)	All NNRTIs; all PIs; most NRTIs; maraviroc	<p><u>Onset:</u> NNRTIs: for NVP, 2/3 within 1st 12 weeks NRTIs: over months to years PIs: generally after weeks to months</p> <p><u>Symptoms/findings:</u> NNRTIs:</p> <ul style="list-style-type: none"> • Asymptomatic to non-specific symptoms, such as anorexia, weight loss, or fatigue. Approximately 1/2 of patients with NVP-associated symptomatic hepatic events present with skin rash. <p>NRTIs:</p> <ul style="list-style-type: none"> • ZDV, ddI, d4T: may cause hepatotoxicity associated with lactic acidosis with microvesicular or macrovesicular hepatic steatosis because of mitochondrial toxicity 	Varies with the different agents	<ul style="list-style-type: none"> • HBV or HCV coinfection • Alcoholism • Concomitant hepatotoxic drugs, particularly rifampin • Elevated ALT &/or AST at baseline • For NVP-associated hepatic events: female w/ pre-NVP CD4 >250 cells/mm³ or male w/ pre-NVP CD4 >400 cells/mm³ • Higher drug concentrations for PIs, particularly TPV 	<ul style="list-style-type: none"> • NVP: monitor liver-associated enzymes at baseline, at 2 & 4 weeks, then monthly for 1st 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 	<ul style="list-style-type: none"> • Rule out other causes of hepatotoxicity, such as alcoholism, viral hepatitis, chronic HBV w/ 3TC, FTC, or TDF withdrawal, HBV resistance, etc. <p><u>For symptomatic patients:</u></p> <ul style="list-style-type: none"> • Discontinue all ARVs and other potential hepatotoxic agents • After symptoms subside & serum transaminases return to normal, construct a new ARV regimen without the potential offending agent(s) <p><u>For asymptomatic patients:</u></p> <ul style="list-style-type: none"> • If ALT >5–10x ULN, some may consider discontinuing ARVs, others may continue therapy with close monitoring unless direct bilirubin iw also elevated • After serum transaminases return to

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		<ul style="list-style-type: none"> •3TC, FTC, or TDF: HBV-coinfected patients may develop severe hepatic flare when these drugs are withdrawn or when resistance develops. <p>PIs:</p> <ul style="list-style-type: none"> •Clinical hepatitis & hepatic decompensation have been reported with TPV/r and also with other PIs to varying degrees. Underlying liver disease increases risk. •Generally asymptomatic, some with anorexia, weight loss, jaundice, etc. 				<p>normal, construct a new ARV regimen without the potential offending agent(s)</p> <p>Note: Refer to information regarding NVP-associated symptomatic hepatic events & NRTI-associated lactic acidosis with hepatic steatosis in this table</p>
Hyperlipidemia	All PIs (except unboosted ATV); d4T; EFV; NVP (to a less extent)	<p><u>Onset:</u> weeks to months after beginning of therapy</p> <p><u>Presentation:</u> All PIs (except unboosted ATV): ↑ in LDL & total cholesterol (TC), & triglyceride (TG). Also, ↑ HDL seen w/ ATV, DRV, FPV, LPV, SQV when boosted w/ RTV</p> <p><u>LPV/r [21] & FPV/r [22]:</u> disproportionate ↑ in TG</p> <p><u>EFV & NVP (to a lesser extent):</u> ↑ in LDL & TC, and slight ↑ TG; also ↑ HDL</p> <p><u>d4T & ZDV:</u> ↑ in LDL, TC, & TG</p>	Varies with different agents <u>Swiss Cohort:</u> ↑TC & TG: 1.7–2.3x higher in patients receiving (non-ATV) PI	<ul style="list-style-type: none"> •Underlying hyperlipidemia •Risk based on ARV therapy <p><u>PI:</u> All RTV-boosted PI may ↑ LDL & TG; ATV/r may produce less of an ↑ in LDL & TG</p> <p><u>NNRTI:</u> EFV >NVP [23]</p> <p><u>NRTI:</u> d4T >ZDV >ABC >TDF [24, 25]</p>	<ul style="list-style-type: none"> •Assess cardiac disease risk factors •Use PIs and NNRTIs with less adverse effect on lipids and non-d4T-based regimen •Fasting lipid profile at baseline, at 3–6 months after starting new regimen, then annually or more frequently if indicated (in high-risk patients or in patients with abnormal baseline levels) 	<ul style="list-style-type: none"> •Lifestyle modification: diet, exercise, and/or smoking cessation •Switching to agents with less propensity for causing hyperlipidemia <p><u>Pharmacologic Management:</u></p> <ul style="list-style-type: none"> •Per HIVMA/ACTG guidelines [26] & National Cholesterol Education Program ATP III guidelines [27] •For potential interactions between ARV and lipid lowering agents, refer to Table 15
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>Usually >2–3 acute symptoms seen with HSR, in descending frequency:</u> high fever, diffuse skin rash, malaise, nausea, headache, myalgia, chills, diarrhea, vomiting, abdominal pain, dyspnea, arthralgia, respiratory symptoms (pharyngitis, dyspnea/tachypnea)</p> <p>With continuation of ABC, symptoms may worsen to include hypotension, respiratory distress, vascular collapse</p> <p><u>Rechallenge reactions:</u> 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-B*5701 screening [16]	<ul style="list-style-type: none"> •HLA-B*5701, HLA-DR7, HLA-DQ3 •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 •Note multiple names for products containing abacavir (ABC, ZIAGEN, EPZICOM or KIVEXA, TRIZIVIR) 	<ul style="list-style-type: none"> •Discontinue ABC and switch to another NRTI •Rule out other causes of symptoms (e.g., intercurrent illnesses such as viral syndromes, and other causes of skin rash) •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, even in patients who are (-) for HLA-B*5701. There are cases of hypersensitivity in HLA-B*5701 (-) patients.</p>
Insulin resistance/diabetes mellitus (DM)	Combination ART, thymidine analogs (ZDV, d4T), some PIs linked to insulin resistance and diabetes mellitus (but this may not be a class effect)	<p><u>Onset:</u> weeks to months after beginning of therapy</p> <p><u>Presentation:</u> Polyuria, polydipsia, polyphagia, fatigue, weakness; exacerbation of hyperglycemia in patients with underlying DM</p>	Up to 3%–5% of patients developed diabetes in some series; D:A:D cohort incidence rate of 5.72 per 1,000 pt-yr f/up (95% CI: 5.31–6.13) [28] Incidence of DM in HIV (+) women in WHIS (2.5–2.9 pt- yrs) not different	<ul style="list-style-type: none"> •Family history of DM 	<ul style="list-style-type: none"> •Use non–thymidine analog–containing regimens or NNRTIs •Fasting blood glucose 1–3 months after starting new regimen, then at least every 3–6 months 	<ul style="list-style-type: none"> •Diet and exercise •Consider switching to non–thymidine analog–containing ART •Consider switching PI to an alternative PI and/or NNRTI •Pharmacotherapeutic management per American Diabetic Association and American Association of Clinical Endocrinologists guidelines [30, 31]

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			from HIV(-) pts [29] and associated with NRTIs			
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 GI 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 (e.g., hepatic failure, acute pancreatitis, encephalopathy, and respiratory failure) <p><u>Laboratory findings:</u></p> <ul style="list-style-type: none"> Increased lactate (often >5 mmol/L) 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>Mortality up to 50% in some case series, esp. in patients with serum lactate >10 mmol/L</p>	<p>Rare</p> <p>Depends on regimen and patient sex:</p> <p><u>U.S.:</u> 0.85 cases per 1,000 pt-yrs [32]</p> <p><u>South Africa:</u> 16.1 per 1,000 pt-yrs in female & 1.2 cases per 1,000 pt-yrs in male patients⁷</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 	<ul style="list-style-type: none"> Routine monitoring of lactic acid 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"> For mild cases, consider switching off offending drugs to safe alternatives For severe lactic acidosis, 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, which 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 for mitochondrial toxicity (e.g., ABC, TDF, 3TC, FTC) Recommend close monitoring of serum lactate after restarting NRTIs Consider NRTI-sparing regimens
Lipodystrophy	<p><u>Lipoatrophy:</u> NRTIs (d4T > ZDV > TDF, ABC, 3TC, FTC), especially when combined with EFV [33]</p> <p><u>Lipohypertrophy:</u> Abdominal fat gain seen with PI- or NNRTI-based regimens & with thymidine analogs (e.g., d4T, ZDV)</p>	<p><u>Onset:</u> gradual: months after initiation of therapy</p> <p><u>Symptoms:</u></p> <ul style="list-style-type: none"> Lipoatrophy: peripheral fat loss manifested as facial thinning and as thinning of extremities and buttocks (d4T) Lipohypertrophy: increase in abdominal girth, breast size, and dorsocervical fat pad (buffalo hump) 	<p>High: exact frequency uncertain and dependent on regimen; increases with duration on offending agents</p>	<ul style="list-style-type: none"> Both lipoatrophy & lipohypertrophy: low baseline body mass index 	<ul style="list-style-type: none"> <u>Lipoatrophy:</u> avoid thymidine analogs (esp. when combined with EFV), or switch from ZDV or d4T to ABC or TDF <u>Lipohypertrophy:</u> pretreatment diet/exercise program may reduce incidence and extent 	<p><u>Lipoatrophy:</u></p> <ul style="list-style-type: none"> Switch from thymidine analogs to TDF or ABC: may slow or halt progression; however, may not fully reverse effects Injectable poly-L-lactic acid or other injectable fillers for treatment of facial lipoatrophy <p><u>Lipohypertrophy:</u></p> <ul style="list-style-type: none"> Liposuction for dorsocervical fat pad enlargement (recurrence common) Diet/exercise Recombinant human growth hormone, under investigation
Nephrolithiasis/urolithiasis/crystalluria	IDV, ATV	<p><u>Onset:</u> any time after beginning of therapy, especially at times of reduced fluid intake</p> <p><u>Laboratory abnormalities:</u> pyuria, hematuria, crystalluria; rarely, rise</p>	IDV: 12.4% of nephrolithiasis reported in clinical trials (4.7%–34.4%)	<ul style="list-style-type: none"> History of nephrolithiasis Patients unable to maintain adequate fluid intake 	<ul style="list-style-type: none"> Drink at least 1.5–2 liters of non-caffeinated fluid (preferably water) per day 	<ul style="list-style-type: none"> Increase hydration Pain control May consider switching to alternative agent or therapeutic drug monitoring (IDV) if treatment option is limited

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		in serum creatinine & acute renal failure <u>Symptoms:</u> flank pain and/or abdominal pain (can be severe), dysuria, frequency	in different trials) ATV: rare; case reports only	<ul style="list-style-type: none"> •High peak IDV concentration (↑ATV levels not found to correlate with risk) •↑duration of exposure •warmer climate 	<ul style="list-style-type: none"> •Increase fluid intake at first sign of darkened urine •Monitor urinalysis and serum creatinine every 3–6 months 	<ul style="list-style-type: none"> •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 progresses to end-stage renal disease TDF: asymptomatic to signs of nephrogenic diabetes insipidus, Fanconi syndrome with weakness and myalgias	Severe toxicity is rare	IDV and TDF: <ul style="list-style-type: none"> •History of renal disease; elevated creatinine at baseline •Concomitant use of nephrotoxic drugs •TDF: advanced age, low body weight, low CD4 count 	<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
Neuro-muscular weakness syndrome (ascending)	Most frequently implicated ARV: d4T	<u>Onset:</u> months after initiation of ARV; then dramatic motor weakness occurring within days to weeks <u>Symptoms:</u> very rapidly progressive ascending demyelinating polyneuropathy, may mimic Guillain-Barré syndrome; some patients may develop respiratory paralysis requiring mechanical ventilation; has resulted in deaths in some patients <u>Laboratory findings may include:</u> <ul style="list-style-type: none"> •lactic acidosis reported in some cases •Markedly increased creatine phosphokinase 	Rare	<ul style="list-style-type: none"> •Prolonged d4T use (found in 61 of 69 [88%] cases in one report) [34] 	<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 •Recovery often takes months and ranges from complete recovery to substantial residual deficits •Symptoms may be irreversible in some patients <p>Do not rechallenge patient with offending agent.</p>
Osteonecrosis	Link to older PIs, but unclear whether it is caused by ARVs or by HIV	<u>Clinical presentation (generally similar to non-HIV-infected population):</u> <ul style="list-style-type: none"> •Insidious in onset, with subtle symptoms of mild to moderate periarticular pain •85% of cases involving one or both femoral heads, but other bones may also be affected •Pain may be triggered by weight bearing or movement 	<u>Symptomatic osteonecrosis:</u> 0.08%–1.33% <u>Asymptomatic osteonecrosis:</u> 4% from MRI reports	<ul style="list-style-type: none"> •Diabetes •Advanced HIV disease •Prior steroid use •Old age •Alcohol use •Hyperlipidemia •Role of ARVs and osteonecrosis is still controversial 	<ul style="list-style-type: none"> •Risk reduction (e.g., limit steroid and alcohol use) •Asymptomatic cases w/ <15% bony head involvement: follow with MRI every 3–6 months x 1 yr, then every 6 months x 1 yr, then annually to assess for disease progression 	<u>Conservative management:</u> <ul style="list-style-type: none"> • ↓ weight bearing on affected joint; • Remove or reduce risk factors • Analgesics as needed <u>Surgical Intervention:</u> <ul style="list-style-type: none"> •Core decompression +/- bone grafting for early stages of disease •For more severe and debilitating disease. total joint arthroplasty
Osteopenia (defined as DEXA scan t-score of 1–2.5 SD from normal) or osteoporosis (t-score >2.5 SD from normal)	Some evidence for early but not progressive bone loss after starting variety of ARVs; Assoc/ with TDF or d4T; ↓ bone density and	<u>Onset:</u> months to years after starting ART <u>Symptoms:</u> generally asymptomatic, bone pain, increased risk of fractures	Wide range depending on methodology & patient population; rate appears much higher than seen in the general population: osteopenia: 20%–54%	<u>General:</u> low body weight, female, white, southeast Asian, older age, alcohol use, smoking, caffeine, hypogonadism, hyperthyroidism, corticosteroids, vitamin D deficiency, history of significant weight loss, TDF	<ul style="list-style-type: none"> •Consider assessment of bone mineral density with DEXA scan (baseline and f/u if abnormal; proper interval in setting of HIV(+) not determined) [36] •Weight-bearing exercise •Calcium & vitamin D 	<ul style="list-style-type: none"> •Switch from potentially contributing ARVs (i.e., d4T or TDF) & stop other contributing drugs • Follow National Osteoporosis Foundation guidelines [37] • Increase exercise, improve diet, decrease alcohol & tobacco use, increase calcium & vitamin D supplementation • Bisphosphonate (e.g., once weekly

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	markers of bone turnover with TDF observed in randomized clinical trials		[35]; osteoporosis: 2%–27% [35]	exposure HIV: low CD4 T-cell count, duration of HIV, lipoatrophy, increased lactic acid levels	supplementation •Hormone replacement	alendronate) • Judicious hormone replacement • Intranasal calcitonin
Pancreatitis	ddI alone; ddi + d4T, 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 ↑ frequency if ddi use w/ d4T, TDF, or ribavirin	•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	•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 •Treat hypertriglyceridemia	•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
Peripheral neuropathy	ddI, d4T, ddC	<u>Onset:</u> weeks to months after initiation of therapy (may be sooner in patients with pre-existing neuropathy) <u>Symptoms:</u> •Begins with numbness & paresthesia of toes and feet •May progress to painful neuropathy of feet and calf •Upper extremities less frequently involved •Can be debilitating for some patients •May be irreversible despite discontinuation of offending agent(s)	ddI: 12%–34% in clinical trials d4T: 52% in monotherapy trial ddC: 22%–35% in clinical trials Incidence increases with prolonged exposure	•Pre-existing peripheral neuropathy; •Combined use of these NRTIs or concomitant use of other drugs that may cause neuropathy •Advanced HIV disease •High dose or concomitant use of drugs that may increase ddi intracellular activities (e.g., HU or RBV)	•Avoid using these agents in patients at risk, if possible •Avoid combined use of these agents •Patient query at each encounter	•Discontinue offending agent if alternative is available; may halt further progression, but symptoms may be irreversible •Substitute alternative ART without potential for neuropathy <u>Pharmacologic management (with variable successes):</u> •Gabapentin (most experience), tricyclic antidepressants, lamotrigine, oxycarbamazepine (potential for CYP interactions), topiramate, tramadol •Narcotic analgesics •Topical capsaicin •Topical lidocaine
Stevens-Johnson syndrome (SJS)/ Toxic epidermal necrosis (TEN)	NVP > EFV, DLV, ETR Also reported with APV, FPV, ABC, DRV, ZDV, ddi, IDV, LPV/r, ATV	<u>Onset:</u> first few days to weeks after initiation of therapy but can occur later <u>Symptoms:</u> •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 •For NVP, may occur with hepatic toxicity •Systemic symptoms (e.g., fever, tachycardia, malaise, myalgia, arthralgia) may be present <u>Complications:</u> ↓ oral intake; fluid depletion; bacterial or fungal superinfection; multiorgan failure	NVP: 0.3%–1%; DLV & EFV: 0.1%; ETR: <0.1% 1–2 case reports for ABC, FPV, ddi, ZDV, IDV, LPV/r, ATV, DRV	•NVP: Female, Black, Asian, Hispanic	•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	•Discontinue all ARVs and any other possible agent(s) (e.g., cotrimoxazole) <u>Aggressive symptomatic support may include:</u> •Intensive care support •Aggressive local wound care (e.g., in a burn unit) •Intravenous hydration •Parenteral nutrition, if needed •Pain management •Antipyretics •Empiric broad-spectrum antimicrobial therapy if superinfection is suspected <u>Controversial management strategies:</u> •Corticosteroid •Intravenous immunoglobulin Do not rechallenge patient with offending agent. • 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.