Adverse Effects of Antiretroviral Medications

Introduction

Background

Antiretroviral therapy has transformed HIV infection into a manageable chronic disease, but antiretroviral medications have the potential to cause short-term and long-term adverse effects. Medication-related adverse effects may manifest in overt symptoms or initially only as laboratory abnormalities.\(^1\) The spectrum of potential antiretroviral drug toxicity is broad, including renal toxicity, mitochondrial and metabolic effects, gastrointestinal symptoms, cardiovascular effects, hypersensitivity, skin reactions, insomnia or other neuropsychiatric manifestations, and many other complications. Furthermore, as life expectancy for individuals with HIV has increased, the long-term safety of antiretroviral therapy has garnered increasing attention. In general, newer antiretroviral medications have improved safety profiles compared with older antiretroviral medications, and this is reflected in the recommendations issued in the Adult and Adolescent ARV Guidelines.\(^2\) Clinicians who provide care to persons living with HIV should have an understanding of the basic toxicity profile of antiretroviral medications, keeping in mind that the potential adverse effects of most antiretroviral medications are less toxic than the effects of untreated HIV. This Topic Review will explore antiretroviral-associated adverse effects by drug class and by specific drug. Issues related to drug interactions with antiretroviral medications are addressed in the Topic Review Drug Interactions with Antiretroviral Therapy.

Safety Laboratory Monitoring in Persons Taking Antiretroviral Therapy

All persons with HIV who initiate antiretroviral therapy should have laboratory studies performed at the initial visit, before initiating or changing a regimen, and as regular monitoring for long-term safety once a regimen is initiated. If abacavir or any abacavir fixed-dose combination is used in the regimen, baseline HLA-B*5701 testing should be performed. The following summarizes key baseline and safety laboratory studies recommended for individuals taking antiretroviral therapy (Table 1).\(^3\)
Nucleoside Reverse Transcriptase Inhibitors

The nucleoside reverse transcriptase inhibitors (NRTIs) have several notable class-wide mitochondrial and metabolic effects, though these adverse effects rarely occur with the newer NRTI agents. Any potential impact of the NRTIs on human mitochondria is important, since mitochondria play an essential role in producing energy for the cell in the form of adenosine triphosphate (Figure 1).[4,5] Mitochondrial toxicity caused by NRTIs induces a wide range of adverse effects, such as lactic acidosis, hepatic steatosis, myopathy, cardiomyopathy, peripheral neuropathy, pancreatitis, and possibly lipodystrophy syndrome.[6,7] Chronic use of older NRTIs, such as didanosine, stavudine, and zidovudine, can inhibit gamma-DNA polymerase-gamma, the key enzyme responsible for mitochondrial DNA replication; this inhibition can decrease cellular oxidative phosphorylation, increase intracellular lipids, and cause accumulation of lactic acid (Figure 2).[1,6,8] The development of peripheral neuropathy and lipatrophy generally only occurs with long-term use of these older NRTIs; these complications only partially reverse, or do not reverse at all, with discontinuation of the offending medication.[6] Such adverse effects are extremely rare with modern NRTIs, such as tenofovir alafenamide, tenofovir DF, abacavir, lamivudine, and emtricitabine.

Hyperlactatemia and Lactic Acidosis

Elevated serum lactate level (hyperlactatemia) is a known complication of older NRTIs (which are now rarely used in the United States). This adverse effect is characterized by a venous lactate level greater than 2 mmol/L (18 mg/dL) and a normal arterial pH.[9,10] Lactic acidosis is a severe form of hyperlactatemia in which patients usually have a serum lactate level greater than 4 mmol/L and evidence of acidosis (pH less than 7.35 or a bicarbonate level less than 20 mmol/L).[10] In some circumstances, coexisting disorders, such as respiratory alkalosis and/or metabolic alkalosis, can alter the serum pH and lactic acidosis can be associated with normal or even elevated serum pH levels. Based on multiple reports of fatal outcomes, NRTI-related lactic acidosis is considered a life-threatening condition.[11] Of the NRTIs, stavudine, didanosine, and the combination of stavudine and zidovudine carry the highest risk of hyperlactatemia and lactic acidosis.[11] The NRTIs abacavir, lamivudine, emtricitabine, tenofovir DF, tenofovir alafenamide, and zidovudine have minimal risk of causing hyperlactatemia and lactic acidosis. Lactic acidosis caused by NRTIs rarely occurs now in the United States.[10] The symptoms of hyperlactatemia can begin months or even years after starting antiretroviral therapy and may include nausea, vomiting, abdominal pain, lethargy, tachycardia, and tachypnea.

Peripheral Neuropathy

Stavudine and didanosine are the most likely of the NRTIs to cause peripheral neuropathy, especially when used in combination; other NRTIs rarely cause peripheral neuropathy. The time frame for developing peripheral neuropathy is controversial, with some studies indicating that risk is highest within the first 90 days of starting NRTI therapy and others suggesting NRTI-induced neurotoxicity results from cumulative exposure.[12,13] The risk of developing peripheral neuropathy is higher among older individuals and those with CD4 counts below 150 cells/mm³.

Hyperlipidemia

The effect of NRTIs on metabolic parameters, in particular lipid levels, are heterogeneous and study findings have been conflicting. Didanosine, stavudine, and zidovudine typically produce unfavorable changes in lipid levels, whereas tenofovir DF usually produces favorable lipid effects; abacavir, emtricitabine, lamivudine, and tenofovir alafenamide have relatively neutral effects on lipids.[14,15] The mechanism for adverse lipid effects associated with didanosine, stavudine, and zidovudine has not been well defined, but switching from zidovudine or stavudine to a more lipid-friendly NRTI can improve lipid profiles.[16,17] Switching from tenofovir DF to tenofovir alafenamide, which is often done in clinical practice nowadays, may lead to a mild rise in all serum lipid parameters, but the clinical implications of this rise is unclear and generally it is not considered a contraindication to
Lipoatrophy

Use of the thymidine analogs ( stavudine and zidovudine) has been associated with the development of lipoatrophy, which is characterized by generalized loss of subcutaneous fat, most prominently in the face, buttocks, legs, and arms. \[18, 19, 20, 21\] Long-term use of thymidine analogs potentially cause mitochondrial dysfunction in adipocytes, which may result in adipocyte apoptosis. \[18\] Lipoatrophy is distinct from AIDS-related wasting syndrome, since the latter involves the loss of muscle in addition to fat tissue. \[1\] Additional risk factors for lipoatrophy syndromes include older age, male sex, lower body mass index, and advanced immunosuppression. \[1, 18, 19\] In 2002, James and coworkers published a facial lipoatrophy severity scale that included a range of severity from 1 to 4 (Figure 3). \[22\] The most important management strategy for patients with lipoatrophy is to discontinue thymidine analog medications (generally by updating them to a newer antiretroviral option). \[23, 24, 25\] Multiple studies have investigated the use of injectable facial filler agents for esthetic treatment of the facial volume loss caused by lipoatrophy; these filler agents included poly-L-lactic acid, calcium hydroxyapatite, hyaluronic acid, polyacrylamide gel, polyalkylimide gel, polymethylmethacrylate, silicone oil, and autologous fat transfer. \[26\] A systematic review performed in 2015 concluded that poly-L-lactic acid was the only facial filler to receive a grade B recommendation. \[26\] The administration of facial fillers should be performed by an expert who has experience and training with this procedure.

Abacavir

Abacavir is an NRTI that is also available in the fixed-dose combination drugs abacavir-lamivudine, abacavir-lamivudine-zidovudine, and dolutegravir-abacavir-lamivudine. Abacavir in any form should only be used in persons who are HLA-B*5701 negative. \[2\]

- **Hypersensitivity Reaction:** The abacavir hypersensitivity reaction is a potentially life-threatening reaction to abacavir that occurs in up to 5% of patients (who do not undergo HLA-B*5701 screening); this reaction is highly associated with positivity for the HLA-B*5701 allele, which stimulates a self-directed immune response (Table 2). \[27, 28\] Signs and symptoms of abacavir hypersensitivity typically develop within 6 weeks of starting abacavir (the median onset of symptoms is at 11 days), and may include fever, rash, malaise, gastrointestinal effects, and respiratory symptoms. \[28, 29\] The reaction occurs more frequently in Caucasians than African Americans, due to a higher HLA-B*5701 allele frequency in Caucasians. The HLA-B*5701 test is highly useful for identifying persons who have a significantly increased risk of developing the abacavir hypersensitivity. Screening for HLA-B*5701 is required before prescribing abacavir, and any patient with a positive HLA-B*5701 screening test should not receive abacavir. \[2, 3\]

- **Cardiovascular Risk:** Abacavir has been associated with cardiovascular disease in some studies, but the data on this issue are conflicting. In the Strategies for the Management of Antiretroviral Therapy (SMART) trial, \[30\] a sub-analysis found that patients taking abacavir had a higher rate of cardiovascular disease than patients taking other NRTIs. \[31\] In addition, a Danish cohort study showed a 2-fold relative risk of hospitalization for myocardial infarction after initiation of abacavir compared with other NRTIs, \[32\] and a large cohort study of veterans with HIV infection found a significant association between abacavir use and cardiovascular disease. \[33\] The Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) cohort study also found an elevated risk of myocardial infarction in persons taking abacavir, with recent abacavir use conferring an increased risk of myocardial infarction (after controlling for traditional cardiovascular risk factors); the increased cardiovascular risk associated with abacavir use did not remain 6 months after discontinuation of abacavir. \[34, 35, 36\] In contrast with the D:A:D study, a meta-analysis that included data from more than 9,000 patients in randomized controlled trials concluded that abacavir does not
confer a higher risk of myocardial infarction or cardiovascular events relative to comparator abacavir-sparing regimens.\cite{37} In light of these conflicting findings, most experts recommend avoiding use of abacavir in patients with cardiovascular disease (or significant risk factors for cardiovascular disease) when other antiretroviral options are available.

**Didanosine**

Didanosine is rarely used now given the potential for multiple adverse effects and serious complications, including pancreatitis, lactic acidosis, and peripheral neuropathy.\cite{38,39} Several studies have identified enhanced risk of didanosine-associated pancreatitis when didanosine is used in combination with stavudine, with incidence rates as high as 60 per 1,000 person-years.\cite{38}

**Emtricitabine and Lamivudine**

Emtricitabine and lamivudine have the best tolerability and safety profile among all the NRTIs.\cite{40,41,42} In clinical trials, discoloration of the skin, nails, and tongue was the only side effect that was more common among people taking emtricitabine compared with other antiretroviral medications.\cite{43}

**Stavudine**

Stavudine is no longer recommended for use in the United States due to an array of adverse effects, including peripheral neuropathy, lactic acidosis, and facial and body lipoatrophy.\cite{20} In addition, cases of severe neuromuscular weakness have been described.\cite{44}

**Tenofovir alafenamide**

Tenofovir alafenamide is available as a component of multiple fixed-dose combination tablets. When compared with tenofovir DF, tenofovir alafenamide generates significantly lower serum tenofovir levels, which may offer a relatively better renal and bone safety profile (Figure 4).\cite{45,46,47,48,49} Switching from tenofovir DF to tenofovir alafenamide results in improved glomerular filtration rate, glomerular and tubular proteinuria, and bone mineral density.\cite{50,51} Overall, in clinical trials, tenofovir alafenamide was well tolerated, except for mild gastrointestinal effects (nausea, vomiting, diarrhea). Tenofovir alafenamide is more likely than tenofovir DF to increase certain lipid parameters (total cholesterol and HDL) but not others (total cholesterol/HDL ratio, triglycerides).\cite{49,52} Tenofovir alafenamide is not recommended in persons who have an estimated creatinine clearance less than 30 mL/min. Some clinical trial and retrospective data suggest that use of tenofovir alafenamide leads to more weight gain than use of tenofovir DF, but the mechanism and clinical significance are not known.\cite{53,54}

**Monitoring on Tenofovir alafenamide**

Patients receiving tenofovir alafenamide should be monitored for renal toxicity as follows:\cite{3}

- Serum creatinine should be obtained at baseline, 2-8 weeks after starting therapy, and every 3-6 months thereafter.
- Urinalysis (including urine glucose and protein) should be obtained at baseline and every 6 months.
- If a urinalysis is performed and shows proteinuria of 1+ or higher, then a quantitative follow-up test is indicated, either an albumin-to-creatinine ratio or a protein-to-creatinine ratio.
- Monitoring of serum phosphorus is indicated if the patient has chronic kidney disease.
- More frequent monitoring may be indicated in patients with risk factors for renal disease.
Tenofovir disoproxil fumarate (Tenofovir DF)

Tenofovir DF is available as a single drug and in multiple fixed-dose combinations. Several studies have shown that persons receiving tenofovir DF had improved lipid profiles when compared with persons receiving abacavir or tenofovir alafenamide. The main adverse effects associated with tenofovir DF are renal and bone toxicity.\(^{[49,57]}\)

- **Nephrotoxicity**: Tenofovir DF-associated renal toxicity includes gradual declines in glomerular filtration rate (GFR), phosphate wasting, and Fanconi syndrome (generalized proximal tubule dysfunction manifesting as type 2 renal tubular acidosis and phosphate wasting).\(^{[58]}\) Reports have also described a unique form of tenofovir-associated interstitial nephritis secondary to a diffuse infiltrative lymphocytosis syndrome.\(^{[59]}\) Tenofovir DF is not recommended for use in persons who have a creatinine clearance less than 60 mL/min. Individuals with tenofovir DF-associated nephrotoxicity may present with declining GFR or new proteinuria on routine screening.

- **Risk Factors for Nephrotoxicity**: Risk factors for tenofovir DF-associated nephrotoxicity include low CD4 cell count, hepatitis C coinfection, diabetes, black race, male gender, older age, and baseline hepatic or renal dysfunction.\(^{[60,61]}\) Some studies have shown that the risk of nephrotoxicity also increases when tenofovir DF is used with a ritonavir-boosted protease inhibitor or with unboosted atazanavir (when compared with tenofovir DF plus a non-nucleoside reverse transcriptase inhibitor); other studies, however, have shown that use of ritonavir-boosted protease inhibitors and unboosted atazanavir independently predicts chronic kidney disease to a similar degree as use of tenofovir DF.

- **Monitoring for Tenofovir DF-Associated Nephrotoxicity**: The 2014 HIVMA CKD Clinical Practice Guideline recommends routine monitoring of kidney function in order to allow timely identification of tenofovir DF-related nephrotoxicity.\(^{[58]}\) This guideline is the most thorough with respect to monitoring and evaluating renal dysfunction in persons with HIV infection. Additional available guidelines for monitoring patients for renal dysfunction include the 2013 HIVMA Primary Care Guidelines and the Adult and Adolescent ARV Guidelines.\(^{[3,62]}\) When clinically indicated, more frequent monitoring may be indicated. The following summarizes recommendations from these guidelines:
  
  - Monitoring serum creatinine and GFR should be performed at baseline, 2 to 8 weeks after starting therapy, and every 3 to 6 months thereafter.
  - Urinalysis (including urine glucose and protein) should be performed at baseline when starting tenofovir-DF and every 6 months thereafter.
  - If a urinalysis is performed and shows proteinuria of 1+ or higher, then a quantitative follow-up test is indicated, either an albumin-to-creatinine ratio or a protein-to-creatinine ratio.
  - More frequent monitoring may be indicated in patients with risk factors for renal disease.

**Evaluation of Suspected Tenofovir DF-Associated Nephrotoxicity**

For patients who develop renal dysfunction in the setting of tenofovir DF use, it can be challenging to determine whether tenofovir DF is the cause of the renal dysfunction. Measuring markers of proximal tubular dysfunction may be helpful in this scenario since these markers can distinguish proximal tubular disease (most likely, tenofovir-induced) from glomerular disease (Figure 5).\(^{[58]}\)

- **Markers for Tubular Dysfunction**: Two indicators have high specificity as markers for tubular dysfunction: (1) glycosuria with normal serum glucose, and (2) urinary phosphorus wasting with low serum phosphorus.

- **Fractional Excretion of Phosphate**: Phosphorus wasting can be determined by fractional excretion of phosphate. Normal fractional excretion of phosphate is generally defined as less than 10% and impaired fractional excretion of phosphate is defined as above 20%; thus, a fractional excretion of phosphate above 20% raises the likelihood of tenofovir DF-related
toxicity, whereas a result below 10% makes tenofovir DF toxicity unlikely. The fractional excretion of phosphate can be determined with a Fractional Excretion of Phosphate (FePO4) calculator and it requires a serum phosphate, urine phosphate, serum creatinine, and urine creatinine (see the FePO4 Calculator in the Tools and Calculators section of this website).

- **Proteinuria**: Although proteinuria is not specific for proximal tubular dysfunction it should also be included in the workup. New onset or worsening proteinuria may be evidence of tenofovir DF-induced proximal tubular wasting (if there is no alternate explanation and if other results suggest proximal tubulopathy) and should prompt additional evaluation for tenofovir DF renal toxicity. New or worsening proteinuria may indicate a need to discontinue tenofovir DF, particularly if associated with decline in renal function. Tests that quantify proteinuria are useful in this scenario and data also suggest that a urine albumin-to-protein ratio of less than 0.4 may be useful in distinguishing proteinuria due to proximal tubular dysfunction (secondary to tenofovir DF toxicity) from proteinuria due to glomerular disease.[58]

- **Discontinuing or Switching Tenofovir DF Because of Nephrotoxicity**: New or worsening proteinuria may indicate a need to change tenofovir DF, particularly if associated with a decline in renal function. Continuing tenofovir DF in the setting of ongoing renal dysfunction, particularly if the dose is not reduced when indicated, can result in severe renal failure. The 2014 HIVMA CKD Clinical Practice Guideline recommends discontinuing tenofovir DF in patients who have a significant reduction in GFR (greater than 25% decrease from baseline and to a level less than 60 mL/minute/1.73 m²), particularly when additional evaluation shows evidence of proximal tubular dysfunction (new onset or worsening of proteinuria, increased urinary phosphorous excretion and hypophosphatemia, euglycemic glycosuria, or increased urinary phosphorous excretion and hypophosphatemia).[58] In a study that enrolled adults with reduced renal function (estimated creatinine clearance of 30 to 69 mL/min) on a tenofovir DF-containing regimen, participants switched to elvitegravir-cobicistat-tenofovir alafenamide-emtricitabine had improvement in proteinuria and minimal change in GFR.

**Evaluation of Bone Demineralization:**

Initiation of antiretroviral therapy accelerates bone demineralization by as much as 6% in the first two years (independent of the specific antiretroviral regimen selected) although this process is not progressive, and bone mineral density stabilizes and may even improve over time.[18,63,64,65,66] Multiple studies have specifically implicated tenofovir DF use as a risk factor for reduced bone mineral density.[49,55] In AIDS Clinical Trials Group (ACTG) trial 5224s, investigators compared the long-term impact on bone mineral density of tenofovir DF-emtricitabine and abacavir-lamivudine and found that patients treated with tenofovir DF-emtricitabine had significantly greater decreases in bone mineral density at the spine and hip.[65] Although the mechanism is incompletely understood, tenofovir DF may affect bone indirectly through proximal tubular toxicity, leading to phosphate wasting and bone turnover.[66] There are no specific recommendations for bone mineral density screening for individuals taking tenofovir DF, but the HIVMA Primary Care Guidelines advise bone mineral density screening with DXA for all postmenopausal women with HIV infection and for men with HIV who are 50 years of age and older.[62]

**Zidovudine**

In the current antiretroviral era, zidovudine is rarely used, primarily because of poor tolerance and substantial risk of long-term adverse effects. An array of adverse effects have been associated with zidovudine use, including fatigue, headache, gastrointestinal upset, lipoatrophy, bone marrow suppression, and myopathy.

- **Bone Marrow Suppression**: Zidovudine is a well-established cause of reversible anemia and leucopenia. The anemia often occurs within the first 6 months after starting zidovudine and can be severe.[67] Significant decreases in hemoglobin are more likely to occur in
patients with advanced immunosuppression (low CD4 cell count), lower baseline hemoglobin levels, and those with coexisting medical conditions. Zidovudine predictably causes an increase in red blood cell mean corpuscular volume (MCV) values.[68] In contrast with its effects on other hematologic cell lines, zidovudine does not typically lower platelet count levels.

- **Myopathy**: Chronic zidovudine use has been associated with myopathy in up to 17% of patients and is marked by progressive generalized muscle pain, weakness, and fatigue; patients may have muscle atrophy and elevated creatine kinase levels. [69] There are several proposed mechanisms for zidovudine-induced myopathy, including zidovudine-induced oxidative stress and mitochondrial depletion of L-carnitine.[69] Virtually all patients experience resolution of myopathy once zidovudine therapy is stopped (assuming zidovudine was the cause of the myopathy).
Non-Nucleoside Reverse Transcriptase Inhibitors

There are six non-nucleoside reverse transcriptase inhibitors (NNRTIs) that have been FDA approved for use: delavirdine, doravirine, efavirenz, etravirine, nevirapine, and rilpivirine.[2] Note that delavirdine is no longer manufactured in the United States and will not be discussed further.

Doravirine

Doravirine is an NNRTI that has been very well tolerated in clinical trials and has been associated with very few adverse effects.[70,71] In clinical trials, doravirine had an improved safety profile compared with efavirenz, with respect to cutaneous and neuropsychiatric adverse effects.[72] Approximately 1% of individuals discontinued doravirine because of neuropsychiatric adverse effects. Compared with ritonavir-boosted darunavir or efavirenz, doravirine clearly had a favorable lipid profile.[72]

Efavirenz

Efavirenz is a highly potent NNRTI, but it is no longer recommended as a component of preferred antiretroviral regimens, primarily due to neuropsychiatric adverse effects. Efavirenz is predominantly eliminated by the cytochrome p450 enzyme CYP2B6 and persons with the CYP2B6*6 allele have reduced clearance of efavirenz and thus greater risk for efavirenz-related toxicity.

- Cardiac QTc Interval Prolongation: Prolonged QTc intervals have been reported with administration of efavirenz and one study has shown that persons homozygous for CYP2B6*6 have an increased risk for developing efavirenz-induced prolongation of QTc.[73,74] This issue is particularly important when patients are taking medications other than efavirenz that may cause QT prolongation; in that situation, consideration should be given to switching efavirenz to another antiretroviral medication.

- Dyslipidemia: Efavirenz has also been shown to increase lipid parameters, including total cholesterol, triglycerides, LDL, and HDL.[17,75] Studies have consistently demonstrated that efavirenz causes more unfavorable lipid changes than the other NNRTI medications.[17] It is unclear, though, what impact efavirenz-induced dyslipidemia has on cardiovascular disease risk, especially given that HDL levels and HDL particle size both increase with efavirenz and these HDL changes may potentially confer a protective effect.[76] One cohort study and a small nested case-control study using Québec’s public health insurance database showed an increased odds ratio of myocardial infarction associated with any exposure to efavirenz (compared to no exposure).[77] whereas the very large D:A:D cohort study with over 180,000 patient-years did not find an association between efavirenz and myocardial infarction.

- Hepatotoxicity: Reports have documented fulminant hepatitis in persons receiving efavirenz; in some cases the hepatitis has progressed to hepatic failure that required liver transplantation, or resulted in death.[78,79,80,81] Efavirenz is not recommended for use in patients with hepatic insufficiency (Child-Turcotte-Pugh class B or C).

- Neuropsychiatric: Efavirenz has significant potential neuropsychiatric side effects that limit its use. Both clinical experience and clinical trials have identified significant neuropsychiatric side effects that include nightmares, impaired concentration, hallucinations, irritability, depression, and acute psychosis.[82] Further, efavirenz may also worsen or unmask underlying or preexisting psychiatric conditions and has been associated with increased risk for suicidal ideation, attempted suicide, and suicide completion.[83] Accordingly, efavirenz should be avoided in persons with preexisting psychiatric conditions. Pharmacokinetic studies have shown that higher plasma efavirenz levels correlate with central nervous system adverse effects (Figure 6) and (Figure 7).[84] Individual patient variation in drug metabolism, as well as food-drug and drug-drug interactions, play a role in determining peak efavirenz levels. Taking efavirenz with food significantly increases efavirenz plasma levels compared
with taking it under fasting conditions. In general, it is recommended that patients take efavirenz on an empty stomach at bedtime to minimize adverse effects.

- **Rash**: Clinical trials have demonstrated that approximately 15% of patients (range 10 to 25%) treated with efavirenz develop a rash (Figure 8), which is significantly higher than reported rates of rash with doravirine, etravirine, or rilpivirine. \[72, 85, 86, 87, 88, 89\] The rash typically presents as a mild-to-moderate erythematous, maculopapular exanthem without systemic involvement, though severe reactions including Stevens-Johnson syndrome and toxic epidermal necrolysis have occurred.

- **Teratogenicity**: Efavirenz has an FDA pregnancy Class D rating. Primate studies have shown fetal malformations associated with maternal efavirenz exposure during the first trimester of pregnancy. There also have been a small number of human case reports of neural tube birth defects.\[90, 91\] Nevertheless, a systematic review and meta-analysis did not find an increased risk of birth defects among human infants exposed to efavirenz during the first trimester of pregnancy (the risk of neural tube defects is similar to incidence in the general population).\[92, 93\] The recommendations in the Perinatal Guidelines do no restrict the use of efavirenz in pregnancy, including during the first 8 weeks.\[94\] In addition, the Perinatal Guidelines now recommend that women who become pregnant while taking a regimen that contains efavirenz can continue on this regimen as long as their HIV RNA levels are suppressed.\[94\]

**Etravirine**

Etravirine is an NNRTI that is primarily used in treatment-experienced individuals who have resistance to another NNRTI. The most common side effect of etravirine is rash, which occurs in approximately 5 to 10% of persons (more commonly in women than men) and is typically mild-to-moderate in severity, with only about 2% of persons needing to discontinue etravirine because of rash.\[95\] Rare (less than 0.1%) of cases of severe rash, including Stevens-Johnson syndrome, toxic epidermal necrosis, erythema multiforme, and DRESS (drug rash with eosinophilia and systemic symptoms) syndrome, have been reported.

**Nevirapine**

Nevirapine confers a risk of serious adverse effects and it may be less potent than other available agents. Earlier in the HIV epidemic, nevirapine was commonly used in antiretroviral regimens, but its use has dramatically declined and it is no longer a recommended or alternative medication for initial therapy.

- **Hypersensitivity Reaction**: Nevirapine has an FDA black box warning for possible life-threatening rash and hepatotoxicity, which can occur together or separately. Initial trials found the incidence of rash to be 48%, with 10% of the cases being life-threatening (Figure 9).\[96\] Rash may be accompanied by fever, general malaise, fatigue, myalgias, arthralgias, blisters, oral lesions, conjunctivitis, facial edema, eosinophilia, granulocytopenia, lymphadenopathy, or renal dysfunction.\[97\] If hepatotoxicity develops, it usually occurs as either an immune-mediated reaction manifesting within the first 4 weeks of therapy, or a non-immune-mediated reaction that develops later (typically after 18 weeks of initiating therapy). The nevirapine-related hypersensitivity reaction occurs more commonly in women, especially during pregnancy. Other identified risk factors for nevirapine toxicity include underlying liver disease (especially chronic hepatitis B or C infection), low body mass index, female sex, and concurrent use of an HIV protease inhibitor.\[98, 99, 100\] In addition, these reactions are more likely to occur in patients with high CD4 cell counts: the risk ratio is 9.8 for women with CD4 counts greater than or equal to 250 cells/mm\(^3\) compared with women with CD4 counts below this threshold, and the risk ratio is 6.4 for men with CD4 counts greater than or equal to 400 cells/mm\(^3\) compared with men who have CD4 counts below 400 cells/mm\(^3\).\[101\] Expert guidelines, therefore, recommend against initiating nevirapine in women with a CD4 count greater than 250 cells/mm\(^3\) or in men with a CD4 count greater than 400 cells/mm\(^3\).\[97\]
Starting nevirapine at a lower dose, and increasing to full dose after two weeks, is a strategy that reduces the risk of rash and possibly hepatotoxicity.[97] Coadministration of corticosteroids is not recommended as they have not been found to prevent hypersensitivity reactions and may increase the risk of developing rash.[102,103] Nevirapine is not recommended for use in patients with hepatic insufficiency (Child-Turcotte-Pugh class B or C).

**Rilpivirine**

Three studies—ECHO, THRIVE, and STaR—compared rilpivirine with efavirenz (given with two background NRTIs) that showed lower rates of drug discontinuation due to adverse effects in patients taking rilpivirine than in those taking efavirenz.[83,89,104]

- **Cardiac QTc Interval Prolongation:** Studies performed with high-dose rilpivirine (3 to 12 times higher than recommended dose) in volunteers without HIV demonstrated QTc prolongation (10.7 msec increase with a 75 mg daily dose and 23.3 msec with a 300 mg once-daily dose); it is recommended to consider using an alternative to rilpivirine in a patient receiving another medication that has known risk for causing torsades de pointes.[87]
- **Elevated Serum Creatinine:** In several trials, rilpivirine caused mild elevations in serum creatinine related to inhibition of tubular secretion of creatinine, but this did not represent a true reduction in renal function, nor did it require discontinuation of rilpivirine.[104]
- **Neuropsychiatric:** Rilpivirine has potential to cause neuropsychiatric side effects, including depression, insomnia, headaches, and dizziness, but the risk is significantly lower than with efavirenz.[89,105]
Integrase Strand Transfer Inhibitors

In general, the integrase strand transfer inhibitors (INSTIs) are well tolerated and cause minimal drug interactions. In clinical trials, the most frequent reported adverse effects were headache, nausea, diarrhea, insomnia, and fatigue, but generally were not significant enough to warrant stopping therapy.[1] Several studies have concluded that INSTIs, particularly dolutegravir, lead to greater weight gain than other classes of antiretrovirals, but the mechanism and clinical significance are unclear.[106,107,108,109] Rare cases of mood changes or new onset of psychiatric disorders have been observed with INSTIs.[110,111]

Bictegravir

Bictegravir is an INSTI that is available only in the single-tablet regimens bictegravir-tenofovir alafenamide-emtricitabine. In clinical trials, the most common adverse effects associated with bictegravir-tenofovir alafenamide-emtricitabine were diarrhea, nausea, and headache.[112,113,114] There are no known serious adverse effects associated with bictegravir. It is unknown whether bictegravir is safe to use in pregnancy. Effects of bictegravir on weight gain have not been as thoroughly studied as those with dolutegravir and are a topic of ongoing investigation. Similar to dolutegravir, bictegravir can cause predictable modest increases in serum creatinine due to inhibition of tubular secretion of creatinine. The typical small increases (less than 0.3 mg/dL) in serum creatinine do not represent reduced true renal glomerular function. Available studies suggest the increases in serum creatinine associated with bictegravir are slightly less than with dolutegravir.[113,115]

Dolutegravir

Overall, dolutegravir is well tolerated and infrequently causes adverse effects. Dolutegravir is widely used in treatment-naïve and treatment-experienced patients.

- **Potential Neural Tube Defects:** On May 18, 2018, an FDA Safety Alert was posted that warned of potential serious neural tube birth defects in infants born to mothers who received dolutegravir at the time of becoming pregnant or early in the first trimester. On May 30, 2018, the HHS Antiretroviral Guideline Panels issued Recommendations Regarding Dolutegravir that address the use of dolutegravir in adults and adolescents with HIV who are pregnant or of child-bearing potential. Note that dolutegravir is also a component of two fixed-dose combinations: dolutegravir-abacavir-lamivudine and dolutegravir-rilpivirine.

- **Elevated Serum Creatinine:** Dolutegravir causes a predictable modest increase in serum creatinine and a decrease in estimated creatinine clearance due to inhibition of active tubular secretion of creatinine via blockade of the organic cation transporter 2 (OCT2) ([Figure 10]).[116] In the kidney, OCT2 is an uptake transporter located on the basolateral (blood) membrane of renal proximal tubular cells and it plays a role in transporting creatinine from the peritubular capillary blood cells into the renal tubular cells (tubular secretion of creatinine). Inhibition of OCT2 by dolutegravir causes more creatinine to remain in the bloodstream and an increase in serum creatinine. Iohexol clearance studies have shown that dolutegravir-related changes in serum creatinine do not reflect a reduction in true renal glomerular function.[58,117] The dolutegravir associated elevations in serum creatinine are typically in the range of 0.1 to 0.2 mg/dL (mean change 0.15 mg/dL), occur within 4 weeks after starting dolutegravir, and remain stable thereafter ([Figure 11]).[118,119] Continued increases in serum creatinine after 2 to 3 months or an increase significantly greater than 0.2 mg/dL should prompt evaluation for a source of elevated creatinine other than dolutegravir.

- **Insomnia:** In randomized trial settings, the incidence of insomnia in patients taking dolutegravir ranged from 3 to 15%.[119,120] Clinical experience has shown that some patients develop insomnia while taking dolutegravir, but this rarely requires discontinuation of dolutegravir.
- **Myopathy and Elevated Creatine Phosphokinase**: Rhabdomyolysis, myopathy, and myositis have been reported in very small numbers of clinical trial participants taking raltegravir.\[120,121\]

**Elvitegravir**

Elvitegravir is an INSTI that is no longer manufactured as a single medication, but it is available in the single-tablet regimens elvitegravir-cobicistat-tenofovir alafenamide-emtricitabine, and elvitegravir-cobicistat-tenofovir DF-emtricitabine. Elvitegravir causes few adverse effects. Elvitegravir itself causes few adverse effects, but the combination with cobicistat may lead to significant gastrointestinal symptoms.\[55,122\]

**Raltegravir**

Raltegravir is the INSTI with which clinicians have the most clinical experience and it has the fewest drug interactions among medications in the INSTI class. In general, it is a well-tolerated medication.

- **Elevated Creatine Kinase**: Raltegravir has been reported to cause elevated creatine kinase enzyme levels in some patients and in some cases has been associated with rhabdomyolysis and myositis.\[123,124\] Concurrent use of a statin medication, which can also cause elevations in creatine kinase elevation, likely increases this risk.\[124\] Other risk factors include comorbid liver or kidney disease.
- **Proximal Myopathy**: Raltegravir has been reported to cause myalgias and proximal myopathy in the setting of normal creatine kinase levels, but the mechanism is unclear and there is no evidence to suggest that raltegravir causes polymyositis or dermatomyositis.\[124\]
- **Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis**: Rash and severe systemic hypersensitivity reactions have been reported rarely in patients taking a regimen that included raltegravir.\[125,126,127\]
Protease Inhibitors

There are currently 10 FDA-approved HIV protease inhibitors (PIs), but in the Adult and Adolescent ARV Guidelines none are designated in the category of Recommended Initial Regimens for Most People with HIV.[2] The following discussion pertains to PIs used to treat HIV infection, not the PIs used to treat hepatitis C virus.

Gastrointestinal Adverse Effects

Gastrointestinal side effects (mainly diarrhea but also nausea, vomiting, and abdominal pain) were common with early PIs, particularly nelfinavir and PIs given with high doses of ritonavir for pharmacokinetic boosting; these adverse effects are less frequent and less severe with more recently developed PIs and when lower doses of ritonavir are used for boosting (100 mg/day versus 200 mg/day).[1] In several trials, boosted darunavir and boosted atazanavir demonstrated lower rates of gastrointestinal side effects compared with the combination of lopinavir-ritonavir.[128,129,130] Nevertheless, PIs overall are linked to higher rates of gastrointestinal side effects than other drug classes, such as the INSTIs or NNRTIs, and even modern PIs can cause some gastrointestinal intolerability.[131,132,133]

Cardiovascular Risk

Protease inhibitors have been associated with dyslipidemia, insulin resistance, premature atherosclerosis, and myocardial infarction.[134] The large, prospective observational D:A:D study found that the incidence of myocardial infarction increased from 1.53 per 1000 person-years in those not exposed to PIs to 6.01 per 1000 person-years in those exposed to PIs for longer than 6 years, with much of this risk attributable to elevated lipid levels.[135] When the D:A:D study results were stratified according to exposure to individual drugs, only indinavir and lopinavir-ritonavir were associated with a statistically significant increased risk of myocardial infarction.[36]

Cardiac Conduction Abnormalities

Several studies have revealed prolonged PR interval as a potential complication of both boosted and unboosted PIs, with the effect being more pronounced with ritonavir-boosted atazanavir, lopinavir, and saquinavir.[136] Although all ritonavir-boosted PIs may potentially prolong the QTc interval, this effect is generally considered minimal, except with the combination of saquinavir with ritonavir.[137] Some patients taking PIs have developed symptomatic atrioventricular (AV) block. Accordingly, ritonavir-boosted PIs should be used with caution in patients who have underlying conduction defects or in patients taking other medications that can prolong the PR interval.

Bleeding Risk in Persons with Hemophilia

Several case studies and case series have reported an increased risk of spontaneous bleeding episodes among hemophiliacs with HIV infection who take HIV PIs.[138,139] In some of these cases, the bleeding was severe. The biologic mechanism remains unknown but may involve platelet dysfunction.[140] Reports have documented individuals with HIV and hemophilia who have safely taken HIV PIs without bleeding complications.[141] In addition, clinical experience has shown that most persons with HIV infection with hemophilia can be safely treated with HIV PIs. Thus, the use of PIs in patients with hemophilia is not contraindicated, but those started on protease inhibitors should be warned about this potential complication and monitored closely.

Lipoaccumulation

Prior use of some first-generation protease inhibitors, particularly indinavir and saquinavir, in combination with thymidine analog NRTIs, has been associated with the development of abnormal central fat accumulation, most often from excessive visceral fat.[6,142] Clinically, the abnormal fat
accumulation has manifested as marked increases in abdominal girth, breast enlargement, and development of a dorsocervical fat pad—often referred to as a buffalo hump (Figure 12) and (Figure 13).[142] The risk of developing lipoaccumulation has markedly declined in the current antiretroviral era since regimens now rarely include thymidine analogs (stavudine or zidovudine) or first-generation PIs.

**Atazanavir**

Although atazanavir was a preferred, first-line agent for many years, relatively lower potency and the potential disadvantage of hyperbilirubinemia (which causes cosmetic concern for many patients) has limited its use compared with newer antiretroviral therapy options.

- **Hyperbilirubinemia:** Atazanavir can block the normal glucuronidation of bilirubin through inhibition of the liver enzyme uridine diphosphate glucuronosyltransferase 1A1 (UGT1A1).[143] The UGT1A1 enzyme is responsible for converting unconjugated bilirubin to conjugated bilirubin (Figure 14).[143] This inhibition of UGT1A1 by atazanavir causes an increase in indirect bilirubin. It does not cause or reflect liver damage but can lead to icterus and jaundice; this is reversible with discontinuation of atazanavir. Discontinuation of atazanavir is sometimes necessary if the icterus is distressing to the patient.[97] The degree of hyperbilirubinemia typically fluctuates, often with a waxing and waning course.

- **Nephrolithiasis:** Atazanavir-induced kidney stones develop in approximately 1% of patients taking ritonavir-boosted atazanavir.[144,145,146] The onset of nephrolithiasis occurs, on average, two years after starting atazanavir.[147] Risk factors identified for atazanavir-induced nephrolithiasis include high atazanavir blood levels (due to slower atazanavir metabolism and/or pharmacologic boosting), high bilirubin levels, alkaline urine (atazanavir is less soluble in an alkaline environment), and prior hepatic or renal disease.[147] Among patients taking long-term ritonavir-boosted atazanavir, the relative rate of developing nephrolithiasis is at least 3-fold higher than with other commonly used antiretroviral medications, including efavirenz, fosamprenavir, or other ritonavir-boosted PIs (darunavir, fosamprenavir, or lopinavir).[146,148] The urine sediment may show rod-shaped crystals and the actual stones often are composed of atazanavir and/or calcium phosphate. Atazanavir stones are typically radiolucent so will not be evident on plain film radiograph or non-contrast computed tomography (CT).[149] Crystal nephropathy can also occur in the absence of stones and should be suspected in patients with rising creatinine levels or sterile pyuria.

- **Cholelithiasis:** Several reports have been published that suggest ritonavir-boosted atazanavir is associated with the development of cholelithiasis.[150] In one study, cumulative treatment with ritonavir-boosted atazanavir for 2 years or longer has been associated with a two-fold increased risk of cholelithiasis compared to shorter term use or treatment with other protease inhibitors, including ritonavir-boosted darunavir or ritonavir-boosted lopinavir.[59,151] A separate study, however, failed to show an increased risk of cholelithiasis with ritonavir-boosted atazanavir when compared with other protease inhibitors.[145,146] Thus, if atazanavir is associated with the development of cholelithiasis, it is an uncommon or rare occurrence.

**Darunavir**

Darunavir is a potent protease inhibitor with a high genetic barrier to resistance. Although no longer a part of recommended initial therapy for most individuals with HIV, it remains a cornerstone of salvage antiretroviral therapy for those who have developed virologic failure with resistance to other classes of antiretroviral medications. Gastrointestinal symptoms and rash are the most commonly reported adverse effects with darunavir use. Abdominal pain and diarrhea are the most common gastrointestinal symptoms and these symptoms occur in approximately 5 to 14% of persons who take this medication. The incidence of rash in patients taking darunavir is approximately 15%, with most cases of mild-moderate severity.[128,152] The rash typically begins during the first 4 weeks of treatment and resolves as patients continue on darunavir. Severe skin rash has been reported in less
than 1% of patients taking darunavir and it can be accompanied by fever and/or increases in hepatic aminotransferase levels. Very rare (less than 0.1%) cases of Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported in patients taking darunavir. Patients who develop a severe skin rash should promptly discontinue darunavir. It is important to be aware that darunavir contains a sulfonamide moiety and patients with a history of skin reaction to a sulfa medication have an increased risk of developing rash when taking darunavir. A history of sulfa allergy is not considered a contraindication for using darunavir, but it is recommended that darunavir should be used with caution in this situation, especially if the sulfa reaction was severe.

**Indinavir**

Indinavir is an older protease inhibitor that is now rarely used in clinical practice due to an increased risk of nephrotoxicity and requirement for twice-daily dosing. Indinavir is classically associated with a wide range of urologic and renal abnormalities, including dysuria, flank pain, renal colic, hematuria, crystalluria, nephrolithiasis, acute renal failure, chronic renal failure, and papillary necrosis.**[153]** Nephrolithiasis, or kidney stones, occurred in about one-fifth of patients treated with indinavir and some of these patients developed significant renal insufficiency. In these cases, renal function typically improved upon withdrawal of indinavir.**[2]**

**Lopinavir-Ritonavir**

Lopinavir is a protease inhibitor that is available only as the coformulated product lopinavir-ritonavir. Although this combination medication was used frequently in the past (including during pregnancy), it is now infrequently used because of its larger pill burden and greater toxicity than with many other currently available antiretroviral medication options.**[2]**

- **Hyperlipidemia**: Lopinavir-ritonavir frequently causes elevations in lipid levels, particularly total cholesterol and triglycerides. In randomized controlled trials, lopinavir-ritonavir led to more substantial lipid abnormalities than either atazanavir or darunavir; in switch-studies, patients experienced an improvement in lipid parameters when they switched off lopinavir-ritonavir to atazanavir, raltegravir, etravirine, or nevirapine.

- **Diarrhea**: Gastrointestinal side effects may occur with any protease inhibitor, but they are more prevalent with lopinavir-ritonavir than with atazanavir or darunavir. In a head-to-head randomized control trial comparing efficacy and safety of twice-daily lopinavir-ritonavir with once-daily atazanavir, diarrhea was reported in 11% of subjects in the lopinavir-ritonavir arm compared with 2% of subjects in the atazanavir arm, and subjects in the lopinavir-ritonavir arm also reported higher rates of nausea compared with the atazanavir arm (8% versus 4%).

- **Alcohol in Liquid Formulation**: The liquid solution of lopinavir-ritonavir contains 42.3% alcohol by volume.**[154]** Standard dosing of liquid solution of lopinavir-ritonavir requires taking 10 mL once daily or 5 mL twice daily.**[154]** The liquid lopinavir-ritonavir solution should not be administered with disulfiram or with any medication that may cause a disulfiram reaction, such as metronidazole. In addition, because the liquid solution of lopinavir-ritonavir contains alcohol, it should not be administered to pregnant women. Use of oral liquid ritonavir solution alone also has 42.3% alcohol by volume and thus has the same alcohol-related issues as lopinavir-ritonavir.

**Saquinavir**

Saquinavir is rarely used in current clinical practice due to the high pill burden, poor tolerability, and potential for serious adverse effects. The combination of saquinavir and ritonavir may cause prolongation of the cardiac QTc and PR intervals, which increases the risk for serious cardiac arrhythmias, including heart block and polymorphic ventricular tachycardia (torsades de pointes). Identified risks for saquinavir-induced QTc prolongation include an underlying heart condition, preexisting prolonged QTc or arrhythmia, older age, female sex, and concomitant use of other
medications that prolong the QTc interval.\textsuperscript{137} The FDA issued a recommendation that the combination of saquinavir and ritonavir should not be used in patients taking other medications known to prolong the QTc interval or in patients with a history of prolonged QTc interval.\textsuperscript{155} All persons who are still taking saquinavir should be switched to a more modern and less toxic agent.

\textbf{Tipranavir}

Tipranavir is almost never used now because of the high pill burden and the potential for serious complications, including intracranial hemorrhage and hepatotoxicity, and the drug carries a black box warning for both conditions. In June 2006, the U.S. Food and Drug Administration (FDA) reported that 14 patients taking tipranavir in combination with ritonavir developed intracranial hemorrhage; among them were 8 fatalities.\textsuperscript{156} From 2005 through 2007, tipranavir was also linked to 12 liver-associated deaths, all of which occurred in patients with underlying risk factors for hepatotoxicity (e.g. advanced HIV, comorbid malignancy, coinfection with hepatitis B or C, or lactic acidosis).\textsuperscript{156} Tipranavir should be avoided in patients at risk for intracranial hemorrhage, including patients with central nervous system lesions, head trauma, recent neurosurgery, coagulopathy, hypertension, alcohol abuse, and in persons receiving anticoagulants or anti-platelet agents (including vitamin E). Tipranavir use is contraindicated in patients with Child-Turcotte-Pugh Class B or C hepatic insufficiency.
### Entry Inhibitors

#### Enfuvirtide

Enfuvirtide is the only fusion inhibitor medication and the fusion inhibitor approved for use by the U.S. FDA. Enfuvirtide is used primarily in treatment-experienced patients who have limited other treatment options; it is administered twice daily by subcutaneous injection. Injection site reactions are common (occurring in up to 98% of patients in some studies) and include erythema, induration, cysts, nodules, and rarely more severe reactions.[158,159] The acute injection site reactions appear within hours after the injection and some patients have persistent sclerotic lesions that can persist for months after discontinuation of enfuvirtide.

#### Ibalizumab

Ibalizumab is an entry inhibitor that is a humanized monoclonal IgG-4 antibody that prevents HIV cell entry by binding to the host CD4 receptor. Ibalizumab requires intravenous infusion. In clinical trials, the most common adverse effects associated with ibalizumab have been diarrhea, dizziness, nausea, and rash.[160] Infusion reactions may also occur.

#### Maraviroc

Maraviroc is an entry inhibitor that exerts its action by directly binding to a host protein—the CCR5 co-receptor. Because maraviroc binds to a human protein, there has been concern it could have unique toxicity. Maraviroc can only be used in individuals who have R5-tropic virus, and thus a co-receptor tropism assay should be performed whenever the use of a CCR5 co-receptor antagonist is being considered.[161] In clinical trials, most participants have tolerated maraviroc well.[162,163]

- **Rash:** Maraviroc has been linked to at least one case of severe rash with systemic symptoms, although most cases of severe reactions (i.e. Stevens-Johnson syndrome, toxic epidermal necrolysis, drug reaction with eosinophilia and systemic symptoms) in patients taking maraviroc have involved patients who were also taking other drugs associated with these conditions.

- **Hepatotoxicity:** Several reports from clinical trials and postmarketing experience have noted sporadic cases of hepatotoxicity accompanied by severe rash and allergic symptoms in patients taking maraviroc, and the FDA labeling now includes a black box warning for hepatotoxicity. Careful monitoring of hepatic laboratory parameters, including alanine aminotransferase (ALT), aspartate aminotransferase (AST), and bilirubin, in patients before and during treatment with maraviroc is recommended, and maraviroc should be used with caution in patients with underlying liver disease or coinfection with hepatitis B or C. Long-term follow-up of patients in the MERIT and MOTIVATE trials indicate no increased risk of hepatotoxicity in patients taking maraviroc over time.[164,165]

- **Impact of Host Immune Function:** Maraviroc is the only antiretroviral drug that acts directly on a host (human) protein—the CCR5 coreceptor. The binding and impairment of the human CCR5 coreceptor by maraviroc has raised concerns for potential maraviroc-induced problems with host immune function or cancer surveillance, but trial data does not show an excess of infections or malignancies, with the exception that blockade of CCR5 receptor may increase the risk of developing symptomatic West Nile virus infection.[162,166,167]
Pharmacologic Boosters

General Considerations

Ritonavir and cobicistat are pharmacokinetic enhancers to boost the concentration of other antiretroviral agents used in the treatment of HIV. Both medications work by interacting with the hepatic metabolism of antiretroviral drugs through the cytochrome P450 (CYP450) system; however, because of this mechanism of action, they can also affect the levels of other medications that are coadministered, leading to clinically significant (and occasionally unpredictable) drug interactions and potential adverse effects.

Ritonavir

Ritonavir is a PI that was previously used at high doses as an independent antiretroviral medication, but due to side effects it is no longer used as a PI. It inhibits the liver enzyme CYP450 3A (CYP3A) and now is used exclusively at lower doses for its boosting effect. The main symptoms associated with ritonavir consist of gastrointestinal effects, including diarrhea, nausea, vomiting, and abdominal pain. These side effects are greater with higher doses of ritonavir.

Cobicistat

Cobicistat is also a CYP34A inhibitor and was developed specifically as a pharmacokinetic enhancer of atazanavir and darunavir; it is also now available in combination form as a booster for elvitegravir. Cobicistat does not have any intrinsic activity against HIV. Cobicistat reduces tubular secretion of creatinine via competitive inhibitor of the multidrug and toxin extrusion protein 1 (MATE1).\[168,169\] In the kidney, MATE1 is located in the luminal (urine) membrane of renal tubular cells and MATE1 can transport creatinine from the renal tubular cell into the renal tubule lumen. The inhibition of MATE1 by cobicistat causes reduced tubular secretion of creatinine and an increase in serum creatinine. This inhibition correlates with a decrease in the estimated glomerular filtration rate (eGFR), but iohexol clearance studies have shown that cobicistat does not impact actual glomerular filtration rate.\[170\] The rise in serum creatinine, which typically is about 0.10 to 0.15 mg/dL, occurs within the first 8 weeks of starting antiretroviral therapy and then stabilizes.\[55,170\] For patients on cobicistat-containing regimens, changes in serum creatinine greater than 0.4 mg/mL from baseline may indicate another cause and should prompt evaluation.\[168\] In clinical trials, cobicistat was also associated with gastrointestinal symptoms, primarily nausea and diarrhea.\[168\]
Summary Points

- Antiretroviral therapy has overwhelming benefits and has transformed HIV infection to a manageable chronic disease for most patients, but antiretroviral therapy may confer adverse effects and sometimes these may be serious.
- The older nucleoside reverse transcriptase inhibitors (NRTIs) were associated with mitochondrial toxicity, which encompasses lactic acidosis, hepatic steatosis, myopathy, cardiomyopathy, peripheral neuropathy, pancreatitis, and lipoatrophy, but these adverse effects are rare with newer, recommended NRTIs.
- Abacavir can cause a hypersensitivity syndrome in persons who are HLA-B*5701 positive. Abacavir may increase the risk of myocardial infarction compared with other NRTIs.
- Tenofovir alafenamide has significantly lower adverse renal and bone mineral density effects than tenofovir DF.
- Tenofovir DF can cause nephrotoxicity, including progressive chronic kidney disease and Fanconi syndrome (generalized proximal tubule dysfunction), which manifests as type 2 renal tubular acidosis and phosphate wasting. Tenofovir DF has also been linked to decreased bone density.
- Efavirenz may cause significant neuropsychiatric side effects, including suicidality, and it is no longer a recommended antiretroviral for most individuals with HIV.
- Medications in the integrase strand transfer inhibitor class are generally well tolerated and moderate to severe side effects are uncommon.
- Dolutegravir can cause headache and insomnia and has been associated with greater weight gain than other INSTIs and other classes of antiretrovirals.
- Protease inhibitors have been traditionally linked to higher rates of gastrointestinal effects, though newer PIs with lower ritonavir-boosting doses are generally better tolerated than older PI options.
- Atazanavir often causes unconjugated hyperbilirubinemia, which is not dangerous but may be cosmetically bothersome and which improves with a switch to another antiretroviral medication. Atazanavir is also associated with nephrolithiasis and cholelithiasis.
- The most common side effects of darunavir include gastrointestinal symptoms (diarrhea, abdominal pain, vomiting) and rash; the rash usually self-resolves and requires discontinuation of the drug in less than 1% of cases.
- Maraviroc can only be used in individuals who have R5-tropic virus, as measured with a coreceptor tropism assay. It is well tolerated and infrequently causes significant side effects.
- Enfuvirtide, the only drug in the fusion inhibitor class, causes injection site reactions (both acute inflammatory responses and persistent sclerotic lesions) in most patients who take it.
- Bictegravir, dolutegravir, rilpivirine, and the pharmacokinetic enhancer cobicistat can increase serum creatinine and decrease estimated creatinine clearance by inhibiting active tubular secretion of creatinine, but these drugs do not typically impact actual glomerular filtration rate.
Citations


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[PubMed Abstract]

[PubMed Abstract]

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Figures

Figure 1 (Image Series) - Human Mitochondrial Function (Image Series) - Figure 1 (Image Series) - Human Mitochondrial Function

Image 1A: Mitochondrial DNA

Each cell has multiple mitochondria and each mitochondrion contains multiple copies of its own DNA (mtDNA). The enzyme DNA polymerase $\gamma$ catalyzes the formation of new mtDNA.

Illustration by David Ehlert, Cognition Studio and David Spach, MD
The new mtDNA encodes for mtRNA that in turn encodes for proteins that function as subunits for 4 of the 5 oxidative phosphorylation complexes. These complexes subsequently become part of the oxidative phosphorylation system.

Illustration by David Ehler, Cognition Studio and David Spach, MD
Figure 1 (Image Series) - Human Mitochondrial Function
Image 1C: Oxidative Phosphorylation System

At the inner mitochondrial membrane, the oxidative phosphorylation complex subunits synthesized from mtDNA join those complexes synthesized from nuclear DNA and comprise the five enzyme complexes of the oxidative phosphorylation system. The system also includes two electron carriers (not shown).

Illustration by David Ehlert, Cognition Studio and David Spach, MD
Figure 1 (Image Series) - Human Mitochondrial Function
Image 1D: H⁺ Gradient and Conversion of ADP to ATP

Electrons (e⁻) and H⁺ are generated from the oxidation of NADH and FADH₂. The electrons are passed down the electron transport system and H⁺ ions are pumped into the intermembrane space to form an H⁺ gradient. Transport of H⁺ back into the mitochondria releases energy for the conversion of ADP to ATP.

Illustration by David Ehler, Cognition Studio and David Spach, MD
Figure 1 (Image Series) - Human Mitochondrial Function

Image 1E: Transport of ATP to Cytosol via Adenine Nucleotide Transporter

The conversion of the ADP to ATP within the mitochondria is followed by the transport of the ATP from the mitochondria to the cytosol via the adenine nucleotide transporter. This transporter shuttles ATP and ADP across the mitochondrial membrane. Within the cytosol, the conversion of ATP to ADP generates energy for the cell.

Illustration by David Ehlert, Cognition Studio and David Spach, MD
The process of glycolysis in the cytosol and β-oxidation in the mitochondria generate acetyl Co-A, which then enters the Krebs cycle, causing a series of redox reactions that reduce electron carrying agents (NAD$^+$ to NADH and FAD to FADH$_2$). The NADH and FADH$_2$ play a critical role in the oxidation phosphorylation process.

Illustration by David Ehlert, Cognition Studio and David Spach, MD
Figure 1 (Image Series) - Human Mitochondrial Function
Image 1G: Conversion of Glucose to Pyruvate or Lactate

Conditions within the cell determine the fate of pyruvate. Aerobic conditions favor a higher NAD$^+$ to NADH ratio and thus a flow of lactate to pyruvate. Anaerobic conditions (or disruption of the oxidative phosphorylation system) favor conversion of pyruvate to lactate because of a higher NADH to NAD$^+$ ratio.

Illustration by David Ehlert, Cognition Studio and David Spach, MD
Some NRTIs have the potential to significantly inhibit DNA polymerase γ and impact mtDNA synthesis. This effect is most prominent with stavudine and didanosine. The decrease in mtDNA synthesis in turn leads to diminished mtRNA, resulting in decreased synthesis of some oxidative phosphorylation system subunits.

Illustration by David Ehler, Cognition Studio and David Spach, MD
The decreased synthesis of mitochondrial components of the oxidative phosphorylation system results in a dysfunctional oxidative phosphorylation system, which leads to diminished conversion of NADH to NAD$^+$ and FADH$_2$ to FAD.

Illustration by David Ehlert, Cognition Studio and David Spach, MD
Figure 2 (Image Series) - NRTI and Increased NADH
Image 2C: Increased NADH leads to Shunting of Pyruvate to Lactate

The drop off in conversion of NADH to NAD$^+$ results in an increased NADH to NAD$^+$ ratio. The NADH reacts with pyruvate to form lactate. Thus, the overall effect of the increased NADH levels is to shift the cytosolic conversion of pyruvate to lactate.

Illustration by David Ehlert, Cognition Studio and David Spach, MD
Figure 3 Facial Lipoatrophy Severity Scale

Facial lipoatrophy most often has been associated with long-term receipt of stavudine, didanosine, or the combination of stavudine plus didanosine.


<table>
<thead>
<tr>
<th>Severity Grade</th>
<th>Tenofovir Dose Adjustment</th>
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<tbody>
<tr>
<td>Grade 1</td>
<td>Mild and localized areas of facial lipoatrophy</td>
</tr>
<tr>
<td>Grade 2</td>
<td>Deeper and longer central cheek atrophy; facial muscles (especially zygomaticus major) beginning to show through</td>
</tr>
<tr>
<td>Grade 3</td>
<td>Atrophic area is even deeper and wider with the muscles clearly showing</td>
</tr>
<tr>
<td>Grade 4</td>
<td>Atrophy covers a wide area and extends up toward the orbit</td>
</tr>
</tbody>
</table>
A 25 mg dose of tenofovir alafenamide has 90% lower circulating plasma tenofovir levels when compared with a 300 mg dose of tenofovir DF.

Figure 4 Metabolism of Tenofovir DF and Tenofovir alafenamide

TDF = tenofovir disoproxil fumarate; TFV = tenofovir; MP = monophosphate; DP = diphosphate
**Figure 5 Common Laboratory Indicators of Proximal Tubule Dysfunction**

Additional nonspecific indicators include proteinuria/albuminuria and hematuria. Investigational markers with limited clinical availability include aminoaciduria, urinary alfa-1 microglobulin, urinary beta-2 microglobulin, urinary retinol binding protein, urinary cytochrome C, and urinary cystatin C.


<table>
<thead>
<tr>
<th>Abnormality</th>
<th>Definition of Abnormality</th>
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<tbody>
<tr>
<td><strong>Serum Abnormalities</strong></td>
<td></td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>Serum potassium concentration below laboratory reference range</td>
</tr>
<tr>
<td>Low serum bicarbonate</td>
<td>Serum bicarbonate concentration below laboratory reference range</td>
</tr>
<tr>
<td>Hypophosphatemia</td>
<td>Serum phosphorous concentration below laboratory reference range</td>
</tr>
<tr>
<td><strong>Urine abnormalities</strong></td>
<td></td>
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<tr>
<td>Urine glucose on dipstick</td>
<td>Glycosuria in the absence of diabetes, or in diabetics with well-controlled blood glucose</td>
</tr>
<tr>
<td>Fractional excretion of phosphate</td>
<td>&lt;10% is normal and &gt;20% is abnormal</td>
</tr>
<tr>
<td>Tubular maximum for phosphate corrected for GFR</td>
<td>Lower than reference value (normal, 2.8–4.4 mg/dL)</td>
</tr>
<tr>
<td>Fractional excretion of uric acid</td>
<td>&lt;15% is normal and &gt;20% is abnormal</td>
</tr>
<tr>
<td>Urine albumin-to-protein ratio</td>
<td>uAPR &lt;0.4 suggests predominantly tubulointerstitial disease, whereas uAPR &gt;0.4 suggests predominantly glomerular disease</td>
</tr>
</tbody>
</table>

Abbreviations: GFR = glomerular filtration rate; uAPR, urine albumin-to-protein ratio;
Figure 6 Central Nervous System Toxicity Related to Plasma Efavirenz Levels

This study involved an analysis of 130 adult on an efavirenz-based antiretroviral regimen. Blood samples for efavirenz levels were drawn at an average of 14 hours after efavirenz intake. The bar graph shows the percentage of patients with central nervous system toxicity based on efavirenz levels. Patients with levels greater than 4.0 µg/ml had an approximately three-fold greater incidence of central nervous system toxicity than patients with levels in the 1.0-4.0 µg/mL range.

**Figure 7 Plasma Efavirenz Levels: Virologic Response and Toxicity**

This graph shows a correlation of plasma efavirenz levels and probability of CNS adverse effects. The probability of viral suppression is shown by the purple line and the central nervous system adverse effects are shown by the blue line. The data shown as stepped lines represent the observed frequency in predefined concentration ranges and the curved lines represent the fitted regression model. The grey box in the middle represents the optimal efavirenz concentration range of 1000-4000 µg/L (equivalent to 1-4 µg/mL).

Figure 8 Efavirenz-Associated Rash

Photograph by David H. Spach, MD
Figure 9 Nevirapine-Associated Rash

Photograph by David H. Spach, MD
Dolutegravir can inhibit the urine organic cation transporter 2 (OCT2), a protein involved in renal tubular secretion of creatinine. The OCT2 transporter protein is located on the basolateral (blood) membrane of the renal tubular cell. The inhibition of OCT2 blocks the secretion of creatinine from the basolateral membrane of the peritubular capillary blood cell into the renal tubular cell. As a result, more serum creatinine remains in the blood and serum creatinine increases.

Illustration by Casandra Mack and David H. Spach, MD
Figure 11 Dolutegravir-Related Changes in Serum Creatinine Level

This graph shows the mean change from baseline in serum creatinine levels for the two arms dolutegravir plus abacavir-lamivudine and efavirenz-tenofovir DF-emtricitabine. The I bars indicate 1 standard deviation. To convert the values for creatinine to milligrams per deciliter, divide by 88.4.

**Figure 12 Fat Redistribution**

This patient developed marked enlargement of the abdominal girth and breasts while taking a regimen of indinavir plus stavudine plus lamivudine.

Photograph by David H. Spach, MD
Figure 13 Fat Redistribution: Neck

Note the dorsocervical fat pad enlargement. This has often been referred to as a buffalo hump.

Photograph by David H. Spach, MD
Atazanavir can increase serum total bilirubin through inhibition of the liver enzyme uridine diphosphate glucuronosyltransferase 1A1 (UGT1A1); this enzyme is a key enzyme in the normal glucuronidation of bilirubin.

Illustration by David Ehlert, Cognition Studio and David Spach, MD
Table 1.
Laboratory Monitoring for Antiretroviral Therapy-Related Toxicities

<table>
<thead>
<tr>
<th>Laboratory Study</th>
<th>ART Initiation</th>
<th>2-8 Weeks after Starting ART</th>
<th>Every 3-6 Months</th>
<th>Every 6 Months</th>
<th>Every 12 Months</th>
</tr>
</thead>
<tbody>
<tr>
<td>HLA-B*5701</td>
<td>√ (if considering abacavir)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Basic Chemistry</td>
<td>√</td>
<td>√</td>
<td>√</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALT, AST, Total bilirubin</td>
<td>√</td>
<td>√</td>
<td>√</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CBC with differential</td>
<td>√</td>
<td>If on zidovudine</td>
<td>√</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fasting lipid profile</td>
<td>√</td>
<td></td>
<td>If abnormal at last measurement</td>
<td>√</td>
<td></td>
</tr>
<tr>
<td>Fasting glucose or HbA1c</td>
<td>√</td>
<td>If abnormal at last measurement</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urinalysis</td>
<td>√</td>
<td></td>
<td>If on tenofovir DF or tenofovir alafenamide</td>
<td>√</td>
<td></td>
</tr>
<tr>
<td>Pregnancy Test</td>
<td>√</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* The information contained in this table is based on information in the Laboratory Testing Schedule for Monitoring HIV-Infected Patients Before and After Initiation of Antiretroviral Therapy.

Source:

- Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in adults and adolescents with HIV. Department of Health and Human Services. Laboratory testing: laboratory testing for initial assessment and monitoring of patients with HIV receiving antiretroviral therapy. October 25, 2018. [AIDSinfo]
Table 2.

**Allele Frequency of HLA-B*5701 in Various Population Groups**

<table>
<thead>
<tr>
<th>Population Group</th>
<th>HLA-B*5701 Carrier Frequency Range (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>European</td>
<td>1.4 – 10.2</td>
</tr>
<tr>
<td>South American</td>
<td>1.1– 3.1</td>
</tr>
<tr>
<td>African</td>
<td>0.0 – 3.2</td>
</tr>
<tr>
<td>Middle Eastern</td>
<td>0.5– 6.0</td>
</tr>
<tr>
<td>Mexican</td>
<td>0.0 – 4.0</td>
</tr>
<tr>
<td>Asian</td>
<td>0.0 – 6.7</td>
</tr>
<tr>
<td>Southwest Asian (Indian)</td>
<td>3.8 – 19.6</td>
</tr>
</tbody>
</table>

Source:
