Adverse Effects of Antiretroviral Medications

Introduction

Background

Antiretroviral therapy has transformed HIV 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 as 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, weight gain, cardiovascular effects, hypersensitivity, skin reactions, insomnia, and neuropsychiatric manifestations.[2] 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 ART Guidelines.[3] Clinicians who provide care to persons with HIV should have an understanding of the basic toxicity profile of antiretroviral medications, keeping in mind that the potential adverse effects of 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 table below summarizes key baseline and safety laboratory studies recommended for individuals taking antiretroviral therapy.[4]

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*The information contained in this table is based on information in the table Laboratory Testing for Initial Assessment and Monitoring of People with HIV Receiving Antiretroviral Therapy.

<sup>a</sup>Serum Na, K, HCO3, Cl, BUN, creatinine, glucose, and Cr-based eGFR. Serum P should be monitored in patients with CKD who are on TDF-containing regimens.

<sup>b</sup>More frequent monitoring may be indicated for patients with evidence of kidney disease (e.g., proteinuria, decreased glomerular dysfunction) or increased risk of renal insufficiency (e.g., patients with diabetes, hypertension).

<sup>c</sup>CBC with differential should be done when a CD4 count is performed. When CD4 count is no longer being monitored, the recommended frequency of CBC with differential is once a year. More frequent monitoring may be indicated for people receiving medications that potentially cause cytopenia (e.g., TMP-SMX).

<sup>d</sup>If random lipids are abnormal, fasting lipids should be obtained. Consult the American College of Cardiology/American Heart Association's 2018 Guideline on the Management of Blood Cholesterol for diagnosis and management of patients with dyslipidemia.

<sup>e</sup>If random glucose is abnormal, fasting glucose should be obtained. HbA1C is no longer recommended for diagnosis of diabetes in people with HIV on ART.

<sup>f</sup>Consult the HIVMA/IDSA’s Clinical Practice Guideline for the Management of Chronic Kidney Disease in Patients Infected with HIV for recommendations.
Laboratory Study | ART Initiation | 4-8 Weeks after ART Initiation or Modification | Every 3 Months | Every 6 Months | Every 12 Months | Clinically Indicated
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on managing patients with renal disease. More frequent monitoring may be indicated for patients with evidence of kidney disease (e.g., proteinuria, decreased glomerular dysfunction) or increased risk of renal insufficiency (e.g., patients with diabetes, hypertension).
9Urine glucose and protein should be assessed before initiating tenofovir alafenamide (TAF)- or tenofovir DF (TDF)-containing regimens and monitored during treatment with these regimens.
9For persons of childbearing potential.

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 people with HIV receiving antiretroviral therapy. September 21, 2022. [HIV.gov]
**Entry Inhibitors**

**Enfuvirtide**

Enfuvirtide is the only fusion inhibitor medication approved for use by the United States Food and Drug Administration (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 more than 90% of patients in some studies) and include erythema, induration, cysts, nodules, and rarely more severe reactions.[5,6] 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. Usage of this drug in the United States has become rare due to approval of other, better tolerated agents for salvage antiretroviral therapy.

**Fostemsavir**

Fostemsavir is the only attachment inhibitor approved for use by the U.S. FDA and it is primarily used in heavily treatment-experienced adults with multidrug-resistant HIV.[7] Fostemsavir is an oral medication that is hydrolyzed after ingestion to its active form temsavir.[7] In the only phase 3 trial completed with fostemsavir, serious side effects were rare; the most commonly observed mild-moderate side effects were nausea, and diarrhea.[8] Fostemsavir given at a dose of 2,400 mg twice daily, which is 4 times the recommended daily dose, was shown to significantly prolong the QTc interval.[9] Caution is also advised if using fostemasavir in patients with a history of QTc prolongation, torsades de pointes, or if taking other medications known to prolong the QT interval.

**Ibalizumab**

Ibalizumab is a post-attachment 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 and is dosed every 2 weeks. In clinical trials, the most common adverse effects associated with ibalizumab have been diarrhea, dizziness, nausea, and rash.[10] Infusion reactions may also occur. Although ibalizumab binds directly to a host cell receptor, there are no known adverse immunologic effects of this medication.

**Maraviroc**

Maraviroc is an entry inhibitor that exerts its action by directly binding to a host protein—the CCR5 co-receptor. 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.[11] In clinical practice and in clinical trials, maraviroc has been well tolerated and serious toxicity has been quite rare.[12,13]

- **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 which may be preceded by severe rash and allergic symptoms in patients taking maraviroc. The FDA labeling now includes a black box hepatotoxicity warning for maraviroc. 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.[14,15] Furthermore, in clinical practice, hepatotoxicity with maraviroc seems to be quite rare.
• Impact of Host Immune Function: Maraviroc binds directly to a host (human) protein—the CCR5 coreceptor. The binding and impairment of the human CCR5 coreceptor by maraviroc initially raised concerns for potential maraviroc-induced problems with host immune function or host cancer surveillance, but clinical trial data and clinical experience have not shown 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.[12, 16, 17]
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] Rare cases of mood changes or new onset of psychiatric disorders have been observed with INSTIs.[18,19]

Adverse Effects Observed with Bictegravir and Dolutegravir

Weight Gain

Several studies have concluded that INSTIs (Figure 1), particularly dolutegravir (Figure 2), lead to greater weight gain than other classes of antiretrovirals, but the mechanism and clinical significance are unclear.[20,21,22,23] Dolutegravir-associated weight gain appears to be more pronounced when dolutegravir is combined with tenofovir alafenamide than with tenofovir DF (Figure 3).[24,25] Available data also suggest weight gain is a complication in persons taking bictegravir-tenofovir alafenamide-emtricitabine.[26] Observations of excess weight gain after a switch to dolutegravir (or bictegravir), with or without a switch to tenofovir alafenamide, are complicated because studies also find associations between older antiretroviral agents (such as efavirenz and tenofovir DF) and suppression of weight gain, so removal of these agents may play a role in post-switch weight change.

Elevated Serum Creatinine

Dolutegravir and bictegravir cause a predictable, modest, benign increase in serum creatinine and thereby 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 4).[27] 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). Normally, approximately 15% of creatinine is secreted into the urine in the proximal tubule. 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.[28,29] These changes in serum creatinine caused by dolutegravir and bictegravir typically are small, occur in the first 2 to 3 months after starting the medication, and then plateau. 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 bictegravir or dolutegravir.

Bictegravir

Bictegravir is an INSTI that is available only as a single-tablet regimen—bictegravir-tenofovir alafenamide-emtricitabine. In clinical trials, the most common adverse effects associated with bictegravir-tenofovir alafenamide-emtricitabine were diarrhea, nausea, and headache.[30,31,32] 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, but available data suggest that effects are likely similar. Available studies suggest the increases in serum creatinine associated with bictegravir are slightly less than with dolutegravir; as described above, these serum creatinine elevations are generally small and are benign.[31,33]

Cabotegravir

For HIV treatment, cabotegravir is available as a long-acting injectable combination of cabotegravir and rilpivirine. For HIV preexposure prophylaxis, long-acting injectable cabotegravir alone can be used. Oral cabotegravir can be used as a lead-in for approximately 1 month. The major adverse effects attributed to long-
acting cabotegravir are injection site reactions, including pain, nodules, induration, and swelling.[34,35,36] The injection site reactions typically become less frequent over time while receiving long-acting injectable cabotegravir.[35]

**Dolutegravir**

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

- **Elevated Serum Creatinine:** 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 5).[37,38]
- **Insomnia:** In randomized trial settings, the incidence of insomnia in patients taking dolutegravir ranged from 3 to 15%.[38,39] Clinical experience has shown that some patients develop insomnia while taking dolutegravir, but this rarely requires discontinuation of dolutegravir.
- **Headache:** In clinical trials, aside from insomnia, headache was the most common side effect of moderate to severe intensity that occurred, though it was still uncommon (2% of participants in one of the phase 3 clinical trials.[38] In practice, it is a rare cause of intolerability of dolutegravir.
- **Myopathy and Elevated Creatine Phosphokinase:** Rhabdomyolysis, myopathy, and myositis have been reported in very small numbers of clinical trial participants taking dolutegravir.[39,40]

**Elvitegravir**

Elvitegravir is an INSTI that is available as a component of two single-tablet regimens: elvitegravir-cobicistat-tenofovir alafenamide-emtricitabine and elvitegravir-cobicistat-tenofovir DF-emtricitabine. Although elvitegravir itself causes few adverse effects, the cobicistat that it is combined with may lead to significant gastrointestinal symptoms and cause benign mild elevations in serum creatinine levels.[41,42] Elvitegravir-based regimens are infrequently used now.

**Raltegravir**

Raltegravir is generally well-tolerated and has the fewest drug interactions among medications in the INSTI class. In current clinical practice, dolutegravir or bictegravir is usually favored over raltegravir, due to raltegravir’s lower barrier to resistance and slightly higher pill burden. Most individuals tolerate raltegravir well. The below potential toxicities have been reported but are rare in clinical practice.

- **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.[43,44] Concurrent use of a statin medication, which can also cause elevations in creatine kinase, likely increases this risk.[44] 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.[44]
- **Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis:** Rash and severe systemic hypersensitivity reactions have rarely been reported in patients taking a regimen that included raltegravir.[45,46,47]
Nucleoside Reverse Transcriptase Inhibitors

Adverse Effects Observed with More than 1 NRTI

Mitochondrial Toxicity

Several of the older nucleoside reverse transcriptase inhibitors (NRTIs)—didanosine, stavudine, and zidovudine—can cause mitochondrial adverse effects; these effects rarely occur with abacavir, emtricitabine, lamivudine, tenofovir alafenamide, or tenofovir DF. Mitochondrial toxicity caused by the NRTIs can result in a wide range of adverse effects, including lactic acidosis, hepatic steatosis, myopathy, cardiomyopathy, peripheral neuropathy, pancreatitis, lipodystrophy, and possibly lipodystrophy syndrome.[48,49,50,51] Since didanosine, stavudine, and zidovudine are rarely used in current clinical practice, these adverse effects are now very uncommon in clinical practice and therefore will not be reviewed in further detail. If NRTI-related peripheral neuropathy and/or lipodystrophy develops, it usually only partially reverses, or does not reverse at all, with discontinuation of the offending medication.[48]

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.[52,53] 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.[54,55] 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 switching; the cause may be removable of the mild lipid-lowering effects of tenofovir DF.

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.[3]

- **Hypersensitivity Reaction**: The abacavir hypersensitivity reaction is a potentially life-threatening reaction to abacavir that occurs in up to 5% of individuals 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).[56,57] 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.[57,58] The reaction occurs more frequently in persons of European descent, as compared to persons of Asian or African descent, due to a higher HLA-B*5701 allele frequency in persons of European descent. The HLA-B*5701 test is highly useful for identifying persons who have a significantly increased risk of developing abacavir hypersensitivity. Screening for HLA-B*5701 is required before prescribing abacavir, and any person with a positive HLA-B*5701 screening test should not receive abacavir.[3,4]

- **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,[59] a sub-analysis found that patients taking abacavir had a higher rate of cardiovascular disease than persons taking other NRTIs.[60] 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,[61] and a large cohort study of veterans with HIV found a significant association between abacavir use and cardiovascular disease.[62] 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. In contrast, a meta-analysis that included data from more than 9,000 persons with HIV in randomized controlled trials concluded abacavir does not confer a higher risk of cardiovascular events relative to comparator abacavir-sparing regimens. In light of these concerning but conflicting findings, most experts recommend avoiding use of abacavir in persons with cardiovascular disease (or significant risk factors for cardiovascular disease). The mechanism by which abacavir may increase risk of ischemic cardiovascular events has been proposed to relate to platelet activation and aggregation.

Didanosine

Didanosine production was discontinued in the United States; this drug is exceedingly rarely used now given the potential for multiple adverse effects and serious complications, including pancreatitis, lactic acidosis, and peripheral neuropathy. 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. Neither drug should be used nowadays and if a patient is still taking either didanosine or stavudine, the medications should be switched to newer, safer options.

Emtricitabine and Lamivudine

Emtricitabine and lamivudine have the best tolerability and safety profile among all the NRTIs. 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, though these effects seem to be rare in clinical practice.

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. In addition, cases of severe neuromuscular weakness have been described. Manufacturing of the drug has been discontinued and any patient who is still taking this medication should be switched to a newer, safer agent.

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 6). Switching from tenofovir DF to tenofovir alafenamide results in improved glomerular filtration rate, glomerular and tubular proteinuria, and bone mineral density. Overall, in clinical trials, tenofovir alafenamide was well tolerated, except for mild gastrointestinal effects (nausea, vomiting, diarrhea). Increases in certain lipid parameters (total cholesterol and HDL) are more likely to occur with tenofovir alafenamide than with tenofovir DF. 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.

- **Renal Monitoring on Tenofovir alafenamide**: Persons receiving tenofovir alafenamide should have serum creatinine should be obtained at baseline, 4-8 weeks after starting therapy, and every 6 months thereafter. Tenofovir alafenamide is not recommended in persons who have an estimated creatinine clearance less than 30 mL/min. Urine glucose and protein) should be obtained at baseline and repeated at least annually.

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.[41,87] The main adverse effects associated with tenofovir DF are decreases in bone mineral density and renal toxicity.[82,88] Tenofovir DF may also suppress weight gain or induce weight loss, though the mechanism has not been confirmed and further research into this observational finding is needed.[89]

- **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.[90,91,92,93,94] Multiple studies have specifically implicated tenofovir DF use as a risk factor for reduced bone mineral density.[41,82,93] Although the mechanism for this effect is incompletely understood, tenofovir DF may affect bone indirectly through proximal tubular toxicity, leading to phosphate wasting and bone turnover.[94] There is also evidence that tenofovir DF may affect bone turnover through effects on parathyroid hormone levels or by direct effects on osteoclasts or osteoblasts.[95,96] There are no specific recommendations for bone mineral density screening for individuals taking tenofovir DF, but the HIVMA/IDSA Primary Care Guidance advise bone mineral density screening with DXA for all postmenopausal women with HIV and for men with HIV who are 50 years of age and older.[97]

- **Nephrotoxicity:** Tenofovir DF-associated renal toxicity may include 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).[29] Persons receiving tenofovir DF as part of HIV treatment, should not receive tenofovir DF if the creatinine clearance is less than 50 mL/min, unless the dose of tenofovir DF can be adjusted based on the degree of renal insufficiency. The HIVMA CKD Clinical Practice Guideline recommends avoiding tenofovir DF in any person with HIV who has a creatinine clearance less than 60 ml/min/1.73m². In addition, for persons taking HIV PrEP, tenofovir DF is not recommended in persons who have a creatinine clearance less than 60 mL/min. Individuals with tenofovir DF-associated nephrotoxicity may present with declining GFR, new proteinuria, new glycosuria, or other manifestations on routine screening.

- **Risk Factors for Nephrotoxicity:** Risk factors for tenofovir DF-associated nephrotoxicity include low CD4 cell count, hepatitis C coinfection, diabetes, older age, and baseline hepatic or renal dysfunction.[98,99] 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. Concomitant use of nephrotoxic, non-antiretroviral medications may also increase the risk of tenofovir DF-associated renal adverse effects.

- **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.[29] 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 are in the Adult and Adolescent ART Guidelines.[4] When clinically indicated, more frequent monitoring may be indicated. The following summarizes the recommendations from these guidelines:
  - Monitoring serum creatinine and GFR should be performed at baseline, 4 to 8 weeks after starting therapy, and every 6 months thereafter. More frequent monitoring may be indicated in persons with chronic kidney disease risk factors.
  - Urinalysis (including urine glucose and protein) should be performed at baseline when starting tenofovir-DF and monitored at least annually.
  - If the urinalysis is performed 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 persons with HIV 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 7). 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 calculating the 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.

• **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). In clinical practice, if tenofovir DF appears to be inducing renal adverse effects, one may consider switching it to an alternate agent or changing the regimen to one that avoids NRTIs altogether or avoids both tenofovir DF and tenofovir alafenamide.

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**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. 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. 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.[3] Note that delavirdine is no longer manufactured in the United States and will not be discussed further. Sine nevirapine is no longer used in clinical p

Doravirine

Doravirine is an NNRTI that is very well tolerated and has been associated with very few adverse effects.[102,103] In clinical trials, doravirine had an improved safety profile compared with efavirenz, with respect to cutaneous and neuropsychiatric adverse effects.[104] 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.[104]

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 the 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.[105,106] 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.[55,107] Studies have consistently demonstrated that efavirenz causes more unfavorable lipid changes than other NNRTI medications.[55] It is unclear, though, what impact efavirenz-induced dyslipidemia has on cardiovascular disease risk, especially given that HDL levels increase with efavirenz and these HDL changes may potentially confer a protective effect.[108,109]
- **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.[110,111,112] 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. These neuropsychiatric side effects include nightmares, impaired concentration, hallucinations, irritability, and depression.[113] 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.[114] 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 8) and (Figure 9).[115] Taking efavirenz with food significantly increases efavirenz plasma levels when compared with taking it without food. Taking efavirenz on an empty stomach at bedtime is recommended 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 10), which is significantly higher than reported rates of rash with doravirine, etravirine, or rilpivirine.[104,116,117] 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.
Hypovitaminosis D: Efavirenz has also been noted in studies to interfere with vitamin D metabolism, causing low vitamin D levels (sometimes leading to severely low levels and associated alkaline phosphatase elevations).\[^{118,119,120}\] The mechanism may be induction of the enzyme 24-hydroxylase, leading to inactivation of 25-hydroxy vitamin D and 1,25-dihydroxy vitamin D.

**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.\[^{121}\] 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 recommended or use to any extent in clinical practice.

- **Hypersensitivity Reaction:** Nevirapine has an FDA black box warning for possible life-threatening rash and hepatotoxicity, which can occur together or separately (Figure 11).\[^{122}\] If hepatotoxicity develops, it usually occurs as either an immune-mediated reaction, manifesting within the first 4 weeks of therapy, or as a nonimmune-mediated reaction that develops later (typically after 18 weeks of initiating therapy). Nevirapine-related hypersensitivity reactions occur more commonly in women and in persons with higher CD4 cell counts.\[^{123,124}\] Expert guidelines, 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\(^3\).\[^{2}\]

**Rilpivirine**

Rilpivirine is available alone, as part of several oral single-tablet regimens (rilpirine-tenofovir DF-emtricitabine, rilpirine-tenofovir alafenamide-emtricitabine, and durtegravir-rilpivirine), and as a component of the long-acting injectable cabotegravir plus rilpivirine. Three studies—ECHO, THRIVE, and STaR—compared oral rilpivirine with efavirenz (each given with two background NRTIs) and all three showed lower rates of drug discontinuation due to adverse effects in patients taking rilpivirine than in those taking efavirenz.\[^{114,116,125}\]

- **Cardiac QTc Interval Prolongation:** Studies performed with high-dose rilpivirine (3 to 12 times higher than the 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.\[^{126}\]
- **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.\[^{125}\]
- **Neuropsychiatric:** Rilpivirine has the potential to cause neuropsychiatric side effects, including depression, insomnia, headaches, and dizziness, but the risk is significantly lower than with efavirenz.\[^{116,127}\]
- **Injection Site Reactions:** With the long-acting injectable cabotegravir and rilpivirine, the major adverse effect associated with rilpivirine injections has been injection site reactions; in clinical trials, most of these reactions were graded as mild to moderate and the vast majority resolved within 7 days. The most frequent type of reaction was pain, followed much less frequently by nodules,
induration, and swelling.[36]
Pharmacologic Boosters

General Considerations

Ritonavir and cobicistat are pharmacokinetic enhancers that 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. As would be expected, both of these medications can significantly impact the levels of other concomitantly administered medications that are metabolized via the cytochrome P450 system, potentially 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).[128,129] 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 results in a benign 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.[130] 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.[41,130] For patients taking cobicistat-containing regimens, changes in serum creatinine greater than 0.4 mg/mL from baseline may indicate another cause and should prompt an evaluation.[129] In clinical trials, cobicistat was also associated with gastrointestinal symptoms, primarily nausea and diarrhea.[129]
Protease Inhibitors

There are currently 10 FDA-approved HIV protease inhibitors (PIs), but in the Adult and Adolescent ART Guidelines, none are designated in the category of Recommended Initial Regimens for Most People with HIV. The following discussion pertains to PIs used to treat HIV, not the PIs used to treat hepatitis C virus or SARS-CoV-2, or other infections. In clinical practice, when PI is used, it is usually darunavir (boosted with either cobicistat or ritonavir).

Gastrointestinal Adverse Effects

Gastrointestinal side effects (mainly diarrhea but also nausea, vomiting, and abdominal pain) were common with early PIs, particularly 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). In several trials, boosted darunavir and boosted atazanavir demonstrated lower rates of gastrointestinal side effects compared with the combination of lopinavir-ritonavir. 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 gastrointestinal intolerance.

Cardiovascular Risk

Protease inhibitors have been associated with dyslipidemia, insulin resistance, premature atherosclerosis, and myocardial infarction. 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. 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.

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. 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. Some persons taking PIs have developed symptomatic atrioventricular (AV) block. Accordingly, ritonavir-boosted PIs should be used with caution in persons 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 persons with hemophilia and HIV who take HIV PIs. In some of these cases, the bleeding was severe. The biologic mechanism remains unknown but may involve platelet dysfunction. Reports have documented individuals with HIV and hemophilia who have safely taken HIV PIs without bleeding complications. 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 persons 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. Clinically, the abnormal fat accumulation has manifested as marked increases in abdominal girth, breast enlargement, and development of a dorsocervical fat pad (Figure 12) and (Figure 13). 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), an enzyme responsible for converting unconjugated bilirubin to conjugated bilirubin (Figure 14). The inhibition of UGT1A1 by atazanavir causes an increase in indirect bilirubin and potentially jaundice, but it does not cause liver damage. The degree of hyperbilirubinemia typically fluctuates and will return to normal with discontinuation of atazanavir.

- **Nephrolithiasis**: Atazanavir-induced kidney stones develop in approximately 1% of persons taking ritonavir-boosted atazanavir. The onset of nephrolithiasis occurs, on average, 2 years after starting atazanavir. The urine sediment may show rod-shaped crystals and the actual stones are often composed of atazanavir and/or calcium phosphate. Atazanavir stones are typically radiolucent and therefore not evident on plain film radiograph or non-contrast computed tomography (CT). Crystal nephropathy can also occur in the absence of stones and should be suspected in persons with rising creatinine levels or sterile pyuria.

- **Cholelithiasis**: Several reports have been published that suggest ritonavir-boosted atazanavir is associated with an approximate two-fold increased risk of developing cholelithiasis. A separate study, however, failed to show an increased risk of cholelithiasis with ritonavir-boosted atazanavir when compared with other protease inhibitors.

Darunavir

Although darunavir is no longer recommended as initial antiretroviral therapy for most individuals with HIV, it remains a cornerstone of second-line and salvage antiretroviral therapy. Abdominal pain and diarrhea are the most common darunavir-related symptoms, occurring in approximately 5 to 14% of persons. The incidence of rash is approximately 10%, with most cases of mild severity. The mild rash typically begins during the first 4 weeks of treatment and resolves, even with continuation of darunavir. Severe skin rash has been reported in less than 1% of persons taking darunavir, which can be accompanied by fever and/or increases in hepatic aminotransferase levels. Darunavir should promptly be discontinued if a severe skin rash develops. Darunavir contains a sulfonamide moiety and persons 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 darunavir contraindication, but darunavir should be used with caution in this situation, especially if the prior sulfa reaction was severe.

Indinavir

Indinavir is an older protease inhibitor that is no longer used in clinical practice due to an increased risk of nephrotoxicity and a 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. Nephrolithiasis, or kidney stones, occurred in about one-fifth of patients treated with indinavir and some of these individuals developed significant renal insufficiency. In most cases, renal function improved upon withdrawal of
Any person with HIV who is still taking indinavir should have this medication switched to a more modern and less toxic agent.

**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.[3]

- **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.[150] Standard dosing of liquid solution of lopinavir-ritonavir requires taking 10 mL once daily or 5 mL twice daily.[150] The liquid lopinavir-ritonavir solution should not be administered with disulfiram. 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 no longer 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, 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.[] Any person with HIV who is still taking saquinavir should have this medication switched to a more modern and less toxic agent.

**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.[] Tipranavir should be avoided in persons at risk for intracranial hemorrhage, and it is contraindicated in persons with Child-Turcotte-Pugh Class B or C hepatic insufficiency.
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.

- Fostemsavir is generally well tolerated but should be used with caution in individuals with QTc prolongation or risk factors for that condition. The other entry inhibitors, like maraviroc and ibalizumab, are also typically well-tolerated, though ibalizumab requires regular infusions and does have a small risk of infusion reactions. 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.

- Dolutegravir can cause headache and insomnia and has been associated with greater weight gain than other INSTIs and other classes of antiretrovirals. Bictegravir has been associated in a similar way with excess weight gain.

- Abacavir can cause a hypersensitivity syndrome in persons who are HLA-B*5701 positive and use of this medication requires a baseline HLA-B*5701 screening test. Abacavir may also increase the risk of myocardial infarction compared with other NRTIs.

- 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. Tenofovir alafenamide has significantly lower adverse renal and bone mineral density effects than tenofovir DF.

- Efavirenz may cause significant neuropsychiatric side effects, including suicidality, and it is no longer a recommended antiretroviral for most individuals with HIV.

- 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.
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Figures

Figure 1 Weight Gain following Initiation of Antiretroviral Therapy

This retrospective observational cohort study analyzed data from 1,152 persons following their initiation of antiretroviral therapy. This included 351 persons receiving an integrase strand transfer inhibitor (135 on dolutegravir, 153 elvitegravir, and 63 raltegravir).

Figure 2 Weight Gain in NA-ACCORD Study by INSTI-Based Regimen

These data from the North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD) show the greatest weight gain at year 1 and 2 with regimens containing dolutegravir when compared to those with raltegravir or elvitegravir.

Figure 3 Impact of NRTI in Dolutegravir Related Weight Gain

This graph shows weight gain at week 48 after starting antiretroviral therapy, based on the regimen used. In both females and males, the combination of dolutegravir with tenofovir alafenamide-emtricitabine was associated with the most weight gain.

Figure 4 (Image Series) - Inhibition of Tubular Secretion of Creatinine (Image Series) - Figure 4 (Image Series) - Inhibition of Tubular Secretion of Creatinine

Image 4A: Renal Tubule and Promial Tubular Secretion of Creatinine

Approximately 15% of creatinine is actively secreted into the urine by the proximal tubule. Dolutegravir can inhibit the urine organic cation transporter 2 (OCT2), a protein involved in renal tubular secretion of creatinine.

Illustration by Casandra Mack and David H. Spach, MD
Image 4B: Organic Cation Transporter 2 (OCT2) and Normal Tubular Secretion of Creatinine

Organic cation transporter 2 (OCT2) is 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.

Illustration: David H. Spach, MD
Figure 4 (Image Series) - Inhibition of Tubular Secretion of Creatinine
Image 4C: Inhibition of Tubular Secretion of Creatinine by Bictegravir and Dolutegravir

Bictegravir and dolutegravir can inhibit OCT2, which 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: David H. Spach, MD
**Figure 5 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 6 Metabolism of Tenofovir DF and Tenofovir alafenamide Cellular Activation

A 25 mg dose of tenofovir alafenamide has 90% lower circulating plasma tenofovir levels when compared with a 300 mg dose of tenofovir DF.

Illustration: David H. Spach, MD
**Figure 7 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.

Figure 8 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 9 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 1000-4,000 µg/L (equivalent to 1-4 µg/mL).

Figure 10 Efavirenz-Associated Rash

Photograph by David H. Spach, MD
Figure 11 Nevirapine-Associated Rash

Photograph by David H. Spach, MD
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
**Figure 14 Mechanism for Atazanavir-Associated Increase in Serum Bilirubin**

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>4-8 Weeks after ART Initiation or Modification</th>
<th>Every 3 Months</th>
<th>Every 6 Months</th>
<th>Every 12 Months</th>
<th>Clinically Indicated</th>
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<td>HLA-B*5701</td>
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<td>If considering abacavir</td>
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<td>When monitoring CD4 count (if required by lab)</td>
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<td>Consider 1–3 months after ARV initiation or modification</td>
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<td>If normal at baseline but with CV risk</td>
<td>If normal at baseline, every 5 years or if clinically indicated</td>
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<tr>
<td>Random or Fasting Glucose$^e$</td>
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<td>Pregnancy Test$^h$</td>
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*The information contained in this table is based on information in the table Laboratory Testing for Initial Assessment and Monitoring of People with HIV Receiving Antiretroviral Therapy.

$^a$Serum Na, K, HCO3, Cl, BUN, creatinine, glucose, and Cr-based eGFR. Serum P should be monitored in patients with CKD who are on TDF-containing regimens.

$^b$More frequent monitoring may be indicated for patients with evidence of kidney disease (e.g., proteinuria, decreased glomerular dysfunction) or increased risk of renal insufficiency (e.g., patients with diabetes, hypertension).

$^c$CBC with differential should be done when a CD4 count is performed. When CD4 count is no longer being monitored, the recommended frequency of CBC with differential is once a year. More frequent monitoring may be indicated for people receiving medications that potentially cause cytopenia (e.g., TMP-SMX).
Laboratory Study | ART Initiation | 4-8 Weeks after ART Initiation or Modification | Every 3 Months | Every 6 Months | Every 12 Months | Clinically Indicated
--- | --- | --- | --- | --- | --- | ---

If random lipids are abnormal, fasting lipids should be obtained. Consult the American College of Cardiology/American Heart Association's [2018 Guideline on the Management of Blood Cholesterol](https://www.cardio.org/guideline) for diagnosis and management of patients with dyslipidemia.

If random glucose is abnormal, fasting glucose should be obtained. HbA1C is no longer recommended for diagnosis of diabetes in people with HIV on ART.

Consult the HIVMA/IDSA's [Clinical Practice Guideline for the Management of Chronic Kidney Disease in Patients Infected with HIV](https://www.hivma.org/guideline/ckd) for recommendations on managing patients with renal disease. More frequent monitoring may be indicated for patients with evidence of kidney disease (e.g., proteinuria, decreased glomerular dysfunction) or increased risk of renal insufficiency (e.g., patients with diabetes, hypertension).

Urine glucose and protein should be assessed before initiating tenofovir alafenamide (TAF)- or tenofovir DF (TDF)-containing regimens and monitored during treatment with these regimens.

For persons of childbearing potential.

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 people with HIV receiving antiretroviral therapy. September 21, 2022. [HIV.gov](https://www.hiv.gov)
### 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:
