



## **Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents Living with HIV**

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## Adverse Effects of Antiretroviral Agents (Last updated October 17, 2017; last reviewed October 17, 2017)

The overall benefits of viral suppression and improved immune function as a result of effective antiretroviral therapy (ART) far outweigh the risks associated with the adverse effects of some antiretroviral (ARV) drugs. However, adverse effects have been reported with the use of all ARV drugs and, in the earlier era of combination ART, adverse effects were among the most common reasons for switching or discontinuing therapy and for medication nonadherence.<sup>1</sup> Fortunately, newer ARV regimens are associated with fewer serious and intolerable adverse effects than regimens used in the past. Generally, less than 10% of ART-naïve patients enrolled in randomized trials have treatment-limiting adverse events. However, the long-term complications of ART can be underestimated, because most clinical trials use highly specific inclusion criteria when enrolling participants and the duration of participant follow-up is relatively short. As ART is now recommended for all patients regardless of CD4 T lymphocyte (CD4) cell count, and because therapy has to be continued indefinitely, the focus of patient management has evolved from identifying and managing early ARV-related toxicities to individualizing therapy to avoid long-term adverse effects such as bone or renal toxicity, dyslipidemia, insulin resistance, or accelerated cardiovascular disease. To achieve sustained viral suppression over a lifetime, both long-term and short-term ART toxicities must be anticipated and overcome. The clinician must consider potential adverse effects when selecting an ARV regimen, as well as the individual patient's comorbidities, concomitant medications, and prior history of drug intolerances.

Several factors may predispose individuals to adverse effects of ARV medications, such as:

- Concomitant use of medications with overlapping and additive toxicities
- Comorbid conditions that increase the risk of or exacerbate adverse effects (e.g., alcoholism or coinfection with viral hepatitis<sup>2,3</sup> may increase the risk of hepatotoxicity; psychiatric disorders may be exacerbated by efavirenz [EFV], rilpivirine [RPV], and, infrequently, by integrase strand transfer inhibitors [INSTIs];<sup>4,5</sup> and borderline or mild renal dysfunction increases the risk of nephrotoxicity from tenofovir disoproxil fumarate [TDF])
- Drug-drug interactions that may increase toxicities of ARV drugs or concomitant medications
- Genetic factors that predispose patients to abacavir (ABC) hypersensitivity reaction,<sup>6,7</sup> EFV neuropsychiatric toxicity **and QTc prolongation**,<sup>8,9</sup> and atazanavir (ATV)-associated hyperbilirubinemia.<sup>10</sup>

Information on the adverse effects of ARVs is outlined in several tables in the guidelines. [Table 14](#) provides clinicians with a list of the most common and/or severe ARV-associated adverse events for each drug class. The most common adverse effects of individual ARV agents are summarized in [Appendix B, Tables 1–6](#).

**Table 14. Common and/or Severe Adverse Effects Associated with Antiretroviral Therapy**, page 1 of 5

N/A indicates either that there are no reported cases for that particular side effect or that data for the specific ARV drug class are not available. See [Appendix B](#) for additional information listed by drug.

| Adverse Effect                    | Drug Class   |  |  |        |     |
|-----------------------------------|--|--|--|--------|-----|
|                                   | NRTIs  | NNRTIs   | PIs  | INSTIs | EIs |
| <b>Bleeding Events</b>            | N/A  | N/A  | Spontaneous bleeding, hematuria in hemophilia<br><br><b>TPV:</b> Intracranial hemorrhage is associated with CNS lesions, trauma, alcohol abuse, hypertension, coagulopathy, anticoagulant or antiplatelet agents, and vitamin E. | N/A    | N/A |
| <b>Bone Density Effects</b>       | <b>TDF:</b> Associated with greater loss of BMD than other NRTIs. Osteomalacia may be associated with renal tubulopathy and urine phosphate wasting.<br><br><b>TAF:</b> Smaller declines in BMD than with TDF. | Decreases in BMD observed after the initiation of any ART regimen. |  |        | N/A |
| <b>Bone Marrow Suppression</b>    | <b>ZDV:</b> Anemia, neutropenia  | N/A  | N/A  | N/A    | N/A |
| <b>Cardiac Conduction Effects</b> | N/A  | <b>RPV, EFV:</b> QTc prolongation                                  | <b>SQV/r, ATV/r, and LPV/r:</b> PR prolongation. Risk factors include pre-existing heart disease and other medications.<br><br><b>SQV/r:</b> QT prolongation. Obtain ECG before administering SQV.                               | N/A    | N/A |
| <b>Cardiovascular Disease</b>     | <b>ABC and ddI:</b> Associated with an increased risk of MI in some cohort studies. Absolute risk greatest in patients with traditional CVD risk factors.  | N/A  | <b>DRV, FPV, IDV, and LPV/r:</b> Associated with cardiovascular events in some cohorts.  | N/A    | N/A |
| <b>Cholelithiasis</b>             | N/A  | N/A  | <b>ATV:</b> Cholelithiasis and kidney stones may present concurrently.<br><br>Median onset is 42 months.   | N/A    | N/A |

Table 14. Common and/or Severe Adverse Effects Associated with Antiretroviral Therapy, page 2 of 5

| Adverse Effect                                  | Drug Class  |   |   |                                   |   |
|---|---|---|---|-----------------------------------|---|
|   | NRTIs   | NNRTIs  | PIs   | INSTIs                            | EIs   |
| <b>Diabetes Mellitus and Insulin Resistance</b> | ZDV, d4T, and ddI   | N/A   | Reported for some (IDV, LPV/r), but not all, PIs.   | N/A                               | N/A   |
| <b>Dyslipidemia</b>                             | <p><b>d4T &gt; ZDV &gt; ABC:</b> ↑ TG and LDL</p> <p><b>TAF:</b> ↑ TG, ↑ LDL, ↑ HDL (no change in TC:HDL ratio)</p> <p>TDF has been associated with lower lipid levels than ABC or TAF.</p>   | EFV: ↑TG, ↑LDL, ↑HDL  | <p><b>All RTV- or COBI-boosted PIs:</b> ↑ TG, ↑ LDL, ↑ HDL</p> <p><b>LPV/r and FPV/r &gt; DRV/r and ATV/r:</b> ↑ TG</p>   | <b>EVG/c:</b> ↑ TG, ↑ LDL, ↑ HDL  | N/A   |
| <b>Gastrointestinal Effects</b>                 | <p><b>ddI and ZDV &gt; other NRTIs:</b> Nausea and vomiting</p> <p><b>ddI:</b> Pancreatitis</p>   | N/A   | <p>GI intolerance (e.g., diarrhea, nausea, vomiting)</p> <p><b>NFV and LPV/r &gt; DRV/r and ATV/r:</b> Diarrhea</p>   | <b>EVG/c:</b> Nausea and diarrhea | N/A   |
| <b>Hepatic Effects</b>                          | <p><b>Reported with most NRTIs.</b></p> <p><b>ZDV, d4T, or ddI:</b> Steatosis</p> <p><b>ddI:</b> Prolonged exposure linked to noncirrhotic portal hypertension and esophageal varices.</p> <p><b>When TAF, TDF, 3TC, and FTC are withdrawn in patients with HBV/HIV coinfection or when HBV resistance develops:</b> Patients with HBV/HIV coinfection may develop severe hepatic flares.</p> | <p><b>EFV:</b> Fulminant hepatitis progressing to hepatic failure requiring transplantation or death have been reported.</p> <p><b>NVP:</b> Severe hepatotoxicity associated with skin rash or hypersensitivity. Two-week NVP dose escalation may reduce risk. Risk is greater for women with pre-NVP CD4 count &gt;250 cells/mm<sup>3</sup> and men with pre-NVP CD4 count &gt;400 cells/mm<sup>3</sup>.</p> <p>NVP should <b>never</b> be used for post-exposure prophylaxis.</p> <p>EFV and NVP <b>are not recommended</b> in patients with hepatic insufficiency (Child-Pugh class B or C).</p> | <p><b>All PIs:</b> Drug-induced hepatitis and hepatic decompensation have been reported; greatest frequency occurs with TPV/r.</p> <p><b>TPV/r:</b> <b>Contraindicated</b> in patients with hepatic insufficiency (Child Pugh class B or C).</p> <p><b>IDV, ATV:</b> Jaundice due to indirect hyperbilirubinemia.</p> | N/A                               | <b>MVC:</b> Hepatotoxicity with or without rash or HSRs reported. |

**Table 14. Common and/or Severe Adverse Effects Associated with Antiretroviral Therapy, page 3 of 5**

| Adverse Effect  | Drug Class   |   |     |  |  |
|---|--|---|-----|--|--|
|   | NRTIs  | NNRTIs  | PIs | INSTIs   | EIs  |
| <p><b>Hypersensitivity Reaction</b></p> <p>Excluding rash alone or Stevens-Johnson syndrome</p> | <p><b>ABC: Contraindicated</b> if HLA-B*5701-positive.</p> <p>Median onset for HSR is 9 days; 90% of reactions occur within first 6 weeks of treatment.</p> <p><b>HSR symptoms (in order of descending frequency):</b> Fever, rash, malaise, nausea, headache, myalgia, chills, diarrhea, vomiting, abdominal pain, dyspnea, arthralgia, and respiratory symptoms</p> <p>Symptoms worsen with continuation of ABC.</p> <p>Patients should not be rechallenged with ABC if HSR is suspected, regardless of their HLA-B*5701 status.</p> | <p><b>NVP:</b> Hypersensitivity syndrome of hepatotoxicity and rash that may be accompanied by fever, general malaise, fatigue, myalgias, arthralgias, blisters, oral lesions, conjunctivitis, facial edema, eosinophilia, renal dysfunction, granulocytopenia, or lymphadenopathy.</p> <p>Risk is greater for ARV-naive women with pre-NVP CD4 count &gt;250 cells/mm<sup>3</sup> and men with pre-NVP CD4 count &gt;400 cells/mm<sup>3</sup>. Overall, risk is higher for women than men. Two-week dose escalation of NVP reduces risk.</p> | N/A | <p><b>RAL:</b> HSR reported when RAL is given with other drugs also known to cause HSR. All ARVs should be stopped if HSR occurs.</p> <p><b>DTG:</b> Reported in &lt;1% of patients in clinical development program.</p> | <p><b>MVC:</b> HSR reported as part of a syndrome related to hepatotoxicity.</p> |
| <p><b>Lactic Acidosis</b></p>   | <p><b>Reported with NRTIs, especially d4T, ZDV, and ddI:</b> Insidious onset with GI prodrome, weight loss, and fatigue. May rapidly progress with tachycardia, tachypnea, jaundice, weakness, mental status changes, pancreatitis, and organ failure. Mortality high if serum lactate &gt;10 mmol/L.</p> <p>Women and obese patients at increased risk.</p>   | N/A   | N/A | N/A  | N/A  |

**Table 14. Common and/or Severe Adverse Effects Associated with Antiretroviral Therapy, page 4 of 5**

| Adverse Effect   | Drug Class   |   |                                  |   |            |
|--|--|---|----------------------------------|---|------------|
|  | NRTIs  | NNRTIs  | PIs                              | INSTIs  | EIs        |
| <b>Lipodystrophy</b>   | <b>Lipoatrophy: d4T &gt; ZDV.</b><br>More likely when NRTIs are coadministered with EFV than with an RTV-boosted PI.   | <b>Lipohypertrophy:</b> Trunk fat increase observed with EFV-, PI-, and RAL-containing regimens; however, causal relationship has not been established.   |                                  |   | N/A        |
| <b>Myopathy/<br/>Elevated<br/>Creatine<br/>Phosphokinase</b> | ZDV: Myopathy  | N/A   | N/A                              | <b>RAL, DTG:</b><br>↑ CPK, rhabdomyolysis, and myopathy or myositis have been reported.   | N/A        |
| <b>Nervous<br/>System/<br/>Psychiatric<br/>Effects</b>       | <b>d4T &gt; ddI:</b> Peripheral neuropathy (can be irreversible)<br><br><b>d4T:</b> Associated with rapidly progressive, ascending neuromuscular weakness resembling Guillain-Barré syndrome (rare). | <b>EFV:</b> Somnolence, insomnia, abnormal dreams, dizziness, impaired concentration, depression, psychosis, and suicidal ideation. Symptoms usually subside or diminish after 2 to 4 weeks. Bedtime dosing may reduce symptoms. Risk factors include presence of psychiatric illness, concomitant use of agents with neuropsychiatric effects, and increased EFV concentrations because of genetic factors or increased absorption with food. An association between EFV and suicidal ideation, suicide, and attempted suicide was found in a retrospective analysis of comparative trials.<br><br><b>RPV:</b> Depression, suicidality, sleep disturbances | N/A                              | <b>All INSTIs:</b> Insomnia, depression, and suicidality have been reported with INSTI use, primarily in patients with pre-existing psychiatric conditions. | N/A        |
| <b>Rash</b>  | <b>FTC:</b> Hyperpigmentation  | All NNRTIs  | <b>ATV, DRV, FPV, LPV/r, TPV</b> | <b>All INSTIs</b>   | <b>MVC</b> |

**Table 14. Common and/or Severe Adverse Effects Associated with Antiretroviral Therapy, page 5 of 5**

| Adverse Effect  | Drug Class   |  |  |   |     |
|---|--|--|--|---|-----|
|   | NRTIs  | NNRTIs   | PIs  | INSTIs  | EIs |
| <b>Renal Effects/<br/>Urolithiasis</b>                        | <p><b>TDF:</b> ↑ SCr, proteinuria, hypophosphatemia, urinary phosphate wasting, glycosuria, hypokalemia, and non-anion gap metabolic acidosis. Concurrent use of TDF with COBI- or RTV-containing regimens appears to increase risk.</p> <p><b>TAF:</b> Less impact on renal biomarkers and lower rates of proteinuria than TDF.</p> | <p><b>RPV:</b> Inhibits Cr secretion without reducing renal glomerular function.</p> | <p><b>ATV and LPV/r:</b> Increased risk of chronic kidney disease in a large cohort study.</p> <p><b>IDV:</b> ↑ SCr, pyuria, renal atrophy, or hydronephrosis</p> <p><b>IDV, ATV:</b> Stone or crystal formation. Adequate hydration may reduce risk.</p> <p><b>COBI (as a boosting agent for DRV or ATV):</b> Inhibits Cr secretion without reducing renal glomerular function.</p> | <p><b>DTG and COBI (as a boosting agent for EVG):</b> Inhibits Cr secretion without reducing renal glomerular function.</p> | N/A |
| <b>Stevens-Johnson Syndrome/<br/>Toxic Epidermal Necrosis</b> | Some reported cases for <b>ddl and ZDV.</b>  | <b>NVP &gt; DLV, EFV, ETR, RPV</b>   | Some reported cases for <b>FPV, DRV, IDV, LPV/r, and ATV.</b>  | <b>RAL</b>  | N/A |

**Key to Abbreviations:** 3TC = lamivudine; ABC = abacavir; ART= antiretroviral therapy; ARV = antiretroviral; ATV = atazanavir; ATV/r = atazanavir/ritonavir; BMD = bone mineral density; CD4 = CD4 T lymphocyte; Cr = creatinine; CNS = central nervous system; COBI = cobicistat; CPK = creatine phosphokinase; CVD = cardiovascular disease; d4T = stavudine; ddC = zalcitabine; ddl = didanosine; DLV = delavirdine; DRV = darunavir; DRV/r = darunavir/ritonavir; DTG = dolutegravir; ECG = electrocardiogram; EFV = efavirenz; EI = entry inhibitor; ETR = etravirine; EVG = elvitegravir; FPV = fosamprenavir; FPV/r = fosamprenavir/ritonavir; FTC = emtricitabine; GI = gastrointestinal; HBV = hepatitis B virus; HDL = high-density lipoprotein; HSR = hypersensitivity reaction; IDV = indinavir; INSTI = integrase strand transfer inhibitor; LDL = low-density lipoprotein; LPV/r = lopinavir/ritonavir; MI = myocardial infarction; MVC = maraviroc; NFV = nelfinavir; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; NVP = nevirapine; PI = protease inhibitor; RAL = raltegravir; RPV = rilpivirine; RTV = ritonavir; SCr = serum creatinine; SQV = saquinavir; SQV/r = saquinavir/ritonavir; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; TG = triglyceride; TPV = tipranavir; TPV/r = tipranavir/ritonavir; ZDV = zidovudine

## Switching Antiretroviral Therapy Because of Adverse Effects

Some patients experience treatment-limiting toxicities associated with ART. In these cases, ART must be modified. ART-associated adverse events can range from acute and potentially life-threatening to chronic and insidious. Serious life-threatening events (e.g., hypersensitivity reaction due to ABC, symptomatic hepatotoxicity, or severe cutaneous reactions) require the immediate discontinuation of all ARV drugs and re-initiation of an alternative regimen without overlapping toxicity. Toxicities that are not life-threatening (e.g., urolithiasis with ATV or renal tubulopathy with TDF) can usually be managed by substituting another ARV agent for the presumed causative agent without interrupting ART. Other, chronic, non-life-threatening adverse events (e.g., dyslipidemia) can be addressed either by switching the potentially causative agent for another agent or by managing the adverse event with additional pharmacological or nonpharmacological interventions. Management strategies must be individualized for each patient.

Switching from an effective ARV regimen (or agent) to a new regimen (or agent) must be done carefully and only when the potential benefits of the change outweigh the potential complications of altering treatment. The fundamental principle of regimen switching is to maintain viral suppression. When selecting a new agent or regimen, providers should be aware that resistance mutations, regardless of when the mutations were identified by genotypic resistance testing, are archived in HIV reservoirs. Even if resistance mutations are absent from subsequent resistance test results, they may reappear under selective drug pressure. It is critical that providers review the following information before implementing any treatment switch:

- The patient's medical and complete ARV history, including prior virologic responses to ART;
- All previous resistance test results;
- Viral tropism (if maraviroc [MVC] is being considered);
- HLA-B\*5701 status (if ABC is being considered);
- Comorbidities;
- Adherence history;
- Prior intolerances to any ARVs; and
- Concomitant medications and supplements, taking into consideration any potential drug interactions with ARVs.

A patient's willingness to accept new food or dosing requirements must also be assessed. In some cases, medication costs may also be a factor to consider before switching treatment. Signs and symptoms of comorbidities, adverse effects of concomitant medications, or HIV itself may mimic those of adverse effects caused by ART. Therefore, clinicians should investigate all potential causes for an adverse event. In the case of a severe adverse event, it may be necessary to discontinue or switch ARVs pending the outcome of such an investigation. For the first few months after an ART switch, the patient should be closely monitored for any new adverse events. The patient's viral load should also be monitored to assure continued viral suppression.

[Table 15](#) lists several major ART-associated adverse events and potential options to appropriately switch agents in an ARV regimen. The table focuses on the ARVs most commonly used in the United States and lists substitutions that are supported by ARV switch studies, the findings of comparative ARV trials and observational cohort studies, or expert opinion. Switching agents in a successful ARV regimen should be done carefully and only when the potential benefits of the change outweigh the potential complications of altering treatment.



**Table 15. Antiretroviral Therapy-Associated Adverse Events That Can Be Managed with Substitution of Alternative Antiretroviral Agent** (page 1 of 3)

| Adverse Event   | ARV Agent(s) or Drug Class                   |   | Comments   |
|---|--|---|--|
|   | Switch from                                  | Switch to   |  |
| <b>Bone Density Effects</b>   | TDF <sup>a</sup>                             | ABC <sup>b</sup> or TAF<br><br>NRTI-sparing regimens or regimens using only 3TC or FTC as the NRTI may be considered, if appropriate. | Declines in BMD have been observed upon initiation of most ART regimens. Switching from TDF to alternative ARV agents has been shown to increase bone density, but the clinical significance of this increase remains uncertain.<br><br>TAF is associated with smaller declines in BMD than TDF, and patients show improvement in BMD upon switching to TAF. The long-term impact of TAF on patients with osteopenia or osteoporosis is unknown; close clinical monitoring is recommended in this setting. |
| <b>Bone Marrow Suppression</b>  | ZDV  | TDF, TAF, or ABC <sup>b</sup>   | ZDV has been associated with neutropenia and macrocytic anemia.  |
| <b>Cardiac QTc Interval Prolongation</b>  | EFV, RPV                                     | A PI- or INSTI-based regimen  | High EFV and RPV exposures may cause QT prolongation.<br><br>Consider switching from EFV- or RPV-based regimens if patient is taking other medications with known risk of torsades de pointes, or in patients at higher risk of torsades de pointes.   |
| <b>Cardiovascular Events</b><br><br>Myocardial infarction, ischemic stroke  | ABC  | TDF, TAF, FTC, 3TC  | ABC use has been associated with cardiovascular disease and cardiac events in some, but not all, observational studies.<br><br>TDF has been associated with lower lipid levels than TAF.   |
|   | RTV- or COBI-boosted PI regimens, EFV, EVG/c | RAL, DTG, RPV   | RAL, DTG, and RPV have less effect on lipids.<br><br>Large observation cohorts have found an association between some PIs (DRV, FPV, IDV, LPV/r) and an increased risk of CV events. However, this association has not been seen with ATV. Further study is needed.  |
| <b>Central Nervous System, Neuropsychiatric Side Effects</b><br><br>Dizziness, suicidal ideation, abnormal dreams, depression | EFV, RPV                                     | ETR or a PI/c or PI/r<br><br>INSTIs may be considered with monitoring (see Comments column).  | In most patients, EFV-related CNS effects subside within 4 weeks after initiation of the drug. Persistent or intolerable effects should prompt substitution of EFV.<br><br>INSTIs are associated with insomnia. Depression and suicidality have been infrequently reported with INSTI use, primarily in patients with pre-existing psychiatric conditions.   |
| <b>Dyslipidemia</b><br><br>Hypertriglyceridemia (with or without elevated LDL level)  | RTV- or COBI-boosted regimens, EFV, EVG/c    | RAL, DTG, RPV   | Elevated TG and LDL levels are more common with LPV/r and FPV/r than with other RTV-boosted PIs. Improvements in TG and LDL levels have been observed with switch from LPV/r to ATV or ATV/r. <sup>c</sup>   |

**Table 15. Antiretroviral Therapy-Associated Adverse Events That Can Be Managed with Substitution of Alternative Antiretroviral Agent** (page 2 of 3)

| Adverse Event   | ARV Agent(s) or Drug Class   |   | Comments  |
|---|--|---|---|
|   | Switch from  | Switch to   |   |
| <b>Gastrointestinal Effects</b><br>Nausea, diarrhea                     | LPV/r  | ATV/c, ATV/r, DRV/c, DRV/r, RAL, DTG, EVG/c       | GI intolerance is common with boosted PIs and is linked to the total dose of RTV. More GI toxicity is seen with LPV/r than with ATV/r or DRV/r. GI effects are often transient, and do not warrant substitution unless persistent and intolerable.                    |
|   | Other RTV- or COBI-boosted regimens  | RAL, DTG, NNRTIs                                  | In a trial of treatment-naïve patients, rates of diarrhea and nausea were similar for EVG/c/TDF/FTC and ATV/r plus TDF/FTC.   |
| <b>Hypersensitivity Reaction</b>  | ABC  | TDF or TAF  | Never rechallenge with ABC following a suspected HSR, regardless of the patient's HLA-B*5701 status.  |
|   | NVP, EFV, ETR, RPV   | Non-NNRTI ART                                     | Risk of HSR with NVP is higher for women and those with high CD4 cell counts.   |
|   | DTG, RAL   | Non-INSTI ART                                     | Reactions to NVP, ETR, RAL, DTG, and MVC may be accompanied by elevated liver transaminases.  |
|   | MVC  | Suitable alternative ART                          |   |
| <b>Insulin Resistance</b>   | LPV/r, FPV/r   | INSTI, RPV  | Results of switch studies have been inconsistent. Studies in HIV-negative patients suggest a direct causal effect of LPV/r (and IDV) on insulin resistance. However, traditional risk factors may be stronger risk factors for insulin resistance than use of any PI. |
| <b>Jaundice and Icterus</b>   | ATV, ATV/c, ATV/r  | DRV/c, DRV/r, INSTI, or NNRTI                     | Increases in unconjugated bilirubin are common with ATV and generally do not require modification of therapy unless resultant symptoms are distressing to the patient.  |
| <b>Lipoatrophy</b><br>Subcutaneous fat wasting of limbs, face, buttocks | d4T, ZDV   | TDF, TAF, or ABC <sup>b</sup>                     | Peripheral lipoatrophy is a legacy of prior thymidine analog (d4T and ZDV) use. Switching from these ARVs prevents worsening lipoatrophy, but fat recovery is typically slow (may take years) and incomplete.   |
| <b>Lipohypertrophy</b>  | Accumulation of visceral, truncal, dorso-cervical, and breast fat has been observed during ART, particularly during use of older PI-based regimens (e.g., IDV), but whether ART directly causes fat accumulation remains unclear. There is no clinical evidence that switching to another first line regimen will reverse weight or visceral fat gain. |   |   |
| <b>Rash</b>   | NNRTIs (especially NVP and EFV)  | PI- or INSTI-based regimen                        | Mild rashes developing after initiation of NNRTIs other than NVP rarely require treatment switch. When serious rash develops due to any NNRTI, switch to another drug class.  |
|   | DRV/c, DRV/r   | ATV/c, ATV/r, or another drug class (e.g., INSTI) | Mild rashes following DRV/r use may resolve with close follow-up only. For more severe reactions, change to an alternative boosted PI or an agent from another drug class.  |

**Table 15. Antiretroviral Therapy-Associated Adverse Events That Can Be Managed with Substitution of Alternative Antiretroviral Agent** (page 3 of 3)

| Adverse Event  | ARV Agent(s) or Drug Class |  | Comments   |
|--|----------------------------|--|--|
|  | Switch from                | Switch to  |  |
| <b>Renal Effects</b><br>Including proximal renal tubulopathy and elevated creatinine | TDF <sup>a</sup>           | ABC, <sup>b</sup> or TAF (for patients with CrCl >30 mL/min), NRTI-sparing regimens, or regimens using only 3TC or FTC as the NRTI may be considered if appropriate. | TDF may cause tubulopathy.<br><br>Switching from TDF to TAF is associated with improvement in proteinuria and renal biomarkers. The long-term impact of TAF on patients with pre-existing renal disease, including overt proximal tubulopathy, is unknown, and close clinical monitoring is recommended in this setting. |
|  | ATV/c, ATV/r, LPV/r        | DTG, RAL, or NNRTI   | COBI and DTG, and to a lesser extent RPV, can increase SCr through inhibition of creatinine secretion. This effect does not affect glomerular filtration. However, assess patient for renal dysfunction if SCr increases by >0.4 mg/dL.  |
| <b>Stones</b><br>Nephrolithiasis and cholelithiasis                                  | ATV, ATV/c, ATV/r          | DRV/c, DRV/r, INSTI, or NNRTI  | Assuming that ATV is believed to be causing the stones.  |

<sup>a</sup> In patients with chronic active HBV infection, another agent active against HBV should be substituted for TDF.

<sup>b</sup> ABC should be used only in patients known to be HLA-B\*5701-negative.

<sup>c</sup> TDF reduces ATV levels; therefore, unboosted ATV should not be coadministered with TDF. Long-term data for unboosted ATV are unavailable.

**Key to Abbreviations:** ABC = abacavir; ART = antiretroviral therapy; ARV = antiretroviral; ATV = atazanavir; ATV/c = atazanavir/cobicistat; ATV/r = atazanavir/ritonavir; BMD = bone mineral density; CD4 = CD4 T lymphocyte; CNS = central nervous system; COBI = cobicistat; CrCl = creatine clearance; CV = cardiovascular; d4T = stavudine; DRV = darunavir; DRV/c = darunavir/cobicistat; DRV/r = darunavir/ritonavir; DTG = dolutegravir; EFV = efavirenz; ETR = etravirine; EVG/c = elvitegravir/cobicistat; FPV/r = fosamprenavir/ritonavir; FTC = emtricitabine; GI = gastrointestinal; HBV = hepatitis B virus; HSR = hypersensitivity reaction; IDV = indinavir; INSTI = integrase strand transfer inhibitor; LDL = low-density lipoprotein; LPV/r = lopinavir/ritonavir; MVC = maraviroc; NNRTI = non-nucleoside reverse transcriptase inhibitor; NVP = nevirapine; PI = protease inhibitor; PI/c = protease inhibitor/cobicistat; PI/r = protease inhibitor/ritonavir; RAL = raltegravir; RPV = rilpivirine; RTV = ritonavir; SCr = serum creatinine; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; TG = triglycerides; ZDV = zidovudine

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