Adverse Effects of Antiretroviral Medications

This is a PDF version of the following document:
Module 3: Antiretroviral Therapy
Lesson 2: Adverse Effects of Antiretroviral Medications

You can always find the most up-to-date version of this document at
https://www.hiv.uw.edu/go/antiretroviral-therapy/adverse-effects/core-concept/all.

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, effects on bone mineralization, metabolic effects, gastrointestinal symptoms, cardiovascular effects, hypersensitivity, skin reactions, liver injury, insomnia, and neuropsychiatric manifestations.[2] In general, newer antiretroviral medications have a markedly improved safety profile compared with older antiretroviral medications, and this is reflected in the recommendations issued in the Adult and Adolescent ARV Guidelines.[3] Clinicians who provide care to persons with HIV should have an understanding of the basic toxicity profile of antiretroviral medications and knowledge of recommended monitoring strategies, keeping in mind that most individuals tolerate antiretroviral medications well and experience only mild or no side effects. This Topic Review will explore antiretroviral-associated adverse effects by medication class and by specific medication. Issues related to drug interactions with antiretroviral medications are addressed in this same module in the lesson on 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]

Table 1.

Laboratory Monitoring for Antiretroviral Therapy-Related Toxicities*

Laboratory Study	ART Initiation	4-8 Weeks after ART Initiation or Modification	Every 3 Months	Every 6 Months	Every 12 Months	Clinically Indicated
HLA-B *5701	√ If considering ab					

Laboratory Study	ART Initiation	4-8 Weeks after ART Initiation or Modification	Every 3 Months	Every 6 Months	Every 12 Months	Clinically Indicated
	acavir					
Basic metabolic[a,b]	√	√		√		√
ALT, AST, total bilirubin	√	√		√		√
CBC with differential[c]	√		√ When monitoring CD4 count	√ When monitoring CD4 count	√ When no longer monitoring CD4 count	√
Lipid[d]	√	Consider 1–3 months after ARV initiation or modification			√ If normal at baseline but with CV risk	If normal at baseline, every 5 years or if clinically indicated
Random or fasting glucose[e]	√					√
Urinalysis[f,g]	√				√ If on tenofovir DF or tenofovir alafenamide	√ E.g., in patients with chronic kidney disease or diabetes me

Laboratory Study	ART Initiation	4-8 Weeks after ART Initiation or Modification	Every 3 Months	Every 6 Months	Every 12 Months	Clinically Indicated
						llitus
Pregnancy test[h]	√					√

*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).

[d]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.

[e]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.

[f]Consult the HIVMA/IDSA's Clinical Practice Guideline for the Management of Chronic Kidney Disease in Patients Infected with HIV for recommendations on managing patients with renal disease. More frequent monitoring may

Laboratory Study	ART Initiation	4-8 Weeks after ART Initiation or Modification	Every 3 Months	Every 6 Months	Every 12 Months	Clinically Indicated
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). [g]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. [h]For women 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 the approval of other, better tolerated agents for salvage antiretroviral therapy.

Fostemsavir

Fostemsavir is the only attachment inhibitor approved for use by the U.S. Food and Drug Administration (FDA), and it is primarily used in heavily treatment-experienced adults with multidrug-resistant HIV.[7] Fostemsavir is an oral medication that, after ingestion, is hydrolyzed to the active drug—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 was shown to significantly prolong the QTc interval when given at a dose of 2,400 mg twice daily, which is 4 times the recommended daily dose.[9] Caution is thus advised if using fostemsavir 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 coreceptor. In clinical practice and in clinical trials, maraviroc has been well tolerated, and serious toxicity has been quite rare.[11,12] Maraviroc has been linked to very rare cases of severe rash with systemic symptoms. In addition, there are rare cases of hepatotoxicity, which may be preceded by severe rash and allergic symptoms in patients taking maraviroc.[13,14] Since maraviroc binds directly to a host (human) CCR5 coreceptor, this initially raised concerns about potential maraviroc-induced problems with host immune function or cancer surveillance. Clinical trial data and clinical experience have not shown an excess of infections or malignancies, with the exception that maraviroc may increase the risk of developing symptomatic West Nile virus infection.[11,15,16]

Integrase Strand Transfer Inhibitors

In general, integrase strand transfer inhibitors (INSTIs) are well tolerated and cause minimal drug interactions. In clinical trials, the most frequently reported adverse effects were headache, nausea, diarrhea, insomnia, and fatigue; these side effects, however, were typically mild and not severe enough to warrant stopping therapy.[1] Rare cases of mood changes or new onset of psychiatric disorders have been observed with INSTIs.[2,17,18]

Adverse Effects Observed with Bictegravir and Dolutegravir

Weight Gain

Several studies have concluded that INSTIs, particularly dolutegravir, lead to greater weight gain than other classes of antiretrovirals; dolutegravir-associated weight gain appears to be more pronounced when dolutegravir is combined with tenofovir alafenamide than with tenofovir DF (Figure 1).[19,20,21,22] Available data also suggest weight gain is relatively greater in persons taking bictegravir-tenofovir alafenamide-emtricitabine than in persons taking antiretroviral therapy with other anchor drugs, such as boosted elvitegravir, a non-nucleoside reverse transcriptase inhibitor, or a boosted protease inhibitor.[23] 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. The mechanism and clinical significance are unclear. Research is ongoing to confirm whether INSTIs directly cause changes to appetite or weight or whether the associations are solely due to comparisons to drugs that suppress weight gain, like efavirenz. Ongoing studies are also evaluating the optimal strategy to address INSTI-associated excess weight gain, if it occurs. To date, guidelines do not recommend altering the choice of initial antiretroviral therapy due to the potential for weight gain and guidelines specify that it remains unclear whether switching from an INSTI to an alternate anchor drug leads to reversal of weight gain.[2]

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 2).[24] 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.[25,26] These changes in serum creatinine caused by dolutegravir and bictegravir are usually 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.[27,28,29] There are no known serious adverse effects associated with bictegravir. Available studies suggest the increases in serum creatinine associated with bictegravir are slightly less than with dolutegravir the increases are benign.[28,30]

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 injectable cabotegravir are injection site reactions, including pain, nodules, induration, and swelling.[31,32,33] The injection site reactions typically become less frequent over time while receiving long-acting injectable cabotegravir.[32]

Dolutegravir

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

- **Insomnia**: In randomized trial settings, the incidence of insomnia in patients taking dolutegravir ranged from 3 to 15%.[34,35] 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).[35] In practice, it is a rare cause of intolerability of dolutegravir.
- **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 3).[35,36]

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.[37,38] Elvitegravir-based regimens are infrequently used now. Compared with boosted elvitegravir, dolutegravir or bictegravir are usually better tolerated and have fewer drug interactions.

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 are usually favored over raltegravir, because raltegravir has a lower barrier to resistance and higher pill burden. Most individuals tolerate raltegravir well. The potential toxicities listed below have been reported, but rarely occur 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.[39,40] Concurrent use of a statin medication, which can also cause elevations in creatine kinase, likely increases this risk.[40]
- **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.[40]
- **Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis**: Rash and severe systemic hypersensitivity reactions have rarely been reported in patients taking a regimen that included raltegravir.[41,42,43]

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, lipoatrophy, and possibly lipodystrophy syndrome.[44,45,46,47] Since didanosine, stavudine, and zidovudine are rarely used in current clinical practice (and manufacturing of didanosine and stavudine has been discontinued), these adverse effects will not be reviewed in further detail. If NRTI-related peripheral neuropathy and/or lipoatrophy develops, it usually only partially reverses or does not reverse at all, when discontinuing the offending medication.[44]

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.[48,49] 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.[50,51] Switching from tenofovir DF to tenofovir alafenamide, which is often done in clinical practice, may lead to a slight rise in all serum lipid parameters; the cause of the increase in lipids is at least partly due to the removal of the mild lipid-lowering effects of tenofovir DF and the long-term clinical consequences have not been confirmed.

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 have a negative HLA-B*5701 screening test.[3]

- **Cardiovascular Risk**: Abacavir has been associated with cardiovascular disease in some studies, but the data on this issue are conflicting.[52,53,54,55] In the Strategies for the Management of Antiretroviral Therapy (SMART) trial, a sub-analysis found that patients taking abacavir had a higher rate of cardiovascular disease than persons taking other NRTIs.[52] 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.[56,57] 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.[55] In light of these concerning but conflicting findings, most experts recommend avoiding abacavir in persons with cardiovascular disease (or significant risk factors for cardiovascular disease). The mechanism by which abacavir may increase the risk of ischemic cardiovascular events has been proposed to relate to platelet activation and aggregation.[58,59,60]
- **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 .[61,62] Signs and symptoms of abacavir hypersensitivity typically develop within 6 weeks of starting abacavir and include fever, rash, malaise, gastrointestinal effects, and respiratory symptoms.[62,63] 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]

Table 2.

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

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

Source:

- Martin MA, Kroetz DL. Abacavir pharmacogenetics--from initial reports to standard of care. Pharmacotherapy. 2013;33:765-75. [PubMed Abstract]

Emtricitabine and Lamivudine

Emtricitabine and lamivudine have the best tolerability and safety profile among all the NRTIs.[64,65,66] 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.[67]

Tenofovir alafenamide

Tenofovir alafenamide is available as a component of multiple fixed-dose combination tablets. When compared with tenofovir DF, tenofovir alafenamide generates significantly lower serum tenofovir levels, which may offer a relatively better renal and bone safety profile (Figure 4).[68,69,70,71] Switching from tenofovir DF to tenofovir alafenamide results in improved glomerular filtration rate, glomerular and tubular proteinuria, and bone mineral density.[72,73] 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.[71,74] Some clinical trials and retrospective data suggest that use of tenofovir alafenamide leads to more weight gain than the use of tenofovir DF, but the mechanism and clinical significance are not known.[21,75]

- **Renal Monitoring on Tenofovir alafenamide**: Persons receiving tenofovir alafenamide should have serum creatinine obtained at baseline, 4-8 weeks after starting therapy, and every 6 months thereafter.[4] 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.[4]

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.[37,76] The main adverse effects associated with tenofovir DF are decreases in bone mineral density and renal toxicity.[71,77] 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.[78]

- **Bone Demineralization**: Multiple studies have specifically implicated tenofovir DF use as a risk factor for reduced bone mineral density.[37,71,79] 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.[80] 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.[81,82] There are no specific recommendations for bone mineral density screening for individuals taking tenofovir DF, but use of tenofovir DF should be considered a risk factor for osteopenia and osteoporosis.
- **Nephrotoxicity**: Tenofovir DF-associated renal toxicity may include gradual declines in glomerular filtration rate (GFR), phosphate wasting, proteinuria, glycosuria, and Fanconi syndrome (generalized proximal tubule dysfunction manifesting as type 2 renal tubular acidosis and phosphate wasting).[26] According to the FDA package insert, the dosing frequency of tenofovir DF can be reduced if the creatinine clearance falls to below 50 mL/min, but most clinicians would instead choose an alternate antiretroviral agent in this setting (both to reduce the risk of inducing further renal insufficiency and because the recommended dosing of tenofovir DF in this situation may be difficult to adhere to, such as dosing every 48 or every 72 to 96 hours). For persons taking HIV PrEP, tenofovir DF is not recommended if the creatinine clearance is less than 60 mL/min.
- **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.[83,84] 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.[26] Additional available guidelines for monitoring patients for renal dysfunction are in the Adult and Adolescent ARV Guidelines.[4] More frequent monitoring may be indicated in certain clinical situations, including the presence of risk factors for renal dissease. 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 and shows proteinuria of 1+ or higher, then a quantitative follow-up test is indicated, either an albumin-to-creatinine ratio or a protein-to-creatinine ratio.
- **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 5).[26] 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.[26] A result between 10 and 20% is considered indeterminate. 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 to 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 a decline in renal function. Tests that quantify proteinuria are useful in this scenario, and 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.[26] New or worsening proteinuria may indicate a need to change tenofovir DF, particularly if associated with a decline in renal function.
- **Discontinuing or Switching Tenofovir DF because of Nephrotoxicity**: 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 m^2), 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).[26] 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. In this setting, if tenofovir DF is stopped, the renal dysfunction tends to improve over time, but sometimes improvement is slow and in rare cases the renal toxicity effects persist.[85]

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.[86,87] In most circumstances, a person taking zidovudine should have their antiretroviral regimen updated to a new regimen that does not include zidovudine.

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] Delavirdine is no longer manufactured in the United States and will not be discussed further.

Doravirine

Doravirine is an NNRTI that is very well tolerated and has been associated with very few adverse effects.[88,89] In clinical trials, doravirine, when compared with efavirenz, had fewer cutaneous and neuropsychiatric adverse effects.[90] 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.[90]

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. Due to the neuropsychiatric risks and other side effects described below, clinicians should choose other options than efavirenz for starting antiretroviral therapy and should have a low threshold to recommend a change of efavirenz to a newer, safer option for individuals still taking this agent.

- **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.[91,92] This issue is particularly important when patients are taking medications other than efavirenz that may cause QT prolongation.
- **Dyslipidemia**: Efavirenz has also been shown to increase lipid parameters.[51,93] 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.[94,95]
- **Hepatotoxicity**: Reports have documented rare cases of fulminant hepatitis in persons receiving efavirenz, progressing in some cases to hepatic failure that required liver transplantation, or resulted in death.[96,97,98] 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, depression, and risk of suicide.[99,100] Efavirenz should be avoided in persons with preexisting mental health conditions. Pharmacokinetic studies have shown that higher plasma efavirenz levels correlate with central nervous system adverse effects (Figure 6).[101] Taking efavirenz with food significantly increases efavirenz plasma levels when compared with taking it without food and thus it is recommended to take efavirenz on a relatively empty stomach.
- **Rash**: Clinical trials have demonstrated that approximately 15% of patients (range 10 to 25%) treated with efavirenz develop a rash (Figure 7), which is significantly higher than reported rates of rash with doravirine, etravirine, or rilpivirine.[90,102,103] 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).[104,105,106]

Etravirine

Etravirine is an NNRTI that is primarily used for 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.[107] There are rare reports (less than 0.1%) of severe rash, including Stevens-Johnson syndrome, toxic epidermal necrosis, erythema multiforme, and DRESS (drug rash with eosinophilia and systemic symptoms) syndrome.

Nevirapine

Nevirapine confers a risk of serious adverse effects. 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 used 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 8).[108] 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.[109,110] 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 (rilpivirine-tenofovir DF-emtricitabine, rilpivirine-tenofovir alafenamide-emtricitabine, and dolutegravir-rilpivirine), and as a component of the long-acting injectable cabotegravir plus rilpivirine. Multiple studies comparing oral rilpivirine with efavirenz (each given with two NRTIs) have shown lower rates of drug discontinuation of rilpivirine due to fewer adverse effects than with efavirenz.[100,102,111]

- **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.[112]
- **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.[111]
- **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.[102,113]
- **Injection Site Reactions**: With the long-acting injectable rilpivirine, which is given in combination with long-acting injectable cabotegravir, the major adverse effect 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.[33]

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 coadministered 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 protease inhibitor (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 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).[114,115] 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 the actual glomerular filtration rate.[116] 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.[37,116] 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.[115] In clinical trials, cobicistat was also associated with gastrointestinal symptoms, primarily nausea and diarrhea.[115]

Protease Inhibitors

The following discussion pertains to the adverse effects of protease inhibitors (PIs) used to treat HIV, not the PIs used to treat hepatitis C virus (HCV), SARS-CoV-2, or other infections. In addition, the following will not include a discussion of the adverse effects of amprenavir, fosamprenavir, indinavir, nelfinavir, saquinavir, or tipranavir, since these PIs have either been discontinued or are very rarely used in clinical practice.[2] In modern clinical practice, when a PI is used, it is usually darunavir (boosted with either cobicistat or ritonavir).

Adverse Effects Observed with More than One PI

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).[1] In several trials, boosted darunavir and boosted atazanavir demonstrated lower rates of gastrointestinal side effects compared with the combination of lopinavir-ritonavir.[117,118,119] 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 intolerability.[120,121,122]

Cardiovascular Risk

Protease inhibitors have been associated with dyslipidemia, insulin resistance, premature atherosclerosis, and myocardial infarction.[123] 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.[124] 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.[56]

Cardiac Conduction Abnormalities

Several studies have revealed PR prolongation as a potential cardiac conduction complication of ritonavir-boosted PIs, including ritonavir-boosted atazanavir and lopinavir-ritonavir.[2,125] 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.

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) have 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 9).[126] 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 when atazanavir is discontinued.[2] .
- **Nephrolithiasis**: Atazanavir-induced kidney stones develop in approximately 1% of persons taking ritonavir-boosted atazanavir.[127,128,129] The onset of nephrolithiasis occurs, on average, 2 years after starting atazanavir.[130] 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).[131] 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 approximately two-fold increased risk of developing cholelithiasis.[132,133,134] A separate study, however, failed to show an increased risk of cholelithiasis with ritonavir-boosted atazanavir when compared with other protease inhibitors.[128,129]

Darunavir

Although darunavir is no longer recommended as initial antiretroviral therapy for most individuals with HIV (unless an individual has received injectable cabotegravir for HIV PrEP prior to the diagnosis of 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.[119,135] The incidence of rash is approximately 10%, with most cases of mild severity.[119,135] The mild rash typically begins during the first 4 weeks of treatment and resolves even with the 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.[119,135] 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.

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 controlled trial comparing the 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.[136] Standard dosing of the lopinavir-ritonavir liquid solution requires taking 10 mL once daily or 5 mL twice daily.[136] 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.

Capsid Inhibitors

Lenacapavir

The FDA has approved one agent in the capsid inhibitor class, lenacapavir, which is approved as part of antiretroviral therapy for heavily treatment-experienced individuals with multiclass drug resistance. The drug is administered as a subcutaneous injection every 6 months (along with a brief oral lead-in, given either as two days of oral pills starting on the same day as the first subcutaneous injection, or given as oral pills on days 1, 2, and 8, followed by an initial injection on day 15).[137] In clinical trials, the most common adverse effects of lenacapavir injections were nausea and injection site reactions; most injection site reactions were mild and did not necessitate discontinuation of the drug.[138] The most common types of injection site reactions were pain, swelling, erythema, nodule formation, and induration. Otherwise, the most common adverse effects were nausea (experienced by 13% of participants), constipation (experienced by 11%), and diarrhea (experienced by 11%); again, most side effects were mild and did not lead to discontinuation of the lenacapavir.

Summary Points

- Antiretroviral therapy has overwhelming benefits and has transformed HIV infection into a manageable chronic disease for most patients, but antiretroviral therapy may have some adverse effects.
- 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 the active tubular secretion of creatinine, but these drugs do not typically impact the actual glomerular filtration rate.
- Dolutegravir can cause headaches and insomnia. Bictegravir and dolutegravir have been associated with greater weight gain than other INSTIs and other classes of antiretrovirals.
- Abacavir can cause 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 proteinuria, 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..
- Atazanavir often causes unconjugated hyperbilirubinemia, which is not dangerous and improves with a switch to another antiretroviral medication. Atazanavir is also associated with nephrolithiasis and cholelithiasis.
- The most common side effects of darunavir (boosted with cobicistat or ritonavir) 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.
- The most common complication of lenacapavir is injection site reactions, which typically are mild and resolve within a few days. Injection site reactions are also the most common adverse effect with long-acting, intramuscular cabotegravir and rilpivirine.

Citations

1. Fernandez-Montero JV, Eugenia E, Barreiro P, Labarga P, Soriano V. Antiretroviral drug-related toxicities - clinical spectrum, prevention, and management. Expert Opin Drug Saf. 2013;12:697-707.
[PubMed Abstract] -

2. 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. Limitations to treatment safety and efficacy: adverse effects of antiretroviral agents. May 26, 2023.
[HIV.gov] -

3. 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. What to Start. Initial Combination Antiretroviral Regimens for People With HIV. September 12, 2024.
[HIV.gov] -

4. 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] -

5. Mirza RA, Turiansky GW. Enfuvirtide and cutaneous injection-site reactions. J Drugs Dermatol. 2012;11:e35-8.
[PubMed Abstract] -

6. Wallace BJ, Tan KB, Pett SL, Cooper DA, Kossard S, Whitfeld MJ. Enfuvirtide injection site reactions: a clinical and histopathological appraisal. Australas J Dermatol. 2011;52:19-26.
[PubMed Abstract] -

7. Cahn P, Fink V, Patterson P. Fostemsavir: a new CD4 attachment inhibitor. Curr Opin HIV AIDS. 2018;13:341-345.
[PubMed Abstract] -

8. Kozal M, Aberg J, Pialoux G, et al. Fostemsavir in Adults with Multidrug-Resistant HIV-1 Infection. N Engl J Med. 2020;382:1232-43.
[PubMed Abstract] -

9. Lagishetty C, Moore K, Ackerman P, Llamoso C, Magee M. Effects of Temsavir, Active Moiety of Antiretroviral Agent Fostemsavir, on QT Interval: Results From a Phase I Study and an Exposure-Response Analysis. Clin Transl Sci. 2020;13:769-776.
[PubMed Abstract] -

10. Emu B, Fessel J, Schrader S, et al. Phase 3 Study of Ibalizumab for Multidrug-Resistant HIV-1. N Engl J Med. 2018;379:645-54.
[PubMed Abstract] -

11. Hardy WD, Gulick RM, Mayer H, et al. Two-year safety and virologic efficacy of maraviroc in treatment-experienced patients with CCR5-tropic HIV-1 infection: 96-week combined analysis of MOTIVATE 1 and 2. J Acquir Immune Defic Syndr. 2010;55:558-64.
[PubMed Abstract] -

12. Sierra-Madero J, Di Perri G, Wood R, et al. Efficacy and safety of maraviroc versus efavirenz, both with

zidovudine/lamivudine: 96-week results from the MERIT study. HIV Clin Trials. 2010;11:125-32.
[PubMed Abstract] -

13. Rockstroh JK, Plonski F, Bansal M, et al. Hepatic safety of maraviroc in patients with HIV-1 and hepatitis C and/or B virus: 144-week results from a randomized, placebo-controlled trial. Antivir Ther. 2017;22:263-269.
[PubMed Abstract] -

14. Wasmuth JC, Rockstroh JK, Hardy WD. Drug safety evaluation of maraviroc for the treatment of HIV infection. Expert Opin Drug Saf. 2012;11:161-74.
[PubMed Abstract] -

15. Glass WG, McDermott DH, Lim JK, et al. CCR5 deficiency increases risk of symptomatic West Nile virus infection. J Exp Med. 2006;203:35-40.
[PubMed Abstract] -

16. Lim JK, McDermott DH, Lisco A, et al. CCR5 deficiency is a risk factor for early clinical manifestations of West Nile virus infection but not for viral transmission. J Infect Dis. 2010;201:178-85.
[PubMed Abstract] -

17. Harris M, Larsen G, Montaner JS. Exacerbation of depression associated with starting raltegravir: a report of four cases. AIDS. 2008;22:1890-2.
[PubMed Abstract] -

18. Kheloufi F, Allemand J, Mokhtari S, Default A. Psychiatric disorders after starting dolutegravir: report of four cases. AIDS. 2015;29:1723-5.
[PubMed Abstract] -

19. Bourgi K, Rebeiro PF, Turner M, et al. Greater Weight Gain in Treatment-naive Persons Starting Dolutegravir-based Antiretroviral Therapy. Clin Infect Dis. 2020;70:1267-74.
[PubMed Abstract] -

20. Bourgi K, Jenkins CA, Rebeiro PF, et al. Weight gain among treatment-naïve persons with HIV starting integrase inhibitors compared to non-nucleoside reverse transcriptase inhibitors or protease inhibitors in a large observational cohort in the United States and Canada. J Int AIDS Soc. 2020;23:e25484.
[PubMed Abstract] -

21. Venter WDF, Moorhouse M, Sokhela S, et al. Dolutegravir plus Two Different Prodrugs of Tenofovir to Treat HIV. N Engl J Med. 2019;381:803-15.
[PubMed Abstract] -

22. Mallon PW, Brunet L, Hsu RK, et al. Weight gain before and after switch from TDF to TAF in a U.S. cohort study. J Int AIDS Soc. 2021;24:e25702.
[PubMed Abstract] -

23. Sax PE, Erlandson KM, Lake JE, et al. Weight Gain Following Initiation of Antiretroviral Therapy: Risk Factors in Randomized Comparative Clinical Trials. Clin Infect Dis. 2020;71:1379-89.
[PubMed Abstract] -

24. Wyatt CM. Antiretroviral therapy and the kidney. Top Antivir Med. 2014;22:655-8.
[PubMed Abstract] -

25. Gutierrez Mdel M, Mateo MG, Vidal F, Domingo P. Drug safety profile of integrase strand transfer inhibitors. Expert Opin Drug Saf. 2014;13:431-45.

[PubMed Abstract] -

26. Lucas GM, Ross MJ, Stock PG, et al. Clinical practice guideline for the management of chronic kidney disease in patients infected with HIV: 2014 update by the HIV Medicine Association of the Infectious Diseases Society of America. Clin Infect Dis. 2014;59:e96-138.
[PubMed Abstract] -

27. Wohl D, Clarke A, Maggiolo F, et al. Patient-Reported Symptoms Over 48 Weeks Among Participants in Randomized, Double-Blind, Phase III Non-inferiority Trials of Adults with HIV on Co-formulated Bictegravir, Emtricitabine, and Tenofovir Alafenamide versus Co-formulated Abacavir, Dolutegravir, and Lamivudine. Patient. 2018;11:561-573.
[PubMed Abstract] -

28. Gallant J, Lazzarin A, Mills A, et al. Bictegravir, emtricitabine, and tenofovir alafenamide versus dolutegravir, abacavir, and lamivudine for initial treatment of HIV-1 infection (GS-US-380-1489): a double-blind, multicentre, phase 3, randomised controlled non-inferiority trial. Lancet. 2017;390:2063-72.
[PubMed Abstract] -

29. Daar ES, DeJesus E, Ruane P, et al. Efficacy and safety of switching to fixed-dose bictegravir, emtricitabine, and tenofovir alafenamide from boosted protease inhibitor-based regimens in virologically suppressed adults with HIV-1: 48 week results of a randomised, open-label, multicentre, phase 3, non-inferiority trial. Lancet HIV. 2018;5:e347-e356.
[PubMed Abstract] -

30. Sax PE, Pozniak A, Montes ML, et al. Coformulated bictegravir, emtricitabine, and tenofovir alafenamide versus dolutegravir with emtricitabine and tenofovir alafenamide, for initial treatment of HIV-1 infection (GS-US-380-1490): a randomised, double-blind, multicentre, phase 3, non-inferiority trial. Lancet. 2017;390:2073-82.
[PubMed Abstract] -

31. Landovitz RJ, Donnell D, Clement ME, et al. N Engl J Med. 2021;385:595-608.
[PubMed Abstract] -

32. Orkin C, Arasteh K, Górgolas Hernández-Mora M, et al. Long-Acting Cabotegravir and Rilpivirine after Oral Induction for HIV-1 Infection. N Engl J Med. 2020;382:1124-35.
[PubMed Abstract] -

33. Swindells S, Andrade-Villanueva JF, Richmond GJ, et al. Long-Acting Cabotegravir and Rilpivirine for Maintenance of HIV-1 Suppression. N Engl J Med. 2020;382:1112-23.
[PubMed Abstract] -

34. Osterholzer DA, Goldman M. Dolutegravir: a next-generation integrase inhibitor for treatment of HIV infection. Clin Infect Dis. 2014;59:265-71.
[PubMed Abstract] -

35. Walmsley SL, Antela A, Clumeck N, et al. Dolutegravir plus abacavir-lamivudine for the treatment of HIV-1 infection. N Engl J Med. 2013;369:1807-18.
[PubMed Abstract] -

36. Curtis L, Nichols G, Stainsby C, et al. Dolutegravir: clinical and laboratory safety in integrase inhibitor-naive patients. HIV Clin Trials. 2014;15:199-208.
[PubMed Abstract] -

37. Sax PE, DeJesus E, Mills A, et al. Co-formulated elvitegravir, cobicistat, emtricitabine, and tenofovir versus co-formulated efavirenz, emtricitabine, and tenofovir for initial treatment of HIV-1 infection: a randomised, double-blind, phase 3 trial, analysis of results after 48 weeks. Lancet. 2012;379:2439-48.
[PubMed Abstract] -

38. DeJesus E, Rockstroh JK, Henry K, et al. Co-formulated elvitegravir, cobicistat, emtricitabine, and tenofovir disoproxil fumarate versus ritonavir-boosted atazanavir plus co-formulated emtricitabine and tenofovir disoproxil fumarate for initial treatment of HIV-1 infection: a randomised, double-blind, phase 3, non-inferiority trial. Lancet. 2012;379:2429-38.
[PubMed Abstract] -

39. Croce F, Vitello P, Dalla Pria A, Riva A, Galli M, Antinori S. Severe raltegravir-associated rhabdomyolysis: a case report and review of the literature. Int J STD AIDS. 2010;21:783-5.
[PubMed Abstract] -

40. Lee FJ, Amin J, Bloch M, Pett SL, Marriott D, Carr A. Skeletal muscle toxicity associated with raltegravir-based combination antiretroviral therapy in HIV-infected adults. J Acquir Immune Defic Syndr. 2013;62:525-33.
[PubMed Abstract] -

41. Thomas M, Hopkins C, Duffy E, et al. Association of the HLA-B*53:01 Allele With Drug Reaction With Eosinophilia and Systemic Symptoms (DRESS) Syndrome During Treatment of HIV Infection With Raltegravir. Clin Infect Dis. 2017;64:1198-1203.
[PubMed Abstract] -

42. Ripamonti D, Benatti SV, Di Filippo E, Ravasio V, Rizzi M. Drug reaction with eosinophilia and systemic symptoms associated with raltegravir use: case report and review of the literature. AIDS. 2014;28:1077-9.
[PubMed Abstract] -

43. Loulergue P, Mir O. Raltegravir-induced DRESS syndrome. Scand J Infect Dis. 2012;44:802-3.
[PubMed Abstract] -

44. Schambelan M, Benson CA, Carr A, et al. Management of metabolic complications associated with antiretroviral therapy for HIV-1 infection: recommendations of an International AIDS Society-USA panel. J Acquir Immune Defic Syndr. 2002;31:257-75.
[PubMed Abstract] -

45. Côté HC, Brumme ZL, Craib KJ, et al. Changes in mitochondrial DNA as a marker of nucleoside toxicity in HIV-infected patients. N Engl J Med. 2002;346:811-20.
[PubMed Abstract] -

46. Carr A, Workman C, Smith DE, et al. Abacavir substitution for nucleoside analogs in patients with HIV lipoatrophy: a randomized trial. JAMA. 2002;288:207-15.
[PubMed Abstract] -

47. James J, Carruthers A, Carruthers J. HIV-associated facial lipoatrophy. Dermatol Surg. 2002;28:979-86.
[PubMed Abstract] -

48. Feeney ER, Mallon PW. HIV and HAART-Associated Dyslipidemia. Open Cardiovasc Med J. 2011;5:49-63.
[PubMed Abstract] -

49. Tungsiripat M, Kitch D, Glesby MJ, et al. A pilot study to determine the impact on dyslipidemia of

adding tenofovir to stable background antiretroviral therapy: ACTG 5206. AIDS. 2010;24:1781-4.
[PubMed Abstract] -

50. Domingo P, Labarga P, Palacios R, et al. Improvement of dyslipidemia in patients switching from stavudine to tenofovir: preliminary results. AIDS. 2004;18:1475-8.
[PubMed Abstract] -

51. Tebas P, Sension M, Arribas J, et al. Lipid levels and changes in body fat distribution in treatment-naive, HIV-1-Infected adults treated with rilpivirine or Efavirenz for 96 weeks in the ECHO and THRIVE trials. Clin Infect Dis. 2014;59:425-34.
[PubMed Abstract] -

52. Strategies for Management of Anti-Retroviral Therapy/INSIGHT1; DAD Study Groups. Use of nucleoside reverse transcriptase inhibitors and risk of myocardial infarction in HIV-infected patients. AIDS. 2008;22:F17-24.
[PubMed Abstract] -

53. Obel N, Farkas DK, Kronborg G, et al. Abacavir and risk of myocardial infarction in HIV-infected patients on highly active antiretroviral therapy: a population-based nationwide cohort study. HIV Med. 2010;11:130-6.
[PubMed Abstract] -

54. Choi AI, Vittinghoff E, Deeks SG, Weekley CC, Li Y, Shlipak MG. Cardiovascular risks associated with abacavir and tenofovir exposure in HIV-infected persons. AIDS. 2011;25:1289-98.
[PubMed Abstract] -

55. Cruciani M, Zanichelli V, Serpelloni G, et al. Abacavir use and cardiovascular disease events: a meta-analysis of published and unpublished data. AIDS. 2011;25:1993-2004.
[PubMed Abstract] -

56. Worm SW, Sabin C, Weber R, et al. Risk of myocardial infarction in patients with HIV infection exposed to specific individual antiretroviral drugs from the 3 major drug classes: the data collection on adverse events of anti-HIV drugs (D:A:D) study. J Infect Dis. 2010;201:318-30.
[PubMed Abstract] -

57. Sabin CA, Worm SW, Weber R, et al. Use of nucleoside reverse transcriptase inhibitors and risk of myocardial infarction in HIV-infected patients enrolled in the D:A:D study: a multi-cohort collaboration. Lancet. 2008;371:1417-26.
[PubMed Abstract] -

58. Baum PD, Sullam PM, Stoddart CA, McCune JM. Abacavir increases platelet reactivity via competitive inhibition of soluble guanylyl cyclase. AIDS. 2011;25:2243-8.
[PubMed Abstract] -

59. Satchell CS, O'Halloran JA, Cotter AG, et al. Increased platelet reactivity in HIV-1-infected patients receiving abacavir-containing antiretroviral therapy. J Infect Dis. 2011;204:1202-10.
[PubMed Abstract] -

60. Trevillyan JM, Arthur JF, Jing J, Andrews RK, Gardiner EE, Hoy JF. Effects of abacavir administration on structural and functional markers of platelet activation. AIDS. 2015;29:2309-13.
[PubMed Abstract] -

61. Hewitt RG. Abacavir hypersensitivity reaction. Clin Infect Dis. 2002;34:1137-42.
[PubMed Abstract] -

62. Martin MA, Kroetz DL. Abacavir pharmacogenetics--from initial reports to standard of care. Pharmacotherapy. 2013;33:765-75.
[PubMed Abstract] -

63. Hughes CA, Foisy MM, Dewhurst N, Higgins N, Robinson L, Kelly DV, Lechelt KE. Abacavir hypersensitivity reaction: an update. Ann Pharmacother. 2008;42:387-96.
[PubMed Abstract] -

64. Kumar PN, Patel P. Lamivudine for the treatment of HIV. Expert Opin Drug Metab Toxicol. 2010;6:105-14.
[PubMed Abstract] -

65. Modrzejewski KA, Herman RA. Emtricitabine: a once-daily nucleoside reverse transcriptase inhibitor. Ann Pharmacother. 2004;38:1006-14.
[PubMed Abstract] -

66. Saag MS. Emtricitabine, a new antiretroviral agent with activity against HIV and hepatitis B virus. Clin Infect Dis. 2006;42:126-31.
[PubMed Abstract] -

67. Skin discoloration with FTC. AIDS Patient Care STDS. 2004;18:616.
[PubMed Abstract] -

68. Lee WA, He GX, Eisenberg E, et al. Selective intracellular activation of a novel prodrug of the human immunodeficiency virus reverse transcriptase inhibitor tenofovir leads to preferential distribution and accumulation in lymphatic tissue. Antimicrob Agents Chemother. 2005;49:1898-906.
[PubMed Abstract] -

69. Birkus G, Wang R, Liu X, et al. Cathepsin A is the major hydrolase catalyzing the intracellular hydrolysis of the antiretroviral nucleotide phosphonoamidate prodrugs GS-7340 and GS-9131. Antimicrob Agents Chemother. 2007;51:543-50.
[PubMed Abstract] -

70. Babusis D, Phan TK, Lee WA, Watkins WJ, Ray AS. Mechanism for effective lymphoid cell and tissue loading following oral administration of nucleotide prodrug GS-7340. Mol Pharm. 2013;10:459-66.
[PubMed Abstract] -

71. Sax PE, Wohl D, Yin MT, et al. Tenofovir alafenamide versus tenofovir disoproxil fumarate, coformulated with elvitegravir, cobicistat, and emtricitabine, for initial treatment of HIV-1 infection: two randomised, double-blind, phase 3, non-inferiority trials. Lancet. 2015;385:2606-15.
[PubMed Abstract] -

72. Gallant JE, Daar ES, Raffi F, et al. Efficacy and safety of tenofovir alafenamide versus tenofovir disoproxil fumarate given as fixed-dose combinations containing emtricitabine as backbones for treatment of HIV-1 infection in virologically suppressed adults: a randomised, double-blind, active-controlled phase 3 trial. Lancet HIV. 2016:e158-65.
[PubMed Abstract] -

73. Pozniak A, Arribas JR, Gathe J, et al. Switching to Tenofovir Alafenamide, Coformulated With Elvitegravir, Cobicistat, and Emtricitabine, in HIV-Infected Patients With Renal Impairment: 48-Week Results From a Single-Arm, Multicenter, Open-Label Phase 3 Study. J Acquir Immune Defic Syndr. 2016;71:530-7.
[PubMed Abstract] -

74. Sax PE, Zolopa A, Brar I, et al. Tenofovir alafenamide vs. tenofovir disoproxil fumarate in single tablet regimens for initial HIV-1 therapy: a randomized phase 2 study. J Acquir Immune Defic Syndr. 2014;67:52-8.
[PubMed Abstract] -

75. Gomez M, Seybold U, Roider J, Härter G, Bogner JR. A retrospective analysis of weight changes in HIV-positive patients switching from a tenofovir disoproxil fumarate (TDF)- to a tenofovir alafenamide fumarate (TAF)-containing treatment regimen in one German university hospital in 2015-2017. Infection. 2019;47:95-102.
[PubMed Abstract] -

76. Moyle GJ, Orkin C, Fisher M, et al. A randomized comparative trial of continued abacavir/lamivudine plus efavirenz or replacement with efavirenz/emtricitabine/tenofovir DF in hypercholesterolemic HIV-1 infected individuals. PLoS One. 2015;10:e0116297.
[PubMed Abstract] -

77. Scherzer R, Estrella M, Li Y, et al. Association of tenofovir exposure with kidney disease risk in HIV infection. AIDS. 2012;26:867-75.
[PubMed Abstract] -

78. Shah S, Pilkington V, Hill A. Is tenofovir disoproxil fumarate associated with weight loss? AIDS. 2021;35:S189-S195.
[PubMed Abstract] -

79. McComsey GA, Kitch D, Daar ES, et al. Bone mineral density and fractures in antiretroviral-naive persons randomized to receive abacavir-lamivudine or tenofovir disoproxil fumarate-emtricitabine along with efavirenz or atazanavir-ritonavir: Aids Clinical Trials Group A5224s, a substudy of ACTG A5202. J Infect Dis. 2011;203:1791-801.
[PubMed Abstract] -

80. McComsey GA, Tebas P, Shane E, et al. Bone disease in HIV infection: a practical review and recommendations for HIV care providers. Clin Infect Dis. 2010;51:937-46.
[PubMed Abstract] -

81. Llamas-Granda P, Martin-Rodríguez L, Largo R, Herrero-Beaumont G, Mediero A. Tenofovir Modulates Semaphorin 4D Signaling and Regulates Bone Homeostasis, Which Can Be Counteracted by Dipyridamole and Adenosine A2A Receptor. Int J Mol Sci. 2021;22: 11490.
[PubMed Abstract] -

82. Van Welzen BJ, Thielen MAJ, Mudrikova T, Arends JE, Hoepelman AIM. Switching tenofovir disoproxil fumarate to tenofovir alafenamide results in a significant decline in parathyroid hormone levels: uncovering the mechanism of tenofovir disoproxil fumarate-related bone loss? AIDS. 2019;33:1531-4.
[PubMed Abstract] -

83. Cohen SD, Chawla LS, Kimmel PL. Acute kidney injury in patients with human immunodeficiency virus infection. Curr Opin Crit Care. 2008;14:647-53.
[PubMed Abstract] -

84. Rodríguez-Nóvoa S, Labarga P, Soriano V, et al. Predictors of kidney tubular dysfunction in HIV-infected patients treated with tenofovir: a pharmacogenetic study. Clin Infect Dis. 2009;48:e108-16.
[PubMed Abstract] -

85. Yoshino M, Yagura H, Kushida H, et al. Assessing recovery of renal function after tenofovir disoproxil

fumarate discontinuation. J Infect Chemother. 2012;18:169-74.
[PubMed Abstract] -

86. Gallant JE, DeJesus E, Arribas JR, et al. Tenofovir DF, emtricitabine, and efavirenz vs. zidovudine, lamivudine, and efavirenz for HIV. N Engl J Med. 2006;354:251-60.
[PubMed Abstract] -

87. Scruggs ER, Dirks Naylor AJ. Mechanisms of zidovudine-induced mitochondrial toxicity and myopathy. Pharmacology. 2008;82:83-8.
[PubMed Abstract] -

88. Colombier MA, Molina JM. Doravirine: a review. Curr Opin HIV AIDS. 2018;13:308-314.
[PubMed Abstract] -

89. Deeks ED. Doravirine: First Global Approval. Drugs. 2018;78:1643-1650.
[PubMed Abstract] -

90. Orkin C, Squires KE, Molina JM, et al. Doravirine/Lamivudine/Tenofovir Disoproxil Fumarate is Non-inferior to Efavirenz/Emtricitabine/Tenofovir Disoproxil Fumarate in Treatment-naive Adults With Human Immunodeficiency Virus-1 Infection: Week 48 Results of the DRIVE-AHEAD Trial. Clin Infect Dis. 2019;68:535-44.
[PubMed Abstract] -

91. Castillo R, Pedalino RP, El-Sherif N, Turitto G. Efavirenz-associated QT prolongation and Torsade de Pointes arrhythmia. Ann Pharmacother. 2002;36:1006-8.
[PubMed Abstract] -

92. Abdelhady AM, Shugg T, Thong N, et al. Efavirenz Inhibits the Human Ether-A-Go-Go Related Current (hERG) and Induces QT Interval Prolongation in CYP2B6*6*6 Allele Carriers. J Cardiovasc Electrophysiol. 2016;27:1206-1213.
[PubMed Abstract] -

93. Crane HM, Grunfeld C, Willig JH, et al. Impact of NRTIs on lipid levels among a large HIV-infected cohort initiating antiretroviral therapy in clinical care. AIDS. 2011;25:185-95.
[PubMed Abstract] -

94. Gotti D, Cesana BM, Albini L, et al. Increase in standard cholesterol and large HDL particle subclasses in antiretroviral-naïve patients prescribed efavirenz compared to atazanavir/ritonavir. HIV Clin Trials. 2012;13:245-55.
[PubMed Abstract] -

95. Durand M, Sheehy O, Baril JG, Lelorier J, Tremblay CL. Association between HIV infection, antiretroviral therapy, and risk of acute myocardial infarction: a cohort and nested case-control study using Québec's public health insurance database. J Acquir Immune Defic Syndr. 2011;57:245-53.
[PubMed Abstract] -

96. Echenique IA, Rich JD. EFV/FTC/TDF-associated hepatotoxicity: a case report and review. AIDS Patient Care STDS. 2013;27:493-7.
[PubMed Abstract] -

97. Manosuthi W, Sukasem C, Lueangniyomkul A, et al. CYP2B6 haplotype and biological factors responsible for hepatotoxicity in HIV-infected patients receiving efavirenz-based antiretroviral therapy. Int J Antimicrob Agents. 2014;43:292-6.
[PubMed Abstract] -

98. Patil R, Ona MA, Papafragkakis H, et al. Acute Liver Toxicity due to Efavirenz/Emtricitabine/Tenofovir. Case Reports Hepatol. 2015;2015:280353.
[PubMed Abstract] -

99. Arendt G, de Nocker D, von Giesen HJ, Nolting T. Neuropsychiatric side effects of efavirenz therapy. Expert Opin Drug Saf. 2007;6:147-54.
[PubMed Abstract] -

100. Mollan KR, Smurzynski M, Eron JJ, et al. Association between efavirenz as initial therapy for HIV-1 infection and increased risk for suicidal ideation or attempted or completed suicide: an analysis of trial data. Ann Intern Med. 2014;161:1-10.
[PubMed Abstract] -

101. Marzolini C, Telenti A, Decosterd LA, Greub G, Biollaz J, Buclin T. Efavirenz plasma levels can predict treatment failure and central nervous system side effects in HIV-1-infected patients. AIDS. 2001;15:71-5.
[PubMed Abstract] -

102. van Lunzen J, Antinori A, Cohen CJ, et al. Rilpivirine vs. efavirenz-based single-tablet regimens in treatment-naive adults: week 96 efficacy and safety from a randomized phase 3b study. AIDS. 2016;30:251-9.
[PubMed Abstract] -

103. Behrens G, Rijnders B, Nelson M, et al. Rilpivirine versus efavirenz with emtricitabine/tenofovir disoproxil fumarate in treatment-naïve HIV-1-infected patients with HIV-1 RNA ≤100,000 copies/mL: week 96 pooled ECHO/THRIVE subanalysis. AIDS Patient Care STDS. 2014;28:168-75.
[PubMed Abstract] -

104. Welz T, Childs K, Ibrahim F, et al. Efavirenz is associated with severe vitamin D deficiency and increased alkaline phosphatase. AIDS. 2010;24:1923-8.
[PubMed Abstract] -

105. Nylén H, Habtewold A, Makonnen E, et al. Prevalence and risk factors for efavirenz-based antiretroviral treatment-associated severe vitamin D deficiency: A prospective cohort study. Medicine (Baltimore). 2016;95:e4631.
[PubMed Abstract] -

106. Brown TT, McComsey GA. Association between initiation of antiretroviral therapy with efavirenz and decreases in 25-hydroxyvitamin D. Antivir Ther. 2010;15:425-9.
[PubMed Abstract] -

107. Girard PM, Campbell TB, Grinsztejn B, et al. Pooled week 96 results of the phase III DUET-1 and DUET-2 trials of etravirine: further analysis of adverse events and laboratory abnormalities of special interest. HIV Med. 2012;13:427-35.
[PubMed Abstract] -

108. Barreiro P, Soriano V, Casas E, et al. Prevention of nevirapine-associated exanthema using slow dose escalation and/or corticosteroids. AIDS. 2000;14:2153-7.
[PubMed Abstract] -

109. Baylor MS, Johann-Liang R. Hepatotoxicity associated with nevirapine use. J Acquir Immun Defic Syndr. 2004;35:538-9.
[PubMed Abstract] -

110. Antinori A, Baldini F, Girardi E, et al. Female sex and the use of anti-allergic agents increase the risk of developing cutaneous rash associated with nevirapine therapy. AIDS. 2001;15:1579-81.
[PubMed Abstract] -

111. Cohen CJ, Andrade-Villanueva J, Clotet B, et al. Rilpivirine versus efavirenz with two background nucleoside or nucleotide reverse transcriptase inhibitors in treatment-naive adults infected with HIV-1 (THRIVE): a phase 3, randomised, non-inferiority trial. Lancet. 2011;378:229-37.
[PubMed Abstract] -

112. Deeks ED. Emtricitabine/rilpivirine/tenofovir disoproxil fumarate single-tablet regimen: a review of its use in HIV infection. Drugs. 2014;74:2079-95.
[PubMed Abstract] -

113. Mills AM, Antinori A, Clotet B, et al. Neurological and psychiatric tolerability of rilpivirine (TMC278) vs. efavirenz in treatment-naïve, HIV-1-infected patients at 48 weeks. HIV Med. 2013;14:391-400.
[PubMed Abstract] -

114. Stray KM, Bam RA, Birkus G, et al. Evaluation of the effect of cobicistat on the in vitro renal transport and cytotoxicity potential of tenofovir. Antimicrob Agents Chemother. 2013;57:4982-9.
[PubMed Abstract] -

115. Sherman EM, Worley MV, Unger NR, Gauthier TP, Schafer JJ. Cobicistat: Review of a Pharmacokinetic Enhancer for HIV Infection. Clin Ther. 2015;37:1876-93.
[PubMed Abstract] -

116. German P, Liu HC, Szwarcberg J, et al. Effect of cobicistat on glomerular filtration rate in subjects with normal and impaired renal function. J Acquir Immune Defic Syndr. 2012;61:32-40.
[PubMed Abstract] -

117. Molina JM, Andrade-Villanueva J, Echevarria J, et al. Once-daily atazanavir/ritonavir versus twice-daily lopinavir/ritonavir, each in combination with tenofovir and emtricitabine, for management of antiretroviral-naive HIV-1-infected patients: 48 week efficacy and safety results of the CASTLE study. Lancet. 2008;372(9639):646-55.
[PubMed Abstract] -

118. Molina JM, Andrade-Villanueva J, Echevarria J, et al. Once-daily atazanavir/ritonavir compared with twice-daily lopinavir/ritonavir, each in combination with tenofovir and emtricitabine, for management of antiretroviral-naive HIV-1-infected patients: 96-week efficacy and safety results of the CASTLE study. J Acquir Immune Defic Syndr. 2010;53:323-32.
[PubMed Abstract] -

119. Madruga JV, Berger D, McMurchie M, et al. Efficacy and safety of darunavir-ritonavir compared with that of lopinavir-ritonavir at 48 weeks in treatment-experienced, HIV-infected patients in TITAN: a randomised controlled phase III trial. Lancet. 2007;370:49-58.
[PubMed Abstract] -

120. Eron JJ, Young B, Cooper DA, et al. Switch to a raltegravir-based regimen versus continuation of a lopinavir-ritonavir based regimen in stable HIV-infected patients with suppressed viraemia (SWITCHMRK 1 and 2): two multicentre, double-blind, randomized controlled trials. Lancet 2010; 375:396-407.
[PubMed Abstract] -

121. Molina JM, Clotet B, van Lunzen J, et al. Once-daily dolutegravir is superior to once-daily

darunavir/ritonavir in treatment-naïve HIV-1-positive individuals: 96 week results from FLAMINGO. J Int AIDS Soc. 2014;17:19490.
[PubMed Abstract] -

122. Molina JM, Clumeck N, Orkin C, Rimsky LT, Vanveggel S, Stevens M. Week 96 analysis of rilpivirine or efavirenz in HIV-1-infected patients with baseline viral load ≤ 100 000 copies/mL in the pooled ECHO and THRIVE phase 3, randomized, double-blind trials. HIV Med. 2014;15:57-62.
[PubMed Abstract] -

123. Zhou H, Pandak WM Jr, Lyall V, Natarajan R, Hylemon PB. HIV protease inhibitors activate the unfolded protein response in macrophages: implication for atherosclerosis and cardiovascular disease. Mol Pharmacol. 2005;68:690-700.
[PubMed Abstract] -

124. Friis-Møller N, Worm SW. Can the risk of cardiovascular disease in HIV-infected patients be estimated from conventional risk prediction tools? Clin Infect Dis. 2007;45:1082-4.
[PubMed Abstract] -

125. Soliman EZ, Lundgren JD, Roediger MP, et al. Boosted protease inhibitors and the electrocardiographic measures of QT and PR durations. AIDS. 2011;25:367-77.
[PubMed Abstract]] -

126. Zhang D, Chando TJ, Everett DW, Patten CJ, Dehal SS, Humphreys WG. In vitro inhibition of UDP glucuronosyltransferases by atazanavir and other HIV protease inhibitors and the relationship of this property to in vivo bilirubin glucuronidation. Drug Metab Dispos. 2005;33:1729-39.
[PubMed Abstract] -

127. Couzigou C, Daudon M, Meynard JL, et al. Urolithiasis in HIV-positive patients treated with atazanavir. Clin Infect Dis. 2007;45:e105-8.
[PubMed Abstract] -

128. Hamada Y, Nishijima T, Komatsu H, et al. Is ritonavir-boosted atazanavir a risk for cholelithiasis compared to other protease inhibitors? PLoS One. 2013;8:e69845.
[PubMed Abstract] -

129. Hamada Y, Nishijima T, Watanabe K, et al. High incidence of renal stones among HIV-infected patients on ritonavir-boosted atazanavir than in those receiving other protease inhibitor-containing antiretroviral therapy. Clin Infect Dis. 2012;55:1262-9.
[PubMed Abstract] -

130. Hara M, Suganuma A, Yanagisawa N, Imamura A, Hishima T, Ando M. Atazanavir nephrotoxicity. Clin Kidney J. 2015;8:137-42.
[PubMed Abstract] -

131. Gentle DL, Stoller ML, Jarrett TW, Ward JF, Geib KS, Wood AF. Protease inhibitor-induced urolithiasis. Urology. 1997;50:508-511.
[PubMed Abstract] -

132. Rakotondravelo S, Poinsignon Y, Borsa-Lebas F, et al. Complicated atazanavir-associated cholelithiasis: a report of 14 cases. Clin Infect Dis. 2012;55:1270-2.
[PubMed Abstract] -

133. Nishijima T, Shimbo T, Komatsu H, et al. Cumulative exposure to ritonavir-boosted atazanavir is associated with cholelithiasis in patients with HIV-1 infection. J Antimicrob Chemother.

2014;69:1385-9.
[PubMed Abstract] -

134. Nishijima T, Yazaki H, Hinoshita F, et al. Drug-induced acute interstitial nephritis mimicking acute tubular necrosis after initiation of tenofovir-containing antiretroviral therapy in patient with HIV-1 infection. Intern Med. 2012;51:2469-71.
[PubMed Abstract] -

135. Ortiz R, Dejesus E, Khanlou H, et al. Efficacy and safety of once-daily darunavir/ritonavir versus lopinavir/ritonavir in treatment-naive HIV-1-infected patients at week 48. AIDS. 2008;22:1389-97.
[PubMed Abstract] -

136. Cvetkovic RS, Goa KL. Lopinavir/ritonavir: a review of its use in the management of HIV infection. Drugs. 2003;63:769-802.
[PubMed Abstract] -

137. Mushtaq A, Kazi F. Lenacapavir: a new treatment of resistant HIV-1 infections. Lancet Infect Dis. 2023;23:286.
[PubMed Abstract] -

138. Segal-Maurer S, DeJesus E, Stellbrink HJ, et al. Capsid Inhibition with Lenacapavir in Multidrug-Resistant HIV-1 Infection. N Engl J Med. 2022;386:1793-1803.
[PubMed Abstract] -

References

- Aberg JA, Gallant JE, Ghanem KG, Emmanuel P, Zingman BS, Horberg MA. Primary care guidelines for the management of persons infected with HIV: 2013 update by the HIV Medicine Association of the Infectious Diseases Society of America. Clin Infect Dis. 2014;58:1-10.
[PubMed Abstract] -

- Abers MS, Shandera WX, Kass JS. Neurological and psychiatric adverse effects of antiretroviral drugs. CNS Drugs. 2014;28:131-45.
[PubMed Abstract] -

- Arenas-Pinto A, Bhaskaran K, Dunn D, Weller IV. The risk of developing peripheral neuropathy induced by nucleoside reverse transcriptase inhibitors decreases over time: evidence from the Delta trial. Antivir Ther. 2008;13:289-95.
[PubMed Abstract] -

- Ayoub A, Alston S, Goodrich J, et al. Hepatic safety and tolerability in the maraviroc clinical development program. AIDS. 2010;24:2743-50.
[PubMed Abstract] -

- Bakal DR, Coelho LE, Luz PM, et al. Obesity following ART initiation is common and influenced by both traditional and HIV-/ART-specific risk factors. J Antimicrob Chemother. 2018;73:2177-2185.
[PubMed Abstract] -

- Bellini C, Keiser O, Chave JP, et al. Liver enzyme elevation after lamivudine withdrawal in HIV-hepatitis B virus co-infected patients: the Swiss HIV Cohort Study. HIV Med. 2009;10:12-8.
[PubMed Abstract] -

- Boyd MA, Truman M, Hales G, Anderson J, Dwyer DE, Carr A. A randomized study to evaluate injection

site reactions using three different enfuvirtide delivery mechanisms (the OPTIONS study). Antivir Ther. 2008;13:449-53.
[PubMed Abstract] -

- Bozzette SA. HIV and Cardiovascular Disease. Clin Infect Dis. 2011;53:92-3.
[PubMed Abstract] -

- Brück S, Witte S, Brust J, et al. Hepatotoxicity in patients prescribed efavirenz or nevirapine. Eur J Med Res. 2008;13:343-8.
[PubMed Abstract] -

- Brinkman K, Kakuda TN. Mitochondrial toxicity of nucleoside analogue reverse transcriptase inhibitors: a looming obstacle for long-term antiretroviral therapy? Curr Opin Infect Dis. 2000;13:5-11.
[PubMed Abstract] -

- Brinkman K, ter Hofstede HJ, Burger DM, Smeitink JA, Koopmans PP. Adverse effects of reverse transcriptase inhibitors: mitochondrial toxicity as common pathway. AIDS. 1998;12:1735-44.
[PubMed Abstract] -

- Brown TT, Glesby MJ. Management of the metabolic effects of HIV and HIV drugs. Nat Rev Endocrinol. 2011;8:11-21.
[PubMed Abstract] -

- Carr A, Samaras K, Burton S, Law M, Freund J, Chisholm DJ, Cooper DA. A syndrome of peripheral lipodystrophy, hyperlipidaemia and insulin resistance in patients receiving HIV protease inhibitors. AIDS. 1998;12:F51-8.
[PubMed Abstract] -

- Carr A. Lactic acidemia in infection with human immunodeficiency virus. Clin Infect Dis. 2003;36:S96-S100.
[PubMed Abstract] -

- Cassetti I, Madruga JV, Suleiman JM, et al. The safety and efficacy of tenofovir DF in combination with lamivudine and efavirenz through 6 years in antiretroviral-naïve HIV-1-infected patients. HIV Clin Trials. 2007;8:164-72.
[PubMed Abstract] -

- Chan-Tack KM, Struble KA, Birnkrant DB. Intracranial hemorrhage and liver-associated deaths associated with tipranavir/ritonavir: review of cases from the FDA's Adverse Event Reporting System. AIDS Patient Care STDS. 2008;22:843-50.
[PubMed Abstract] -

- Cohen CJ, Molina JM, Cassetti I, et al. Week 96 efficacy and safety of rilpivirine in treatment-naive, HIV-1 patients in two Phase III randomized trials. AIDS. 2013;27:939-50.
[PubMed Abstract] -

- Cooper DA, Heera J, Ive P, et al. Efficacy and safety of maraviroc vs. efavirenz in treatment-naive patients with HIV-1: 5-year findings. AIDS. 2014;28:717-25.
[PubMed Abstract] -

- Cotter AG, Powderly WG. Endocrine complications of human immunodeficiency virus infection: hypogonadism, bone disease and tenofovir-related toxicity. Best Pract Res Clin Endocrinol Metab. 2011;25:501-15.
[PubMed Abstract] -

- D'Abbraccio M, Busto A, De Marco M, Figoni M, Maddaloni A, Abrescia N. Efficacy and Tolerability of Integrase Inhibitors in Antiretroviral-Naive Patients. AIDS Rev. 2015;17:171-85.
[PubMed Abstract] -

- Dao CN, Patel P, Overton ET, et al. Low vitamin D among HIV-infected adults: prevalence of and risk factors for low vitamin D Levels in a cohort of HIV-infected adults and comparison to prevalence among adults in the US general population. Clin Infect Dis. 2011;52:396-405.
[PubMed Abstract] -

- De Santis M, Carducci B, De Santis L, Cavaliere AF, Straface G. Periconceptional exposure to efavirenz and neural tube defects. Arch Intern Med. 2002;162:355.
[PubMed Abstract] -

- Domingo P, Gutierrez Mdel M, Gallego-Escuredo JM, et al. Effects of switching from stavudine to raltegravir on subcutaneous adipose tissue in HIV-infected patients with HIV/HAART-associated lipodystrophy syndrome (HALS). A clinical and molecular study. PLoS One. 2014;9:e89088.
[PubMed Abstract] -

- Dore GJ, Soriano V, Rockstroh J, et al. Frequent hepatitis B virus rebound among HIV-hepatitis B virus-coinfected patients following antiretroviral therapy interruption. AIDS. 2010;24:857-65.
[PubMed Abstract] -

- El-Sadr WM, Lundgren J, Neaton JD, et al. CD4+ count-guided interruption of antiretroviral treatment. N Engl J Med. 2006;355:2283-96.
[PubMed Abstract] -

- Estrada V, Portilla J. Dyslipidemia related to antiretroviral therapy. AIDS Rev. 2011;13:49-56.
[PubMed Abstract] -

- Fessel J, Hurley LB. Incidence of pancreatitis in HIV-infected patients: comment on findings in EuroSIDA cohort. AIDS. 2008;22:145-7.
[PubMed Abstract] -

- Ford N, Mofenson L, Kranzer K, et al. Safety of efavirenz in first-trimester of pregnancy: a systematic review and meta-analysis of outcomes from observational cohorts. AIDS. 2010;24:1461-70.
[PubMed Abstract] -

- Ford N, Mofenson L, Shubber Z, et al. Safety of efavirenz in the first trimester of pregnancy: an updated systematic review and meta-analysis. AIDS. 2014;28 Suppl 2:S123-31.
[PubMed Abstract] -

- Freiberg MS, Chang CC, Kuller LH et al. HIV Infection and the risk of acute myocardial infarction. JAMA Intern Med. 2013;173:614-22.
[PubMed Abstract] -

- Fundarò C, Genovese O, Rendeli C, Tamburrini E, Salvaggio E. Myelomeningocele in a child with intrauterine exposure to efavirenz. AIDS. 2002;16:299-300.
[PubMed Abstract] -

- Griesel R, Maartens G, Chirehwa M, et al. CYP2B6 Genotype and Weight Gain Differences Between Dolutegravir and Efavirenz. Clin Infect Dis. 2021;73:e3902-e3909.
[PubMed Abstract] -

- Grinspoon S, Carr A. Cardiovascular risk and body-fat abnormalities in HIV-infected adults. N Engl J Med. 2005;352:48-62.
[PubMed Abstract] -

- Grinsztejn B, Di Perri G, Towner W, Woodfall B, De Smedt G, Peeters M. A review of the safety and tolerability profile of the next-generation NNRTI etravirine. AIDS Res Hum Retroviruses. 2010;26:725-33.
[PubMed Abstract] -

- Hollmig KA, Beck SB, Doll DC. Severe bleeding complications in HIV-positive haemophiliac patients treated with protease inhibitors. Eur J Med Res. 2001;6:112-4.
[PubMed Abstract] -

- Huang SH, Huang WC, Lin SW, et al. Impact of Efavirenz Mid-dose Plasma Concentration on Long-Term Weight Change Among Virologically Suppressed People Living With HIV. J Acquir Immune Defic Syndr. 2021;87:834-41.
[PubMed Abstract] -

- Hunt K, Hughes CA, Hills-Nieminen C. Protease inhibitor-associated QT interval prolongation. Ann Pharmacother. 2011;45:1544-50.
[PubMed Abstract] -

- Jagdeo J, Ho D, Lo A, Carruthers A. A systematic review of filler agents for aesthetic treatment of HIV facial lipoatrophy (FLA). J Am Acad Dermatol. 2015;73:1040-54.e14.
[PubMed Abstract] -

- Khalili H, Farasatinasab M, Hajiabdolbaghi M. Efavirenz severe hypersensitivity reaction: case report and rapid desensitization protocol development. Ann Pharmacother. 2012;46:e12.
[PubMed Abstract] -

- Kim AH, Jang W, Kim Y, Park YJ, Han K, Oh EJ. Mean corpuscular volume (MCV) values reflect therapeutic effectiveness in zidovudine-receiving HIV patients. J Clin Lab Anal. 2013;27:373-8.
[PubMed Abstract] -

- Knobel H, Miro JM, Domingo P, et al. Failure of a short-term prednisone regimen to prevent nevirapine-associated rash: a double-blind placebo-controlled trial: the GESIDA 09/99 study. J Acquir Immune Defic Syndr. 2001;28:14-8.
[PubMed Abstract] -

- Kopp JB, Miller KD, Mican JM, et al. Crystalluria and urinary tract abnormalities associated with indinavir. Ann Intern Med. 1997;127:119-25.
[PubMed Abstract] -

- Lactic Acidosis International Study Group 2007. Risk factors for lactic acidosis and severe hyperlactataemia in HIV-1-infected adults exposed to antiretroviral therapy. AIDS. 2007;21:2455-64.
[PubMed Abstract] -

- Lake JE, Trevillyan J. Impact of Integrase inhibitors and tenofovir alafenamide on weight gain in people with HIV. Curr Opin HIV AIDS. 2021;16:148-151.
[PubMed Abstract] -

- Lea AP, Faulds D. Stavudine: a review of its pharmacodynamic and pharmacokinetic properties and clinical potential in HIV infection. Drugs. 1996;51:846-64.
[PubMed Abstract] -

- Leung JM, O'Brien JG, Wong HK, Winslow DL. Efavirenz-induced hypersensitivity reaction manifesting in rash and hepatitis in a Latino male. Ann Pharmacother. 2008;42:425-9.
[PubMed Abstract] -

- Mallolas J, Podzamczer D, Milinkovic A, et al. Efficacy and safety of switching from boosted lopinavir to boosted atazanavir in patients with virological suppression receiving a LPV/r-containing HAART: the ATAZIP study. J Acquir Immune Defic Syndr. 2009;51:29-36.
[PubMed Abstract] -

- Martínez E, Ribera E, Clotet B, et al. Switching from zidovudine/lamivudine to tenofovir/emtricitabine improves fat distribution as measured by fat mass ratio. HIV Med. 2015;16:370-4.
[PubMed Abstract] -

- Matthews LT, Giddy J, Ghebremichael M, et al. A risk-factor guided approach to reducing lactic acidosis and hyperlactatemia in patients on antiretroviral therapy. PLoS One. 2011;6:e18736.
[PubMed Abstract] -

- Menard A, Meddeb L, Tissot-Dupont H, et al. Dolutegravir and weight gain: an unexpected bothering side effect? AIDS. 2017;31:1499-1500.
[PubMed Abstract] -

- Merry C, McMahon C, Ryan M, O'Shea E, Mulcahy F, Smith OP. Successful use of protease inhibitors in HIV-infected haemophilia patients. Br J Haematol. 1998;101:475-9.
[PubMed Abstract] -

- Mocroft A, Kirk O, Reiss P, et al. Estimated glomerular filtration rate, chronic kidney disease and antiretroviral drug use in HIV-positive patients. AIDS. 2010;24:1667-78.
[PubMed Abstract] -

- Molina JM, Squires K, Sax PE, et al. Doravirine versus ritonavir-boosted darunavir in antiretroviral-naive adults with HIV-1 (DRIVE-FORWARD): 48-week results of a randomised, double-blind, phase 3, non-inferiority trial. Lancet HIV. 2018;5:e211-e220.
[PubMed Abstract] -

- Montaner JS, Cahn P, Zala C, et al. Randomized, controlled study of the effects of a short course of prednisone on the incidence of rash associated with nevirapine in patients infected with HIV-1. J Acquir Immune Defic Syndr. 2003;33:41-6.
[PubMed Abstract] -

- Nelson MR, Elion RA, Cohen CJ, et al. Rilpivirine versus efavirenz in HIV-1-infected subjects receiving emtricitabine/tenofovir DF: pooled 96-week data from ECHO and THRIVE Studies. HIV Clin Trials. 2013;14:81-91.
[PubMed Abstract] -

- Nolan D, Mallal S. Antiretroviral-therapy-associated lipoatrophy: current status and future directions. Sex Health. 2005;2:153-63.
[PubMed Abstract] -

- Nolan D, Mallal S. The role of nucleoside reverse transcriptase inhibitors in the fat redistribution syndrome. J HIV Ther. 2004;9:34-40.
[PubMed Abstract] -

- Norwood J, Turner M, Bofill C, et al. Brief Report: Weight Gain in Persons With HIV Switched From

Efavirenz-Based to Integrase Strand Transfer Inhibitor-Based Regimens. J Acquir Immune Defic Syndr. 2017;76:527-31.
[PubMed Abstract] -

- 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: co-receptor tropism assays. October 25, 2018.
[HIV.gov] -

- Panel on Treatment of HIV During Pregnancy and Prevention of Perinatal Transmission. Recommendations for the Use of Antiretroviral Drugs During Pregnancy and Interventions to Reduce Perinatal HIV Transmission in the United States. Recommendations for Use of Antiretroviral Drugs During Pregnancy. Teratogenicity. January 31, 2024.
[HIV.gov] -

- Perry CM, Balfour JA. Didanosine. An update on its antiviral activity, pharmacokinetic properties and therapeutic efficacy in the management of HIV disease. Drugs. 1996;52:928-62.
[PubMed Abstract] -

- Phillips DR, Hay P. Current perspectives on the management and prevention of antiretroviral-associated lipoatrophy. J Antimicrob Chemother. 2008;62:866-71.
[PubMed Abstract] -

- Poeta J, Linden R, Antunes MV, et al. Plasma concentrations of efavirenz are associated with body weight in HIV-positive individuals. J Antimicrob Chemother. 2011;66:2601-4.
[PubMed Abstract] -

- Pollmann H, Richter H, Jürgens H. Platelet dysfunction as the cause of spontaneous bleeding in two haemophilic patients taking HIV protease inhibitors. Thromb Haemost. 1998;79:1213-4.
[PubMed Abstract] -

- Racoosin JA, Kessler CM. Bleeding episodes in HIV-positive patients taking HIV protease inhibitors: a case series. Haemophilia. 1999;5:266-9.
[PubMed Abstract] -

- Rockwood N, Mandalia S, Bower M, Gazzard B, Nelson M. Ritonavir-boosted atazanavir exposure is associated with an increased rate of renal stones compared with efavirenz, ritonavir-boosted lopinavir and ritonavir-boosted darunavir. AIDS. 2011;25:1671-3.
[PubMed Abstract] -

- Ryom L, Mocroft A, Kirk O, et al. Association between antiretroviral exposure and renal impairment among HIV-positive persons with normal baseline renal function: the D:A:D study. J Infect Dis. 2013;207:1359-69.
[PubMed Abstract] -

- Sabin CA, Reiss P, Ryom L, et al. Is there continued evidence for an association between abacavir usage and myocardial infarction risk in individuals with HIV? A cohort collaboration. BMC Med. 2016;14:61.
[PubMed Abstract] -

- Sanne I, Mommeja-Marin H, Hinkle J, et al. Severe hepatotoxicity associated with nevirapine use in HIV-infected subjects. J Infect Dis. 2005;191:825-9.
[PubMed Abstract] -

- Sulkowski MS, Thomas DL, Mehta SH, Chaisson RE, Moore RD. Hepatotoxicity associated with nevirapine or efavirenz-containing antiretroviral therapy: role of hepatitis C and B infections. Hepatology. 2002;35:182-9.
[PubMed Abstract] -

- Tebas P. Insulin resistance and diabetes mellitus associated with antiretroviral use in HIV-infected patients: pathogenesis, prevention, and treatment options. J Acquir Immune Defic Syndr. 2008;49 Suppl 2:S86-92.
[PubMed Abstract] -

- U.S. Food and Drug Administration. FDA Drug Safety Communication: Ongoing safety review of *Invirase* (saquinavir) and possible association with abnormal heart rhythms
[FDA Alert] -

- Vogel M, Rockstroh JK. Hepatotoxicity and liver disease in the context of HIV therapy. Curr Opin HIV AIDS. 2007;2:306-13.
[PubMed Abstract] -

- White AJ. Mitochondrial toxicity and HIV therapy. Sex Transm Infect. 2001;77:158-73.
[PubMed Abstract] -

- Wit FWNM, Wood R, Horban A, et al. Prednisolone does not prevent hypersensitivity reactions in antiretroviral drug regimens containing abacavir with or without nevirapine. AIDS. 2001;15:2423-9.
[PubMed Abstract] -

- Wooltorton E. HIV drug stavudine (*Zerit*, d4T) and symptoms mimicking Guillain-Barré syndrome. CMAJ. 2002;166:1067.
[PubMed Abstract] -

- Yombi JC, Pozniak A, Boffito M, et al. Antiretrovirals and the kidney in current clinical practice: renal pharmacokinetics, alterations of renal function and renal toxicity. AIDS. 2014;28:621-32.
[PubMed Abstract] -

Figures

Figure 1 (Image Series) - Dolutegravir-Associated Weight Gain (Image Series) - Figure 1 (Image Series) - Dolutegravir-Associated Weight Gain
Image 1A: 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 on elvitegravir, and 63 on raltegravir).

Source: Bourgi K, Rebeiro PF, Turner M, et al. Greater Weight Gain in Treatment-naive Persons Starting Dolutegravir-based Antiretroviral Therapy. Clin Infect Dis. 2020;70:1267-74.

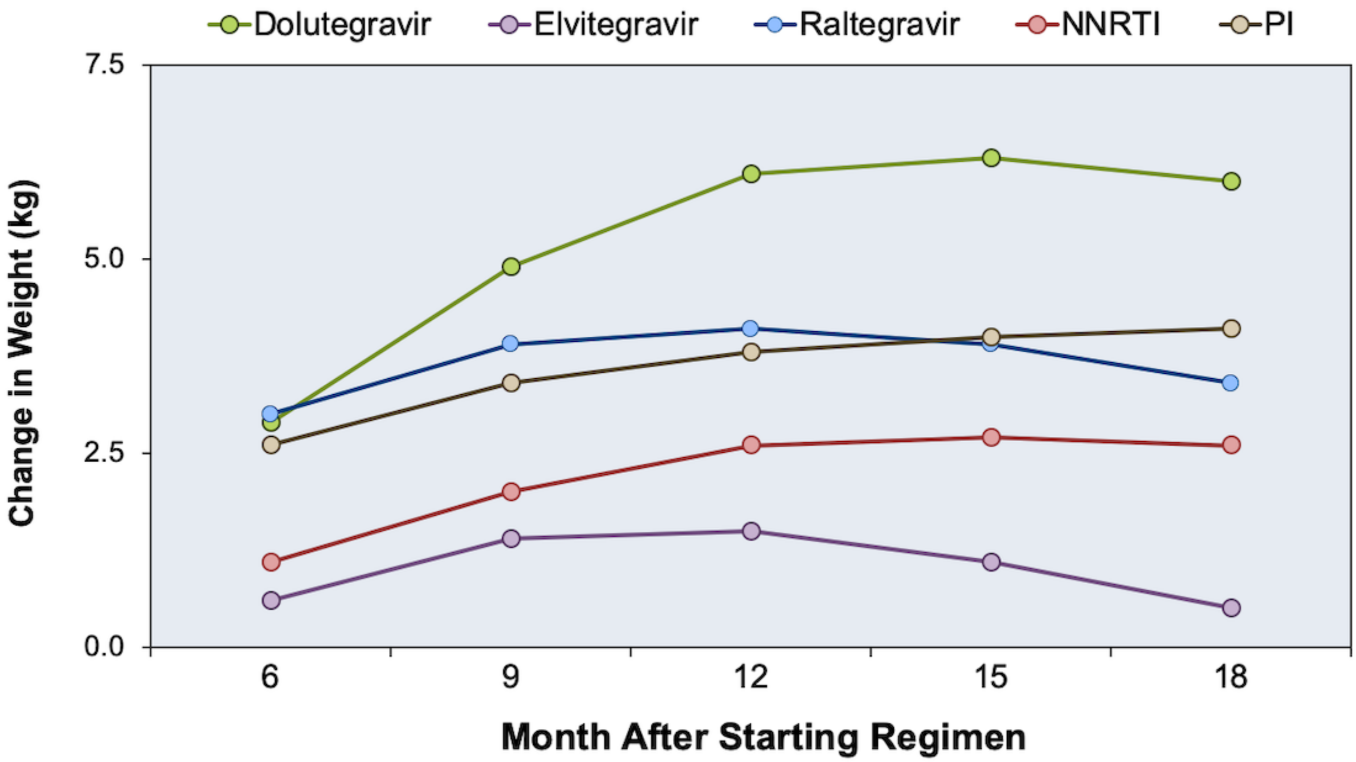

Figure 1 (Image Series) - Dolutegravir-Associated Weight Gain
Image 1B: Weight Gain in NA-ACCORD Study by INSTI-Based Regimen

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

Source: Bourgi K, Jenkins CA, Rebeiro PF, et al. Weight gain among treatment-naïve persons with HIV starting integrase inhibitors compared to non-nucleoside reverse transcriptase inhibitors or protease inhibitors in a large observational cohort in the United States and Canada. J Int AIDS Soc. 2020;23:e25484.

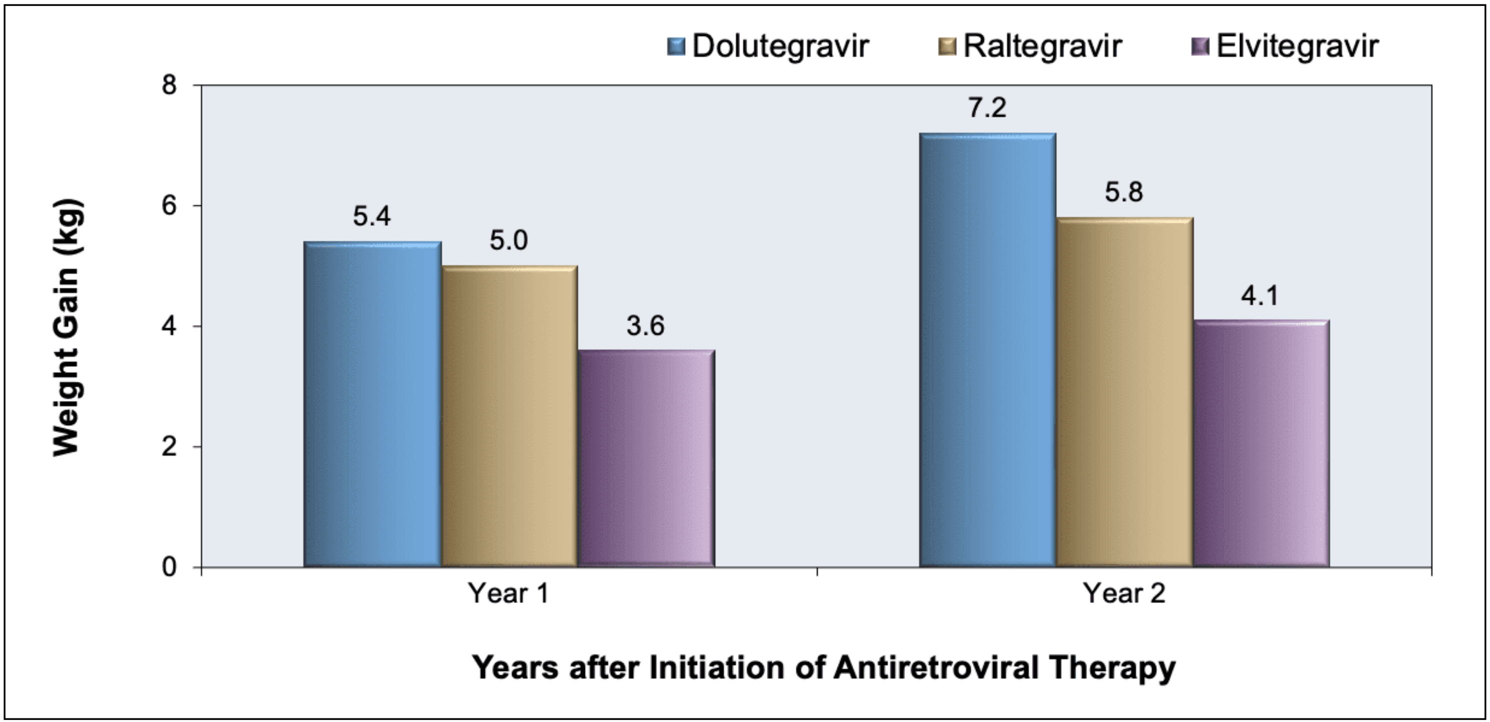

Figure 1 (Image Series) - Dolutegravir-Associated Weight Gain
Image 1C: Impact of NRTI on Dolutegravir-Related Weight Gain

This graph shows weight gain at week 48 after starting antiretroviral therapy, based on the regimen used. The combination of dolutegravir with tenofovir alafenamide-emtricitabine was associated with the most weight gain.
Abbreviations: DTG = dolutegravir; EFV = efavirenz; TDF = tenofovir DF; TAF = tenofovir alafenamide; FTC = emtricitabine

Source: Venter WDF, Moorhouse M, Sokhela S, et al. Dolutegravir plus Two Different Prodrugs of Tenofovir to Treat HIV. N Engl J Med. 2019;381:803-15

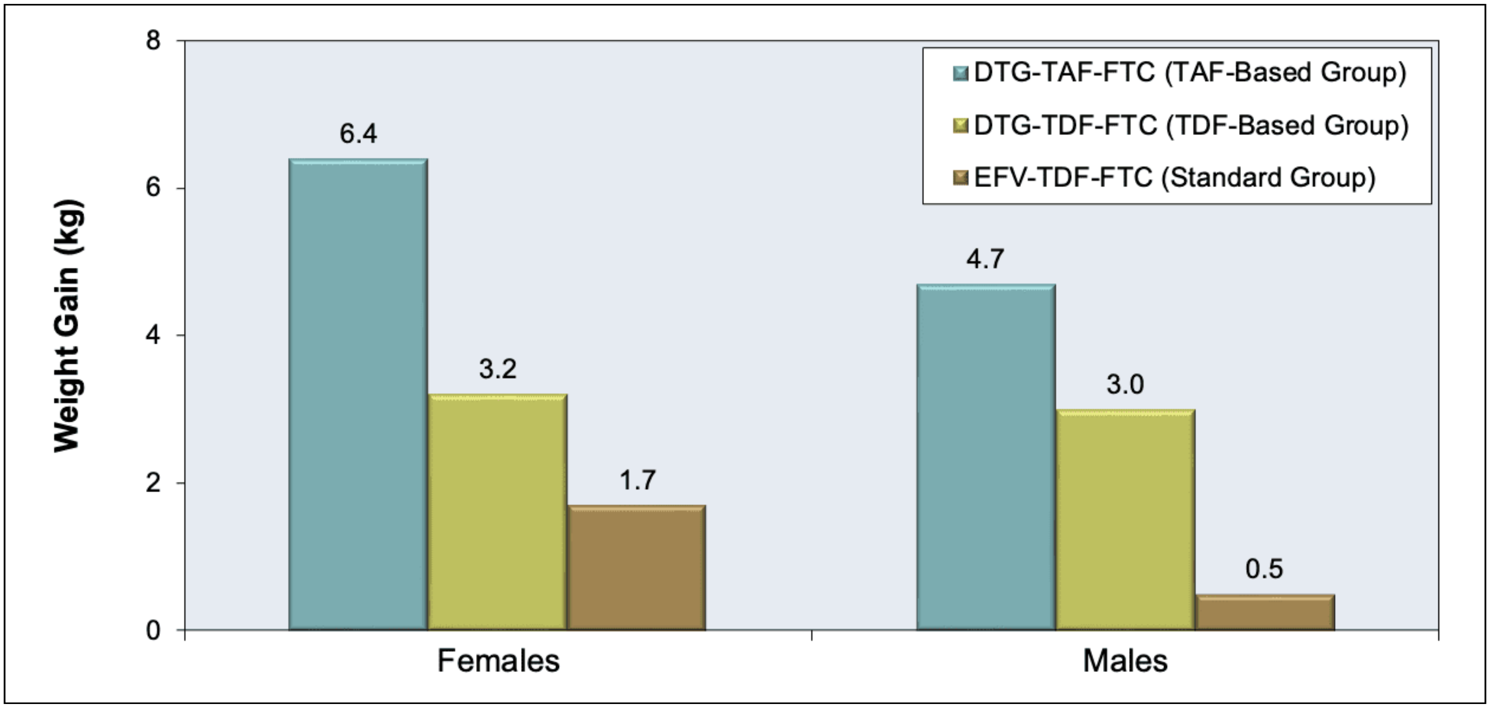

Figure 2 (Image Series) - Inhibition of Tubular Secretion of Creatinine (Image Series) - Figure 2 (Image Series) - Inhibition of Tubular Secretion of Creatinine
Image 2A: Renal Tubule and Promial Tubular Secretion of Creatinine

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

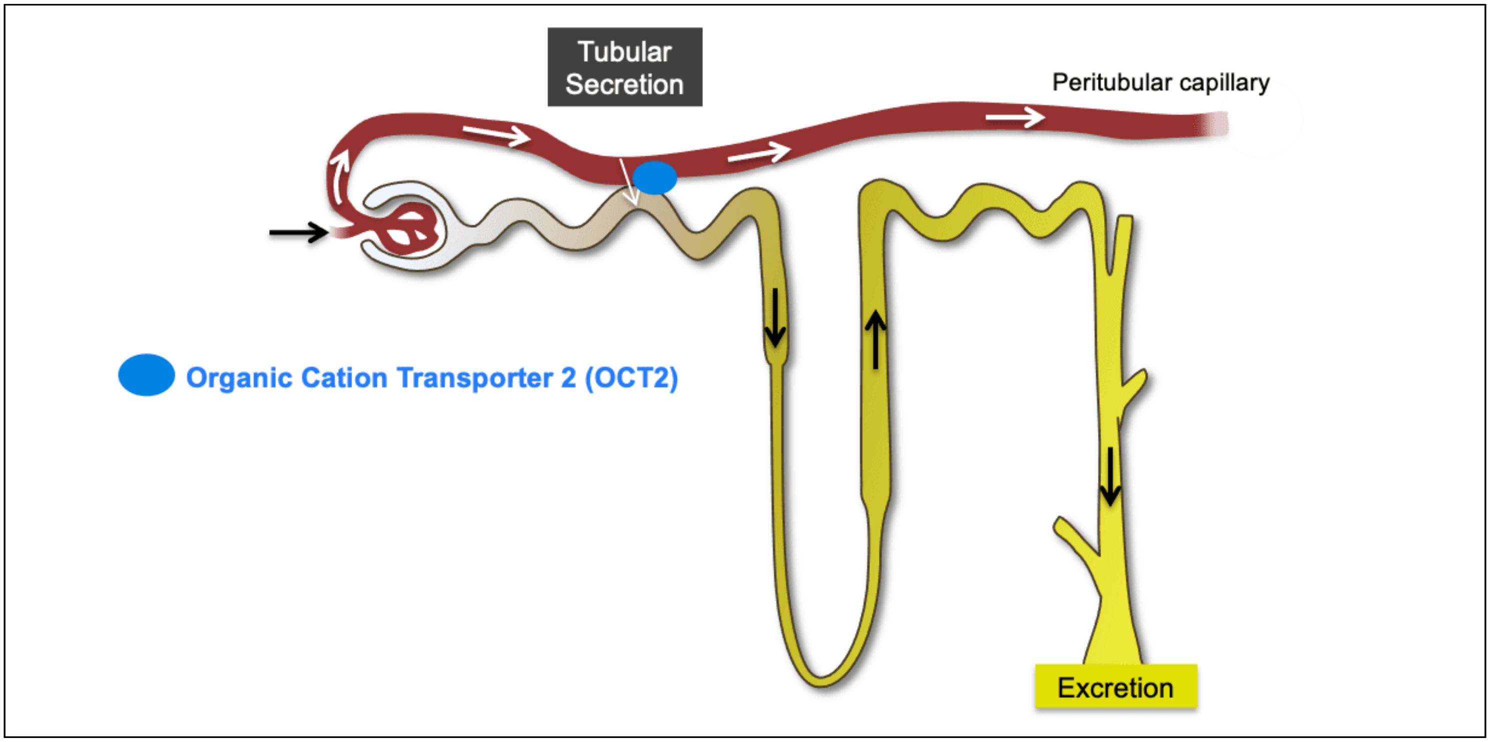

Figure 2 (Image Series) - Inhibition of Tubular Secretion of Creatinine
Image 2B: Organic Cation Transporter 2 (OCT2) and Normal Tubular Secretion of Creatinine

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

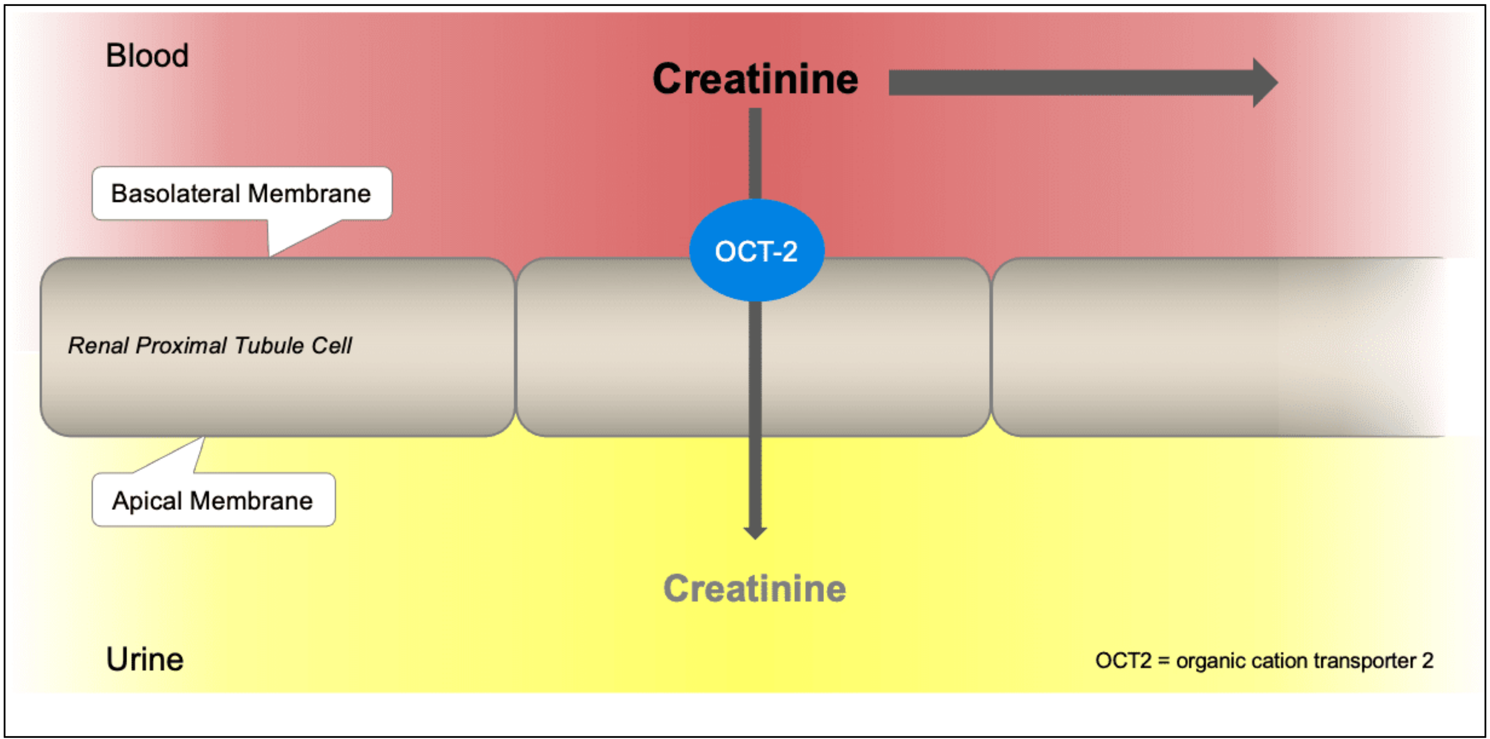

Figure 2 (Image Series) - Inhibition of Tubular Secretion of Creatinine
Image 2C: Inhibition of Tubular Secretion of Creatinine by Bictegravir and Dolutegravir

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

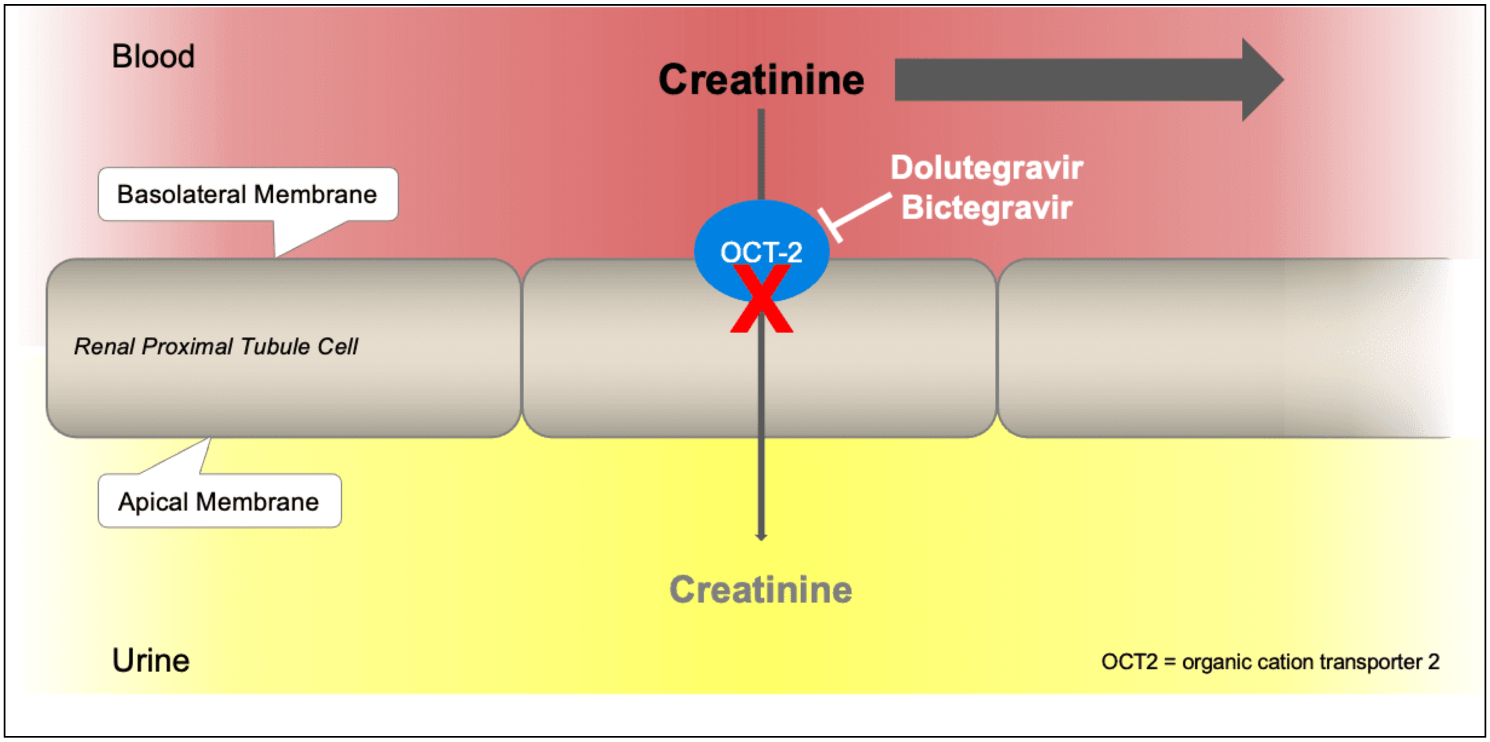

Figure 3 Dolutegravir-Related Changes in Serum Creatinine Level

This graph shows the mean change in serum creatinine levels from baseline for two antireretroviral regimens: 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.

Source: Walmsley SL, Antela A, Clumeck N, et al. Dolutegravir plus abacavir-lamivudine for the treatment of HIV-1 infection. N Engl J Med. 2013;369:1807-18. ©2013 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

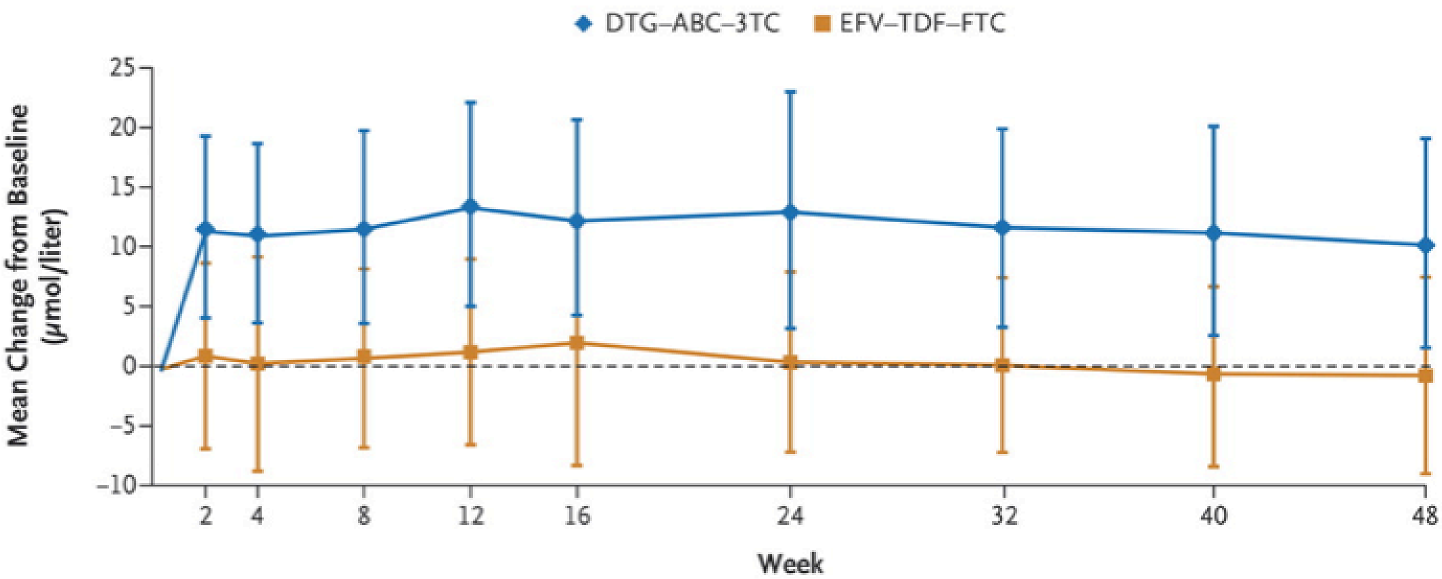

Figure 4 Metabolism of Tenofovir DF and Tenofovir Alafenamide Cellular Activation

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

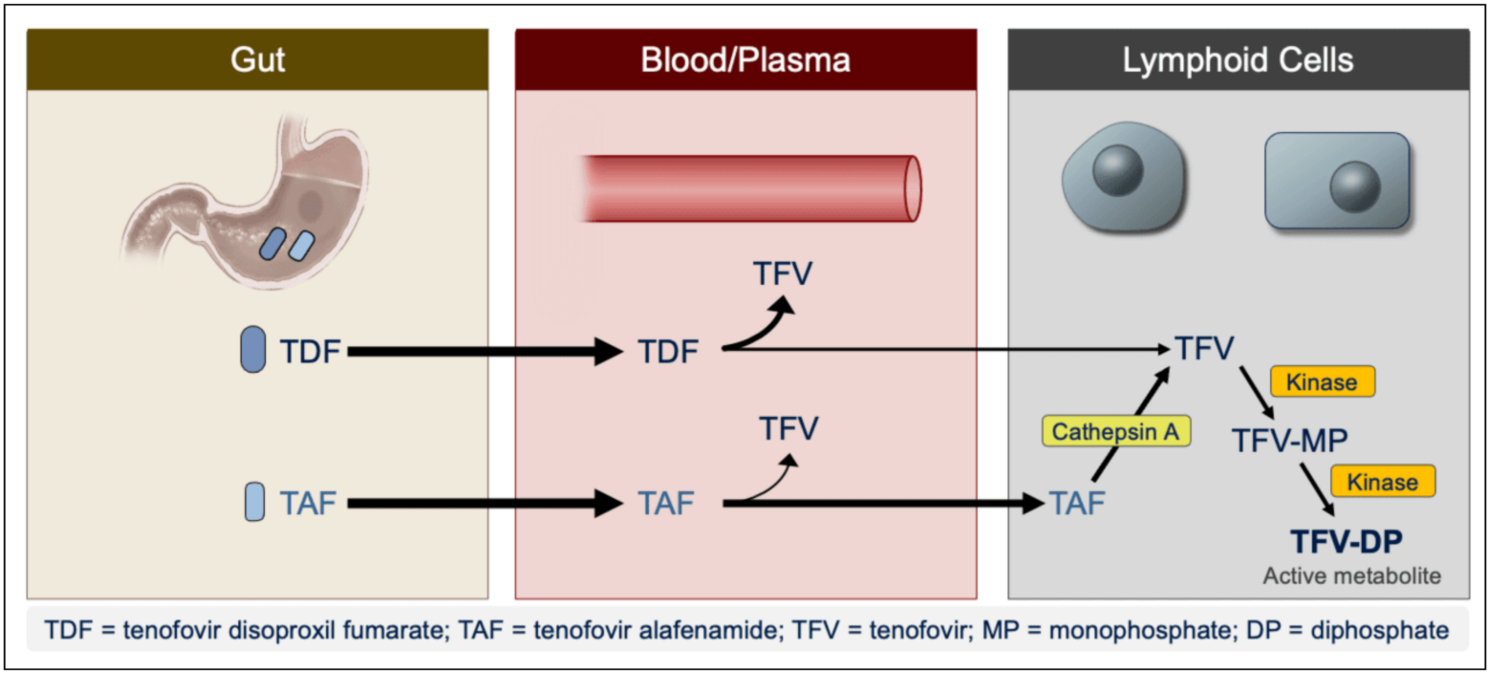

Figure 5 Common Laboratory Indicators of Proximal Tubule Dysfunction

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

Source: modified from Lucas GM, Ross MJ, Stock PG, et al. Clinical practice guideline for the management of chronic kidney disease in patients infected with HIV: 2014 update by the HIV Medicine Association of the Infectious Diseases Society of America. Clin Infect Dis. 2014;59:e96-138.

Common Laboratory Indicators of Proximal Tubular Dysfunction	
Abnormality	**Definition of Abnormality**
Serum Abnormalities	
Hypokalemia	Serum potassium concentration below laboratory reference range
Low serum bicarbonate	Serum bicarbonate concentration below laboratory reference range
Hypophosphatemia	Serum phosphorous concentration below laboratory reference range
Urine abnormalities	
Urine glucose on dipstick	Glycosuria in the absence of diabetes, or in diabetics with well-controlled blood glucose
Fractional excretion of phosphate	<10% is normal and >20% is abnormal
Tubular maximum for phosphate corrected for GFR	Lower than reference value (normal, 2.8–4.4 mg/dL)
Fractional excretion of uric acid	<15% is normal and >20% is abnormal
Urine albumin-to-protein ratio	uAPR <0.4 suggests predominantly tubulointerstitial disease, whereas uAPR >0.4 suggests predominantly glomerular disease
Abbreviations: GFR = glomerular filtration rate; uAPR, urine albumin-to-protein ratio;	

Figure 6 Central Nervous System Toxicity Related to Plasma Efavirenz Levels

This study involved an analysis of 130 adults taking an efavirenz-based antiretroviral regimen. Blood samples for efavirenz levels were drawn at an average of 14 hours after efavirenz intake.

Source: Marzolini C, Telenti A, Decosterd LA, Greub G, Biollaz J, Buclin T. Efavirenz plasma levels can predict treatment failure and central nervous system side effects in HIV-1-infected patients. AIDS. 2001;15:71-5.

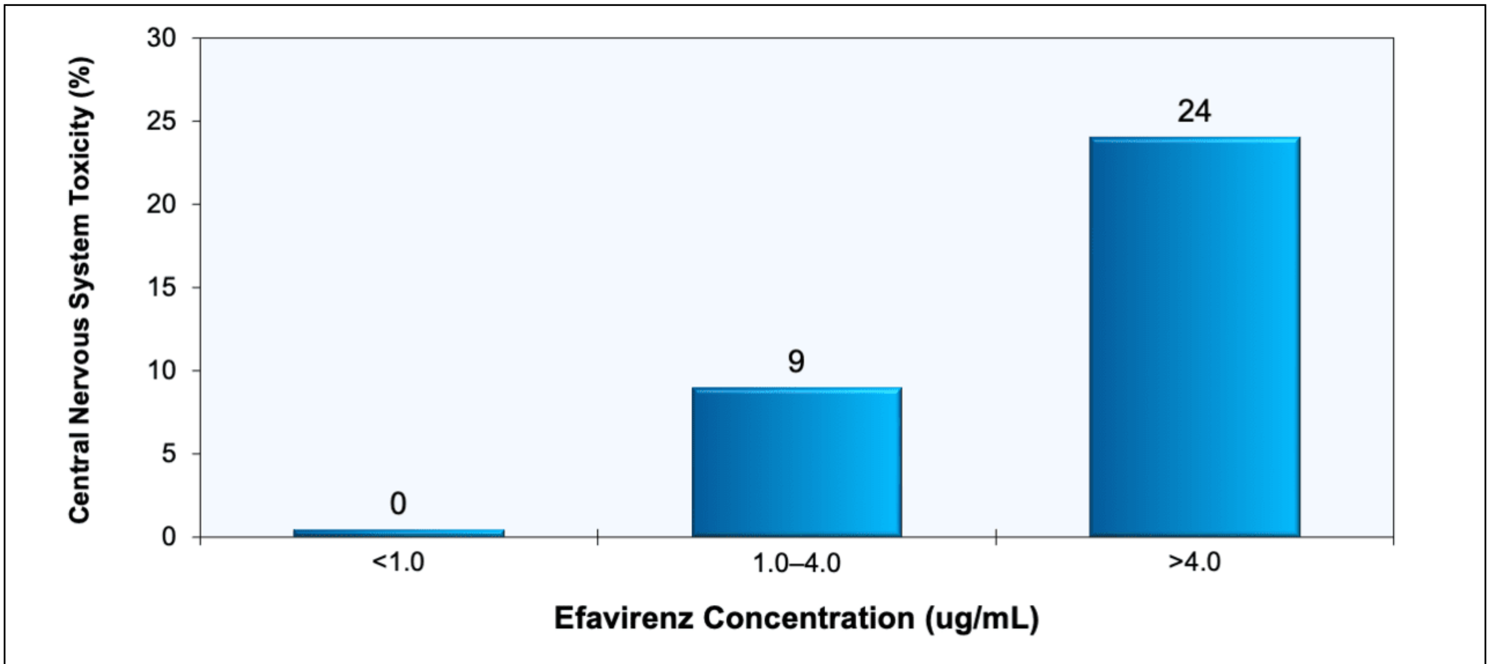

Figure 7 Efavirenz-Associated Rash

Photograph by David H. Spach, MD

Figure 8 Nevirapine-Associated Rash

Photograph by David H. Spach, MD

Figure 9 Mechanism for Atazanavir-Associated Increase in Serum Bilirubin

Abbreviation: UGT1A1 = uridine diphosphate glucuronosyltransferase 1A

Illustration: David Spach, MD

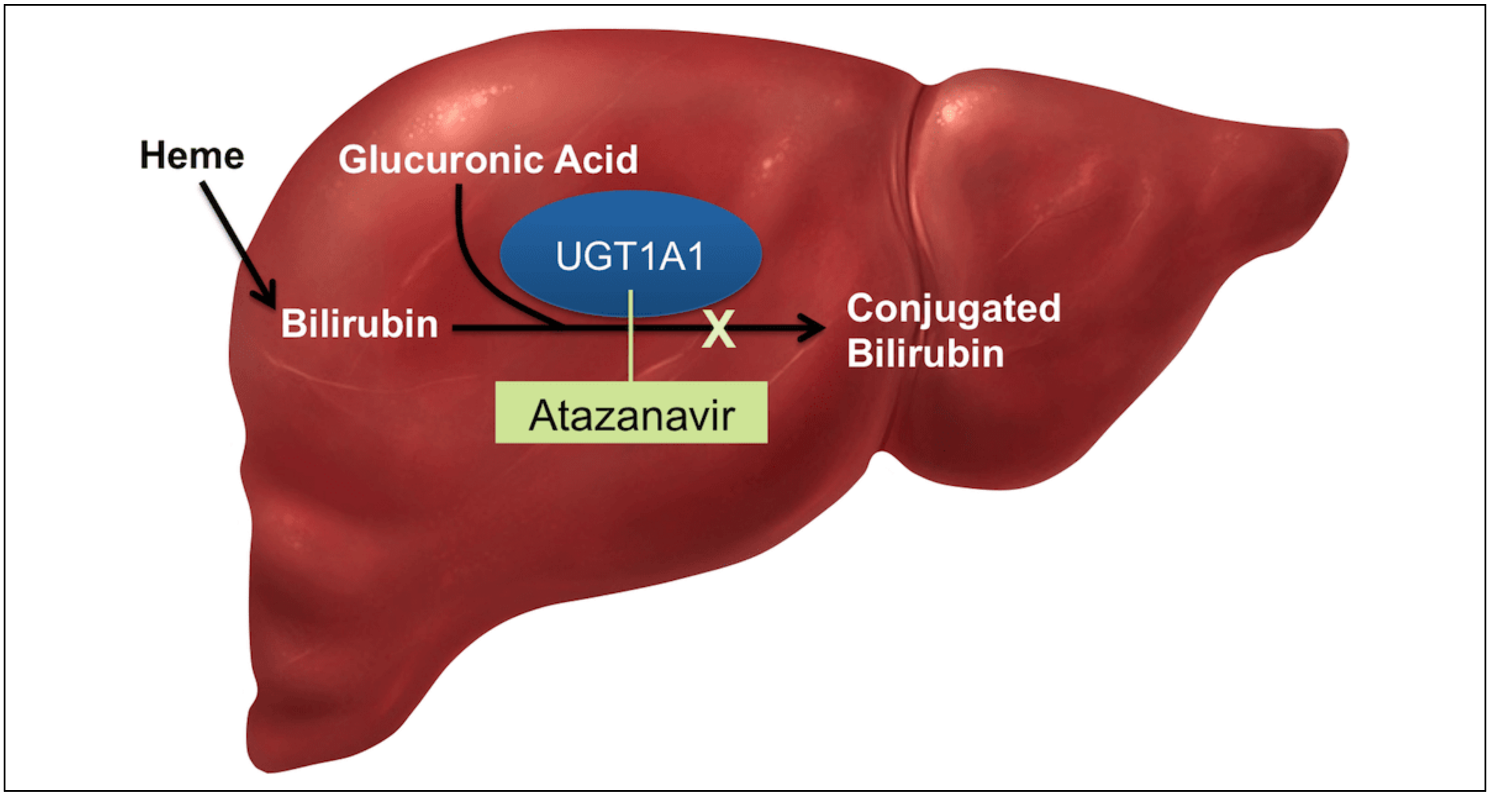

Table 1.

Laboratory Monitoring for Antiretroviral Therapy-Related Toxicities*

Laboratory Study	ART Initiation	4-8 Weeks after ART Initiation or Modification	Every 3 Months	Every 6 Months	Every 12 Months	Clinically Indicated
HLA-B*5701	√ If considering abacavir					
Basic metabolic panel[a,b]	√	√		√		√
ALT, AST, total bilirubin	√	√		√		√
CBC with differential[c]	√		√ When monitoring CD4 count	√ When monitoring CD4 count	√ When no longer monitoring CD4 count	√
Lipid profile[d]	√	Consider 1–3 months after ARV initiation or modification			√ If normal at baseline but with CV risk	If normal at baseline, every 5 years or if clinically indicated
Random or fasting glucose[e]	√					√
Urinalysis[f,g]	√				√ If on tenofovir DF or tenofovir alafenamide	√ E.g., in patients with chronic kidney disease or diabetes mellitus
Pregnancy test[h]	√					√

*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).
[d]If random lipids are abnormal, fasting lipids should be obtained. Consult the American

<table>
<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></tr>
<tr><td colspan="6">College of Cardiology/American Heart Association’s 2018 Guideline on the Management of Blood Cholesterol for diagnosis and management of patients with dyslipidemia.
[e]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.
[f]Consult the HIVMA/IDSA’s Clinical Practice Guideline for the Management of Chronic Kidney Disease in Patients Infected with HIV 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).
[g]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.
[h]For women of childbearing potential.</td><td></td></tr>
</table>

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]

Table 2.

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

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

Source:

- Martin MA, Kroetz DL. Abacavir pharmacogenetics--from initial reports to standard of care. Pharmacotherapy. 2013;33:765-75. [PubMed Abstract]