Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents

Downloaded from https://aidsinfo.nih.gov/guidelines on 9/19/2017

Adverse Effects of Antiretroviral Agents (Last updated July 14, 2016; last reviewed July 14, 2016)

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

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

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

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

Table 14. Antiretroviral Therapy-Associated Common and/or Severe Adverse Effects (page 1 of 5)

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

Adverse Effect	NRTIs	NNRTIs	PIs	INSTI	EI
Bleeding Events	N/A	N/A	Spontaneous bleeding, hematuria in hemophilia. **TPV:** Intracranial hemorrhage associated with CNS lesions, trauma, alcohol abuse, hypertension, coagulopathy, anticoagulant or antiplatelet agents, vitamin E	N/A	N/A
Bone Density Effects	**TDF:** Associated with greater loss of BMD than other NRTIs; osteomalacia may be associated with renal tubulopathy and urine phosphate wasting **TAF:** Smaller declines in BMD than with TDF.	Decreases in BMD observed after the initiation of any ART regimen.			N/A
Bone Marrow Suppression	**ZDV:** Anemia, neutropenia	N/A	N/A	N/A	N/A
Cardiovascular Disease	**ABC and ddI:** Associated with an increased risk of MI in some cohort studies. Absolute risk greatest in patients with traditional CVD risk factors.	**RPV:** QTc prolongation	Associated with MI and stroke in some cohorts. **SQV/r, ATV/r, and LPV/r:** PR prolongation (risks include pre-existing heart disease, other medications). **SQV/r:** QT prolongation. Obtain ECG before administering SQV.	N/A	N/A
Cholelithiasis	N/A	N/A	**ATV:** Cholelithiasis and kidney stones may present concurrently. Median onset is 42 months.	N/A	N/A
Diabetes Mellitus/ Insulin Resistance	ZDV, d4T, and ddI	N/A	Reported for some (IDV, LPV/r), but not all PIs	N/A	N/A

Table 14. Antiretroviral Therapy-Associated Common and/or Severe Adverse Effects (page 2 of 5)

Adverse Effect	NRTIs	NNRTIs	PIs	INSTI	EI
Dyslipidemia	**d4T > ZDV > ABC:** ↑TG and LDL **TAF > TDF:** ↑TG, ↑LDL, ↑HDL (no change in TC:HDL ratio)	**EFV:** ↑TG, ↑LDL, ↑HDL	**All RTV- or COBI-boosted PIs:** ↑TG, ↑LDL, ↑HDL **LPV/r = FPV/r and LPV/r > DRV/r and ATV/r:** ↑TG	**EVG/c:** ↑TG, ↑LDL, ↑HDL	N/A
Gastrointestinal Effects	**ddI and ZDV > other NRTIs:** Nausea and vomiting **ddI:** Pancreatitis	N/A	GI intolerance (eg, diarrhea, nausea, vomiting) **Common with LPV/r and more frequent than with DRV/r and ATV/r:** Diarrhea	**EVG/c:** Nausea and diarrhea	N/A
Hepatic Effects	Reported with most NRTIs. **ZDV, d4T, or ddI:** Steatosis most common **ddI:** Prolonged exposure linked to noncirrhotic portal hypertension, esophageal varices. **When TAF, TDF, 3TC, and FTC are withdrawn or when HBV resistance develops:** HIV/HBV-coinfected patients may develop severe hepatic flares.	NVP > other NNRTIs **NVP:** Severe hepatotoxicity associated with skin rash or hypersensitivity. Two-week NVP dose escalation may reduce risk. Risk is greater for women with pre-NVP CD4 count >250 cells/mm^3 and men with pre-NVP CD4 count >400 cells/mm^3. NVP should **never** be used for postexposure prophylaxis, or in patients with hepatic insufficiency (Child-Pugh B or C).	**All PIs:** Drug-induced hepatitis and hepatic decompensation have been reported; greatest frequency with TPV/r. **IDV, ATV:** Jaundice due to indirect hyperbilirubinemia **TPV/r: Contraindicated** in patients with hepatic insufficiency (Child-Pugh B or C)	N/A	**MVC:** Hepatotoxicity with or without rash or HSRs reported

Table 14. Antiretroviral Therapy-Associated Common and/or Severe Adverse Effects (page 3 of 5)

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

Table 14. Antiretroviral Therapy-Associated Common and/or Severe Adverse Effects (page 4 of 5)

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

Table 14. Antiretroviral Therapy-Associated Common and/or Severe Adverse Effects (page 5 of 5)

Adverse Effect	NRTIs	NNRTIs	PIs	INSTI	EI
Renal Effects/ Urolithiasis	**TDF:** ↑SCr, proteinuria, hypophosphatemia, urinary phosphate wasting, glycosuria, hypokalemia, non-anion gap metabolic acidosis. Concurrent use of TDF with COBI or RTV-containing regimens appears to increase risk. **TAF:** Less impact on renal biomarkers and lower rates of proteinuria than TDF.	N/A	**ATV and LPV/r:** Increased risk of chronic kidney disease in a large cohort study. **IDV:** ↑SCr, pyuria, renal atrophy or hydronephrosis **IDV, ATV:** Stone, crystal formation; adequate hydration may reduce risk.	**COBI and DTG:** Inhibits Cr secretion without reducing renal glomerular function.	N/A
Stevens-Johnson Syndrome/Toxic Epidermal Necrosis	**ddI, ZDV:** Reported cases	NVP > DLV, EFV, ETR, RPV	**FPV, DRV, IDV, LPV/r, ATV:** Reported cases	RAL	N/A

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

Switching Antiretroviral Therapy Because of Adverse Effects

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

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

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

A patient's acceptance of new food or dosing requirements must also be assessed. In some cases, medication costs may also be a factor to consider before switching treatment. Signs and symptoms of ART-associated adverse events may mimic those of comorbidities, adverse effects of concomitant medications, or HIV infection. Therefore, concurrent with ascribing a particular clinical event to ART, alternative causes for the event should be investigated. In the case of a severe adverse event, it may be necessary to discontinue or switch ARVs pending the outcome of such an investigation. For the first few months after an ART switch, the patient should be closely monitored for any new adverse events. The patient's viral load should also be monitored to assure continued viral suppression.

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

Table 15. Antiretroviral Therapy-Associated Adverse Events That Can Be Managed with Substitution of Alternative Antiretroviral Agent (page 1 of 2)

Adverse Event	ARV Agent(s) or Drug Class		Comments
	Switch from	Switch to	
Bone Density Effects	TDF[a]	ABC[b] or TAF NRTI-sparing regimens or regimens using only 3TC or FTC as NRTI may be considered if appropriate.	Declines in BMD have been observed upon initiation of most ART regimens. Switching from TDF to alternative ARV agents has been shown to increase bone density, but the clinical significance of this increase remains uncertain. TAF is associated with smaller declines in BMD than TDF, and with improvement in BMD upon switching from TDF. The long-term impact of TAF on patients with osteopenia or osteoporosis is unknown; close clinical monitoring is recommended in this setting.
Bone Marrow Suppression	ZDV	TDF, TAF, or ABC[b]	ZDV has been associated with neutropenia and macrocytic anemia.
Central Nervous System, Neuropsychiatric Side Effects Dizziness, suicidal ideation, abnormal dreams, depression	EFV, RPV	ETR or a PI/c or PI/r INSTIs may be considered (see Comments column).	In most patients, EFV-related CNS effects subside within 4 weeks after initiation of the drug. Persistent or intolerable effects should prompt substitution of EFV. INSTIs are associated with insomnia. Depression and suicidality have been infrequently reported with INSTI use, primarily in patients with pre-existing psychiatric conditions.
Dyslipidemia Hypertriglyceridemia (with or without elevated LDL level)	RTV- or COBI-boosted regimens; EFV; EVG/c	RAL, DTG, RPV	Elevated TG and LDL levels are more common with LPV/r and FPV/r than with other RTV-boosted PIs. Improvements in TG and LDL levels have been observed with switch from LPV/r to ATV or ATV/r.[c]
Gastrointestinal Effects Nausea, diarrhea	LPV/r	ATV/c, ATV/r, DRV/c, DRV/r, RAL, DTG, EVG/c	GI intolerance is common with boosted PIs and is linked to the total dose of RTV. More GI toxicity is seen with LPV/r than with ATV/r or DRV/r. GI effects are often transient, and do not warrant substitution unless persistent and intolerable.
	Other RTV- or COBI-boosted regimens	RAL, DTG, NNRTIs	In a trial of treatment-naive patients, rates of diarrhea and nausea were similar for EVG/c/TDF/FTC and ATV/r plus TDF/FTC.
Hypersensitivity Reaction	ABC	TDF or TAF	Never rechallenge with ABC following a suspected HSR, regardless of the patient's HLA-B*5701 status.
	NVP, EFV, ETR, RPV	Non-NNRTI ART	Risk of HSR with NVP is higher for women and those with high CD4 cell counts.
	DTG, RAL MVC	Non-INSTI ART Suitable alternative ART	Reactions to NVP, ETR, RAL, DTG and MVC may be accompanied by elevated liver transaminases.
Insulin Resistance	LPV/r, FPV/r	INSTI, RPV	Results of switch studies have been inconsistent. Studies in HIV-negative patients suggest a direct causal effect of LPV/r (and IDV) on insulin resistance. However, traditional risk factors may be stronger risk factors for insulin resistance than use of any PI.
Jaundice and Icterus	ATV, ATV/c, ATV/r	DRV/c, DRV/r, INSTI, or NNRTI	Increases in unconjugated bilirubin are common with ATV and generally do not require modification of therapy unless resultant symptoms are distressing to the patient.

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

Adverse Event	ARV Agent(s) or Drug Class		Comments
	Switch from	Switch to	
Lipoatrophy Subcutaneous fat wasting of limbs, face, buttocks	d4T, ZDV	TDF, TAF, or ABC[b]	Peripheral lipoatrophy is a legacy of prior thymidine analog (d4T and ZDV) use. Switching from these ARVs prevents worsening lipoatrophy, but fat recovery is typically slow (may take years) and incomplete.
Lipohypertrophy	Accumulation of visceral, truncal, dorso-cervical, and breast fat has been observed during ART, particularly during use of older PI-based regimens (eg, IDV), but whether ART directly causes fat accumulation remains unclear. There is no clinical evidence that switching to another first line regimen will reverse weight or visceral fat gain.		
Rash	NNRTIs (especially NVP and EFV)	PI- or INSTI-based regimen	Mild rashes developing after initiation of NNRTIs other than NVP rarely require treatment switch. When serious rash develops due to any NNRTI, switch to another drug class.
	DRV/c, DRV/r	ATV/c, ATV/r, or another drug class (eg, INSTI)	Mild rashes following DRV/r use may resolve with close follow-up only. For more severe reactions, change to an alternative boosted PI or an agent from another drug class.
Renal Effects Including proximal renal tubulopathy, elevated creatinine	TDF[a]	ABC[b] or TAF (for patients with CrCl >30mL/min) or NRTI-sparing regimens, or regimens using only 3TC or FTC as NRTI may be considered if appropriate.	TDF may cause tubulopathy. Switching from TDF to TAF is associated with improvement in proteinuria and renal biomarkers. The long-term impact of TAF on patients with pre-existing renal disease, including overt proximal tubulopathy, is unknown, and close clinical monitoring is recommended in this setting.
	ATV/c, ATV/r, LPV/r	DTG, RAL, or NNRTI	COBI and DTG, and to a lesser extent RPV, can increase SCr through inhibition of creatinine secretion. This effect does not affect glomerular filtration. However, assess for renal dysfunction if SCr increases by >0.4 mg/dL.
Stones Nephrolithiasis and cholelithiasis	ATV, ATV/c, ATV/r	DRV/c, DRV/r, INSTI, or NNRTI	Assuming that ATV is believed to be causing the stones.

[a] In patients with chronic active HBV infection, another agent active against HBV should be substituted for TDF.

[b] ABC should be used only in patients known to be HLA-B*5701 negative.

[c] TDF reduces ATV levels; therefore, unboosted ATV should not be co-administered with TDF. Long-term data for unboosted ATV are unavailable.

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

References

1. O'Brien ME, Clark RA, Besch CL, et al. Patterns and correlates of discontinuation of the initial HAART regimen in an urban outpatient cohort. *J Acquir Immune Defic Syndr*. 2003;34(4):407-414. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=14615659.
2. den Brinker M, Wit FW, Wertheim-van Dillen PM, et al. Hepatitis B and C virus co-infection and the risk for hepatotoxicity of highly active antiretroviral therapy in HIV-1 infection. *AIDS*. Dec 22 2000;14(18):2895-2902. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=11153671.
3. Saves M, Raffi F, Clevenbergh P, et al. Hepatitis B or hepatitis C virus infection is a risk factor for severe hepatic cytolysis after initiation of a protease inhibitor-containing antiretroviral regimen in human immunodeficiency virus-infected patients. The APROCO Study Group. *Antimicrob Agents Chemother*. Dec 2000;44(12):3451-3455. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=11083658.
4. Harris M, Larsen G, Montaner JS. Exacerbation of depression associated with starting raltegravir: a report of four cases. *AIDS*. Sep 12 2008;22(14):1890-1892. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18753871.
5. Kheloufi F, Allemand J, Mokhtari S, Default A. Psychiatric disorders after starting dolutegravir: report of four cases. *AIDS*. Aug 24 2015;29(13):1723-1725. Available at http://www.ncbi.nlm.nih.gov/pubmed/26372287.
6. Mallal S, Phillips E, Carosi G, et al. HLA-B*5701 screening for hypersensitivity to abacavir. *N Engl J Med*. 2008;358(6):568-579. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=18256392.
7. Saag M, Balu R, Phillips E, et al. High sensitivity of human leukocyte antigen-b*5701 as a marker for immunologically confirmed abacavir hypersensitivity in white and black patients. *Clin Infect Dis*. 2008;46(7):1111-1118. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=18444831.
8. Gounden V, van Niekerk C, Snyman T, George JA. Presence of the CYP2B6 516G> T polymorphism, increased plasma Efavirenz concentrations and early neuropsychiatric side effects in South African HIV-infected patients. *AIDS Res Ther*. 2010;7:32. Available at http://www.ncbi.nlm.nih.gov/pubmed/20723261.
9. Rodriguez-Novoa S, Martin-Carbonero L, Barreiro P, et al. Genetic factors influencing atazanavir plasma concentrations and the risk of severe hyperbilirubinemia. *AIDS*. Jan 2 2007;21(1):41-46. Available at http://www.ncbi.nlm.nih.gov/pubmed/17148966.