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

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Limitations to Treatment Safety and Efficacy

Adherence to Antiretroviral Therapy (Last updated May 1, 2014; last reviewed May 1, 2014)

Strict adherence to antiretroviral therapy (ART) is key to sustained HIV suppression, reduced risk of drug resistance, improved overall health, quality of life, and survival,[1,2] as well as decreased risk of HIV transmission.[3] Conversely, poor adherence is the major cause of therapeutic failure. Achieving adherence to ART is a critical determinant of long-term outcome in HIV infected patients. For many chronic diseases, such as diabetes or hypertension, drug regimens remain effective even after treatment is resumed following a period of interruption. In the case of HIV infection, however, loss of virologic control as a consequence of non-adherence to ART may lead to emergence of drug resistance and loss of future treatment options. Many patients initiating ART or already on therapy are able to maintain consistent levels of adherence with resultant viral suppression, CD4+ T-lymphocyte (CD4) count recovery, and improved clinical outcomes. Others, however, have poor adherence from the outset of ART and/or experience periodic lapses in adherence over the lifelong course of treatment. Identifying those with adherence-related challenges that require attention and implementing appropriate strategies to enhance adherence are essential roles for all members of the treatment team.

Recent data underscore the importance of conceptualizing treatment adherence broadly to include early engagement in care and sustained retention in care. The concept of an HIV "treatment cascade" has been used to describe the process of HIV testing, linkage to care, initiation of effective ART, adherence to treatment, and retention in care. The U.S. Centers for Disease Control and Prevention estimates that only 36% of the people living with HIV in the United States are prescribed ART and that among these individuals, only 76% have suppressed viral loads.[4] Thus, to achieve optimal clinical outcomes and to realize the potential public health benefit of treatment as prevention, attention to each step in the treatment cascade is critical.[5] Therefore, provider skill and involvement to retain patients in care and help them achieve high levels of medication adherence are crucial.

This section provides updated guidance on assessing and monitoring adherence and outlines strategies to help patients maintain high levels of adherence.

Factors Associated with Adherence Success and Failure

Adherence to ART can be influenced by a number of factors, including the patient's social situation and clinical condition; the prescribed regimen; and the patient-provider relationship.[6] It is critical that each patient receives and understands information about HIV disease including the goals of therapy (achieving and maintaining viral suppression, decreasing HIV-associated morbidity and mortality, and preventing sexual transmission of HIV), the prescribed regimen (including dosing schedule and potential side effects), the importance of strict adherence to ART, and the potential for the development of drug resistance as a consequence of suboptimal adherence. However, information alone is not sufficent to assure high levels of adherence; patients must also be positively motivated to initiate and maintain therapy.

From a patient perspective, nonadherence is often a consequence of one or more behavioral, structural, and psychosocial barriers (e.g., depression and other mental illnesses, neurocognitive impairment, low health literacy, low levels of social support, stressful life events, high levels of alcohol consumption and active substance use, homelessness, poverty, nondisclosure of HIV serostatus, denial, stigma, and inconsistent access to medications).[7-9] Furthermore, patient age may affect adherence. For example, some adolescent and young adult HIV patients, in particular, have substantial challenges in achieving levels of adherence necessary for successful therapeutic outcomes (see HIV-Infected Adolescents section).[10,11] In additon, failure to adopt practices that facilitate adherence, such as linking medication taking to daily activities or using a medication reminder system or a pill organizer, is also associated with treatment failure.[12]

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Characteristics of one or more components of the prescribed regimen can affect adherence. Simple, once-daily regimens,[13] including those with low pill burden, without a food requirement, and few side effects or toxicities, are associated with higher levels of adherence.[14,15] Many currently available ARV regimens are much easier to take and better tolerated than older regimens. Studies have shown that patients taking once-daily regimens have higher rates of adherence than those taking twice-daily dosing regimens.[15] However, data to support or refute the superiority of fixed-dose combination product of 1-pill versus 3-pills (of individual drug products), once-daily regimens—as might be required for the use of some soon-to-be-available generic-based ARV regimens—are limited.

Characteristics of the clinical setting can also have important structural influences on the success or failure of medication adherence. Settings that provide comprehensive multidisciplinary care (e.g., with case managers, pharmacists, social workers, psychiatric care providers) are often more successful in supporting patients' complex needs, including their medication adherence-related needs. Further, specific settings, such as prisons and other institutional settings, may thwart or support medication adherence. Drug abuse treatment programs are often best suited to address substance use that may confound adherence and may offer services, such as directly observed therapy, that promote adherence.

Finally, a patient-provider relationship that enhances patient trust through non-judgmental and supportive care and use of motivational strategies can positively influence medication adherence.

Routine Monitoring of Adherence and Retention in Care

Although there is no gold standard for assessing adherence,[1] properly implemented validated tools and assessment strategies can prove valuable in most clinical settings. Viral load suppression is one of the most reliable indicators of adherence and can be used as positive reinforcement to encourage continuous adherence. When patients initiating ART fail to achieve viral suppression by 24 weeks of treatment, the possibility of suboptimal adherence and other factors must be assessed. Similarly, treatment failure as measured by detectable viral load during chronic care is most likely the result of non-adherence. Patient self-report, the most frequently used method for evaluating medication adherence, remains a useful tool for assessing adherence over time. However, self-reports must be properly and carefully assessed as patients may overestimate adherence. While carefully assessed patient self report of high-level adherence to ART has been associated with favorable viral load responses,[16,17] patient admission of suboptimal adherence is highly correlated with poor therapeutic response. The reliability of self report often depends on how the clinican elicits the information. It is most reliable when ascertained in a simple, nonjudgmental, routine, and structured format that normalizes less-than-perfect adherence and minimizes socially desirable or "white coat adherence" responses. Some patients may selectively adhere to components of a regimen believed to have the fewest side effects or the lowest dosing frequency or pill burden. To allow patients to more accurately disclose lapses in adherence, some experts suggest that providers inquire about the number of missed doses during a defined time period rather than directly asking "Are you taking your medicines?" Others advocate simply asking patients to rate their adherence during the last 4 weeks on a 5- or 6-point Likert scale.[18,19] Regardless of how obtained, patient self-report, in contrast to other measures of adherence, allows for immediate patient-provider discussion to identify reasons for missed doses and to explore corrective strategies.

Other measures of adherence include pharmacy records and pill counts. Pharmacy records can be valuable when medications are obtained exclusively from a single source so that refills can be traced. Pill counts are commonly used but can be altered by patients. Other methods of assessing adherence include the use of therapeutic drug monitoring and electronic measurement devices (e.g., MEMS bottle caps and dispensing systems). However, these methods are costly and are usually done primarily in research settings.

Interventions to Improve Adherence and Retention in Care

A continuum of ART adherence support services is necessary to meet individual patient needs. All health care

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team members, including physicians, physician assistants, nurse practitioners, nurse midwives, nurses, pharmacists, medication managers, and social workers play integral roles in successful adherence programs.[17,20-22]

Effective adherence interventions vary in modality and duration, and by clinical setting, provider, and patient. There are many options that can be customized to suit a range of needs and settings (see Table 13). An increasing number of interventions have proven effective in improving adherence to ART. For descriptions of the interventions, see: http://www.cdc.gov/hiv/topics/research/prs/ma-good-evidence-interventions.htm.[23]

Clinicians should provide all patients with a basic level of adherence-related information and support. Before writing the first prescription(s) for patients initiating or reinitiating ART, clinicians should assess the patient's adherence readiness. Clinicians should evaluate patients' knowledge about HIV disease, treatment, and prevention and provide basic information about ART, viral load and CD4 count and the expected outcome of ART based on these parameters, the importance of strict adherence to ART, and the consequences of non-adherence. In addition, clinicians should assess patients' motivation to successfully adhere to ART and identify and support facilitating factors and address potential barriers to adherence. Finally, clinicians should be assured that patients have the necessary medication taking skills to follow the regimen as prescribed.

Given the wide array of treatment options, individualizing treatment with patient involvement in decision making is the cornerstone of treatment planning and therapeutic success. The first principle of successful treatment is to design an understandable plan to which the patient can commit.[24,25] It is important to consider the patient's daily schedule; patient tolerance of pill number, size and frequency; and any issues affecting absorption (e.g., use of acid reducing therapy and food requirements). With the patient's input, a medication choice and administration schedule should be tailored to his/her routine daily activities. If necessary, soliciting help from family members may also improve adherence. Patients who are naive to ART should understand that their first regimen usually offers the best chance for taking a simple regimen that affords long-term treatment success and prevention of drug resistance. Establishing a trusting patient-provider relationship over time and maintaining good communication will help to improve adherence and long-term outcomes. Medication taking can also be enhanced by the use of pill organizers and medication reminder aids (e.g., alarm clock, pager, calendar).

Positive reinforcement can greatly help patients maintain high levels of adherence. This technique to foster adherence includes informing patients of their low or suppressed HIV viral load levels and increases in CD4 cell counts. Motivational interviewing has also been used with some successes. Recognizing high levels of adherence with incentives and rewards can facilitate treatment success in some patients. Adherence-contingent reward incentives such as meal tickets, grocery bags, lotto tickets, and cash have been used in the treatment of HIV and other chronic diseases. The effectiveness of using cash incentives to promote HIV testing, entry to care, and adherence to ART is currently being studied in the multi-site HPTN 065 trial. Other effective interventions include nurse home visits, a five-session group intervention, pager messaging, and couples or family-based interventions. To maintain high levels of adherence in some patients, it is critically important to provide substance abuse therapy and to strengthen social support. Directly observed therapy (DOT) has been effective in providing ART to active drug users[26] but not to patients in a general clinic population.[27]

To determine whether additional adherence or retention interventions are warranted, assessments should be done at each clinical encounter and should be the responsibility of the entire health care team. Routine monitoring of HIV viral load, pharmacy records, and indicators that measure retention in care are useful to determine if more intense efforts are needed to improve adherence. Patients with a history of non-adherence to ART are at risk for poor adherence when re-starting therapy with the same or new drugs. Special attention should be given to identify and address any reason for previous poor adherence. Preferential use of ritonavir-boosted protease inhibitor-(PI/r)-based ART, which has a higher barrier to the development of resistance than

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other treatment options, should be considered if poor adherence is predicted.

The critical elements of adherence go hand in hand with linkage-to-care and retention in care. A recently released guideline provides a number of strategies to improve entry and retention in care and adherence to therapy for HIV infected patients.[5] As with adherence monitoring, research advances offer many options for systematic monitoring of retention in care that may be used in accordance with local resources and standards. The options include surveillance of visit adherence, gaps in care, and the number of visits during a specified period of time.[28]

Conclusion

Adherence to ART is central to therapeutic success. Given the many available assessment strategies and interventions, the challenge for the treatment team is to select the techniques that best fit each patient and patient population, and, according to available resources, the treatment setting. In addition to maintaining high levels of medication adherence, attention to effective linkage to care, engagement in care, and retention in care is critical for successful treatment outcomes. To foster treatment success, there are interventions to support each step in the cascade of care, as well as guidance on systematic monitoring of each step in the cascade.[5]

Table 13. Strategies to Improve Adherence to Antiretroviral Therapy and Retention in Care
(page 1 of 3)

Strategies	Examples
Use a multidisciplinary team approach. Provide an accessible, trustworthy health care team.	• Nonjudgmental providers, nurses, social workers, pharmacists, and medication managers
Strengthen early linkage to care and retention in care.	• Encourage healthcare team participation in linkage to and retention in care.
Assess patient readiness to start ART.	
Evaluate patient's knowledge about HIV disease, prevention and treatment and, on the basis of the assessment, provide HIV-related information.	• Considering the patient's current knowledge base, provide information about HIV, including the natural history of the disease, HIV viral load and CD4 count and expected clinical outcomes according to these parameters, and therapeutic and prevention consequences of non-adherence.
Identify facilitators, potential barriers to adherence, and necessary medication management skills before starting ART medication.	• Assess patient's cognitive competence and impairment. • Assess behavioral and psychosocial challenges including depression, mental illnesses, levels of social support, high levels of alcohol consumption and active substance use, non-disclosure of HIV serostatus and stigma. • Identify and address language and literacy barriers. • Assess beliefs, perceptions, and expectations about taking ART (e.g., impact on health, side effects, disclosure issues, consequences of non-adherence). • Ask about medication taking skills and foreseeable challenges with adherence (e.g., past difficulty keeping appointments, adverse effects from previous medications, issues managing other chronic medications, need for medication reminders and organizers). • Assess structural issues including unstable housing, lack of income, unpredictable daily schedule, lack of prescription drug coverage, lack of continuous access to medications.
Provide needed resources.	• Provide or refer for mental health and/or substance abuse treatment. • Provide resources to obtain prescription drug coverage, stable housing, social support, and income and food security.

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Table 13. Strategies to Improve Adherence to Antiretroviral Therapy and Retention in Care
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Strategies	Examples
Involve the patient in ARV regimen selection.	• Review regimen potency, potential side effects, dosing frequency, pill burden, storage requirements, food requirements, and consequences of nonadherence. • Assess daily activities and tailor regimen to predictable and routine daily events. • Consider preferential use of PI/r-based ART if poor adherence is predicted. • Consider use of fixed-dose combination formulation. • Assess if cost/co-payment for drugs can affect access to medications and adherence.
Assess adherence at every clinic visit.	• Monitor viral load as a strong biologic measure of adherence. • Use a simple behavioral rating scale. • Employ a structured format that normalizes or assumes less-than-perfect adherence and minimizes socially desirable or "white coat adherence" responses. • Ensure that other members of the health care team also assess adherence.
Use positive reinforcement to foster adherence success.	• Inform patients of low or non-detectable levels of HIV viral load and increases in CD4 cell counts. • When needed, consider providing incentives and rewards for achieving high levels of adherence and treatment success.
Identify the type of and reasons for nonadherence.	• Failure to fill the prescription(s) • Failure to understand dosing instructions • Complexity of regimen (e.g., pill burden, size, dosing schedule, food requirements) • Pill aversion • Pill fatigue • Adverse effects • Inadequate understanding of drug resistance and its relationship to adherence • Cost-related issues • Depression, drug and alcohol use, homelessness, poverty • Stigma • Non-disclosure • Other potential barriers
Select from among available effective treatment adherence interventions.	• See http://www.cdc.gov/hiv/topics/research/prs/ma-good-evidence-interventions.htm. • Use adherence-related tools to complement education and counseling interventions (e.g., pill boxes, dose planners, reminder devices). • Use community resources to support adherence (e.g., visiting nurses, community workers, family, peer advocates). • Use patient prescription assistance programs. • Use motivational interviews.

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Table 13. Strategies to Improve Adherence to Antiretroviral Therapy and Retention in Care
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Strategies	Examples
Systematically monitor retention in care.	• Record and follow up on missed visits.
On the basis of any problems identified through systematic monitoring, consider options to enhance retention in care given resources available.	• Provide outreach for those patients who drop out of care. • Use peer or paraprofessional treatment navigators. • Employ incentives to encourage clinic attendance or recognize positive clinical outcomes resulting from good adherence. • Arrange for directly observed therapy (if feasible).

Key to Acronyms: ART = antiretroviral therapy; CD4 = CD4 T lymphocyte; PI = protease inhibitor; PI/r = ritonavir-boosted protease inhibitor

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Adverse Effects of Antiretroviral Agents (Last updated May 1, 2014; last reviewed May 1, 2014)

Adverse effects have been reported with the use of all antiretroviral (ARV) drugs and are among the most common reasons cited for switching or discontinuing therapy and for medication non-adherence.[1] However, with the use of newer ARV regimens, rates of treatment-limiting adverse events in antiretroviral therapy (ART)-naive patients enrolled in randomized trials appear to be declining and are generally now occurring in less than 10% of study participants. However, because most clinical trials have a relatively short follow-up duration, the longer term complications of ART can be underestimated. In the Swiss Cohort study during 6 years of follow-up, the presence of laboratory adverse events was associated with higher rates of mortality, which highlights the importance of adverse events in overall patient management.[2]

Several factors may predispose individuals to adverse effects of ARV medications. For example, compared with men, women (especially ART-naive women with CD4 counts >250 cells/mm^3) seem to have a higher propensity to develop Stevens-Johnson syndrome, rashes, and hepatotoxicity from nevirapine (NVP)[3-5] and have higher rates of lactic acidosis due to nucleoside reverse transcriptase inhibitors.[6-8] Other factors may also contribute to the development of adverse events:

- Concomitant use of medications with overlapping and additive toxicities;
- Comorbid conditions that may increase the risk of or exacerbate adverse effects (e.g., alcoholism[9] or coinfection with viral hepatitis[10-12] may increase the risk of hepatotoxicity);
- Drug-drug interactions that may lead to an increase in drug toxicities (e.g., interactions that result from concomitant use of statins with protease inhibitors); or
- Genetic factors that predispose patients to abacavir (ABC) hypersensitivity reaction.[10,11]

The therapeutic goals of ART include achieving and maintaining viral suppression and improving immune function, but an overarching goal of treatment should be to select a regimen that is not only effective but also safe. To accomplish this goal, the clinician must consider the toxicity potential of an ARV regimen, as well as the individual patient's underlying conditions, concomitant medications, and prior history of drug intolerances. In addition, it should be appreciated that, in general, the overall benefits of ART outweigh its risks and that some conditions (e.g., anemia, cardiovascular disease, renal impairment), may be more likely in the absence of ART.[12,13]

Information on the adverse events 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 by drug class. The most common adverse effects of individual ARV agents are summarized in Appendix B, Tables 1–6.

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Table 14. Antiretroviral Therapy-Associated Common and/or Severe Adverse Effects (page 1 of 7)

See Appendix B for additional information listed by drug. Empty cells in the table may mean that there are no reported cases for the particular side effect or that data for the specific ARV drug class are not available.

Adverse Effect	NRTIs	NNRTIs	PIs	INSTI	EI
Bleeding Events	N/A	N/A	PIs: Increased spontaneous bleeding, hematuria in patients with hemophilia reported with some PIs TPV: Reports of intracranial hemorrhage. Risks include CNS lesions, trauma, surgery, hypertension, alcohol abuse, coagulopathy, and concomitant use of anti-coagulant or anti-platelet agents, including vitamin E	N/A	N/A
Bone Density Effects	TDF: Associated with greater loss of BMD than ZDV, d4T, and ABC. Osteomalacia reported in association with proximal renal tubulopathy.	Decreases in BMD observed in studies of regimens containing different NRTIs combined with NNRTIs, PIs, or INSTIs.			N/A
Bone Marrow Suppression	ZDV: Anemia, neutropenia	N/A	N/A	N/A	N/A
CVD	ABC and ddI: Associated with an increased risk of MI in some, but not all, cohort studies. Absolute risk is greatest in patients with traditional CVD risk factors.	N/A	PIs: Associated with MI and stroke in some cohort studies. Data on newer PIs (ATV, DRV, and TPV) are limited. SQV/r, ATV/r, and LPV/r: PR interval prolongation. Risks include structural heart disease, conduction system abnormalities, cardiomyopathy, ischemic heart disease, and co-administration with drugs that prolong PR interval. SQV/r: QT interval prolongation in patients in a healthy volunteer study. Risks include underlying heart conditions, pre-existing prolonged QT or arrhythmia, or use with other QT-prolonging drugs. ECG is recommended before SQV initiation and should be considered during therapy.	N/A	N/A

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Table 14. Antiretroviral Therapy-Associated Common and/or Severe Adverse Effects (page 2 of 7)

Adverse Effect	NRTIs	NNRTIs	PIs	INSTI	EI
Cholelithiasis	N/A	N/A	ATV: • History of kidney stones increases risk. • Patients may present with cholelithiasis and kidney stones concurrently. • Typically presents as abdominal pain. • Reported complications include cholecystitis, pancreatitis, choledocholithiasis, and cholangitis. • Median time to onset is 42 months (range 1 to 90 months).	N/A	N/A
DM/Insulin Resistance	ZDV, d4T, and ddI	N/A	Reported for some PIs (IDV, LPV/r), but not all PIs	N/A	N/A
Dyslipidemia	d4T > ZDV > ABC: ↑LDL and TG	EFV: ↑TG, ↑LDL, ↑HDL	↑LDL, ↑TG, ↑HDL: All RTV-boosted PIs ↑TG: LPV/r = FPV/r and LPV/r > DRV/r and ATV/r	EVG/cobi/TDF/FTC: ↑TG, ↑LDL, ↑HDL	N/A
GI Effects	Nausea and vomiting: ddI and ZDV > other NRTIs Pancreatitis: ddI	N/A	GI intolerance (e.g., diarrhea, nausea, vomiting) Diarrhea: Common with NFV; also seen with LPV/r > DRV/r and ATV/r	Nausea and diarrhea: EVG/cobi/TDF/FTC	N/A

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Table 14. Antiretroviral Therapy-Associated Common and/or Severe Adverse Effects (page 3 of 7)

Adverse Effect	NRTIs	NNRTIs	PIs	INSTI	EI
Hepatic Effects	Reported with most NRTIs ddI: Prolonged exposure has been linked to non-cirrhotic portal hypertension, including some cases with esophageal varices. Steatosis: Most commonly seen with ZDV, d4T, or ddI Flares: HIV/HBV-co-infected patients may develop severe hepatic flares when TDF, 3TC, and FTC are withdrawn or when HBV resistance develops.	NVP > Other NNRTIs NVP: • Severe hepatotoxicity with NVP is often associated with skin rash or symptoms of hypersensitivity. • In ARV-naive patients, 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. Overall risk is higher for women than men. • Risk is greatest in the first few months of treatment. • 2-week dose escalation of NVP reduces risk of rash and possibly hepatotoxicity if related to hypersensitivity. • NVP is contraindicated in patients with moderate to severe hepatic insufficiency (Child-Pugh classification B or C). • Liver failure observed in HIV-uninfected individuals receiving NVP for post-exposure prophylaxis. NVP should **never** be used for this indication.	All PIs: Drug-induced hepatitis and hepatic decompensation (and rare cases of fatalities) have been reported with all PIs. The frequency of hepatic events is higher with TPV/r than with other PIs. IDV, ATV: Jaundice due to indirect hyperbilirubinemia TPV/r: Contraindicated in patients with moderate to severe hepatic insufficiency (Child Pugh classification B or C)	N/A	MVC: Hepatotoxicity with or without rash or HSRs reported

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Table 14. Antiretroviral Therapy-Associated Common and/or Severe Adverse Effects (page 4 of 7)

Adverse Effect	NRTIs	NNRTIs	PIs	INSTI	EI
HSR Excluding rash alone or SJS	ABC: • HLA-B*5701 screening should be performed before initiation of ABC. ABC should not be started if the HLA-B*5701 test result is positive. • Symptoms of HSR (in descending frequency): fever, skin rash, malaise, nausea, headache, myalgia, chills, diarrhea, vomiting, abdominal pain, dyspnea, arthralgia, and respiratory symptoms • Symptoms worsen with continuation of ABC. • Median onset of reactions is 9 days; approximately 90% of reactions occur within the first 6 weeks of treatment. • Patients, regardless of HLA-B*5701 status, should not be re-challenged with ABC if HSR is suspected.	NVP: • Hypersensitivity syndrome of hepatic toxicity and rash that may be accompanied by fever, general malaise, fatigue, myalgias, arthralgias, blisters, oral lesions, conjunctivitis, facial edema, eosinophilia, granulocytopenia, lymphadenopathy, or renal dysfunction. • In ARV-naive patients, 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. Overall, risk is higher for women than men. • 2-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

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Table 14. Antiretroviral Therapy-Associated Common and/or Severe Adverse Effects (page 5 of 7)

Adverse Effect	NRTIs	NNRTIs	PIs	INSTI	EI
Lactic Acidosis	NRTIs, Especially d4T, ZDV, and ddI: • Insidious onset with GI prodrome, weight loss, and fatigue. May be rapidly progressive with tachycardia, tachypnea, jaundice, muscular weakness, mental status changes, respiratory distress, pancreatitis, and organ failure. • Mortality up to 50% in some case series, especially in patients with serum lactate >10 mmol/L • Females and obese patients at increased risk Laboratory Findings: • ↑ lactate (often >5 mmol/L), anion gap, AST, ALT, PT, bilirubin • ↑ amylase and lipase in patients with pancreatitis • ↓ arterial pH, serum bicarbonate, serum albumin	N/A	N/A	N/A	N/A
Lipodystrophy	Lipoatrophy: Thymidine analogs (d4T > ZDV). May be more likely when NRTIs combined with EFV than with a 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 CPK	ZDV: Myopathy	N/A	N/A	RAL: ↑ CPK Muscle weakness and rhabdomyolysis	N/A

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Table 14. Antiretroviral Therapy-Associated Common and/or Severe Adverse Effects (page 6 of 7)

Adverse Effect	NRTIs	NNRTIs	PIs	INSTI	EI
Nervous System/ Psychiatric Effects	Peripheral neuropathy (pain and/or paresthesia, lower extremities > upper extremities): d4T > ddI and ddC (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 2–4 weeks. Bedtime dosing may reduce symptoms. Risks include history of psychiatric illness, concomitant use of agents with neuropsychiatric effects, and increased plasma 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 one retrospective analysis of several comparative trials.	N/A	All INSTIs: insomnia RAL: Depression and suicidal ideation (uncommon)	N/A
Rash	FTC: Hyperpigmentation	All NNRTIs	ATV, DRV, FPV, LPV/r, TPV	RAL, EVG/cobi/ TDF/FTC: Uncommon	MVC
Renal Effects/ Urolithiasis	TDF: ↑ SCr, proteinuria, hypophosphatemia, urinary phosphate wasting, glycosuria, hypokalemia, non-anion gap metabolic acidosis Concurrent use with PI appears to increase risk.	N/A	ATV and LPV/r: Associated with increased risk of chronic kidney disease in a large cohort study. IDV: ↑ SCr, pyuria; hydronephrosis or renal atrophy IDV, ATV: Stone, crystal formation; adequate hydration may reduce risk.	cobi (a component of EVG/cobi/TDF/ FTC) and DTG: Can increase SCr by reducing tubular secretion of Cr without reducing renal glomerular function; however, assess for renal dysfunction, especially if SCr increase by >0.4 mg/dL.	N/A

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Table 14. Antiretroviral Therapy-Associated Common and/or Severe Adverse Effects (page 7 of 7)

Adverse Effect	NRTIs	NNRTIs	PIs	INSTI	EI
SJS/TEN	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; ALT = alanine aminotransferase; ARV = antiretroviral; AST = aspartate aminotransferase; ATV = atazanavir; ATV/r = ritonavir-boosted atazanavir; BMD = bone mineral density; CrCl = creatinine clearance; CNS = central nervous system; cobi= cobicistat; CPK = creatine phosphokinase; CVD = cardiovascular disease; d4T = stavudine; ddC = zalcitabine; ddI = didanosine; DLV = delavirdine; DM = diabetes mellitus; DRV = darunavir; DRV/r = ritonavir-boosted darunavir; DTG = dolutegravir; ECG = electrocardiogram; EFV = efavirenz; EI = entry inhibitor; ETR = etravirine; EVG = elvitegravir; FPV = fosamprenavir; FPV/r = ritonavir-boosted fosamprenavir; 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 = ritonavir-boosted lopinavir; MI = myocardial infarction; MVC = maraviroc; NFV = nelfinavir; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; NVP = nevirapine; PI = protease inhibitor; PT = prothrombin time; RAL = raltegravir; RPV = rilpivirine; RTV = ritonavir; SCr. = serum creatinine; SJS = Stevens-Johnson syndrome; SQV = saquinavir; SQV/r = ritonavir-boosted saquinavir; TDF = tenofovir disoproxil fumarate; TEN = toxic epidermal necrosis; TG = triglyceride; TPV = tipranavir; TPV/r = ritonavir-boosted tipranavir; ZDV = zidovudine

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Switching Antiretroviral Therapy Because of Adverse Effects

Most patients do not experience treatment-limiting ART-associated toxicities; however, some patients do, and in these cases, ART must be modified. ART-associated adverse events can range from acute and potentially life threatening to chronic and insidious. Acute life-threatening events (e.g., acute hypersensitivity reaction due to ABC, lactic acidosis due to stavudine [d4T] and didanosine [ddI], liver and/or severe cutaneous toxicities due to NVP) usually require the immediate discontinuation of all ARV drugs and re-initiation of an alternative regimen without overlapping toxicity. Non-life threatening toxicities (e.g., urolithiasis with atazanavir [ATV], renal tubulopathy with tenofovir [TDF]) can usually be handled by substituting another ARV agent for the presumed causative agent without interruption of ART. Other, more chronic, non-life threatening adverse events (e.g., dyslipidemia) can be addressed either by switching the potentially causative agent for another agent or by managing the adverse event with additional pharmacological or non-pharmacological interventions. Management strategies must be individualized for each patient.

Switching from an effective ARV regimen to a new regimen 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 and even if absent from subsequent resistance test results, 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; resistance test results; viral tropism (when maraviroc [MVC] is being considered); HLA B*5701 status (when ABC is being considered); co-morbidities; adherence history; prior intolerances to any medications; and concomitant medications and supplements and their potential for drug interactions with ARVs. Patient 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, other concomitant medications, or HIV infection itself. 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 switching ARVs pending the outcome of such an investigation. For the first few months after a switch in ART is made, the patient should be closely monitored for any new adverse events, and viral load should 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.

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

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. The fundamental principle of regimen switching is to maintain viral suppression. Before any treatment switch is implemented, it is critical to review the patient's medical and full ARV history including the patient's prior virologic responses, resistance test results, viral tropism (when MVC is being considered), HLA B*5701 status (when ABC is being considered), co-morbidities, adherence history, concomitant medications and supplements and their potential for drug interactions, and prior intolerances to any ARV drugs.

Adverse Event	ARV Agent(s)/Drug Class		Comments
	Switch from	Switch to	
Bone Density Effects	TDF[a]	ABC[b]	Declines in BMD have been observed with the start of most ART. Modification of ART because of reduced BMD should be predicated on the clinical significance of the decline. Switching from TDF to alternative ARV agents has been shown to increase bone density, but the clinical significance of this increase remains uncertain.
Bone Marrow Suppression Anemia, leukopenia	ZDV	TDF or ABC[b]	N/A
CNS/Neuropsychiatric Side Effects Dizziness, suicidal ideation, sleep disturbance, abnormal dreams, depression	EFV	Alternative NNRTI (RPV, ETR, NVP), a PI, or an INSTI	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 with an alternate ARV agent.
Dyslipidemia Hypertriglyceridemia (with or without high low-density LDL level)	RTV- or cobi-boosted regimens or EFV	RAL, DTG, RPV, NVP, or unboosted ATV[c]	Elevated TG and LDL levels are more common with LPV/r and FPV/r than with other RTV-boosted PIs. Improved TG and LDL levels have been seen following a switch from LPV/r to RTV-boosted and -unboosted ATV.[c]
GI Effects Nausea, diarrhea	LPV/r	ATV/r, DRV/r, RAL, DTG, EVG/cobi/TDF/FTC	GI intolerance is relatively 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 in nature, and do not warrant switching therapy. If GI adverse effects are persistent or intolerable, consider drug substitution.
	Other RTV-boosted regimens or EVG/cobi/TDF/FTC	RAL, DTG, unboosted ATV,[c] NNRTIs	In a trial of treatment-naive patients, rates of diarrhea and nausea were similar for boosted EVG/cobi/TDF/FTC and ATV/r plus TDF/FTC.

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

Adverse Event	ARV Agent(s)/Drug Class		Comments
	Switch from	Switch to	
HSR	ABC	TDF	Never re-challenge 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	NNRTI (NVP or RPV), INSTI, unboosted ATV[c]	Results of switch studies have been inconsistent. Studies in HIV-negative patients given short courses of a PI suggest a direct causal effect of LPV/r (and IDV) on insulin resistance. However, traditional risk factors, such as obesity and family history of diabetes, may be stronger risk factors for insulin resistance than use of any PIs.
Jaundice and Icterus	ATV, ATV/r	DRV/r, INSTI, or NNRTI	Increases in unconjugated bilirubin are commonly seen with ATV and generally do not require modification of therapy unless jaundice/icterus is distressing to the patient.
Lipoatrophy Subcutaneous fat wasting of limbs, face, buttocks	d4T, ZDV	TDF 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, incomplete, and may take years.
Lipohypertrophy Accumulation of visceral abdominal, truncal, dorsocervical, and breast fat	Lipohypertrophy has been observed during ART, particularly during use of older PI-based regimens (e.g., IDV), but whether ART directly causes increases in fat depots remains unclear. There is no clinical evidence that switching to any currently recommended first line regimen will reverse weight or visceral fat gain.		
Rash	NNRTIs (especially NVP and EFV)	PI- or INSTI- based regimen	Rash can be seen with any NNRTI but occurs more frequently and is more severe with use of NVP, followed by EFV. Mild rashes developing after initiation of NNRTIs other than NVP rarely require treatment switch. When serious rash develops with use of any NNRTI, a switch to an agent from another ARV drug class is recommended.
	DRV/r	ATV/r or another class, such as INSTI	Mild rashes following DRV/r initiation do not necessarily require treatment switch. Close follow-up until the rash subsides is recommended. For more severe reactions, therapy can be changed to an alternative RTV-boosted PI or an agent from another drug class.

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

Adverse Event	ARV Agent(s)/Drug Class		Comments
	Switch from	Switch to	
Renal Effects Including proximal renal tubulopathy, elevated creatinine	TDF [a]	ABC [b]	Phosphate wasting as a consequence of TDF nephrotoxicity may lead to osteomalacia.
	ATV/r, LPV/r	DTG, RAL, or NNRTI	cobi and DTG, and to a lesser extent RTV, RPV, and RAL, can increase SCr soon after treatment initiation because of inhibition of tubular secretion of creatinine. This effect does not affect glomerular filtration. However, assess for renal dysfunction, especially if SCr increases by >0.4 mg/dL.
Stones Nephrolithiasis and cholelithiasis	ATV, ATV/r	DRV/r, INSTI, or NNRTI	Nephrolithiasis (a frequent complication of IDV) has been observed with ATV. Cholelithiasis is also reported with ATV.

[a] For patients with chronic active HBV infection, another agent active against HBV should be added to substitute 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/r = ritonavir-boosted atazanavir; BMD = bone mineral density; CNS = central nervous system; cobi = cobicistat; d4T = stavudine; ddI = didanosine; DRV/r = ritonavir-boosted darunavir; DTG = dolutegravir; EFV = efavirenz; ETR = etravirine; EVG = elvitegravir; FPV/r = ritonavir-boosted fosamprenavir; FTC = emtricitabine; GI = gastrointestinal; HBV = hepatitis B virus; HSR = hypersensitivity reaction; IDV = indinavir; INSTI = integrase strand transfer inhibitor; LDL = low-density lipoprotein; LPV/r = ritonavir-boosted lopinavir; MVC = maraviroc; 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; TDF = tenofovir disoproxil fumarate; TG = triglycerides; ZDV = zidovudine

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Cost Considerations and Antiretroviral Therapy (Last updated May 1, 2014; last reviewed May 1, 2014)

Although antiretroviral therapy (ART) is expensive (see Table 16 below), the cost-effectiveness of ART has been demonstrated in analyses of older[1] and newer regimens,[2,3] as well as for treatment-experienced patients with drug-resistant HIV.[4] Given the recommendations for immediate initiation of lifelong treatment and the increasing number of patients taking ART, the Panel now introduces cost-related issues pertaining to medication adherence and cost-containment strategies, as discussed below.

Costs as They Relate to Adherence from a Patient Perspective

Cost sharing: Cost sharing is where the patient is responsible for some of the medication cost burden (usually accomplished via co-payments, co-insurance, or deductibles); these costs are often higher for branded medications than for generic medications. In one comprehensive review, increased patient cost sharing resulted in decreased medical adherence and more frequent drug discontinuation; for patients with chronic diseases, increased cost sharing was also associated with increased use of the medical system.[5] Conversely, co-payment reductions, such as those that might be used to incentivize prescribing of generic drugs, have been associated with improved adherence in patients with chronic diseases.[6] Whereas cost-sharing disproportionately affects low income patients, resources (e.g., the Ryan White AIDS Drug Assistance Program [ADAP]) are available to assist eligible patients with co-pays and deductibles. Given the clear association between out-of-pocket costs for patients with chronic diseases and the ability of those patients to pay for and adhere to medications, clinicians should minimize patients' out-of-pocket drug-related expenses whenever possible.

Prior authorizations: As a cost-containment strategy, some programs require that clinicians obtain prior authorizations or permission before prescribing newer or more costly treatments rather than older or less expensive drugs. Although there are data demonstrating that prior authorizations do reduce spending, several studies have also shown that prior authorizations result in fewer prescriptions filled and increased non-adherence.[7-9] Prior authorizations in HIV care specifically have been reported to cost over $40 each in provider personnel time (a hidden cost) and have substantially reduced timely access to medications.[10]

Generic ART: The impact of the availability of generic antiretroviral (ARV) drugs on selection of ART in the United States is unknown. Because U.S. patent laws currently limit the co-formulation of some generic alternatives to branded drugs, generic options may result in increased pill burden. To the extent that pill burden, rather than drug frequency, results in reduced adherence, generic ART could lead to decreased costs but at the potential expense of worsening virologic suppression rates and poorer clinical outcomes.[11,12] Furthermore, prescribing the individual, less-expensive generic components of a branded co-formulated product rather than the branded product itself could, under some insurance plans, lead to higher copays—an out-of-pocket cost increase that may reduce medication adherence.

Potential Cost Containment Strategies from a Societal Perspective

Given resource constraints, it is important to maximize the use of resources without sacrificing clinical outcomes. Evidence-based revisions to these guidelines recommend tailored laboratory monitoring for patients with long-term virologic suppression on ART as one possible way to provide overall cost savings. Data suggest that continued CD4 monitoring yields no clinical benefit for patients whose viral loads are suppressed and CD4 counts exceed 200 cells/mm^3 after 48 weeks of therapy.[13] A reduction in laboratory use from biannual to annual CD4 monitoring could save ~$10 million per year in the United States[14] (see the Laboratory Monitoring section). Although this is a small proportion of the overall costs associated with HIV care, such a strategy could reduce patients' personal expenses if they have deductibles for laboratory tests. The present and future availability of generic formulations of certain ARV drugs, despite the potential caveats of increased pill burden and reduced adherence, offers other money-saving possibilities on a much

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greater scale. One analysis suggests the possibility of saving approximately $900 million nationally in the first year of switching from a branded fixed-dose combination product to a three-pill regimen containing generic efavirenz.[3]

In summary, understanding HIV and ART-related costs in the United States is complicated because of the wide variability in medical coverage, accessibility, and expenses across regions, insurance plans, and pharmacies. In an effort to retain excellent clinical outcomes in an environment of cost-containment strategies, providers should remain informed of current insurance and payment structures, ART costs (see Table 16 below for estimates of drugs' average wholesale prices), discounts among preferred pharmacies, and available generic ART options. Providers should work with patients and their case managers and social workers to understand their patients' particular pharmacy benefit plans and potential financial barriers to filling their prescriptions. Additionally, providers should familiarize themselves with ARV affordability resources (such as ADAP and pharmaceutical company patient assistance programs for patients who qualify) and refer patients to such assistance if needed.

Table 16: Monthly Average Wholesale Price[a] of Antiretroviral Drugs (Last updated January 2014; last reviewed January 2014) (page 1 of 4)

ARV Drug (Generic and Brand Names)	Strength	Dosing	Tablets/Capsules/ mLs per Month	AWP[a] (Monthly)
Nucleoside Reverse Transcriptase Inhibitors (NRTIs)				
Abacavir				
• Generic	300 mg tab	2 tabs daily	60 tabs	$602.66
• Ziagen	300 mg tab	2 tabs daily	60 tabs	$670.30
• Ziagen	20 mg/mL soln	30 mL daily	900 mL	$660.86
Didanosine Delayed-Release				
• Generic	400 mg cap	1 cap daily	30 caps	$368.72
• Videx EC	400 mg cap	1 cap daily	30 caps	$515.84
Emtricitabine				
• Emtriva	200 mg cap	1 cap daily	30 tabs	$602.27
• Emtriva	10 mg/mL soln	24 mL daily	680 mL (28-day supply)	$568.88
Lamivudine				
• Generic	300 mg tab	1 tab daily	30 tabs	$429.66
• Epivir	300 mg tab	1 tab daily	30 tabs	$498.89
• Epivir	10 mg/mL soln	30 mL daily	900 mL	$498.90
Stavudine				
• Generic	40 mg cap	1 cap twice daily	60 caps	$410.70
• Zerit	40 mg cap	1 cap twice daily	60 caps	$553.12
Tenofovir				
• Viread	300 mg tab	1 tab daily	30 tabs	$1,047.73
Zidovudine				
• Generic	300 mg tab	1 tab twice daily	60 tabs	$360.97
• Retrovir	300 mg tab	1 tab twice daily	60 tabs	$476.70

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Table 16: Monthly Average Wholesale Price[a] of Antiretroviral Drugs (Last updated January 2014; last reviewed January 2014) (page 2 of 4)

ARV Drug (Generic and Brand Names)	Strength	Dosing	Tablets/Capsules/ mLs per Month	AWP[a] (Monthly)
NRTI Combination Products				
Abacavir/Lamivudine				
• Epzicom	600/300 mg tab	1 tab daily	30 tabs	$1,239.41
Tenofovir Disoproxil Fumarate/ Emtricitabine				
• Truvada	300/150 mg tab	1 tab daily	30 tabs	$1,539.90
Zidovudine/Lamivudine				
• Generic	300/150 mg tab	1 tab twice daily	60 tabs	$931.61
• Combivir	300/150 mg tab	1 tab twice daily	60 tabs	$1,081.70
Abacavir Sulfate/Zidovudine/ Lamivudine				
• Generic	300/300/150 mg tab	1 tab twice daily	60 tabs	$1,738.46
• Trizivir	300/300/150 mg tab	1 tab twice daily	60 tabs	$1,931.64
Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)				
Efavirenz				
• Sustiva	600 mg tab	1 tab daily	30 tabs	$862.14
Etravirine				
• Intelence	200 mg tab	1 tab twice daily	60 tabs	$1,123.52
Nevirapine				
• Generic	200 mg tab	1 tab twice daily	60 tabs	$650.05
• Viramune	200 mg tab	1 tab twice daily	60 tabs	$812.45
• Viramune XR (nevirapine extended release)	400 mg tab	1 tab daily	30 tabs	$753.52
Rilpivirine				
• Endurant	25 mg tab	1 tab daily	30 tabs	$923.47
Protease Inhibitors (PIs)				
Atazanavir				
• Reyataz	150 mg cap[b]	2 caps daily	60 caps	$1,422.83
• Reyataz	200 mg cap	2 caps daily	60 caps	$1,422.83
• Reyataz	300 mg cap[b]	1 cap daily	30 caps	$1,409.39
Darunavir				
• Prezista	600 mg tab[b]	1 tab twice daily	60 tabs	$1,399.25
• Prezista	800 mg tab[b]	1 tab daily	30 tabs	$1,399.25
• Prezista	100 mg/mL soln[b]	8 mL daily 6 mL twice daily	240 mL 360 mL	$932.83 $1,399.25
Fosamprenavir				
• Lexiva	700 mg tab	2 tabs twice daily	120 tabs	$2,088.40
• Lexiva	700 mg tab	1 tab twice daily[b]	60 tabs	$1,044.20
• Lexiva	700 mg tab	2 tabs once daily[b]	60 tabs	$1,044.20

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Table 16: Monthly Average Wholesale Price[a] of Antiretroviral Drugs (Last updated January 2014; last reviewed January 2014) (page 3 of 4)

ARV Drug (Generic and Brand Names)	Strength	Dosing	Tablets/Capsules/ mLs per Month	AWP[a] (Monthly)
Protease Inhibitors (PIs), continued				
Lopinavir/Ritonavir • Kaletra	200 mg/50 mg tab	2 tabs twice daily or 4 tabs once daily	120 tabs	$977.22
• Kaletra	80 mg/20 mg per mL soln	5 mL twice daily	300 mL	$916.13
Ritonavir Total Daily Dose Depends On Concomitant PI • Norvir	100 mg tab	1 tab once daily	30 tabs	$308.60
• Norvir	100 mg tab	1 tab twice daily	60 tabs	$617.20
• Norvir	100 mg tab	2 tabs twice daily	120 tabs	$1,234.40
Saquinavir • Invirase	500 mg tab[b]	2 tabs twice daily	120 tabs	$1,177.58
Tipranavir • Aptivus	250 mg cap[b]	2 caps twice daily	120 caps	$1,500.17
Integrase Strand Transfer Inhibitors (INSTIs) Please refer to Co-formulated Combination Antiretroviral Drugs for cost of elvitegravir/cobicistat/tenofovir/emtricitabine (Stribild)				
Dolutegravir • Tivicay	50 mg tab	1 tab once daily	30 tabs	$1,410.48
• Tivicay	50 mg tab	1 tab twice daily	60 tabs	$2,820.96
Raltegravir • Isentress	400 mg tab	1 tab twice daily	60 tabs	$1,352.05
Fusion Inhibitor				
Enfuviritide • Fuzeon	90 mg injection kit	1 injection twice daily	60 doses (1 kit)	$3,513.49
CCR5 Antagonist				
Maraviroc • Selzentry	150 mg tab	1 tab twice daily	60 tabs	$1,297.62
• Selzentry	300 mg tab	1 tab twice daily	60 tabs	$1,297.62
• Selzentry	300 mg tab	2 tabs twice daily	120 tabs	$2,595.24
Co-Formulated Combination Products as Complete Antiretroviral Regimens				
Efavirenz/Tenofovir Disoproxil Fumarate/Emtricitabine • Atripla	600/300/200 mg tab	1 tab daily	30 tabs	$2,402.04
Rilpivirine/Tenofovir Disoproxil Fumarate/Emtricitabine • Complera	25/300/200 mg tab	1 tab daily	30 tabs	$2,463.37
Elvitegravir/Cobicistat/Tenofovir Disoproxil Fumarate/ Emtricitabine • Stribild	150/150/300/200 mg tab	1 tab daily	30 tabs	$2,948.70

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Table 16: Monthly Average Wholesale Price[a] of Antiretroviral Drugs (Last updated January 2014; last reviewed January 2014) (page 4 of 4)

[a] AWP = Average Wholesale Price. Note that this price may not represent the pharmacy acquisition price or the price paid by consumers.

Source: Red Book Online. Available at http://aapredbook.aappublications.org. Accessed January 2014

[b] Should be used in combination with ritonavir. Please refer to Appendix B, Table 3 for ritonavir doses.

Key to Abbreviations: cap = capsule; EC = enteric coated; soln = solution; AWP = average wholesale price; tab = tablet; XR = extended release

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