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 March 27, 2012; last reviewed March 27, 2012)

Adherence to antiretroviral therapy (ART) has been correlated strongly with HIV viral suppression, reduced rates of resistance, an increase in survival, and improved quality of life.[1-2] In the past few years, ART regimens have been greatly simplified. Although newer regimens include more fixed-dose combination products and offer once-daily dosing, adherence remains a challenge. Because HIV treatment is a lifelong endeavor, and because many patients will initiate therapy when they are generally in good health, feel well, and demonstrate no obvious signs or symptoms of HIV disease, adherence poses a special challenge and requires commitment from the patient and the health care team.

Adherence remains a challenging and complicated topic. This section provides clinicians with some guidance in their approaches to assist patients in maintaining adherence.

Factors Associated with Nonadherence

Adherence to ART can be influenced by characteristics of the patient, the regimen, the clinical setting, and the provider/patient relationship.[3] To assure adherence, it is critical that the patient receive and understand information about HIV disease, the goal of therapy, and the specific regimen prescribed. A number of factors have been associated with poor adherence, including the following:

- low levels of health literacy[4] or numeracy (ability to understand numerical-related health information);[5]
- certain age-related challenges (e.g., polypharmacy, vision loss, cognitive impairment)[6];
- younger age;
- psychosocial issues (e.g., depression, homelessness, low social support, stressful life events, or psychosis);[7]
- nondisclosure of HIV serostatus[8]
- neurocognitive issues (e.g., cognitive impairment, dementia)
- active (but not history of) substance abuse, particularly for patients who have experienced recent relapse;
- stigma[9];
- difficulty with taking medication (e.g., trouble swallowing pills, daily schedule issues);
- complex regimens (e.g., high pill burden, high-frequency dosing, food requirements);
- adverse drug effects;
- nonadherence to clinic appointments[10]
- cost and insurance coverage issues; and
- treatment fatigue.

Adherence studies conducted in the early era of combination ART with unboosted protease inhibitors (PIs) found that virologic failure is much less likely to occur in patients who adhere to more than 95% of their prescribed doses than in those who are less adherent.[11] More recent adherence studies were conducted using boosted PIs and non-nucleoside reverse transcriptase inhibitors (NNRTIs). These studies suggest that the longer half-lives of boosted PIs and efavirenz may make the drugs more forgiving of lapses in adherence.[12-13] Nonetheless, clinicians should encourage patients to adhere as closely as possible to the prescribed doses and schedules for all ART regimens.

Measurement of Adherence

There is no gold standard for the assessment of adherence,[1] but there are many validated tools and strategies to choose from. Although patient self-report of adherence predictably overestimates adherence by as much as 20%,[14] this measure still is associated with viral load responses.[15] Thus, a patient's report of suboptimal adherence is a strong indicator of nonadherence and should be taken seriously.

When ascertained in a simple, nonjudgmental, routine, and structured format that normalizes less-than-perfect adherence and minimizes socially desirable responses, patient self-report remains the most useful method for the assessment and longitudinal monitoring of a patient's adherence in the clinical setting. A survey of all doses missed during the past 3 days or the past week accurately reflects longitudinal adherence and is the most practical and readily available tool for adherence assessments in clinical trials and in clinical practice.[1] Other strategies also may be effective. One study found that asking patients to rate their adherence on a six-point scale during 1 month was more accurate than asking them about the frequency of missed doses or to estimate the percentage of doses taken during the previous 3 or 7 days.[16] Pharmacy records and pill counts also can be used in addition to simply asking the patient about adherence.[17] Other methods of assessing adherence include the use of electronic measurement devices (e.g., bottle caps, dispensing systems). However, these methods may not be feasible in some clinical settings.

Interventions to Improve Adherence

Before writing the first prescriptions, the clinician should assess the patient's readiness to take medication, including information such as factors that may limit adherence (psychiatric illness, active drug use, etc.) and make additional support necessary; the patient's understanding of the disease and the regimen; and the patient's social support, housing, work and home situation, and daily schedules.

During the past several years, a number of advances have simplified many regimens dramatically, particularly those for treatment-naive patients. Prescribing regimens that are simple to take, have a low pill burden and low-frequency dosing, have no food requirements, and have low incidence and severity of adverse effects will facilitate adherence.[18] The Panel considered both regimen simplicity and effectiveness when making current treatment recommendations (see What to Start).

Patients should understand that their first regimen usually offers the best chance for a simple regimen that affords long-term treatment success and prevention of drug resistance. Given that effective response to ART is dependent on good adherence, clinicians should identify barriers to adherence such as a patient's schedule, competing psychosocial needs, learning needs, and literacy level before treatment is initiated. As appropriate, resources and strategies that will help the patient to achieve and maintain good adherence should be employed.

Individualizing treatment with involvement of the patient in decision making is the cornerstone of any treatment plan.[17] The first principle of successful treatment is negotiation of an understandable plan to which the patient can commit.[19-20] Establishing a trusting relationship over time and maintaining good communication will help to improve adherence and long-term outcomes.

An increasing number of interventions have demonstrated efficacy in improving adherence to ART. A meta-analysis of 19 randomized controlled trials of ART adherence interventions found that intervention participants were 1.5 times as likely to report 95% adherence and 1.25 times as likely to achieve an undetectable viral load as participants in comparison conditions.[21]

In a more recent synthesis, CDC provides new guidance to assist providers in selecting from among the many possible adherence interventions. According to efficacy criteria described by the CDC HIV/AIDS Prevention Research Synthesis (PRS) project, CDC has identified a subset of best-evidence medication adherence interventions. In December 2010, CDC published a new online Medication Adherence chapter of

the Compendium of Evidence-Based HIV Behavioral Interventions that includes eight medication adherence behavioral interventions identified from the scientific literature published or in press from January 1996 through December 2009. For descriptions of the interventions, see: http://www.cdc.gov/hiv/topics/research/prs/ma-good-evidence-interventions.htm.[22] Since these reviews have been conducted, additional evidence also has accumulated regarding the efficacy and benefits of motivational interviewing.[23]

In summary, effective adherence interventions vary in their modality and duration, providing clinics, providers, and patients with options to suit a range of needs and settings. Some effective interventions identified include multiple nurse home visits, five-session group intervention, pager messaging, and couples-based interventions. Substance abuse therapy and strengthening social support also can improve adherence. All health care team members, including nurses, nurse practitioners, pharmacists, medication managers, and social workers, have integral roles in successful adherence programs.[24-27] Directly observed therapy (DOT) has been shown to be effective in provision of ART to active drug users.[28] However, the benefits cannot be sustained after transitioning the drug users out of the methadone clinics and halting the provision of ART by DOT.[29]

To routinely determine whether such additional adherence intervention is 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 and pharmacy records are useful determinants for the need of intensified efforts.

Conclusion

Significant progress has been made regarding determinants, measurements, and interventions to improve adherence to ART. Given the various assessment strategies and potential interventions available, the challenge for the treatment team is to select the techniques that provide the best fit for the treatment setting, resources available, and patient population. The complexity and the importance of adherence encourage clinicians to continue to seek novel, patient-centered ways to improve adherence and to tailor adherence interventions. Early detection of nonadherence and prompt intervention can reduce greatly the development of viral resistance and the likelihood of virologic failure.

Table 12. Strategies to Improve Adherence to Antiretroviral Therapy

Strategies	Examples
Use a multidisciplinary team approach Provide an accessible, trusting health care team	• Nurses, social workers, pharmacists, and medications managers
Establish a trusting relationship with the patient	
Establish patient readiness to start ART	
Assess and simplify the regimen, if possible	
Identify potential barriers to adherence before starting ART	• Psychosocial issues • Active substance abuse or at high risk of relapse • Low literacy • Low numeracy • Busy daily schedule and/or travel away from home • Nondisclosure of HIV diagnosis • Skepticism about ART • Lack of prescription drug coverage • Lack of continuous access to medications
Provide resources for the patient	• Referrals for mental health and/or substance abuse treatment • Resources to obtain prescription drug coverage • Pillboxes
Involve the patient in ARV regimen selection	• For each option, review regimen potency, potential side effects, dosing frequency, pill burden, storage requirements, food requirements, and consequences of nonadherence
Assess adherence at every clinic visit	• Use a simple checklist that the patient can complete in the waiting room • Ensure that other members of the health care team also assess adherence • Ask the patient open-ended questions (e.g., *In the last 3 days, please tell me how you took your medicines*.)
Identify the type of nonadherence	• Failure to fill the prescription(s) • Failure to take the right dose(s) at the right time(s) • Nonadherence to food requirements
Identify reasons for nonadherence	• Adverse effects from medications • Complexity of regimen (pill burden, dosing frequency, etc.) • Difficulty swallowing large pills • Forgetfulness • Failure to understand dosing instructions • Inadequate understanding of drug resistance and its relationship to adherence • Pill fatigue • Other potential barriers
If resources allow, select from among available effective interventions	• See http://www.cdc.gov/hiv/topics/research/prs/ma-good-evidence-interventions.htm

Key to Abbreviations: ART = antiretroviral therapy; ARV = antiretroviral

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Adverse Effects of Antiretroviral Agents (Last updated February 12, 2013; last reviewed February 12, 2013)

Adverse effects have been reported with use of all antiretroviral (ARV) drugs; they are among the most common reasons for switching or discontinuing therapy and for medication nonadherence.[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 (NRTIs).[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 [PIs]); or
- Genetic factors that predispose patients to abacavir (ABC) hypersensitivity reaction (HSR).[13, 14]

The therapeutic goals of ART include achieving and maintaining viral suppression and improving immune function, but an overarching goal should be to select a regimen that is not only effective but also safe. This requires consideration of 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 [CVD], renal impairment), may be more likely in the absence of ART.[15, 16]

Information on adverse events of ARVs is outlined in several tables in the guidelines. Table 13 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.

Table 13. Antiretroviral Therapy-Associated Common and/or Severe Adverse Effects (page 1 of 5)

(See Appendix B for additional information listed by drug. Empty spaces in the table may mean no reported cases for the particular side effect or no data are available for the specific ARV drug class)

Adverse Effects	NRTIs	NNRTIs	PIs	INSTI	EI
Bleeding events			**All PIs:** Increased spontaneous bleeding, hematuria in patients with hemophilia **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		
Bone marrow suppression	**ZDV:** Anemia, neutropenia				
Cardiovascular disease (CVD)	**ABC and ddI:** Associated with an increased risk of MI in some, but not all, cohort studies. Absolute risk greatest in patients with traditional CVD risk factors.		**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 coadministration 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.		
Central nervous system (CNS) effects	**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 due to genetic factors or increased absorption with food.		**RAL:** Depression (uncommon)	

Table 13. Antiretroviral Therapy-Associated Common and/or Severe Adverse Effects (page 2 of 5)

Adverse Effects	NRTIs	NNRTIs	PIs	INSTI	EI
Cholelithiasis			**ATV:** • History of kidney stones increases risk and 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 1–90 months)		
Diabetes mellitus (DM)/insulin resistance	**ZDV**, **d4T**, and **ddI**		• Reported for some **PIs** (**IDV**, **LPV/r**), but not all PIs		
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**		
Gastrointestinal (GI) effects	**Nausea and vomiting:** **ddI** and **ZDV** > other **NRTIs** **Pancreatitis: ddI**		GI intolerance (e.g., diarrhea, nausea, vomiting) **Diarrhea:** Common with **NFV**; **LPV/r** > **DRV/r** and **ATV/r**	**Nausea and diarrhea:** **EVG/COBI/TDF/FTC**	

Table 13. Antiretroviral Therapy-Associated Common and/or Severe Adverse Effects (page 3 of 5)

Adverse Effects	NRTIs	NNRTIs	PIs	INSTI	EI
Hepatic effects	Reported for most **NRTIs** **ddI:** Prolonged exposure linked to non-cirrhotic portal hypertension, some cases with esophageal varicees **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 hepatic toxicity 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** to varying degrees. 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)		**MVC:** Hepatotoxicity with or without rash or HSRs reported

Table 13. Antiretroviral Therapy-Associated Common and/or Severe Adverse Effects (page 4 of 5)

Adverse Effects	NRTIs	NNRTIs	PIs	INSTI	EI
Hypersensitivity reaction (HSR) (excluding rash alone or Stevens-Johnson syndrome [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 include (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. • The onset of re-challenge reactions is within hours of re-challenge dose • 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.		**RAL**	**MVC:** Reported as part of a syndrome related to hepatotoxicity
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 <u>Laboratory findings</u>: • ↑ lactate (often >5 mmol/L), anion gap, AST, ALT, PT, bilirubin • ↑ amylase and lipase in patients with pancreatitis • ↓ arterial pH, serum bicarbonate, serum albumin				

Table 13. Antiretroviral Therapy-Associated Common and/or Severe Adverse Effects (page 5 of 5)

Adverse Effects	NRTIs	NNRTIs	PIs	INSTI	EI
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.			
Myopathy/elevated creatine phosphokinase (CPK)	**ZDV:** Myopathy			**RAL:** ↑ CPK Muscle weakness and rhabdomyolysis	
Nephrotoxicity/urolithiasis	**TDF:** ↑ serum creatinine, proteinuria, hypophosphatemia, urinary phosphate wasting, glycosuria, hypokalemia, non-anion gap metabolic acidosis Concurrent use with **PI** appears to increase risk.		**IDV:** ↑ serum creatinine, pyuria; hydronephrosis or renal atrophy **IDV, ATV**: Stone, crystal formation; adequate hydration may reduce risk.	**EVG/COBI/TDF/FTC:** • **COBI** can cause non-pathologic decrease in CrCl. • May increase risk of **TDF**-related nephrotoxicity	
Osteopenia/osteoporosis	**TDF:** Associated with greater loss of BMD than with **ZDV**, **d4T**, and **ABC**.	Decreases in BMD observed in studies of regimens containing different **NRTIs** combined with either **NNRTIs** or **PIs**.			
Peripheral neuropathy	**Peripheral neuropathy** (pain and/or paresthesias, lower extremities > upper extremities): **d4T** > **ddI** and **ddC** (can be irreversible)				
Rash		**All NNRTIs**	**ATV, DRV, FPV**	**RAL, EVG/COBI/TDF/FTC:** Uncommon	**MVC**
Stevens-Johnson syndrome (SJS)/ toxic epidermal necrosis (TEN)	**ddI, ZDV:** Reported cases	**NVP > DLV, EFV, ETR, RPV**	**FPV, DRV, IDV, LPV/r, ATV:** Reported cases	**RAL**	

Key to Abbreviations: 3TC = lamivudine, ABC = abacavir, ALT = alanine aminotransferase, ARV = antiretroviral, AST = aspartate aminotransferase, ATV = atazanavir, ATV/r = atazanavir + ritonavir, 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 = delaviridine, DM = diabetes mellitus, DRV = darunavir, DRV/r = darunavir + ritonavir, 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, PT = prothrombin time, RAL = raltegravir, RPV = rilpivirine, RTV = ritonavir, SJS = Stevens-Johnson syndrome, SQV = saquinavir, SQV/r = saquinavir + ritonavir, TDF = tenofovir disoproxil fumarate, TEN = toxic epidermal necrosis, TG = triglyceride, TPV = tipranavir, TPV/r = tipranavir + ritonavir, ZDV = zidovudine

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