



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

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## Limitations to Treatment Safety and Efficacy

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### 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.<sup>1-2</sup> 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.<sup>3</sup> 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<sup>4</sup> or numeracy (ability to understand numerical-related health information);<sup>5</sup>
- certain age-related challenges (e.g., polypharmacy, vision loss, cognitive impairment)<sup>6</sup>;
- younger age;
- psychosocial issues (e.g., depression, homelessness, low social support, stressful life events, or psychosis);<sup>7</sup>
- nondisclosure of HIV serostatus<sup>8</sup>
- neurocognitive issues (e.g., cognitive impairment, dementia)
- active (but not history of) substance abuse, particularly for patients who have experienced recent relapse;
- stigma<sup>9</sup>;
- 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<sup>10</sup>
- 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.<sup>11</sup> 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.<sup>12-13</sup> 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,<sup>1</sup> 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%,<sup>14</sup> this measure still is associated with viral load responses.<sup>15</sup> 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.<sup>1</sup> 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.<sup>16</sup> Pharmacy records and pill counts also can be used in addition to simply asking the patient about adherence.<sup>17</sup> 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-naïve 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.<sup>18</sup> 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.<sup>17</sup> The first principle of successful treatment<sup>17</sup> is negotiation of an understandable plan to which the patient can commit.<sup>19-20</sup> 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.<sup>21</sup>

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>.<sup>22</sup> Since these reviews have been conducted, additional evidence also has accumulated regarding the efficacy and benefits of motivational interviewing.<sup>23</sup>

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.<sup>24-27</sup> Directly observed therapy (DOT) has been shown to be effective in provision of ART to active drug users.<sup>28</sup> However, the benefits cannot be sustained after transitioning the drug users out of the methadone clinics and halting the provision of ART by DOT.<sup>29</sup>

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	<ul style="list-style-type: none"> <li>• Nurses, social workers, pharmacists, and medications managers</li> </ul>
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	<ul style="list-style-type: none"> <li>• Psychosocial issues</li> <li>• Active substance abuse or at high risk of relapse</li> <li>• Low literacy</li> <li>• Low numeracy</li> <li>• Busy daily schedule and/or travel away from home</li> <li>• Nondisclosure of HIV diagnosis</li> <li>• Skepticism about ART</li> <li>• Lack of prescription drug coverage</li> <li>• Lack of continuous access to medications</li> </ul>
Provide resources for the patient	<ul style="list-style-type: none"> <li>• Referrals for mental health and/or substance abuse treatment</li> <li>• Resources to obtain prescription drug coverage</li> <li>• Pillboxes</li> </ul>
Involve the patient in ARV regimen selection	<ul style="list-style-type: none"> <li>• For each option, review regimen potency, potential side effects, dosing frequency, pill burden, storage requirements, food requirements, and consequences of nonadherence</li> </ul>
Assess adherence at every clinic visit	<ul style="list-style-type: none"> <li>• Use a simple checklist that the patient can complete in the waiting room</li> <li>• Ensure that other members of the health care team also assess adherence</li> <li>• Ask the patient open-ended questions (e.g., <i>In the last 3 days, please tell me how you took your medicines.</i>)</li> </ul>
Identify the type of nonadherence	<ul style="list-style-type: none"> <li>• Failure to fill the prescription(s)</li> <li>• Failure to take the right dose(s) at the right time(s)</li> <li>• Nonadherence to food requirements</li> </ul>
Identify reasons for nonadherence	<ul style="list-style-type: none"> <li>• Adverse effects from medications</li> <li>• Complexity of regimen (pill burden, dosing frequency, etc.)</li> <li>• Difficulty swallowing large pills</li> <li>• Forgetfulness</li> <li>• Failure to understand dosing instructions</li> <li>• Inadequate understanding of drug resistance and its relationship to adherence</li> <li>• Pill fatigue</li> <li>• Other potential barriers</li> </ul>
If resources allow, select from among available effective interventions	<ul style="list-style-type: none"> <li>• See <a href="http://www.cdc.gov/hiv/topics/research/prs/ma-good-evidence-interventions.htm">http://www.cdc.gov/hiv/topics/research/prs/ma-good-evidence-interventions.htm</a></li> </ul>

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

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