Factors Affecting Adherence to Antiretroviral Therapy
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In both clinical trials and clinical practice, nonadherence to medications is widespread among patients with chronic diseases. The shift to combination therapies for treating human immunodeficiency virus (HIV)–infected individuals has increased adherence challenges for both patients and health-care providers. Estimates of average rates of nonadherence to antiretroviral therapy range from 50% to 70%. Adherence rates of <80% are associated with detectable viremia in a majority of patients. The principal factors associated with nonadherence appear to be patient-related, including substance and alcohol abuse. However, other factors may also contribute, such as inconvenient dosing frequency, dietary restrictions, pill burden, and side effects; patient–health-care provider relationships; and the system of care. We discuss the major reasons reported by HIV-infected individuals for not taking their medications. Improving adherence probably requires clarifying the treatment regimen and tailoring it to patient lifestyles.

Measurement of Adherence

The shift to the use of highly active antiretroviral therapy (HAART) for treating human immunodeficiency virus (HIV) disease has led to increasingly complex drug regimens. These present significant challenges to both patients and health-care providers with respect to adherence. Without adequate adherence, antiretroviral agents are not maintained at sufficient concentrations to suppress HIV replication in infected cells and to lower the plasma viral load. In addition to being associated with poor short-term virological response, poor adherence to antiviral medication accelerates development of drug-resistant HIV. Therefore, identifying and overcoming the factors that reduce adherence to combination antiretroviral agents is of utmost importance for prolonged viral load suppression.

There are a number of key issues in the study of adherence to antiretroviral therapy, including accurate measurement of adherence, assessment of the impact of adherence on viral load and clinical outcome, determination of the factors that affect adherence, and the development of interventions. Addressing these issues may provide valuable information about which patients are most at risk for nonadherence and about how adherence might be improved. The critical factors that influence adherence fall into 4 main groups: (1) patient factors, such as drug use, alcohol use, age, sex, or ethnicity; (2) medication regimen, such as dosing complexity, number of pills, or food requirements; (3) the patient–health-care provider relationship; and (4) the system of care.

Adherence to therapy is difficult to measure accurately. Four basic techniques have been developed for quantifying adherence, all of which have limitations. First and most common are patient self-reports. These have the advantages of low cost and flexibility of design (questionnaires suit individual language abilities). The data are easily collected and can help to determine the reasons why patients are nonadherent. They assume, however, that patients can accurately recall their behavior and are providing honest answers. A major limitation of self-reports is that they reflect only short-term or average adherence and may often overestimate it. Nevertheless, some studies show significant relationships between data from self-reports and viral load [1, 2]. Other studies that compare data from self-reports to pill counts or electronic measurements found differences, suggesting that self-reports provide inflated estimates of adherence behavior [3, 4].

Second are patients’ reports of missing pills, which are almost always reliable [5], so self-reports can be helpful for understanding the dynamics surrounding missed medication. Pill counts have been widely used. The return of excess pills provides tangible evidence of nonadherence. However, pill counts require patients to return the medication packaging to the clinician. Even in clinical trial situations, patients tend to forget the packages or inadvertently discard them. There have also been reports that patients other than those with HIV, aware that pill counts are being conducted, engage in “pill dumping” to appear adherent. As a result, pill counts typically overestimate adherence.

Third, assays of drug levels have been used in clinical trials to measure the last dose taken; however, these assays are often impractical because of their expense and lack of general availability. In addition, serum concentrations of nucleoside analogues may not reflect intracellular concentration of the active
Adherence to HIV Therapy

Large-scale studies of the impact of adherence on viral load and clinical outcome in HIV therapy are underway within the AIDS Clinical Trials Group (ACTG) and at clinical sites in the United States and abroad. However, findings have not yet been reported. A small study by Paterson et al. [6] examined patient adherence to protease inhibitor therapy by use of MEMS. The investigators found that poor adherence correlated with clinical and virological failure at 3 months of follow-up (table 1). These results suggest that a high degree of adherence is necessary for maintenance of drug efficacy. Further similar studies are needed to corroborate these data and to establish whether adherence requirements vary for different drugs.

Although very little published information is available on medication adherence of HIV-infected patients, new data from a number of studies were presented at numerous conferences, including the 12th World AIDS Conference in Geneva and the 38th Annual Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC) in San Diego. Because the study of adherence is in its infancy, study designs and end points vary widely, making study comparisons difficult. Self-reported adherence, as defined in research studies, has been reported to range from 0% to 100% [6–13]. Although the results of some of these studies appear to conflict, important information is emerging about the extent of and factors associated with adherence. The earliest reports of nonadherence suggested that slightly >10% of patients missed ≥1 dose of medication each day [1, 14]. Rates of nonadherence may be as high as 50% when averaged over time and with an arbitrary cutoff point of <80% of medication taken [8]. This figure is supported by observations from 2 larger studies: an international multicenter study of 235 HIV-infected patients and a United States study of 244 HIV-infected Medicaid-insured patients. The reported rates of patients who take <80% of doses in these studies were 46% and 40%, respectively [9, 10]. It is interesting to note that these results are consistent with estimates of adherence in other chronic diseases and support the view that nonadherence is a common behavior that should be expected, even with a serious disease such as HIV infection.

In order to implement measures to improve adherence, it is first essential to identify the principal factors that contribute to the inability of patients to take their medication. Those factors identified to date are summarized in table 2.

A published study of adherence by Eldred et al. [10] required 244 patients who were receiving antiretroviral therapy and Pneumocystis carinii pneumonia (PCP) prophylaxis to report the medications they were taking, their pattern of use, and their knowledge and attitudes about HIV therapies [10]. Most of the patients in the study were receiving monotherapy. Eldred et al. found that 60% of patients reported >80% adherence to treatment regimens in the previous 7 days. When PCP prophylaxis was analyzed by assaying urinary sulfamethoxazole levels, a correlation of ~80% was found between self-report and levels of sulfamethoxazole in the urine. This leads to the conclusion that at least 40% of patients were getting <80% of their antiviral medication. Good adherence was associated with dosing twice a day or less, the likelihood that patients take medication when away from home, and self-efficacy (i.e., patients' belief in their

### Table 1. Poor medication adherence correlates with virologic failure: a study of 45 HIV-infected patients.

<table>
<thead>
<tr>
<th>Medication adherence, % of patients</th>
<th>Virologic failure, % of patients</th>
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<tbody>
<tr>
<td>&lt;80</td>
<td>87</td>
</tr>
<tr>
<td>80–90</td>
<td>47</td>
</tr>
<tr>
<td>&gt;95</td>
<td>10</td>
</tr>
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</table>

NOTE. Seventy-two percent of patients were treated with a single protease inhibitor (nelfinavir, 65%; indinavir, 26%; other inhibitors, 9%); 28% received a combination of saquinavir and ritonavir. Adapted from [6].

Medication adherence, % of patients

<table>
<thead>
<tr>
<th>Patient factors</th>
<th>Medication factors</th>
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<tbody>
<tr>
<td>Active substance abuse (drugs and/or alcohol)</td>
<td>Dose frequency of more than twice a day</td>
</tr>
<tr>
<td>Male sex</td>
<td>Type of drug</td>
</tr>
<tr>
<td>Youth</td>
<td>Inability to take medication when away from home</td>
</tr>
<tr>
<td>Active depression</td>
<td>Food requirement</td>
</tr>
<tr>
<td>Lower level of education</td>
<td>Side effects</td>
</tr>
<tr>
<td>Lack of self-efficacy l</td>
<td>Poor doctor–health-care provider relationship</td>
</tr>
<tr>
<td>Extreme anxiety</td>
<td>System of care</td>
</tr>
<tr>
<td>Extreme pain</td>
<td>Dissatisfaction with past experience of health-care system, leading to avoidance</td>
</tr>
<tr>
<td>No change in health status</td>
<td></td>
</tr>
<tr>
<td>Non-white</td>
<td></td>
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</table>

NOTE. Based on data from [2, 6–8, 12, 13, 15–19].

a “Self-efficacy” refers to patients’ belief in their ability to take medication as prescribed.
ability to take their medication). The major factor associated with nonadherence was active illicit drug use. In particular, patients who had used crack cocaine were significantly less adherent. These findings, although not directly applicable to combination therapy, may shed light on adherence issues for patients who are receiving HAART.

Preliminary data from a number of studies of adherence to antiretroviral agents have been presented in abstract form [4, 6, 12, 15, 19–22]. Specific findings vary from study to study, due at least in part to the different samples and measures used. In general, it appears that the most important factors that affect adherence are patient-related. The most common reasons given by patients for nonadherence are summarized in table 3; the principal reasons are that they forgot or were busy. Data from a large cohort of HIV-infected patients (1322 persons living with HIV/AIDS) who were receiving antiviral combination therapies demonstrated that characteristics that predict nonadherence included youth, government-subsidized health insurance, extreme anxiety or pain, and no perceived change in health status as a result of drug therapy [15]. These data suggest that vulnerable subgroups of HIV-infected patients need to be identified and targeted [15].

Reduction of the administration frequency of current drug regimens may be limited by the relatively short half-lives of the nonnucleoside reverse transcriptase inhibitors (NNRTIs) and protease inhibitors. Although it has been assumed that reducing dosing frequency or pill burden will increase adherence, it is important to note that this may not be the case. In the above-mentioned trial of 179 patients and in another smaller trial of 45 patients, there was no association between dose frequency or pill burden and nonadherence [6, 10]. There are indications from a number of other studies that meal restrictions and other factors, and not simply pill burden, are predictors of nonadherence [2, 4, 10, 13, 19]. It is worth noting that the pharmaceutical industry is investing considerable effort to develop new compounds or regimens with longer half-lives in order to reduce pill count and dosing frequency and is also trying to find other ways to simplify drug regimens. The simplification of existing regimens may prove worthwhile as therapies continue to fail in nonadherent patients and even more medications are added to regimens.

A good patient–health-care provider relationship may be an important motivating factor for taking and adhering to complex combination drug therapies [20]. A qualitative study of homosexual youths showed that primary-care providers exhibited judgmental behavior, stereotyping, homophobia, and failure to address cultural issues when administering care [17]. Such experiences are likely to lead some people with HIV infection to avoid the health care system. On the other hand, factors that have been identified as strengthening patient–health-care provider relationships include perceptions of health-care provider competence, communication quality and clarity, compassion, willingness to include patients in treatment decisions, adequacy of referrals, and convenience of visiting the doctor [21]. Conversely, frustration for health-care providers is associated with lack of patient adherence to treatment, misinformation, missed appointments, complexity of treatment regimens, and medication side effects [21, 23]. In light of these problems, it is heartening to find that initiatives are underway to encourage health-care providers to work with patients as “partners” in care and to involve representatives from the entire HIV community [24].

Other important adherence issues have arisen, particularly with regard to economically disadvantaged patients with multiple social problems. Many clinicians feel that lifestyle factors, such as homelessness, substance abuse, lack of education, and mental illness, are predictors of nonadherence and therefore are withholding HAART from these patients. A review of these studies indicates that some, but not all, have found an association between nonadherence and youth, female sex, less education, or a current or past history of substance abuse [25]. Therefore, health-care providers should be cautious in making assumptions about patients’ likelihood to encounter problems. It is of interest that results of trials show that health-care providers are not very good at predicting which patients will be adherent to medication [6, 22, 26]. For example, a comparison of health-care providers’ opinions and self-reports from 193 HIV-infected patients revealed that the health-care providers overestimated the influence of social factors on adherence [22]. In this study, social factors made no significant difference. Results of another study of 45 patients indicated that health-care providers predicted adherence of patients poorly: 33% of nonadherent patients were identified by health-care providers as adherent, and 36% of patients with better than 95% adherence (measured by MEMS Caps) were identified as being poorly adherent [3]. In addition, the results of a recent study of 31 HIV-infected youths found that homelessness, current living situation, years of education, clinical depression, and substance abuse did not predict adherence to combination therapy [26]. These data do not support the routine withholding of HAART from specific social groups, since adherence cannot reliably be predicted on the basis of patient characteristics [27].

Special issues with adherence exist for HIV-infected children and adolescents. Infants and young children are dependent on adults for administration of their medications, which means

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**Table 3.** Frequent causes for medication nonadherence by HIV-infected patients who are receiving highly active antiretroviral therapy.

<table>
<thead>
<tr>
<th>Reason for nonadherence</th>
<th>Prevalence, % of patients</th>
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<tbody>
<tr>
<td>Forgot or busy</td>
<td>34–52</td>
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<tr>
<td>Away from home</td>
<td>27–42</td>
</tr>
<tr>
<td>Change in daily routine</td>
<td>40</td>
</tr>
<tr>
<td>Side effects</td>
<td>19–25</td>
</tr>
<tr>
<td>Depression or illness</td>
<td>9–23</td>
</tr>
<tr>
<td>Lack of interest or drug “holidays”</td>
<td>4–19</td>
</tr>
</tbody>
</table>

NOTE: Based on data from [4, 11, 19].
that their adherence is only as good as that which their caregivers are able to achieve. Unfortunately, liquid formulations are often not particularly palatable, and food requirements for some antiretroviral agents make therapies difficult to administer to infants who require frequent formula feeding. These factors can affect the willingness of the caregiver to administer the medication and the willingness of the child to take it. Another barrier to adherence for children and adolescents with HIV may be their families’ desire for secrecy about the condition. For example, parents may be unwilling to fill prescriptions at local pharmacies and/or may send their child to school without their medication to hide the fact that the child is HIV-infected. Adolescents find adherence particularly challenging as they enter a stage of life when they are particularly self-conscious and do not want to be different from their peers. A detailed assessment of the barriers to adherence should be implemented for all minors who require antiretroviral therapy. Case managers and counselors may often be able to work with families to resolve specific issues.

The Way Ahead

A variety of methods for improving adherence have been suggested, and descriptions from clinicians, pilot studies, and 1 trial [28] provide encouraging positive results. A study by Workman et al. [18] describes a practice that implemented a number of patient management interventions aimed at improving adherence. These included extended consultation time to explain and to reinforce medication instructions, tailoring the choice of drug regimen to patient lifestyle, frequent follow-up when initiating or changing drug regimens, rapid viral load feedback, and the use of reminder calls and alarms [18]. Adherence rates of 80%–100% (with 73% reporting 100% adherence) were reported by 99% of 77 HIV-infected patients [18].

The authors concluded that the interventions significantly enhanced adherence, compared with mean adherence rates reported in the literature [6, 8–10]. The effectiveness of an alarm set to alert patients when their drugs should be taken was tested in another study of 49 HIV-infected patients [29]. After 3 months, the frequency of 100% pill adherence was 89%; 80% adherence was observed in 99% of patients. The patients also exhibited good adherence to timing and diet requirements. All the patients were enthusiastic about the alarm device; however, concerns were raised as to its durability, since malfunctions occurred in the devices issued to half of the patients. Managed social support and perceived health-care provider support for promoting adherence have also been investigated. In 2 separate studies, patient support systems were found to enhance adherence and were particularly helpful with regard to enabling patients to better follow advice and instructions [30, 31].

As the previous review demonstrates, the major factors associated with nonadherence are related to patient behavior, and a variety of strategies by health care professionals are beginning to yield improved adherence. Some of the interventions that have been studied are listed in table 4. Of particular importance is the tailoring of medication to the patient’s lifestyle [18, 25, 28]. This can be illustrated by consideration of dosing requirements and the need for special instructions that take into account the life patterns of patients. For some patients, certain dosing intervals might be easier to adhere to; for others, lack of ready access to refrigeration or water may prove problematic. Moreover, if a patient’s treatment fails, the patient should be approached to review adherence before the regimen is changed. This should help ensure that patients begin a new regimen with optimal adherence.

Future clinical trials that study safety and efficacy of antiretroviral agents with respect to virologic and immunologic endpoints may be considered deficient if they do not include
at least 1 acceptable measure of adherence to therapy. Indeed, simultaneous measurement of adherence by 2 different methods may be the best approach. In addition, there is a need for studies that directly assess strategies that are designed to increase adherence.

Finally, important lessons can be drawn from studies of adherence among patients with other chronic diseases, where there is a larger body of published literature. Both the factors related to adherence and many of the interventions to improve adherence to other medications may largely overlap with those important to antiretrovirals [27]. For example, a recent review of hypertension stated the following: “Once-daily dosing should be coupled with selection of a drug with long duration of action to overcome problems of missed doses. Widespread adoption of simple compliance enhancement methods could lead to decreased morbidity and mortality” [32]. Incomplete compliance with any long-term medication is a multifactorial problem, but it is a problem that can and must be addressed.

Summary

It is important to recognize that some degree of nonadherence is common and should be expected in all patients who are receiving antiretroviral therapy. The first step toward addressing the problem of medication nonadherence is to accurately identify patients whose risk of nonadherence is sufficient to underpin clinical outcomes. However, a number of studies have demonstrated that health-care providers cannot accurately identify those patients likely to be nonadherent. Studies of large samples suggest that substance abuse is associated with nonadherence. Therefore, health-care providers may want to be careful to ask patients with histories of substance abuse about adherence. It does not follow, however, that all patients who abuse substances will be nonadherent. Similarly, homelessness, lack of education, and mental illness are not necessarily predictors of nonadherence, but might warrant extra attention and support. Furthermore, the absence of alcohol and drug abuse does not predict good adherence. Steps to maximize adherence, therefore, should be reviewed with all patients. Although self-reports tend to overestimate adherence, they are inexpensive and fairly accurate for providing an indication of problems. In particular, reports of nonadherence are reliable and call for action. Such reports also help to determine why HIV-infected patients are nonadherent. Of the available methods, self-reports are the most practical for routine use in the clinic. Once nonadherent patients are identified, health-care providers may want to implement a variety of interventions to enhance adherence. Strategies for intervention are likely to be based on tailoring the drug regimen to the lifestyle of the patient and assessing adherence as part of a follow-up program.

References


