

## Future implications: Compliance and failure with antiretroviral treatment

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### ABSTRACT

HIV management is currently in an era of effective, potent antiretroviral therapy. Modern drug discovery and development have transformed HIV-1 disease into a treatable, chronic infectious disease. Complete suppression of viral replication is critical for long-term durability of antiretroviral therapy. Partial suppression, even at very low levels, is likely to lead to virologic failure and ultimately to the appearance of drug resistance. The relationship between adherence and resistance to HIV antiretroviral therapy is more complex than to state 'non-adherence increases the risk of drug resistance.' In many patients who fail to respond to initial therapy, the primary reason for failure is their inability to take the prescribed drug regimen or nonadherence.

**KEY WORDS:** Adherence, protease inhibitor, non-nucleoside reverse transcriptase inhibitor, antiretroviral treatment

HIV management is currently in an era of effective, potent antiretroviral therapy. In the last 22 years since the isolation of HIV-1, modern drug discovery and development have transformed HIV-1 disease into a treatable, chronic infectious disease. Intention-to-treat analyses of recent clinical trials have shown that as many as 73% of patients who are naive to therapy can have viral replication effectively suppressed for a period of several years.<sup>[1]</sup> On-treatment analyses of the same trials suggest that over 90% of such patients will achieve and maintain viral loads at undetectable levels. Since the on-treatment results largely reflect patients who were actually able to take their medications, these results suggest that if taken reliably, current potent regimens are extremely effective. Thus, for many patients who fail to respond to initial therapy, inability to take their drug regimen (nonadherence / noncompliance) is the primary reason for failure.

It is well recognized that complete suppression of viral replication is critical for long-term durability of antiretroviral therapy. Partial suppression, even at very low levels, is likely to lead to virologic failure and ultimately to the appearance of drug resistance.<sup>[2,3]</sup> For this reason, adherence is a critical component of success and "a key determinant in the degree and duration of virologic suppression."<sup>[4]</sup> Other reasons often given for failure of an antiviral regimen like inadequate potency, interindividual pharmacologic variability (pharmacogenomics) and drug-drug interactions are now very rare causes of failure

of the first regimen.<sup>[4]</sup> Failure of treatment increases the accumulation of drug resistant mutations in patients. Recently multidrug resistant virus transmission has been detected.<sup>[5]</sup> With increasing use and access to combination antiretroviral treatment (cART), we expect a rise in the prevalence of drug resistant virus in naïve patients. This may have future therapeutic implications regarding failure to achieve complete suppression in similar proportions of patients. Recognition of the factors that influence the adherence and the use of regimens that can strengthen the adherence are crucial for the long-term success of antiretroviral therapy.

### *Importance of patient adherence*

#### *How much adherence is necessary?*

Paterson and colleagues showed that adherence of 95% or greater to unboosted protease inhibitor (PI) based regimens, resulted in superior virologic outcomes at 3 months of treatment.<sup>[6]</sup> This and similar studies led to the commonly accepted wisdom that patients had to be essentially 100% adherent and missing even a single dose per week might potentially compromise success. However these observations with unboosted protease inhibitor (PI) based regimens do not apply to other regimens as currently available potent non-nucleoside reverse transcriptase inhibitor (NNRTI) based regimens having intrinsically more "forgiveness" than unboosted PI based regimens. The data regarding relationship between specific levels of adherence and virologic outcomes in the current era of boosted PI or potent NNRTI based regimens is in fact unknown. The relationship between adherence and the emergence of drug resistance is complex. Resistance is more likely in patients whose adherence is "pretty

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good” as opposed to patients who are completely nonadherent. Patients who are completely nonadherent have essentially no circulating or intracellular drug levels and certainly there is insufficient antiviral activity to apply selective pressure on the virus to select mutations that would counteract the antiviral activity. On the other hand taking some (but not enough) drug will result in some antiviral activity that would select for emergence of drug-resistant mutants, which is inevitable if the antiviral activity is inadequate to completely suppress viral replication. The potency of the regimen will also influence the relationship between adherence and resistance. Although 100% adherence to a highly potent regimen should be sufficient to completely suppress viremia and prevent resistance, 100% adherence to a regimen that does not have the intrinsic potency to achieve virologic suppression may present a *higher* likelihood of resistance than would a lesser degree of adherence to the same regimen [Figure 1].<sup>[7]</sup>

In a study in the urban poor in San Francisco, Bangsberg and colleagues estimated that 23% of all drug resistance occurs among patients in the top quintile of adherence (92 to 100%) and over 50% of all drug resistance mutations occur among patients in the top 2 quintile of adherence (79 to 100%).<sup>[7]</sup> Recent work by another research group found resistance most likely with good, but imperfect adherence similar to the levels reported by Bangsberg and colleagues.<sup>[8]</sup> However, recent data also suggest that each antiretroviral therapeutic class has a unique adherence / resistance relationship.<sup>[9]</sup> The balance between viral suppression and resistance to NNRTIs is precarious. Because both efavirenz and nevirapine have long half-lives, a missed or delayed dose may not allow an immediate surge in viral replication. But if HIV does escape NNRTI control, resistant virus emerges swiftly and a single NNRTI mutation can defeat an NNRTI regimen. Resistance to protease inhibitors requires multiple mutations, each of which has a potential to reduce enzymic efficiency and viral fitness. For unboosted PI based regimens, most resistance occurs in patients who take most of their medications and there is likely to be a bell-shaped relationship between adherence and resistance accumulation (with the peak of the curve near 70-80% adherence). For boosted PI regimens, limited resistance occurs at any level of adherence. For NNRTI, resistance mutations are uncommon in highly adherent patients but will

likely be very common in patients with any level of adherence insufficient for full viral suppression.<sup>[9]</sup> Thus, for each of the commonly used regimens, additional research is needed to determine whether there is a threshold at which the likelihood of negative consequences of poor adherence is greater, ultimately determining whether certain regimens are more “forgiving” than others.

**Patient/provider related issues in adherence**

Measurement of adherence is imperfect and currently lacks established standards. While self-reporting by patients of complete adherence has been an unreliable predictor of adherence, a patient’s estimate of suboptimal adherence is a strong predictor and should be taken seriously.<sup>[10,11]</sup> The clinician’s estimate of the likelihood of a patient’s adherence has also been proven to be an unreliable predictor of patient adherence.<sup>[12]</sup> This is not to say that it is impossible to predict patients who may be more likely to have problems. Several studies have helped to identify factors that put patients at higher risk of antiretroviral treatment failure [Table 1].<sup>[13-15]</sup>

Providers must recognize that their ability to predict adherence is limited because they have shown a tendency to underprescribe antiretroviral therapy to those whom they anticipate to be nonadherent and this problem disproportionately affects minority populations.<sup>[16,17]</sup> Effective treatment of psychiatric conditions improves adherence and results in effective treatment of HIV infection and improves overall health outcomes.

**Medication-related factors and adherence**

1. Adverse effects are the most common reason for HIV-infected patients discontinuing their antiretroviral therapy. In an Italian cohort study of treatment-naive patients, conducted in the era of first-generation PI use, 36% of patients discontinued initial treatment and the primary reason in the majority of these patients (58%) was toxicity.<sup>[18]</sup> Not just the serious side effects but even the common side effects like nausea (with or without vomiting), abdominal discomfort or cramping and diarrhea are frequently reported by patients, as reasons for stopping their medications. Providers must keep in mind that most patients are asymptomatic when treatment is started and the development of symptoms, even those considered minor in character can be distressing to patients, both physically and mentally and sufficient to lead to discontinuation of treatment. It is almost as important to warn patients about minor side effects as it is to offer the more standard warnings about serious and life-threatening

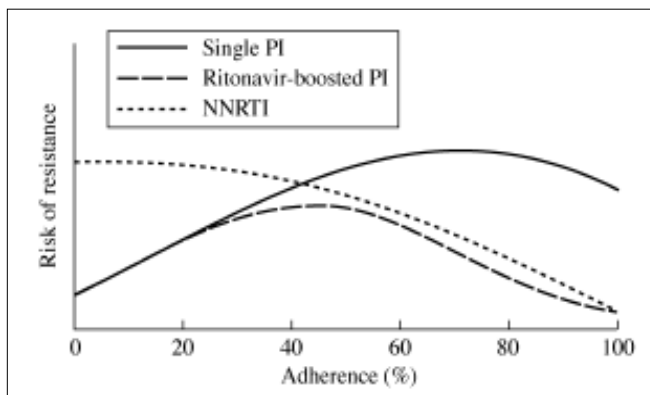


Figure 1: Relationship between adherence, potency and evolution of resistance

Table 1: Factors influencing adherence to antiretroviral therapy

Factors associated with increased adherence	Patient belief in HAART Physician experience Social support, regular clinic visit
Factors associated with decreased adherence	Active injection drug abuse, active alcohol abuse, psychiatric disease (especially depression), young age, chaotic lifestyle, low literacy

side effects of the treatment. It is particularly important to remind patients not to try to self-diagnose which drug is causing their side effects by stopping one of their medications. This strategy carries a high risk for inadequate viral suppression and development of resistance. Fear of side effects may also play a role in nonadherence. In a survey conducted by the Gay Men's health crisis, concerns about body shape change were cited by a large number of individuals (70%) as a factor that affected their willingness to take medications.<sup>[19]</sup>

2. Dosing frequency and pill burden are commonly cited as issues in patient adherence. There is little information as to whether patients generally do better on once-daily compared with twice-daily therapy. The group from Moore's clinic at Johns Hopkins reported an 80% adherence rate in patients who were taking medications on a once- or twice-daily basis but did not distinguish between once- or twice-daily therapy.<sup>[20]</sup>
3. The complexity of drug-dosing is also important. Data from the early years of HAART indicated that patients often had difficulties with agents that required multiple daily doses as well as separation of medications and/or food restrictions. Dietary restrictions significantly increase the risk of patients skipping doses.<sup>[21]</sup> Thus, the ability to take medications together with food and the avoidance of food restrictions are important factors in simplifying a patient's regimen and increasing the likelihood of successful therapy. With regard to more simplified therapy, a number of surveys have attempted to determine patient preferences as to pill burden and side effects. It has been suggested that the ideal regimen from a patient's perspective is 2 or fewer pills per day, dosed all together once daily, with no dietary restrictions and with a smaller pill size.<sup>[22]</sup> Stone and colleagues from Boston, Massachusetts, more recently conducted a patient survey to examine the relative importance of different regimen characteristics on adherence.<sup>[23]</sup> They found that the four most important issues for patients were total number of pills per day, dosing frequency, dietary restrictions and side effects. Many of these were predictable responses, but an interesting finding was that, although patients had a strong preference for a regimen consisting only of once-daily agents if all of those drugs could be taken together, they expressed a preference for a twice-daily regimen in which all agents could be taken together if the once-daily drug regimen was subjected to restrictions that required the individual drugs to be taken at separate times.
4. Lack of knowledge about HAART dosing requirements and low levels of literacy are associated with poor adherence to anti-HIV treatment. Miller LG *et al* in his study found that low literacy levels were found to be an independent factor of poor medication knowledge and poor adherence.<sup>[24]</sup> On the basis of their finding the patients who have recently started HAART or changed their treatment regimen should be questioned soon after to assess adherence and those with low levels of literacy should be asked to verbally describe their understanding of the medication's dosing requirements. Then one should try specific interventions in patients with low levels of education and literacy to help

them learn dosing instructions.

### *Assessing, monitoring and improving adherence*

The first principle of success is to negotiate an understandable treatment plan to which the patient can commit.<sup>[25,26]</sup> Trusting relationships between the patient, clinician and health care team (including nurses, case managers, social workers, pharmacists and others) are essential for optimal adherence. This often requires several clinic visits and the patience of clinicians, before therapy can be started. Prior to writing the first prescription, clinicians need to assess the patient's readiness to take medication. Patients need to understand that the first regimen has the best chance for long-term success.<sup>[27]</sup> Resources need to be identified to assist in success. Interventions can also assist with identifying the need for educating the patients about adherence and the strategies to be adopted for each patient. Examples include adherence support groups, adherence counselors, behavioral interventions,<sup>[28]</sup> using community-based case managers and peer educators. Lastly and most importantly, adherence counseling and assessment should be done at each clinical encounter. Early detection of non-adherence and prompt intervention can greatly reduce the chance of virologic failure and development viral resistance.

In summary, the relationship between adherence and resistance to HIV antiretroviral therapy is more complex than 'non-adherence increases the risk of drug resistance.' For many patients who fail the initial therapy, inability to take their drug regimen (or nonadherence) is the primary reason for failure. Recognition of the factors that influence adherence and the use of regimens that can strengthen adherence are key factors for the long-term success of antiretroviral therapy. The association between adherence and outcomes (i.e. the degree of "forgiveness" of missed doses) in the current era of boosted protease inhibitors or potent NNRTI-based regimens containing antiretroviral agents with longer half-lives is unknown. Dosing frequency and pill burden are commonly cited as issues in patient adherence.

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