Forgiveness of non-adherence to HIV-1 antiretroviral therapy

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Superior adherence to HIV-1 antiretroviral therapy is a mainstay of successful HIV management. Studies performed in the early era of highly active antiretroviral therapy demonstrated the need for ≥95% adherence in order to achieve and sustain viral suppression. High rates of viral suppression have been observed at moderate levels of adherence with newer antiretroviral regimens. The term ‘forgiveness’ is being used to describe the ability of a regimen to achieve and sustain viral suppression, despite suboptimal adherence. A variety of pharmacological, viral and host properties determine the level of forgiveness of any specific regimen. As the choice of treatment options continues to expand, forgiveness of non-adherence is likely to emerge as an increasingly important factor in therapeutic decision-making.

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Introduction

The term ‘forgiveness’ has entered the lexicon of HIV management.1–4 When applied to antiretroviral therapy, it refers to the ability to achieve or maintain complete viral suppression, despite imperfect medication adherence. It is generally used as a comparative descriptor of different classes of highly active antiretroviral therapy (HAART) regimens, based upon the ‘anchor drug’ of the regimen. For example, ritonavir-boosted protease inhibitor (PI)-based regimens and non-nucleoside reverse transcriptase inhibitor (NNRTI)-based regimens are more forgiving than unboosted PI-based regimens.1–4 This article will review the current state of knowledge on factors that determine the forgiveness of various antiretroviral treatment strategies and will discuss the relevance of this important attribute to clinical practice.

The issue of adherence to HAART came to the forefront in 2000 when Paterson et al.5 showed that extraordinarily high rates of adherence were necessary to achieve viral suppression in a group of HIV-infected patients receiving primarily unboosted indinavir or nelfinavir-based HAART. Additional studies lent support to the view that very high rates of adherence were required to achieve complete viral suppression.5,7 These findings, taken together with the bleak outlook for those failing their first PI-based regimen in the early HAART era,8,9 gave birth to the ‘95% rule’, namely, that patients must take at least 95% of the prescribed antiretroviral doses in order to control viral replication.10 This, in turn, led to an unprecedented emphasis on achieving and sustaining near-perfect adherence in all recipients of antiretroviral therapy. The necessity for near-perfect adherence to unboosted PI-based regimens was a driving force for a standard of care that still includes aggressive adherence monitoring and management.

Two recent studies employing rigorous measures of adherence have demonstrated high rates of viral suppression at more moderate levels of adherence in patients treated with NNRTI and ritonavir-boosted PI-based HAART.4,11 In the REACH cohort, a group of 110 marginally housed, HIV-infected individuals in San Francisco, CA, USA, underwent electronic adherence monitoring and periodic measurement of HIV viral load. Recipients of NNRTI-based regimens (primarily nevirapine) achieved high rates of viral suppression at adherence rates as low as 54%.11 Shuter et al. used electronic adherence monitoring to evaluate the relationship between adherence and viral suppression in 64 patients receiving lopinavir/ritonavir-based HAART in the Bronx, New York. In this study, there was no significant decline in rates of viral suppression with decreasing adherence rates, even in the lowest adherence stratum. The mean adherence rate in those who achieved complete viral suppression was 75%.4 These studies, and others employing alternative measures of adherence, have provided compelling evidence that NNRTI and ritonavir-boosted PI-based HAART are more forgiving of non-adherence than unboosted PI-based HAART.1–4

Most pharmacological parameters in common usage can be defined with precision. In contrast, forgiveness currently lacks an established, quantitative measure. Notwithstanding the lack of a specific forgiveness scale, the medical community has embraced the concept that some regimens are more forgiving of non-adherence than others, and this recognition influences therapeutic choices that are made every day in offices and clinics. Forgiveness, like many properties related to antimicrobial treatment, depends on...
pharmacological, viral and host factors. Although the ‘drug, bug and host’ schema provides a useful method of categorizing different determinants of forgiveness, the artificiality of the construct must be acknowledged. Viral setpoint, for example, is the end result of a complex interaction between the virus and the host’s immune response. Likewise, medication half-life depends on both intrinsic pharmacological properties and host metabolism. The ensuing summary of the various determinants of forgiveness attempts to assign each factor to the most appropriate category while recognizing that extensive overlap exists.

Pharmacological factors

Medication half-life and antiviral efficacy are critical factors in forgiveness of non-adherence. Research into these properties and their relationship to virological outcomes generally focus on the anchor drug of the regimen, as will this discussion. However, the potential influence of the other antiretroviral agents in a regimen, although less-well delineated, should not be forgotten. Unboosted PIs, such as saquinavir, indinavir, and nelfinavir, have relatively short half-lives and are likely to fall to subinhibitory levels after a missed dose. Unboosted atazanavir has a longer half-life than earlier unboosted PIs, but the effect of its improved pharmacokinetic profile on forgiveness of non-adherence remains unexplored. Ritonavir-boosted PIs and NNRTIs have substantially longer half-lives and are likely to maintain inhibitory levels after a missed dose. In general, therefore, a longer elimination half-life favours greater forgiveness. Under certain circumstances, however, a long half-life can confer a forgiveness disadvantage. The very prolonged half-lives of the NNRTIs, efavirenz and nevirapine, may result in de facto monotherapy (the ‘NNRTI tail’) when patients miss sequential doses of their regimen. NNRTI monotherapy promotes the development of resistance, especially when drug levels fall to subinhibitory levels. Sustained exposure to subinhibitory levels makes NNRTI-based regimens less forgiving of prolonged periods of non-adherence, e.g. treatment interruptions or drug holidays, than other regimens. The complex relationship between adherence and resistance is discussed in greater detail below.

The efficacy of a regimen at producing complete viral suppression (often referred to as ‘potency’) is another intrinsic drug characteristic that affects forgiveness. By definition, patients receiving less efficacious regimens are more likely to experience incomplete viral suppression than those receiving more efficacious regimens at similar levels of adherence. When regimens with limited efficacy are used, failure to achieve and sustain complete viral suppression may be a direct result of suboptimal antiviral activity and does not necessarily require the acquisition of drug resistance. The relatively high virological failure rate coupled with the low resistance mutation rate among recipients of zidovudine, lamivudine and indinavir in the Trilege study illustrates that the poor forgiveness profile attributable to suboptimal pharmacokinetic properties and antiviral efficacy of a regimen may be independent of the acquisition of genotypic resistance.

Viral factors

HIV’s primary route to continued replication in the presence of antiretroviral medication is via the development of resistance. Its error-prone replicative machinery provides an ongoing source of mutated virus, and the selection pressure exerted by antiretroviral medications, especially at subinhibitory levels, is a powerful promotor of viral resistance. At any level of adherence to HAART, resistance to one or more components of a regimen increases the likelihood of virological failure and hence decreases forgiveness. The development of genotypic resistance depends on several viral factors. Exposed to the same level of antiviral selection pressure, a virus with a high replicative rate is more likely to accumulate resistance mutations per unit time than one with a low replicative rate. Higher viral setpoints and higher levels of viral replication in the setting of incomplete suppression by HAART are, consequently, risk factors for the development of resistance. Many resistance mutations exact a price in terms of replication competence, thereby mitigating their deleterious effect on forgiveness. Some mutations, however, particularly those that affect viral regions distant from the site of the target enzyme, are replication competence neutral or may even result in increased replication competence. Many of the mutations that confer resistance to the NNRTI class are associated with increased rates of viral replication and tend to diminish forgiveness of non-adherence. For some regimens, an individual resistance mutation may lead to high rates of virological failure, whereas for others, multiple mutations may be required. Moreover, the sequential accumulation of resistance mutations does not necessarily occur at a constant rate. A mutation or a set of mutations may either facilitate or inhibit the acquisition of additional mutations.

Host factors

Host factors also play a role in forgiveness. Varying levels of absorption, drug distribution, metabolism and elimination affect the exposure of the virus to the drug(s) and hence have the potential to affect forgiveness. Important examples of such phenomena include impaired absorption of atazanavir in patients with high gastric pH and delayed metabolism of efavirenz in subjects with cytochrome P450 CYP2B6 polymorphisms. Recent research has also demonstrated an association of certain human leukocyte antigen alleles with specific antiretroviral resistance mutations, suggesting another potential avenue by which host determinants could influence forgiveness. The effect of CCR5 heterozygosity on forgiveness in recipients of CCR5 antagonists remains to be studied.

The adherence–resistance relationship

Bangsberg et al. have synthesized many of the aforementioned factors into a cohesive model that explains the complex relationship between antiretroviral adherence and the development of resistance. This model is central to our current understanding of...
 forgiveness. Two basic tenets underlie the adherence–resistance relationship. First, the frequency of acquisition of new resistance mutations approaches zero in treated patients with undetectable viral loads.\(^2\) Secondly, the ideal environment for the acquisition of new resistance mutations consists of actively replicating virus in the presence of subinhibitory concentrations of drug (i.e. antimicrobial selection pressure).\(^2\) Depending on the level of resistance conferred by a mutation, resistance may be overcome by improved adherence to a regimen or it may be insurmountable regardless of the adherence level.\(^2,3\)

Several studies have demonstrated that among recipients of non-boosted PI-based regimens, the majority of new PI resistance mutations occur in those with higher adherence rates.\(^3,4,5\) In contrast, the development of new NNRTI resistance mutations occurs most frequently in patients with lower adherence rates, including those who experience substantial interruptions in therapy, and in those receiving single-dose NNRTI therapy.\(^1,9,36,37\) On the basis of these findings, Bangsberg et al.\(^3\) proposed an adherence–resistance relationship that is depicted in Figure 1. According to the model, the high frequency of mutation acquisition associated with unboosted PI-based regimens is a result of the inferior antiviral efficacy of these regimens together with the relatively short half-life of the drugs. Highly efficacious regimens, by definition, yield very high rates of complete virological suppression in subjects who adhere well. As mutations are unlikely to occur in the absence of active viral replication, adherence to highly efficacious regimens discourages the development of resistance. In contrast, the substantial proportion of patients who have ongoing viral replication despite excellent adherence to unboosted PIs (as a result of limited antiviral efficacy and inferior pharmacokinetic profile) are likely to accumulate resistance mutations over time, because their virus is often replicating in the presence of drug. In the lower adherence strata, the short half-lives of unboosted PIs and their resultant rapid disappearance from circulation during non-adherent periods lessen selection pressure and lead to a proportionately lower frequency of new mutations. Clinically significant PI resistance generally develops in a stepwise pattern, with incremental increases in phenotypic resistance as each new mutation occurs.\(^2\) As PI resistance mutations exact a relatively high cost in terms of viral fitness,\(^2,3\) the ratio of resistance conferred per mutation/viral fitness cost per mutation is low for PIs. As a result of this resistance–viral fitness relationship, more constant exposure to drug tends to amplify the emergence of PI-resistant strains (i.e. in higher adherence strata), whereas less constant exposure encourages the proliferation of more replication-competent PI-susceptible strains (i.e. in lower adherence strata).\(^2,3\)

The situation in recipients of NNRTI-based regimens is very different.\(^11\) NNRTI-based regimens combine a high degree of antiviral efficacy and a prolonged elimination half-life (at least of the NNRTI component). These two features together render NNRTI-based regimens forgiving of occasional missed doses. In patients with fully suppressed viral replication, there is a lag period after the interruption of therapy before viral rebound occurs,\(^18\) so sporadic missed doses of the NNRTIs are unlikely to produce the high-risk combination of actively replicating virus and subtherapeutic levels of NNRTI. Because of the long half-lives of NNRTIs, patients with lengthy periods of non-adherence or with treatment interruptions who stop all their antiretrovirals simultaneously may be exposed to the ‘NNRTI tail’.\(^17,18\) Waning levels of the NNRTI in the face of rebounding viral replication set the stage for the acquisition of NNRTI resistance mutations. Unlike PI resistance, NNRTI resistance exacts little or no cost in terms of viral fitness,\(^24\) and single mutations can confer high-level resistance against all currently available members of the NNRTI class.\(^3\) The ratio of resistance conferred per mutation/viral fitness cost per mutation is high for NNRTIs. Circumstances that attenuate the protection against resistance acquisition conferred by the NNRTIs’ antiviral efficacy and long half-lives may compromise the forgiveness of NNRTI-based regimens. This is consistent with observations in extremely non-adherent patients, patients who have experienced treatment interruptions, and recipients of single-dose nevirapine therapy administered in an attempt to interrupt vertical transmission.\(^19,36,37\) In contrast to unboosted PIs, NNRTIs are more forgiving of sporadic, short-term non-adherence (probably the most common form of non-adherence), but may be less forgiving of long-term treatment interruptions. This distinction highlights the importance of understanding the non-adherence patterns of our patients. Take, for example, two different 75% adherence scenarios over a 4 month period. In the first scenario, the patient misses every fourth dose of medications throughout, and in the second scenario, she/he takes every dose for 3 months and takes a self-imposed drug holiday for the entire fourth month. The patient in the first scenario would be at high risk for virological failure and acquisition of PI resistance if treated with an unboosted PI-based regimen, but at low risk for virological failure and acquisition of NNRTI resistance if treated with an NNRTI-based regimen. The patient in the second scenario would be at low risk for the acquisition of PI resistance if treated with an unboosted PI-based regimen and at high risk for the acquisition of NNRTI resistance if treated with an NNRTI-based regimen. Although conventional wisdom designates NNRTI-based regimens as more forgiving than unboosted PI-based regimens,\(^11\) extreme patterns of non-adherence can alter this relationship. These considerations take on increased importance in resource-poor areas of the world where NNRTI-based regimens dominate HIV therapy, and inventory shortfalls as well as patients’ inability to pay for continuous medication supplies result in frequent treatment hiatuses.\(^37\)

Ritonavir-boosted PIs have a high degree of antiviral efficacy and half-lives that are longer than those of unboosted PIs, but shorter than those of the NNRTIs.\(^39\) Their effective viral suppression discourages the development of resistance in the setting of sporadic missed doses, and their intermediate half-lives

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**Figure 1.** A proposed model of the adherence–resistance relationship (reproduced from Bangsberg *et al.*,\(^31\) with permission of the author and publisher.)
combined with the fitness cost of PI resistance are impediments to the development of resistance mutations in patients with longer treatment interruptions. These characteristics appear to make ritonavir-boosted PI-based regimens the most forgiving of the regimens in common use. They may also help to explain the surprisingly high levels of viral suppression seen in even the lowest adherence strata in a recent study of lopinavir/ritonavir.

Regimens that are not NNRTI- or PI-based

Rigorous studies of adherence and virological outcomes in patients receiving unboosted PI-based regimens, NNRTI-based regimens and boosted-PI regimens have allowed for a clearer understanding of forgiveness of non-adherence to these treatments. Little is known about the forgiveness of modern NRTI-only regimens. High failure rates in recipients of a lamivudine, abacavir, tenofovir combination were due, at least in part, to the low genetic barrier to resistance of the regimen. The available evidence suggests that the forgiveness of such regimens is low. However, Rawlings et al. used electronic monitoring to demonstrate a more favourable adherence–resistance relationship in subjects receiving zidovudine/lamivudine/abacavir combination therapy. The forgiveness profiles of zidovudine/lamivudine/tenofovir and zidovudine/lamivudine/abacavir/tenofovir combinations and of regimens containing enfuvirtide, CCR5 antagonists, integrase inhibitors, and the next generation of NNRTIs remain to be studied.

The collective experience of investigators studying adherence to antiretrovirals has taught us that, on average, patients take ~75% of their prescribed doses. Patients and providers should not be satisfied with this figure and should constantly strive for better. Non-adherence, however, is a fact of life. The virological outcomes of patients who fall at the extreme ends of the adherence spectrum are fairly predictable. Those who take none of their prescribed therapy fail to suppress viral replication, and those who take every dose generally achieve full suppression of viral replication. The fate of the vast majority of individuals who fall in between these extremes is more variable. An understanding of forgiveness of antiretroviral non-adherence sheds light on these varied outcomes and reinforces the view that they are not haphazard occurrences, but rather the end result of a complex interaction between key pharmacological, viral and host factors.

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