

Paradoxes of adherence and drug resistance to HIV antiretroviral therapy

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Public health debates about providing HIV antiretroviral therapy to impoverished populations have centred on the relationship between adherence and risk of drug resistance. Recent data indicate that each antiretroviral therapeutic class has a unique adherence–resistance relationship. Resistance to single protease inhibitor therapy occurs most frequently at moderate to high levels of adherence, resistance to non-nucleoside reverse transcriptase inhibitor therapy occurs at low to moderate levels of adherence, and resistance to ritonavir-boosted protease inhibitor therapy is most likely to occur at middle ranges of adherence. These dynamic relationships should be considered in balancing the individual and public health benefits of therapy.

Keywords: resource-constrained countries, drug users, protease inhibitors, non-nucleoside reverse transcriptase inhibitors, public health

'Non-adherence leads to drug-resistant HIV.' Or, at least, this is what we have been trained to believe. Failure to take the prescribed doses of antiretroviral drugs leads to ongoing viral replication in the presence of drug and the selection of drug-resistant HIV. This view forms the basis of domestic^{1–5} and international⁶ public health debates regarding the potential benefits and dangers of providing antiretroviral therapy to populations at risk for non-adherence. Some have argued that the risk of spreading resistant virus justifies withholding therapy, both domestically and internationally, until adherence support mechanisms are in place.^{1,7,8} These debates hinge on an accurate understanding of the relationship between adherence and resistance to HIV antiretroviral therapy. However, only recently have empirical studies directly addressed this issue. As we will discuss here, these studies indicate that the relationship between adherence and HIV drug resistance is more complicated than assumed initially. For some regimens, resistance may be more likely in those who take more rather than less of their medications. For others, the opposite may be true.

The association between antiretroviral adherence and viral suppression,^{9–12} progression to AIDS¹³ and progression to death^{14,15} is well established. Initial studies of adherence and resistance were limited by a small sample size, the use of monotherapy,¹⁶ or the use of incompletely characterized measures of adherence.¹⁷ Given the limitations in these early studies, the early proposition that non-adherence leads to resistance was influenced heavily by the prior epidemic of multi-drug-resistant tuberculosis in New York City where resistance was almost exclusively seen in individuals at risk for non-adherence due to addiction, mental illness and unstable housing.^{5,18}

The widely accepted premise that non-adherence breeds resistance is now being challenged, at least as it pertains to anti-HIV therapy. Recent data from cohorts of individuals with well-characterized measures of adherence suggest that resistance to both protease and nucleoside reverse transcriptase inhibitors occurs primarily in *highly* adherent patients.⁹ In separate studies, Walsh *et al.*¹⁹ and Howard *et al.*²⁰ demonstrated linear and direct associations between adherence and the number of drug resistance mutations. Gallego *et al.*²¹ found protease inhibitor resistance was limited to those individuals reporting more than 90% adherence.

The above studies were largely cross-sectional and were limited by the possibility that resistance occurred during unmeasured lapses in adherence. Subsequent studies with more extensive, concurrently obtained longitudinal adherence and resistance measures have confirmed the early findings. Longitudinal studies by our group and by Miller *et al.* found that increasing adherence independently predicts the rate of accumulation of drug resistance mutations among patients with persistent detectable viraemia.^{22,23} When all patients were included in our study, including those with undetectable viraemia, we estimated that one-quarter of all drug resistance mutations occurred in patients with 92–100% adherence. A subsequent mathematical model based on these data estimated that population-level resistance occurs most frequently at 81% adherence and declines only modestly with perfect adherence.²⁴ This estimate is remarkably similar to independent estimates recently provided in abstract form by Harrigan *et al.*²⁵ and King *et al.*²⁶ Both of these longitudinal studies involved well-characterized individuals treated with standard treatment regi-

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mens, and both concluded that drug resistance is most common in patients with 80–90% adherence. Since the average level of adherence in most studies with objective measures of adherence is 70%,²⁷ clearly it is not the ‘non-adherent’ who are at highest risk of drug resistance.

Most of the preceding data were derived from cohorts of individuals treated with either sequential monotherapy or earlier, less potent three-drug regimens (e.g. two nucleoside analogues and a single protease inhibitor). Given the inherent lack of anti-HIV potency when antiretroviral drugs are used in this manner, it is not surprising that high-level adherence did not routinely suppress all viral replication nor that high-level adherence did not prevent the emergence of resistant variants. Standard of care now focuses on the use of more effective first-line regimens, including two nucleoside analogues and either a non-nucleoside reverse transcriptase inhibitor (e.g. efavirenz) or a ritonavir-boosted protease inhibitor (e.g. ritonavir/lopinavir). We estimate that any regimen that durably suppresses viraemia to undetectable levels (<50 copies/mL) in 95% of perfectly adherent patients will reduce the population burden of resistance by 45% compared to historical regimens.²⁴ Given the very high virological suppression rates observed with either efavirenz- or ritonavir/lopinavir-based regimens,^{28,29} it is reasonable to predict that the balance will shift towards more complete viral suppression and less drug resistance in highly-adherent individuals.

Emerging data indicating that antiretroviral classes may have different adherence–resistance relationships complicate the choice between efavirenz- and ritonavir/lopinavir-based regimens. A direct adherence–resistance relationship appears strongest for non-ritonavir-boosted protease inhibitors,^{19–21,23,26} and it has also been observed for most nucleoside analogues.^{9,30} No such relationship has been observed for the non-nucleoside reverse transcriptase inhibitors (NNRTIs). In contrast to studies of protease inhibitors, Parienti *et al.* found that NNRTI resistance is associated with interruptions of therapy,³¹ and in a mostly NNRTI-treated cohort, Sethi *et al.* found resistance occurring at lower levels of adherence than that observed in patients who develop resistance to protease inhibitor therapy.³² A different adherence–resistance relationship for NNRTIs is also consistent with reports of resistance to these medications occurring after single-dose or after short-course therapy given during perinatal HIV prevention trials.^{33,34} Since single-dose therapy is analogous to the lowest level of adherence possible, it appears that the NNRTIs have an adherence–resistance relationship wherein almost any exposure in the absence of full viral suppression is sufficient to cause resistance.

Why would the relationship between adherence and resistance differ substantially between drug classes? Although the answer to this question remains unknown, substantial *in vivo* data and theoretical considerations suggest that NNRTIs have several characteristics that might result in an unfavourable adherence/resistance relationship. First, NNRTIs are very potent and therefore exert a strong selective pressure. Second, NNRTIs act at a site distant from the active site of their target enzyme. Therefore, mutations that confer drug resistance do not dramatically impact enzymic efficiency and—by extension—viral replicative capacity (or viral ‘fitness’). Third, NNRTIs have long half-lives and remain in plasma for extended periods after several missed doses; this allows the virus an opportunity to replicate in the presence of suboptimal drug exposure (note that this pharmacological property might be beneficial in some instances since a few missed doses separated in time will be unlikely to allow the virus to replicate). Fourth, resistance to one NNRTI almost universally confers cross-resistance to all other NNRTIs. Finally, NNRTI resistance persists indefinitely after the drug is discontinued.³⁵ Thus, many factors

appear to favour the virus over the drug in terms of NNRTI resistance. NNRTIs should be considered a relatively fragile drug class across the entire range of adherence too low to suppress viral replication.

Many of these factors regarding adherence and resistance to NNRTIs do not apply to ritonavir-boosted protease inhibitors. For example, resistance to protease inhibitors requires multiple mutations, each of which significantly reduces enzymic efficiency and viral fitness. Therefore, high-level drug resistance requires both viral replication and sufficient drug exposure to create a selective advantage for less-fit, resistant virus and should emerge over a relatively narrow range of drug exposure. Also, since the half-life of a protease inhibitor is relatively short, protease inhibitor concentrations are likely to remain in a suboptimal therapeutic range for only a brief time during periods of non-adherence.²⁵ Given these factors, it is perhaps not surprising that protease inhibitor resistance is rarely observed during early virological failure of ritonavir-boosted protease inhibitor-based regimens.^{26,28} Even if resistance does emerge during protease inhibitor therapy, there are theoretical arguments and some empirical data that indicate that these variants will be less fit and therefore less infectious than NNRTI-resistant variants.^{36,37}

Based simply on these resistance arguments, it would appear that the widespread use of NNRTIs will have greater public health costs than the widespread use of ritonavir-boosted protease inhibitors. Although these issues argue for the use of dual protease inhibitor-based regimens over NNRTI-based regimens, it remains difficult to ignore the fact that NNRTIs are far less expensive than protease inhibitors (especially generic formulations available in the developing world), and that NNRTIs are generally easy to store and easy to administer. In our opinion, regimen choice on both an individual- and a population-based level should be driven by many factors, including fiscal constraints, clinical effectiveness, tolerability and the risk of drug 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 non-boosted protease-based regimens, most drug 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 ritonavir-boosted protease inhibitor regimens, limited resistance occurs at any level of adherence. For NNRTIs, 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 (Figure 1).

How should these data be used to formulate treatment strategies? Most physicians’ first priority is to prevent illness in individual patients rather than to bring down the population burden of resistant HIV. This therapeutic framework may change, however, with the increasing need to maximize treatment benefit on a community basis in resource-constrained areas. Since governments and other large funding agencies will be purchasing drugs in such settings, the public health implications of any treatment strategy will likely become more relevant. Rational predictions of how deployment of therapy will impact population levels of drug resistance will require a sound understanding of the complex relationships between adherence and development of drug resistance. Since this relationship appears to be drug-specific, we propose that defining this relationship be a critical part of the drug development process. Recently, resistance to HIV has been the price for patients adhering to therapy so that they can live longer. Hopefully, a better understanding of adherence and resistance

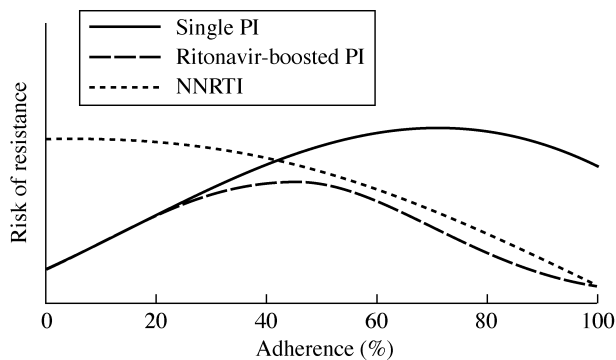


Figure 1. Schematic figure outlining the relationship between medication adherence and the risk of developing PI or NNRTI drug resistance. NNRTI-treated individuals rarely develop resistance at high levels of adherence due to the virological effectiveness of these regimens. NNRTI resistance develops rapidly at moderate to low levels of adherence due to the low 'fitness' costs associated with single mutations. Single PI-treated individuals may develop resistance at high levels of adherence because residual viral replication is often seen in such patients. PI resistance is uncommon at low levels of adherence because of the significant fitness costs associated with these mutations. Resistance to a ritonavir-boosted PI is only possible in a narrow range of adherence where there is sufficient residual viral replication. Data in this figure are conceptual and based on trends observed in a number of recent studies (see text). PI, protease inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor.

in combination with more complete viral suppression will better align the individual and public health benefits of antiretroviral therapy.

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