Modeling the HIV Protease Inhibitor Adherence–Resistance Curve by Use of Empirically Derived Estimates

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The standard view postulates a bell-shaped relationship between adherence to therapy and development of drug-resistant human immunodeficiency virus (HIV), with a resistance peak at a moderate level of adherence. This relationship has not been confirmed empirically. We statistically modeled the relationship between adherence and development of drug resistance, using empirically defined relationships of the rate of viral suppression and drug-resistance–mutation accumulation derived from patients receiving protease-inhibitor–based therapy. We found that the maximal rate of drug resistance occurs at 87% adherence and declines modestly at 100% adherence. Higher levels of viral suppression at 100% adherence (a marker of greater regimen potency) progressively reduce the overall population rate of drug resistance and shift the peak resistance rate to lower levels of adherence.

Nonadherence to therapy is closely associated with incomplete viral suppression [1] and disease progression [2], and it is thought to be a risk factor for the development of drug resistance [3, 4]. The relationship between adherence and the risk of drug resistance to HIV antiretroviral therapy is postulated to be a “bell-shaped curve” [5]. This bell-shaped curve is based on 2 assumptions: first, the presence of antiretroviral drugs during viral replication creates a selective advantage for drug-resistant virus; second, levels of adherence high enough to completely halt viral replication will prevent the development of drug resistance.

This theoretical model, however, has not been empirically confirmed, nor has the risk of resistance been estimated numerically at various levels of adherence. We set out to model the relationship between adherence and the rate of evolution of protease-inhibitor–drug resistance. The model was based on empirical estimates of adherence, viral suppression, and the rate of accumulation of protease-inhibitor mutations [6]. We assumed that viral evolution to <50 copies/mL terminated the evolution of drug resistance [7]. On the basis of previous observations demonstrating a consistent relationship between the level of adherence and the risk of resistance to this drug class, we limited the model to the development of protease-inhibitor–drug resistance [1, 6, 8–10].

Methods. We used a statistical model to estimate the rate of accumulation of protease-inhibitor–drug resistance, on the basis of previously published relationships between adherence, viral suppression, and the rate of accumulation of drug resistance in patients with plasma HIV RNA levels >50 copies RNA/mL [6]. We first estimated the probability that viral suppression could be achieved at different levels of adherence. Next, we estimated the probability of new resistance mutations at each level of adherence (given a failure of viral suppression). Finally, we multiplied the probability of detectable viremia by the rate of accumulating new resistance mutations for each level of adherence.

The relationship between adherence and viral suppression was based on results from 87 patients receiving protease-inhibitor therapy, monthly viral-load (VL) determinations, and adherence monitoring based on unannounced pill counts conducted at their usual place of residence over 12 months. We have demonstrated elsewhere that unannounced pill counts are closely associated with electronic medication monitoring, viral suppression, and progression to AIDS [1, 2, 11]. The probability that, at each level of adherence, plasma HIV RNA level <50 copies/mL would be achieved was estimated by a logistic regression relationship derived from the primary adherence-VL data (intercept, −3.141 [SE, 1.12]; adherence, 3.061 [SE, 1.417]; P = .03).

In a previous report, the relationship between adherence and the rate of development of HIV protease-inhibitor drug-resistance mutations was based on published estimates for 41 patients who had incomplete viral suppression (VL >50 copies) and unannounced pill-count adherence monitoring over 6 months [6]. The rate of new drug-resistance mutations was estimated on the
basis of modeled VL for each modeled patient. For patients predicted to have an HIV RNA level <50 copies RNA/mL, we assumed a drug-resistance–mutation rate of zero [7]. For those with VL >50 copies RNA/mL, we used Poisson regression to estimate the rate of new protease-inhibitor drug-resistance mutations. This regression equation (intercept, −0.0069 [SE, 0.135]; adherence, 1.052 [SE, 0.289]; P = .0001) was based on previously observed rates of accumulation of protease-inhibitor drug-resistance mutations by level of adherence [6].

We computed the statistical properties of the modeled adherence–resistance relationship from 10,000 bootstrap replications drawn independently from both sets of data. For each bootstrap replication, as before, we computed the probability of suppression, using logistic regression, and the rate of mutation accumulation, using Poisson regression; then we computed the overall curve.

We conducted a sensitivity analysis of the model by varying, from 65% to 95%, the theoretical rates of viral suppression at 100% adherence.

**Results.** The population used to determine the parameter estimates is described in table 1. The population was heavily pretreated, with a significant number of patients receiving single- or dual-nucleoside exposure prior to 3-drug combination therapy.

The model was constructed on the basis of the probability of detectable viremia at >50 copies in all patients and the rate of accumulation of drug resistance in viremic patients. On the basis of results for 87 patients studied, the probability of viral suppression increased with higher levels of adherence such that, at 100% adherence, 48% of individuals were estimated to have a viral load of <50 copies/mL (figure 1). In viremic patients, the rate of drug-resistance mutations increased to 2.08 per person over 12 months, at 100% adherence (figure 1). When viremic and nonviremic patients were considered together, the maximal rate of accumulation of new protease-resistance mutations was 1.12 (95% bootstrap confidence interval [CI], 0.574–1.83) and occurred at 87% adherence. At 100% adherence, the rate declined to 1.08 (95% bootstrap CI, 0.455–1.95) mutations per person-year (figure 1, "Empirically derived DRM").

We conducted sensitivity analyses to assess the impact of more-potent regimens on the relationship between adherence and resistance. The effectiveness of the regimen was defined as the percentage of individuals who achieved an undetectable VL at 100% adherence. In these sensitivity analyses, more-suppressive regimens decreased the rate of drug-resistance mutations and shifted the peak rate of drug resistance to lower levels of adherence (figure 1). When 95% of individuals have viral suppression at 100% adherence, the peak rate of protease-inhibitor resistance occurs at 44% adherence. The population burden of drug resistance, reflected by the area under the adherence–resistance curve, declined to 86%, 76%, 64%, and 45% of that under the reference curve, when the assumed viral suppression in 100% adherent individuals increased to 65%, 75%, 85%, and 95%, respectively.

**Discussion.** Our model suggests that, in a treatment-experienced population on single–protease-inhibitor therapy, maximum drug resistance occurs at 87% adherence. The drug-resistance peak is close to the 70%–80% adherence range observed in most studies using objective measures of adherence [12]. Our finding is consistent with the results of a preliminary prospective study by King et al., which demonstrates that, in single–protease-inhibitor regimens, protease-inhibitor mutations accumulate most rapidly in patients with high levels of adherence and incomplete viral suppression [13]. Our findings also are consistent with several cross-sectional studies demonstrating that drug resistance is most common in patients with high

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**Table 1. Patient characteristics for parameter estimates.**

<table>
<thead>
<tr>
<th></th>
<th>Adherence group (N = 87)</th>
<th>Genotype subgroup (N = 44)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), years</td>
<td>43.7 (8.7)</td>
<td>42.9 (7.0)</td>
</tr>
<tr>
<td>Male, no. (%)</td>
<td>75 (86.2)</td>
<td>37 (84.1)</td>
</tr>
<tr>
<td>Nonwhite, no. (%)</td>
<td>52 (59.8)</td>
<td>28 (63.6)</td>
</tr>
<tr>
<td>IDU ever, no. (%)</td>
<td>50 (58.1)</td>
<td>25 (58.1)</td>
</tr>
<tr>
<td>CD4 count, mean (SD), cells/mm³</td>
<td>360 (226)</td>
<td>352 (236)</td>
</tr>
<tr>
<td>Treatment, no. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Indinavir</td>
<td>20 (23.0)</td>
<td>11 (25.0)</td>
</tr>
<tr>
<td>Nelfinavir</td>
<td>51 (58.6)</td>
<td>23 (52.3)</td>
</tr>
<tr>
<td>Ritonavir</td>
<td>1 (1.1)</td>
<td>1 (2.3)</td>
</tr>
<tr>
<td>Saquinavir</td>
<td>6 (6.9)</td>
<td>5 (11.4)</td>
</tr>
<tr>
<td>Ritonavir-indinavir</td>
<td>6 (6.9)</td>
<td>1 (2.3)</td>
</tr>
<tr>
<td>Ritonavir-saquinavir</td>
<td>3 (3.4)</td>
<td>3 (6.8)</td>
</tr>
<tr>
<td>ARV naive, no. (%)</td>
<td>5 (5.8)</td>
<td>3 (6.8)</td>
</tr>
<tr>
<td>Single- or dual-nucleoside exposure, no. (%)</td>
<td>44 (50.6)</td>
<td>24 (54.5)</td>
</tr>
<tr>
<td>PC adherence, mean (SD), %</td>
<td>62.3 (28.1)</td>
<td>65.5 (20.5)</td>
</tr>
</tbody>
</table>

**NOTE.** ARV, antiretroviral therapy; IDU, injection drug user; PC, unannounced pill count.
levels of adherence but incomplete viral suppression [1, 8–10, 14]. In the present study, we found that the highest risk of drug resistance at the population level occurs at the most commonly observed levels of adherence. This may explain why 50% of HIV-infected people are estimated to have drug-resistant virus [15].

The model suggests that, at higher levels of adherence, the rate of accumulation of new drug-resistance mutations in pre-treated individuals receiving a single-protease-inhibitor regimen declines only modestly; even 100% adherence will not prevent the accumulation of resistance mutations in such regimens. These data paradoxically suggest that effective adherence interventions in such patients may increase drug resistance.

Our sensitivity analysis suggests that more-effective treatment strategies (e.g., the use of efavirenz or lopinavir-ritonavir in a treatment-naive population) will decrease population levels of resistance and lower the level of adherence that maximally selects for drug-resistant virus; for example, a regimen that leads to 95% viral suppression at 100% adherence reduces the population burden of drug resistance by 55% and shifts the location of the peak rate of resistance from 87% to 44% adherence.

There are several limitations to our study. First, our data are relevant to only a single class of drugs. Nonnucleoside reverse-transcriptase inhibitors and lamivudine likely have fundamentally different adherence–resistance relationships [6]. Longer half-life regimens seen with ritonavir boosting also may lead to different adherence–resistance relationships. Second, our model is based on data on individuals accumulating drug resistance during stable virologic failure. The rates of accumulation of drug resistance may be different—and, perhaps, more rapid—in early virologic failure. Finally, we assumed that the rate of development of new mutations was independent of VL and the number of accumulated mutations.

In summary, we find that the relationship between adherence and resistance to protease inhibitors is driven largely by the proportion of individuals who have complete suppression at
each level of adherence. The conceptual view of a symmetric bell-shaped curve requires viral suppression to be <50 copies/mL in ≥95% of individuals with 100% adherence. At commonly observed levels of adherence—or even with 100% adherence—lower rates of viral suppression, often seen in treatment-experienced patients, may lead to high rates of drug-resistance mutations. The development of regimens leading to complete viral suppression in the vast majority of patients at moderate and high levels of adherence is essential to the limiting of the development of drug resistance.

References