Interruption of Treatment with Individual Therapeutic Drug Classes in Adults with Multidrug-Resistant HIV-1 Infection

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Background. Many antiretroviral-treated human immunodeficiency virus (HIV)–infected patients experience sustained immunologic and virologic benefit despite the presence of multidrug-resistant HIV. We hypothesized that the use of simplified regimens could maintain treatment benefit while preventing viral evolution and reducing drug-related toxicity and costs.

Methods. We conducted a 48-week nonrandomized study of adults with multidrug-resistant HIV type 1 infection. Subjects interrupted protease inhibitor (PI) or reverse-transcriptase inhibitor (RTI) treatment.

Results. At study entry, subjects had a median reduction in HIV RNA levels of 1.2 log10 copies/mL relative to pretreatment levels. Interruption of PI treatment was associated with stable HIV RNA levels (mean change per week, +0.005 log10 copies/mL; P = .36). PI mutations waned and replicative capacity and HIV RNA levels increased after long-term observation. HIV RNA levels also remained stable in subjects interrupting NNRTI treatment. In contrast, all subjects who interrupted RTI treatment exhibited immediate increases in HIV RNA levels, and most exhibited a subsequent loss of the M184V mutation.

Conclusions. These data indicate that nucleoside analogues often exert continued antiviral activity in the setting of drug-resistance mutations and that both nucleoside analogues and PIs can select for drug-resistance mutations that reduce viral fitness. These observations support the evaluation of treatment strategies aimed at maintaining the treatment benefit of therapy while reducing drug exposure.

The optimal treatment response to combination antiretroviral therapy (ART) is complete viral suppression, generally defined as the achievement and maintenance of undetectable levels of plasma HIV RNA [1]. Failure to achieve a complete response results in ongoing viral replication in the presence of drug, the emergence of drug resistance–associated mutations, and the eventual loss of future therapeutic options [2, 3]. Many treatment-experienced patients with drug-resistant HIV are unable to achieve an optimal virologic response to subsequent “salvage” ART, either because effective agents are not available or because toxicity and/or drug costs preclude the use of aggressive multidrug salvage regimens. For such patients, the goal of therapy is to maintain or enhance immunologic function.

Many HIV-infected patients who remain on a stable protease inhibitor (PI)–based treatment regimen despite the emergence of drug-resistant virus maintain some degree of partial viral suppression, and there exists a strong inverse relationship between the degree of partial viral suppression and the magnitude of the CD4+ T cell benefit [4]. The mechanism for this continued benefit of therapy is multifactorial and includes residual activity of therapy against the drug-resistant variant,
the selective maintenance of a virus population with reduced replicative capacity, preserved intrathymic T cell production, reduced peripheral T cell activation, and a sustained increase in the number and function of HIV-specific T cells [5–11].

We hypothesized that a treatment strategy aimed at preventing the emergence of wild-type HIV while maintaining the less fit and, perhaps, less virulent drug-resistant variant may be beneficial for patients with multidrug-resistant viremia. Specifically, we hypothesized that a simplified regimen including a limited number of drugs from a single therapeutic class could achieve this goal and that this strategy would maintain treatment benefit while reducing drug exposure, drug toxicity, and drug costs. Moreover, this strategy should prevent further accumulation of mutations conferring resistance to the interrupted treatment class. We tested this hypothesis in a "proof of principle" nonrandomized study in which individuals selectively interrupted all PI treatment or all reverse-transcriptase inhibitor (RTI) treatment. Because our initial study design did not allow us to distinguish the relative contributions of nonnucleoside RTIs (NNRTIs) and nucleoside RTIs (NRTIs), a subsequent substudy was performed in which individuals interrupted only the NNRTI component of their regimen.

**SUBJECTS AND METHODS**

**Study design and subjects.** The present study was a nonrandomized prospective study. Eligibility criteria included (1) continuous therapy, including at least 1 PI and 1 NRTI, for at least 12 months; (2) persistent plasma HIV-1 RNA levels >400 copies/mL during the preceding 6 months; (3) genotypic resistance testing demonstrating at least 1 drug-resistance mutation; and (4) >90% self-reported adherence to therapy during the month preceding study entry. To ascertain that the subject’s PIs were truly bioavailable, a 6-h pharmacokinetic study was performed at baseline, and subjects who did not have quantifiable PI levels were excluded.

The study included a 4-week lead-in period aimed at establishing the on-therapy steady-state plasma HIV RNA levels and CD4+ T cell counts. This period was followed by the interruption period, in which subjects were followed weekly for the first 4 weeks, then every 2 weeks for the next 8 weeks, and then every 4 weeks. All subjects were followed for a minimum of 48 weeks or until study treatment was modified. This study was approved by the University of California, San Francisco Committee on Human Research. All subjects provided written, informed consent.

**Intervention.** The decision to interrupt either PI or RTI treatment was made by the primary care provider in consultation with the investigators. Because the perceived benefit to the subject was reduction of drug-associated toxicity, the decision of which drug class to interrupt was individualized and based on regimen-associated adverse effects and dosing requirements. Genotypic and/or phenotypic resistance data were not used to determine which therapeutic class to discontinue. The decision of when to restart or modify therapy was also made by the primary care provider. Subjects were encouraged to resume or modify therapy in the event of a >1 log10 increase in HIV RNA levels or a >50% decrease in CD4+ T cell counts.

**NNRTI interruptions substudy.** Both NRTI treatment and NNRTI treatment were discontinued in those interrupting RTI treatment. Because it was not clear whether the change in HIV RNA levels was due to selective removal of the NRTIs, the NNRTIs, or both, we subsequently studied subjects who were taking a failing regimen containing an NNRTI and who were willing to discontinue only treatment with this therapeutic drug class. Eligible subjects had stable detectable HIV RNA levels (>400 copies/mL) while taking a regimen containing 1 NNRTI. Subjects were evaluated at baseline and at weeks 2 and 4 after the interruption.

**Measurements.** Routine T cell immunophenotyping and plasma HIV-1 RNA levels were measured at each visit. Plasma HIV-1 RNA levels were determined using a polymerase chain reaction assay (AmpliCoral HIV Monitor version 1.5; Roche Diagnostics; lower limit of quantification, 50 copies/mL). Phenotypic susceptibility to ART was determined using a recombinant virus–based assay that measures the IC50 of the drug-resistant variant, compared with that of a wild-type reference strain (PhenoSense HIV; ViroLogic). The same assay was also used to measure replicative capacity. Genotypic resistance measurements were performed using the GeneSeq assay (ViroLogic), as described in detail elsewhere [12].

Fasting total cholesterol, triglyceride, high-density–lipoprotein (HDL) cholesterol, and low-density–lipoprotein (LDL) cholesterol levels were evaluated twice at baseline and at weeks 4, 8, 12, 24, and 36. The non-HDL cholesterol level, which reflects the sum of all atherogenic lipoproteins and is a strong prognostic marker for atherosclerotic disease, was also calculated at each time point.

**Statistical analysis.** The virologic and immunologic outcomes were evaluated by Kaplan-Meier and repeated-measures analyses. In Kaplan-Meier analyses, virologic failure was defined as the first of 2 consecutive increases in HIV RNA levels of at least 0.5 log10 copies/mL, and immunologic failure was defined as the first of 2 consecutive decreases in CD4+ T cell counts of least 25% relative to the count at study entry. Repeated-measures analyses were performed using mixed-effects linear models, implemented in proc MIXED in SAS. Two models of change after interruption of therapy were evaluated. The first was a model that assumed that a change in plasma HIV RNA levels (or CD4+ T cell counts) occurred shortly after treatment interruption and was sustained (i.e., abrupt increase or decrease and then plateau). The second was a model that assumed that change occurred at a continuous and monotonic rate over time. In both models,
The median baseline CD4+ T cell count and plasma HIV RNA level for all participants were 333 cells/mm³ and 3.93 log₁₀ copies/mL, respectively (table 2). Importantly, all subjects had evidence of sustained treatment-mediated increases in CD4+ T cell counts relative to pretreatment nadir (median gain, 203 cells/mm³ [range, 70–460 cells/mm³]), and all but 1 subject had sustained decreases in HIV RNA levels relative to pretreatment levels (median change, −1.1 log₁₀ copies/mL [range, −2.77 to +0.31 log₁₀ copies/mL]). Virus from most subjects exhibited moderate to high levels of drug resistance, with a median fold change in IC₅₀ of 5.0 (interquartile range [IQR], 3.7–6.1) for abacavir and 36 (IQR, 16–96) for the specific PI that the participant was using (tables 1 and 2). Major and minor genotypic resistance mutations for each subject are presented in table 3.

**Impact of RTI treatment interruptions on HIV RNA levels and CD4+ T cell counts.** Interruption of all RTI treatment (and continuation of all PI treatment) was associated with an increase in baseline HIV RNA level, with median change of 3.37 log₁₀ copies/mL (IQR, 2.98–3.96). The median baseline CD4+ T cell count and plasma HIV RNA level for all participants were 333 cells/mm³ and 3.93 log₁₀ copies/mL, respectively (table 2). Importantly, all subjects had evidence of sustained treatment-mediated increases in CD4+ T cell counts relative to pretreatment nadir (median gain, 203 cells/mm³ [range, 70–460 cells/mm³]), and all but 1 subject had sustained decreases in HIV RNA levels relative to pretreatment levels (median change, −1.1 log₁₀ copies/mL [range, −2.77 to +0.31 log₁₀ copies/mL]). Virus from most subjects exhibited moderate to high levels of drug resistance, with a median fold change in IC₅₀ of 5.0 (interquartile range [IQR], 3.7–6.1) for abacavir and 36 (IQR, 16–96) for the specific PI that the participant was using (tables 1 and 2). Major and minor genotypic resistance mutations for each subject are presented in table 3.

### Table 1. Treatment outcomes by individual.

<table>
<thead>
<tr>
<th>Interrupted drug class, subject</th>
<th>Baseline regimen</th>
<th>Interrupted drug(s)</th>
<th>Fold change in IC₅₀ᵃ</th>
<th>Baseline HIV RNA level, log₁₀ copies/mL</th>
<th>Change in HIV RNA level, log₁₀ copies/mLᵇ</th>
<th>Change in CD4+ T cell count, cells/mm³</th>
</tr>
</thead>
<tbody>
<tr>
<td>All RTIs</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3002 IDV/RTV/3TC/EFV</td>
<td></td>
<td>ddI/ddI/3TC/EFV</td>
<td>2.7</td>
<td>4.6</td>
<td>&gt;200</td>
<td></td>
</tr>
<tr>
<td>3017 NFV/3TC</td>
<td></td>
<td>ZDV/3TC</td>
<td>0.4</td>
<td>&gt;200</td>
<td>39</td>
<td></td>
</tr>
<tr>
<td>3024 IDV/3TC</td>
<td></td>
<td>d4T</td>
<td>0.7</td>
<td>NA</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>3030 ZDV/3TC</td>
<td></td>
<td>NRTI 1</td>
<td>8.0</td>
<td>&gt;200</td>
<td>350</td>
<td></td>
</tr>
<tr>
<td>3031 NRTI 2</td>
<td></td>
<td>NRTI 2</td>
<td>0.4</td>
<td>&gt;200</td>
<td>350</td>
<td></td>
</tr>
<tr>
<td>3032 NRTI 3</td>
<td></td>
<td>NRTI 3</td>
<td>0.4</td>
<td>&gt;200</td>
<td>350</td>
<td></td>
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<tr>
<td>All PIs</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3005 IDV/RTV/3TC/EFV</td>
<td></td>
<td>ZDV/3TC</td>
<td>0.4</td>
<td>&gt;200</td>
<td>39</td>
<td></td>
</tr>
<tr>
<td>3016 NRTI 1</td>
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<td>NRTI 1</td>
<td>8.0</td>
<td>&gt;200</td>
<td>350</td>
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<tr>
<td>3017 NRTI 2</td>
<td></td>
<td>NRTI 2</td>
<td>0.4</td>
<td>&gt;200</td>
<td>350</td>
<td></td>
</tr>
<tr>
<td>3018 NRTI 3</td>
<td></td>
<td>NRTI 3</td>
<td>0.4</td>
<td>&gt;200</td>
<td>350</td>
<td></td>
</tr>
</tbody>
</table>

**NOTE.** All plasma HIV RNA levels were log₁₀ transformed. 3TC, lamivudine; ABC, abacavir; APV, amprenavir; d4T, stavudine; ddI, didanosine; DLV, delavirdine; EFV, efavirenz; IDV, indinavir; LPV, lopinavir; NA, not applicable; NFV, nelfinavir; NVP, nevirapine; RTV, ritonavir; SQV, saquinavir; TFN, tenofovir; ZDV, zidovudine.

ᵃ Phenotypic data are expressed as fold decrease in drug susceptibility for the baseline virus relative to the wild-type control. The fold change in IC₅₀ refers to each nucleoside reverse-transcriptase inhibitor (NRTI) and to the non-ritonavir protease inhibitor (PI). NRTI 1, 2, and 3 refer to the NRTIs listed in the second column (in order).

ᵇ Change from baseline level to the level at either week 2 or week 16 of the treatment interruption period.
Table 2. Baseline characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Treatment interruption</th>
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</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RT (n = 6)</td>
<td>PI (n = 18)</td>
<td>All (n = 24)</td>
<td></td>
</tr>
<tr>
<td>Age, years</td>
<td>52.4</td>
<td>46.1</td>
<td>49.6</td>
<td></td>
</tr>
<tr>
<td>CD4+ T cell count, cells/mm³</td>
<td>314 (276–352)</td>
<td>333 (209–400)</td>
<td>333 (251–398)</td>
<td></td>
</tr>
<tr>
<td>CD8+ T cell count, cells/mm³</td>
<td>1499 (1261–2035)</td>
<td>1309 (942–1705)</td>
<td>1360 (961–1777)</td>
<td></td>
</tr>
<tr>
<td>Plasma HIV RNA level, log₁₀ copies/mL</td>
<td>3.62 (3.55–3.81)</td>
<td>4.03 (3.84–4.64)</td>
<td>3.93 (3.63–4.55)</td>
<td></td>
</tr>
<tr>
<td>Treatment-mediated change in CD4+ T cell count relative to pretreatment nadir, cells/mm³</td>
<td>+216 (199–263)</td>
<td>+173 (145–345)</td>
<td>+203 (152–309)</td>
<td></td>
</tr>
<tr>
<td>Treatment-mediated change in plasma HIV RNA level relative to pretreatment baseline, log₁₀ copies/mL</td>
<td>−1.29 (−1.39 to −1.16)</td>
<td>−1.03 (−1.36 to −0.72)</td>
<td>−1.08 (−1.38 to −0.81)</td>
<td></td>
</tr>
<tr>
<td>Fold change in IC₅₀</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abacavir</td>
<td>4.1 (3.0–5.1)</td>
<td>5.2 (4.4–6.2)</td>
<td>5.0 (3.7–6.1)</td>
<td></td>
</tr>
<tr>
<td>Subject-specific PI</td>
<td>36.0 (25.0–38.4)</td>
<td>32.0 (11.7–117)</td>
<td>36.0 (15.9–95.5)</td>
<td></td>
</tr>
<tr>
<td>Replicative capacity, % of NL4-3 control</td>
<td>26.0 (16.1–37.5)</td>
<td>41.3 (19.8–57.3)</td>
<td>36.0 (19.5–51.3)</td>
<td></td>
</tr>
<tr>
<td>Total fasting cholesterol level, mg/dL</td>
<td>224 (219–243)</td>
<td>200 (173–214)</td>
<td>209 (175–223)</td>
<td></td>
</tr>
<tr>
<td>Triglyceride level, mg/dL</td>
<td>301 (225–652)</td>
<td>299 (160–533)</td>
<td>299 (183–573)</td>
<td></td>
</tr>
<tr>
<td>HDL cholesterol level, mg/dL</td>
<td>30 (22–36)</td>
<td>32 (27–50)</td>
<td>31 (27–40)</td>
<td></td>
</tr>
<tr>
<td>Non-HDL cholesterol level, mg/dL</td>
<td>191 (181–228)</td>
<td>160 (143–184)</td>
<td>173 (149–189)</td>
<td></td>
</tr>
</tbody>
</table>

**NOTE.** Data are medians (interquartile ranges). HDL, high-density lipoprotein; PI, protease inhibitor; RT, reverse transcriptase.

*a Abacavir susceptibility was used as a surrogate for nucleoside RT inhibitor resistance, because resistance to this drug is strongly correlated with resistance to other drugs and because resistance is not dramatically affected by M184V.
Interruption of Antiretroviral Treatment

Table 3. Baseline genotypic resistance data.
The table is available in its entirety in the online edition of the Journal of Infectious Diseases.

immediate increase in HIV RNA levels in all 6 subjects studied (figure 1). The median increase at week 2 was 0.78 log_{10} copies/mL (range, 0.46–1.00 log_{10} copies/mL). This increase in plasma HIV RNA levels was sustained over time, as evidenced by a mean increase of 0.66 log_{10} copies/mL (95% confidence interval [CI], 0.46–0.87 log_{10} copies/mL; P < .001) relative to study entry levels at each of the time points during the first 16 weeks. The mean decrease in CD4⁺ T cell counts during 16 weeks was 14.9% (95% CI, 24.1%–3.6%; P = .012). By use of Kaplan-Meier analysis, the median time to a 25% loss of CD4⁺ T cells was calculated as 22 weeks (figure 2).

Two additional subjects who enrolled in the PI-interruption arm of this study subsequently interrupted either all RTI treatment (subject 3158) or treatment with 2 of 3 RTIs (subject 3153, who discontinued stavudine and didanosine but continued to receive lamivudine). Both subjects experienced immediate increases in HIV RNA levels (increase at week 2, 0.80 and 0.60 log_{10} copies/mL, for subjects 3158 and 3153, respectively).

Impact of PI treatment interruptions on HIV RNA levels and CD4⁺ T cell counts. Interruption of PI treatment was associated with stable HIV RNA levels in most subjects, at least through the first 24 weeks of observation (figure 1). In contrast to the interruption of RTI treatment, which was associated with an increase of at least 0.5 log_{10} copies/mL in HIV RNA levels by week 2 in all subjects, no subject interrupting PI treatment experienced a ≥0.5-log_{10} copies/mL increase in plasma HIV RNA levels at week 2 (median change, +0.04 log_{10} copies/mL; range, −0.40 to +0.36 log_{10} copies/mL).

HIV RNA level changes within the first 24 weeks—when they occurred—tended to exhibit a monotonic increase over time rather than an immediate increase and plateau, as was seen when RTI treatment was interrupted. When all data through week 24 were considered, the mean change per week in HIV RNA levels was +0.005 log_{10} copies/mL (95% CI, −0.006 to +0.017 log_{10} copies/mL), which was not significantly different from 0 (P = .36).

CD4⁺ T cell count changes were more variable. Over the first 24 weeks, there was a nonsignificant trend toward a decrease in CD4⁺ T cell counts (mean change, −0.67% of cells/week [95% CI, −1.5% to +0.14% of cells/week]; P = .10). By use of Kaplan-Meier analysis, the median time to a 25% loss of CD4⁺ T cells was calculated as 37 weeks (figure 2).

Viral evolution after interruption of RTI treatment. We did not observe the emergence of a fully susceptible virus after interruption of RTI treatment. Viral evolution was evident, however, in most subjects interrupting RTI treatment. Specifically, 5 of 6 lamivudine-treated subjects exhibited a loss of the lamivudine-associated M184V mutation during the interruption period. This loss first became apparent after a median of 20 weeks (range, 12–36 weeks) and was temporally associated with an increase in replicative capacity (median fold increase from baseline, 2.2 [range 1.1–3.2]; n = 5). Between the time points when lamivudine resistance was present and then lost, plasma HIV RNA levels increased by a median of 0.41 log_{10} copies/mL (range, 0.25–0.64 log_{10} copies/mL; n = 5).

Figure 1. Change in plasma HIV RNA levels and CD4⁺ T cell counts after interruption of protease inhibitor (PI) or reverse-transcriptase inhibitor (RTI) treatment. Graphs show the change in log_{10} plasma HIV RNA levels (A) and CD4⁺ T cell counts (B) in subjects with drug-resistant viremia interrupting either all PI or all RTI treatment. Three of 6 subjects interrupting RTI treatment modified therapy at or near week 16, because of increasing plasma HIV RNA levels. Three of 18 subjects interrupting PI treatment modified therapy before week 24, because of increasing plasma HIV RNA levels and/or decreasing CD4⁺ T cell counts. Median changes and interquartile ranges are shown. The week-2 change in plasma HIV RNA levels (log_{10} transformed) for all subjects interrupting RTI, PI, or nonnucleoside RTI (NNRTI) treatment is also shown (C).
Figure 2. Time to virologic and immunologic failure in subjects interrupting either protease inhibitor (PI) or reverse-transcriptase inhibitor (RTI) treatment. Virologic failure was defined as the first of 2 consecutive increases in plasma HIV RNA levels of at least $0.5 \log_{10}$ copies/mL, relative to study entry levels. Immunologic failure was defined as the first of 2 consecutive decreases in CD4+ T cell counts of least 25%, relative to study entry levels.

**Viral evolution after interruption of PI treatment.** Among the 18 subjects who interrupted PI treatment, we observed no loss (or accumulation) of PI-associated mutations during the first 12 weeks of observation. Notably, no subject experienced a rapid rebound of a nucleoside analogue–resistant, PI-susceptible virus during the first 12 weeks of observation, even though all but 2 subjects had received sequential nucleoside analogue therapy during the pre-PI era and, therefore, potentially harbored nucleoside analogue–resistant, PI-susceptible virus [14]. Loss of PI-associated mutations and increased PI susceptibility was first observed at week 12 in 2 subjects and at or near week 36 in 4 subjects, whereas no change in protease was observed in the remaining subjects through a median of 42 weeks of observation.

Genotypic and phenotypic changes in protease resistance were associated with increased replicative capacities and increased plasma HIV RNA levels. The median fold increase in replicative capacity relative to baseline values in subjects experiencing a shift in resistance genotype/phenotype was 2.1 (IQR, 1.5–4.3). This was significantly higher than the increase in replicative capacity observed in subjects who did not exhibit a change in protease genotype/phenotype (median fold increase, 1.2 [IQR, 1.1 to 1.7]; $P = .04$, Wilcoxon rank sum). Increases in plasma HIV RNA levels were also higher in subjects experiencing a shift in protease genotype (median change, $+0.86$ vs. $−0.01 \log_{10}$ copies/mL, in those experiencing a shift vs. those not experiencing a shift, respectively; $P = .03$, Wilcoxon rank sum).

**Metabolic changes during partial treatment interruptions.** Triglyceride and cholesterol levels were elevated at baseline in both study groups (table 2). On the basis of repeated-measures analyses, PI treatment interruption was associated with significant and rapid decreases in fasting triglyceride levels ($P < .001$), total cholesterol levels ($P < .001$), and non-HDL cholesterol levels ($P < .001$). Among subjects who interrupted RTI treatment, there was a significant decrease in triglyceride levels ($P = .03$).

**Impact of nonnucleoside RTI treatment interruption on plasma HIV RNA levels.** Of the 6 individuals interrupting RTI treatment, 1 was also taking an NNRTI. Of the 18 subjects who continued to take RTIs, 2 were taking an NNRTI. To more fully define the relative contribution of the NNRTIs, we analyzed the changes in HIV RNA levels in 6 subjects with multidrug-resistant HIV who interrupted the NNRTI component of their regimen while continuing to take their other antiretroviral medications (3 discontinued nevirapine, 2 discontinued efavirenz, and 1 discontinued delavirdine). Three subjects (subjects 3025, 3062, and 3168) had completed previously interrupted PI treatment in the context of this study and subsequently reconsented to interrupt their NNRTI treatment. All subjects had evidence of phenotypic or genotypic resistance to NNRTIs at the time that treatment with these drugs was interrupted (see table 3). Interruption of the NNRTI resulted in no change in plasma HIV RNA levels at week 2 (median fold change, $−0.18 \log_{10}$ copies/mL [range, $−0.40$ to $+0.08 \log_{10}$ copies/mL]) (figure 1) or at week 4 (median fold change, $+0.08 \log_{10}$ copies/mL [range, $−1.31$ to $+0.29 \log_{10}$ copies/mL]).

**DISCUSSION**

Many patients who continue stable combination ART despite the presence of drug-resistant HIV-1 achieve a steady-state level of viremia that remains below pretreatment levels. Several factors likely contribute to this partial control of viral replication, including the selective maintenance of a less-fit virus population and the persistent antiviral activity of therapy against the drug-resistant variant. In this pilot study, interruption of RTI treatment (and continuation of PI treatment) was associated with an immediate and substantial increase in HIV RNA levels before any genotypic changes within reverse transcriptase, indicating that these drugs may retain direct antiviral activity against the resistant variant. In contrast, interruption of PI treatment (and continuation of RTI treatment) was associated, through 24 weeks,
with stable HIV RNA levels in most subjects, indicating that resistance to these drugs is often complete. Although PI-associated mutations remained stable in the absence of PIs for most subjects, a delayed loss of resistance mutations that was temporally associated with increased replicative capacity and increased HIV RNA levels was observed in a few subjects. Similar observations were made with regard to the loss of the lamivudine-associated M184V mutation in patients interrupting RTI treatment.

These data may have clinical implications for the management of treatment-experienced patients. With regard to NRTIs, our data, as well as recent data from other groups [15–17], indicate that these drugs retain significant antiviral activity against the drug-resistant variant and that this activity persists even after prolonged replication of HIV in the presence of drug pressure. These drugs should, therefore, remain critical components of any salvage regimen. The use of the NRTI lamivudine appears to have an additional beneficial effect on viral fitness, as evidenced by the temporal association between the loss of the lamivudine-associated M184V mutation and an increase in both replicative capacity and HIV RNA levels. With regard to the PI class, our data suggest that resistance to these drugs in heavily pretreated patients may be complete and that these drugs exert their residual benefit by selectively maintaining drug-resistance mutations associated with reduced replicative capacity. Since these mutations persist for months in the absence of drug pressure, studies aimed at using either low-dose or intermittent PIs, with the goal of preventing wild-type reversion, may be considered. Such strategies may reduce drug toxicity and drug costs while preventing ongoing viral evolution and the emergence of additional mutations. Finally, with regard to the management of individuals who are maintained on a partially effective regimen, our data suggest that phenotypic and, perhaps, genotypic resistance assays may be able to define which drugs should be maintained and which can be discontinued because of lack of activity. Alternatively, clinical assays that quantify both residual antiviral activity and fitness costs in the presence of drug may enhance clinical management [18].

Why did PI resistance persist in the absence of PI exposure for many subjects? Under the assumption that the wild-type protease is more efficient than the resistant protease (and, therefore, more fit in the absence of PI therapy), strong selective pressures should have resulted in either gradual loss of protease mutations or the escape of an archived NRTI-resistant, protease wild-type variant. However, for most individuals, this was not observed during the first 6–12 months of observation. Several mechanisms may account for the failure of PI resistance to wane. First, increasing PI resistance may be associated with the accumulation of compensatory mutations within pol and/or gag; these mutations act to increase the relative fitness of the PI-resistant virus. Back mutations within protease may require remodeling within these regions, thus necessitating an initial decrease in relative fitness before an increase (i.e., viral evolution may need to go through a fitness valley before restoring wild-type levels of protease efficiently) [19–21]. Second, archived NRTI-resistant, PI-susceptible variants likely contain fewer NRTI-associated mutations than do the more recent variants. Thus, the archived virus may be more susceptible to NRTIs and therefore less likely to emerge in presence of these drugs [22].

Several limitations should be considered with regard to our conclusions. First, since this study population was not randomized, it is difficult to directly compare the 2 treatment arms. This is particularly true given the small number of subjects who interrupted RTI treatment and the relatively lower levels of resistance in that group. It is notable, however, that several recent studies of patients infected with drug-resistant HIV-1 who interrupted zidovudine, lamivudine, or stavudine treatment demonstrated results similar to those observed in our 6 subjects [15–17]. Second, our data are not generalizable to all treatment-experienced patients. We enrolled a cohort of extensively pretreated patients. Patients with more-limited treatment experience would likely have very different outcomes. For example, early failure of a PI-based regimen is often associated with the presence of a virus population that exhibits only moderate reductions in drug susceptibility. Significant rebounds in HIV RNA levels would be expected if PI treatment were interrupted in such patients. Also, most of the subjects enrolled in the present study had evidence of durable partial viral suppression at study entry. The level of residual anti-HIV activity would be expected to be lower in patients with more-complete virologic failure. Finally, it should also be noted that the level of resistance to PIs was very high in this cohort, whereas the level of resistance to the nucleoside analogues was more variable and often low. Determining the degree to which nucleoside analogues maintain residual activity in patients with highly resistant variants will require additional studies.

In summary, our study suggests that the therapeutic benefit of ART in the presence of drug-resistant HIV is due to both residual activity of drugs against the resistant variant and the selective maintenance of a virus with reduced replicative capacity. Moreover, our data suggest that the roles of these mechanisms differ by therapeutic drug class. Finally, our data support the need for further randomized studies regarding how to maintain therapeutic benefit of therapy in patients with limited options for complete viral suppression.

References


