Determining the Relative Efficacy of Highly Active Antiretroviral Therapy

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Despite the clinical benefits of combination antiviral therapy, whether maximal antiviral potency has been achieved with current drug combinations remains unclear. We studied the first phase of decay of human immunodeficiency virus type 1 (HIV-1) RNA in plasma, one early indicator of antiviral activity, after the administration of a novel combination of lopinavir/ritonavir, efavirenz, tenofovir disoproxil fumarate, and lamivudine and compared it with that observed in matched cohorts treated with alternative combination regimens. On the basis of these comparisons, we conclude that the relative potency of highly active antiretroviral therapy may be augmented by as much as 25%–30%. However, it is important to emphasize that further study is warranted to explore whether these early measurements of relative efficacy provide long-term virologic and clinical benefits. Nevertheless, we believe that optimal treatment regimens for HIV-1 have yet to be identified and that continued research to achieve this goal is warranted.

Despite the substantial benefits of highly active antiretroviral therapy (HAART) in reducing human immunodeficiency virus type 1 (HIV-1)–related morbidity and mortality [1, 2], current regimens do not completely suppress viral replication in most treated individuals [3]. This inability, as well as the persistence of a pool of latently infected CD4+ T cells harboring infectious virus, are 2 clearly identified immediate obstacles to the development of alternatives to life-long treatment of HIV-1–infected individuals with HAART [4]. The ability of current antiviral therapy to suppress HIV-1 replication could be improved, in theory, by an increase in drug efficacy (defined as the ability to suppress in vivo production of infectious virions).

After HAART is initiated, a rapid and exponential decrease in the plasma virus load occurs, referred to as the “first phase” of viral decay [5]. This first phase represents the clearance of free plasma HIV-1 virions and the death of productively HIV-1–infected CD4+ T cells. Because the clearance of plasma virions is extremely rapid and thus negligible (compared with the rate of clearance of cells producing these particles), the rate of change or slope of the first phase of plasma HIV-1 decay is the product of 2 parameters: δ, the decay constant of productively infected CD4+ T cells, and ε, efficacy, the ability of the intervention to suppress viral replication. If we assume that the rate of decay of virus-producing CD4+ T cells, δ, is constant in comparable
patient cohorts, then the slope of the first phase is directly proportional to the efficacy of the intervention applied [6]. Therefore, the more negative the slope of the first phase of HIV-1 RNA decay, the greater the efficacy of the antiretroviral therapy being used.

To explore whether the efficacy of HAART can be augmented, we studied early virologic events indicative of antiviral activity after the administration of a novel combination of lopinavir/ritonavir (533/133 mg twice daily), efavirenz (600 mg daily), tenofovir disoproxil fumarate (300 mg daily), and lamivudine (150 mg twice daily) (regimen A). The average initial rate of decrease in plasma HIV-1 RNA, the first-phase slope, was compared to the decreases observed in matched individuals treated with 2 different HAART regimens. The first comparator, the group receiving regimen B, included subjects treated during acute and early HIV-1 infection with lamivudine (150 mg twice daily), abacavir (300 mg twice daily) in combination with indinavir (800 mg 3 times daily), and amprenavir (900 mg twice daily). The second comparator, the group receiving regimen C, included subjects treated during chronic infection with zidovudine (300 mg twice daily) and lamivudine (150 mg twice daily) in combination with ritonavir (400–600 mg twice daily) and saquinavir (400–600 mg twice daily).

SUBJECTS AND METHODS

Forty-four individuals, 39 antiretroviral naive and 5 treatment experienced, were enrolled and began receiving treatment with regimen A between July 2000 and August 2001. Subjects were divided into 2 groups, those with acute and early infection (n = 33) and those with chronic infection (n = 11). By definition, “acute and early infection” included subjects who tested positive for HIV-1 RNA; had no antibody response or an evolving response to HIV-1 infection or a documented negative serologic test result for HIV-1 antibodies within 120 days of screening; and had a clinical history compatible with new infection. Identical entry criteria were used to identify 29 subjects who were enrolled and began receiving treatment with regimen B between March 1997 and June 1998. A total of 9 individuals were excluded from the analysis as a result of inadequate data collection or known treatment adherence issues.

Of the 33 newly infected individuals who received treatment with regimen A, 6 subjects were excluded from the analysis as a result of nonadherence or inadequate data collection. Of the remaining 27, we selected 20 subjects for inclusion in the analysis who had baseline CD4+ T cell counts and pretreatment HIV-1 RNA levels that most closely matched those of the 20 patients treated during acute and early infection with regimen B. Eleven patients who received treatment with regimen C during chronic infection and who had matching baseline CD4+ T cell counts and HIV-1 RNA levels served as controls for the 11 chronically infected subjects who were treated with regimen A. In all of these studies, adherence was assessed mainly by history and drug reconciliation. Failure of patients to report taking all prescribed doses of all medications at the appropriate times during the initial 7-day period of treatment was considered to indicate nonadherence. Baseline characteristics were analyzed using the Mann-Whitney U test. P ≤ .05 was considered to be statistically significant.

Plasma samples from all study subjects receiving regimens A and B were subjected to reverse-transcription polymerase chain reaction and sequencing of pol, using Trugene (Visible Genetics) in accordance with the manufacturer’s instructions. In addition, viral phenotypes were identified using a commercial recombinant virus assay (Virologic).

The mean baseline (day 0) to day 7 viral decay slopes were determined using methods published elsewhere [5] and analyzed with the Mann-Whitney U test. The relative efficacies of the treatment regimens were calculated by dividing the mean day-0–7 HIV-1 decay slope of each of the matched treatment groups (regimens B and C) by the mean day-0–7 decay slope for patients treated with regimen A.

To over-accurately characterize early virologic events that occurred after initiation of treatment, 9 chronically HIV-1–infected subjects were enrolled in a viral dynamics substudy in which plasma HIV-1 RNA was determined every 6 h for the first 72 h and then daily until day 10. For each participant in the viral dynamics substudy, the first-phase plasma HIV-1 RNA decay slope was calculated by nonlinear least-squares fitting of the 2-compartment (long-lived infected cell) or 3-compartment (latently and long-lived infected cell) model of HIV-1 decay to the data, as described elsewhere [7]. This procedure is more accurate than simple linear regression for analyzing the slope of the first phase of decay, because it does not rely on an arbitrary assignment of the end of the first phase.

RESULTS

The baseline characteristics of the subjects treated during acute and early and chronic infection were comparable (table 1). The vast majority of participants were men who have sex with men (98%). Phenotyping of viruses from all patients treated with regimens A and B indicated that the viruses were drug susceptible, and genotype analyses were consistent with wild-type HIV-1. The chronically infected individuals treated with the ritonavir and saquinavir–based regimen C were drug naive and began receiving therapy in June 1996.

Mean baseline plasma HIV-1 RNA levels (±SE) in the acute and early cohorts treated with regimens A and B were 5.6 ± 0.2 log10 copies/mL (range, 4.2–7.2 log10 copies/mL) and 5.4 ± 0.2 log10 copies/mL (range, 3.8–6.8 log10 copies/mL), respectively (table 1). There were no statistically significant dif-

Determining the Efficacy of HAART • JID 2003:187 (15 March) • 897
Chronic infection

124–665 cells/mm$^3$) (Table 1).

3.9–5.9 log$_{10}$ copies/mL), respectively (Table 1). CD4

HIV-1 RNA levels (A and C, baseline characteristics included mean pretreatment regimen.

served in previous studies of ritonavir monotherapy [5, 8].

The first-phase, day-0–7 slopes of HIV-1 RNA decay were $-0.52 \pm 0.03$ per day (d$^{-1}$) (range, $-0.23$ to $-0.82$ d$^{-1}$) for the acute and early regimen A group and $-0.40 \pm 0.4$ d$^{-1}$ (range, $-0.03$ to $-0.65$ d$^{-1}$) for the regimen B group. Slopes for patients with acute and early infection treated with regimen A were significantly more negative than those calculated in the comparator study (regimen B) ($P = .02$; figure 1A). Using the slope obtained for the novel 4-drug regimen (regimen A) as a reference, we calculated that the control regimen (regimen B) had a relative efficacy of 0.75. In other words, the control regimen was 75% as effective in interrupting the production of infectious virions as was the novel drug combination regimen.

In the 22 chronically infected patients treated with regimens A and C, baseline characteristics included mean pretreatment HIV-1 RNA levels (±SE) of 4.7 ± 0.2 log$_{10}$ copies/mL (range, 4.0–5.9 log$_{10}$ copies/mL) and 4.9 ± 0.2 log$_{10}$ copies/mL (range, 3.9–5.9 log$_{10}$ copies/mL), respectively ($P = .38$; Table 1). CD4$^+$ cell counts were similarly comparable: 364 ± 43 cells/mm$^3$ (range, 150–689 cells/mm$^3$) versus 335 ± 44 cells/mm$^3$ (range, 124–665 cells/mm$^3$) ($P = .49$; Table 1).

The mean day-0–7 decay slope (±SE) observed for chronically infected subjects treated with regimen A was, again, significantly more negative than that observed for the control treatment combination, regimen C: $-0.54 \pm 0.07$ d$^{-1}$ (range, $-0.23$ to $-1.046$) versus $-0.37 \pm 0.02$ d$^{-1}$ (range, $-0.27$ to $-0.53$) ($P < .05$) (figure 1B). Using the rate of change in HIV-1 RNA levels obtained with regimen A as a reference, we calculated that the relative efficacy of regimen C was 0.68, or 68%.

Interestingly, despite obvious differences in baseline characteristics, including a statistically significant different in baseline HIV-1 RNA levels, there appears to be no substantial difference between the mean slope observed for subjects treated with regimen A during acute and early infection ($-0.52$ d$^{-1}$) and those treated with regimen A during chronic infection ($-0.54$ d$^{-1}$).

We calculated the mean first-phase slope of HIV-1 RNA decay using methods published elsewhere [8] in the 9 intensively sampled substudy participants. By more frequent sampling, which allowed determination of the delay in the onset of HIV-1 RNA decay, we determined the slope to be $-1.03$ d$^{-1}$, substantially more acute than the mean plasma virus load decay slope calculated from the day-0–7 decreases. Furthermore, the mean duration of the first phase of viral decay among the substudy participants was 4.1 days (range, 2.5–7.0 days), which is considerably shorter than the range of 7–10 days observed in previous studies of ritonavir monotherapy [5, 8].

**DISCUSSION**

We embarked on this trial to test whether HAART regimens containing combinations of nucleoside reverse-transcriptase inhibitors and protease inhibitors had indeed reached maximal potency. We took advantage of our understanding of the relationship between changes in HIV-1 RNA levels that occur shortly after initiation of therapy and the degree of suppression of viral replication in vivo to assess the relative efficacy of a novel 4-drug regimen incorporating compounds of all 3 classes of antiretroviral agents available. For comparators, we chose 2 combination regimens incorporating nucleoside reverse-transcriptase inhibitors and protease inhibitors that provide identically matched cohorts for baseline characteristics. This is critical, because it has been suggested that the rate of change in HIV-1 RNA levels may be different in patients at different stages of infection [9]. Here we have demonstrated, by analyzing decreases in plasma HIV-1 RNA levels from day 0 to day 7, that the relative efficacy of antiretroviral regimens may be augmented substantially, by 25%–30%, although we must empha-

<table>
<thead>
<tr>
<th>Variable</th>
<th>Acute and early infection</th>
<th>Chronic infection</th>
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<tbody>
<tr>
<td></td>
<td>Regimen A (n = 20)</td>
<td>Regimen B (n = 20)</td>
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<tr>
<td>Plasma HIV RNA load, mean log$_{10}$ copies/mL ± SE (range)</td>
<td>5.6 ± 0.2 (4.2–7.2)</td>
<td>5.4 ± 0.2 (3.8–6.8)</td>
</tr>
<tr>
<td>CD4$^+$ T cell count, mean cells/mm$^3$ ± SE (range)</td>
<td>444 ± 33 (259–720)</td>
<td>420 ± 26 (119–572)</td>
</tr>
<tr>
<td>HIV-1 RNA decay, mean slope change per day ± SE</td>
<td>$-0.52 \pm 0.03$</td>
<td>$-0.40 \pm 0.04$</td>
</tr>
<tr>
<td>Relative efficacy</td>
<td>1.0</td>
<td>0.75</td>
</tr>
</tbody>
</table>

**NOTE.** Regimen A included lopinavir/ritonavir, efavirenz, tenofovir disoproxil fumarate, and lamivudine; regimen B included abacavir, lamivudine, indinavir, and amprenavir; regimen C included zidovudine, lamivudine, ritonavir, and saquinavir.

### Table 1. Baseline laboratory values and treatment results for subjects who received 1 of 3 regimens of highly active antiretroviral therapy at the acute and early or chronic stage of human immunodeficiency virus type 1 (HIV-1) infection.
Figure 1.  

A, Change in plasma human immunodeficiency virus type 1 (HIV-1) RNA levels from baseline (day 0) to day 7 in individuals treated during acute and early HIV-1 infection with regimen A (lopinavir/ritonavir, efavirenz, tenofovir disoproxil fumarate, and lamivudine; left panel) or regimen B (abacavir, lamivudine, indinavir, and amprenavir; right panel). 

B, Change in plasma HIV-1 RNA levels from baseline (day 0) to day 7 in individuals with chronic HIV-1 infection treated with regimen A (left panel) or regimen C (zidovudine, lamivudine, ritonavir, and saquinavir; right panel). Mean change in HIV-1 RNA levels is shown (dotted black lines).
issues have motivated clinical investigators to seek alternatives, such as treatment interruptions and delayed initiation of treatment. However, attempts to discontinue therapy in the majority of HIV-1–infected individuals treated with prolonged HAART have been disappointing [15, 16]. Maximally potent, optimized treatment regimens are critical requirements for development of alternatives that allow limited exposure to antiretroviral agents. Furthermore, we believe that, as new antiviral agents directed against existing and new targets are developed and the number of potential drug combinations increases, relative efficacy determinations may be useful in selecting specific combinations for larger comparative clinical trials.

Acknowledgments

We acknowledge the clinical assistance of Andrew Talal, Rhonda Kost, Bharat Ramratnam, Beth Captan, and The Rockefeller University Hospital clinical staff. We thank Bruce Richards for logistical and operational support and Wendy Chen for her help in preparing the table and figure. Finally, we would like to thank our many study participants, without whom these analyses would not have been possible.

References