A Randomized Study of the Utility of Human Immunodeficiency Virus RNA Measurement for the Management of Antiretroviral Therapy

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To compare frequent measurement with infrequent measurement of human immunodeficiency virus (HIV) RNA levels in the management of antiretroviral therapy, we conducted a clinical strategy study of 206 HIV-infected patients who had <500 CD4 cells/mm3. Patients were randomized (1.5:1) to undergo frequent monitoring (at baseline and every 2 months) or infrequent monitoring (at baseline and twice yearly), with CD4 cell counts determined every 2 months. Patients received unrestricted antiretroviral therapy. In the primary analysis (at month 6), the frequent group had a mean HIV RNA reduction (± standard deviation) of 0.93 ± 0.79 log10 copies/mL, versus 0.48 ± 0.83 log10 copies/mL for the infrequent group (P = .0002). A trend toward improved survival was seen in the frequent group. Given this improved virological response, more frequent HIV RNA measurement than is recommended in published guidelines (every 3–4 months) may be appropriate.

Quantitation of plasma HIV RNA levels (virus load) in HIV-infected patients has greatly improved our understanding of the dynamics of HIV infection, has improved assessment of patient prognosis and management of antiretroviral therapy, and has facilitated development of new therapeutics against HIV [1–10]. The prognostic value of HIV RNA levels was initially demonstrated with use of a single baseline value for HIV RNA level that predicted the time to progression of AIDS or death [11]. In an expanded analysis, the HIV RNA level was found to be independent of and complementary to the CD4 cell count as a predictor of disease progression [12].

Several studies have demonstrated that the reduction in virus load induced by antiretroviral treatment correlates with improved clinical outcome [13–19]. In a large study of combinations of nucleosides, the value of both pretherapy and therapy-induced changes in HIV RNA level was demonstrated [13]. Overall, pa-
tients with a 1 log₁₀ reduction in HIV RNA level from baseline were 65% less likely to develop AIDS or to die during the study, which is a significant effect, even after controlling for baseline HIV RNA level. Analysis of a randomized trial of zidovudine, lamivudine, and indinavir demonstrated that patients whose HIV RNA levels were suppressed to <500 copies/mL were much less likely to have an AIDS-defining event during follow-up than were those with HIV RNA levels >500 copies/mL [20].

Although baseline and treatment-induced changes in HIV RNA levels correlate with outcomes in randomized clinical trials, no study has addressed the impact of frequent monitoring of HIV RNA levels during individualized therapy. In the absence of controlled data to support sequential monitoring of HIV RNA levels, several expert panels have recommended the routine use of this measure [8, 21, 22]. Despite the availability of practice guidelines based on these expert opinions, medical decisions should be evidence-based. Given these considerations, the California Collaborative Treatment Group (CCTG) initiated a randomized clinical strategy study designed to determine the utility of monitoring individual patients’ HIV RNA levels. The purpose of this study was to compare frequent HIV RNA monitoring (every 2 months) to semiannual virus load testing.

PATIENTS AND METHODS

Our study (CCTG 570) was a multicenter clinical strategy study of frequent versus infrequent HIV RNA monitoring of antiretroviral therapy. After stratification by CD4 cell count (≤50 or >50 cells/mm³) and duration of prior antiretroviral therapy (≤12 or >12 months), patients infected with HIV were randomized into 1 of 2 groups, the “frequent group” and the “infrequent group.” For the frequent group, both plasma HIV RNA levels and CD4 cell counts were measured and reported in real time at baseline and every 2 months thereafter, with additional determinations of HIV RNA levels at times when antiretroviral treatment was changed. For the infrequent group, CD4 cell counts and HIV RNA levels were determined as in the other group, but HIV RNA levels were recorded only at baseline and at most twice per year, at times that were determined by each patient’s health care provider.

The original protocol design called for HIV RNA levels to be reported only at baseline for the infrequent group, but it was amended 6 months after the start of the study to allow 2 additional measurements. The central randomization was weighted 1:5:1 in favor of the frequent group. A central laboratory determined HIV RNA levels, which were provided to the treating physicians, plus cumulative numeric and graphic reports of HIV RNA and CD4 values.

Each patient’s physician, after initial training by the investigators, selected antiretroviral regimens without protocol-imposed restrictions or fixed criteria that mandated treatment switches. Treatment with investigational antiretrovirals were allowed, if the investigational protocol neither restricted the selection of therapy nor determined HIV RNA levels. All investigators received standardized guidelines for using CD4 cell counts and HIV RNA levels to monitor antiretroviral therapy, which were updated as new information became available.

Investigators from the primary care practices of 6 university-affiliated clinical sites enrolled patients who had CD4 cell counts <500/mL and had HIV-1 RNA levels of ≥5000 copies/mL within 30 days of entry. Eligible patients were ≥18 years of age, had been receiving treatment with a stable antiretroviral regimen for ≥4 weeks, had a Karnofsky score ≥80, and had an estimated life expectancy of >12 months. Patients had at least 2 available antiretroviral medications that they were not currently receiving and could potentially tolerate. Patients were excluded for any of the following reasons: (1) they were unable or unwilling to take a series of antiretroviral regimens; (2) they had symptoms suggestive of an undiagnosed opportunistic infection or cancer; (3) they required systemic chemotherapy; (4) they had active drug or alcohol addiction that would compromise active follow-up or adherence to a treatment regimen; (5) they were pregnant or breast-feeding; (6) they were undergoing long-term therapy that would limit antiretroviral treatment; (7) they were receiving or had received treatment with immune modulators, therapeutic vaccines, gene therapy, antisense compounds, or ribozymes within the previous 90 days; or (8) they were having HIV-1 RNA levels measured outside of the study.

Patients were seen by their primary providers at least every 2 months or more frequently, if needed. The antiretroviral regimens used were carefully recorded. AIDS-defining events [23] and hospital days were recorded.

Laboratory tests. For all patients, CD4 cell counts and plasma HIV RNA levels were determined in real time at a screening visit and a day 0 visit (which were 30 days apart), every 2 months, and as requested by their treating physician at times of treatment changes. Plasma was processed and frozen at −70°C within 6 h of being obtained, and HIV RNA levels were determined with use of the Roche Amplicor kit (Roche Molecular Systems; limit of detection, 400 copies/mL), according to the manufacturer’s directions.

Statistical analysis. The primary end point was the area about the change from baseline (ACFB) of log₁₀ HIV RNA levels, which was calculated with use of the trapezoidal rule (see Appendix). Since antiretroviral therapy could be changed at any time, the area-based measure was considered more informative than a simple change from baseline. To avoid excess extrapolation of ACFB, the a priori analysis plan called for inclusion of patients in the primary analysis with at least 4 months of follow-up. HIV RNA and CD4 cell levels that were determined after month 8 were excluded from this analysis. All area-based measures were normalized to 6 months for presen-
Table 1. Baseline characteristics for a population of patients infected with HIV and receiving antiretroviral therapy, as related to infrequent versus frequent monitoring of HIV RNA levels.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Infrequent group (n = 85)</th>
<th>Frequent group (n = 121)</th>
<th>Overall (n = 206)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, no. (%) of patients</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>13 (14)</td>
<td>10 (8)</td>
<td>23 (10)</td>
</tr>
<tr>
<td>Male</td>
<td>72 (86)</td>
<td>111 (92)</td>
<td>183 (90)</td>
</tr>
<tr>
<td>Age, median years (range)</td>
<td>37 (21–64)</td>
<td>38 (23–63)</td>
<td>37 (21–64)</td>
</tr>
<tr>
<td>Stratum, a no. (%) of patients</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;50 cells/mm³, &lt;12 months</td>
<td>9 (11)</td>
<td>13 (11)</td>
<td>22 (11)</td>
</tr>
<tr>
<td>≥50 cells/mm³, ≥12 months</td>
<td>12 (14)</td>
<td>14 (12)</td>
<td>26 (13)</td>
</tr>
<tr>
<td>≥50 cells/mm³, &lt;12 months</td>
<td>23 (27)</td>
<td>34 (28)</td>
<td>57 (28)</td>
</tr>
<tr>
<td>Race or ethnicity, no. (%) of patients</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>38 (45)</td>
<td>55 (46)</td>
<td>93 (45)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>33 (39)</td>
<td>45 (37)</td>
<td>78 (38)</td>
</tr>
<tr>
<td>Black</td>
<td>10 (12)</td>
<td>14 (12)</td>
<td>24 (12)</td>
</tr>
<tr>
<td>Asian American</td>
<td>1 (1)</td>
<td>2 (2)</td>
<td>3 (2)</td>
</tr>
<tr>
<td>Other</td>
<td>3 (4)</td>
<td>5 (4)</td>
<td>8 (4)</td>
</tr>
<tr>
<td>CD4 count, cells/mm³, mean (range)</td>
<td>136 (3–516)</td>
<td>144 (4–494)</td>
<td>140 (3–516)</td>
</tr>
<tr>
<td>HIV RNA (log₁₀ copies/mL), mean (SD)</td>
<td>4.7 (0.6)</td>
<td>4.7 (0.6)</td>
<td>4.7 (0.6)</td>
</tr>
<tr>
<td>Total duration of prior therapy, median months</td>
<td>18</td>
<td>16</td>
<td>17</td>
</tr>
<tr>
<td>Prior treatment, % of patients</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment naive</td>
<td>9</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Protease inhibitor naive</td>
<td>71</td>
<td>61</td>
<td>65</td>
</tr>
<tr>
<td>Lamivudine naive</td>
<td>22</td>
<td>23</td>
<td>23</td>
</tr>
</tbody>
</table>

* According to CD4 count and duration of prior antiretroviral therapy.

Results

Study population. Two-hundred six patients were enrolled in the study from May 1996 through July 1997. Baseline characteristics of these patients are shown in Table 1. As planned, 59% (121 of 206) were randomized to the frequent group. Age, sex, race or ethnicity, randomization stratum (baseline CD4 cell count and length of prior therapy), and assignment within the 6 clinics were balanced between the 2 monitoring strategies. The mean baseline CD4 cell count and HIV RNA level were...
similar in the infrequent group (136 cells/mm$^3$ and 4.7 log$_{10}$ copies/mL, respectively) and frequent group (144 cells/mm$^3$ and 4.7 log$_{10}$ copies/mL, respectively). Antiretroviral therapy histories were also similar in the 2 strategy groups (table 1). Overall, 10% of patients had received no prior therapy, 23% were naive to lamivudine, and 65% were naive to protease inhibitors. Most patients initiated a change in therapy at or shortly after baseline.

Patients were followed in the randomized strategy groups until 30 September 1997, at which time the patients were all switched to frequent monitoring of HIV RNA levels, and all prior HIV RNA values were unmasked for the infrequent group, because of the results of a preplanned interim analysis. All patients were followed for survival and new clinical end points until 15 July 1998. Forty-six patients withdrew during the randomized portion of the study: 26 in the infrequent group and 20 in the frequent group. The mean time until premature withdrawal was shorter for the infrequent group than the frequent group (357 vs. 412 days, respectively; $P = .02$). Eleven percent of patients in the infrequent group (9 of 85) withdrew in the first 60 days after randomization, compared with 3% (4 of 121) in the frequent group. The primary reasons for early termination were as follows: failure to follow up or change of residence (27 patients), desire to stop therapy (11), perceived lack of benefit (4), desire to increase monitoring of HIV RNA levels (3), and toxicity (1). The reasons for termination were similar for both groups, except that more patients in the infrequent group stopped therapy (8, vs. 3 in the frequent group).

The planned primary analysis called for inclusion of all patients who had at least 4 months of follow-up ($n = 159$). There was no difference in baseline characteristics between the 26 patients in the infrequent group and the 20 patients in the frequent group (total, 47 patients) who were excluded from the primary analysis. In addition, the baseline characteristics of these 47 patients were no different than those of the 159 patients included in the analysis. All other analyses were intent-to-treat and included all available data.

**Area-based changes in HIV RNA levels and CD4 cell counts.** For patients in the primary analysis, regimen changes in both strategy groups resulted in reductions in HIV RNA levels from baseline. The mean ($\pm$SD) ACFB in HIV RNA levels for the frequent group was -0.93 ($\pm$0.79) log$_{10}$ copies/mL, compared with -0.48 ($\pm$0.83) log$_{10}$ copies/mL for the infrequent group ($P = .0002$; weighted $t$ test). Analyses without variance weighting yielded almost identical results (data not shown). Thus, more frequent HIV RNA monitoring resulted in a reduction in virus load nearly twice that seen with less frequent virus-load monitoring. Analyses of ACFB of HIV RNA levels were similar for patients completing 4, 6, 8, 10, and 12 months of follow-up (intent-to-treat) and showed statistically significant differences between the 2 monitoring strategies for all time points (data not shown). Patients in both the frequent group and infrequent group who were enrolled in the first 6 months of the study had a reduction in HIV RNA levels that was 0.2 log$_{10}$ copies less than did patients who were enrolled in the second 6 months. Thus, the difference in HIV RNA suppression ($\sim 0.5$ log$_{10}$) between groups was consistent across the enrollment period.

For patients in the frequent monitoring group, mean CD4 cell counts ($\pm$SD) increased by 49 ($\pm$54) cells/mm$^3$ (on the basis of ACFB calculations). Patients in the infrequent monitoring group had a slightly lower increase: 40 ($\pm$56) cells/mm$^3$, a value that did not reach statistical significance ($P = .26$), possibly because of the large standard deviations of this measure. Intent-to-treat analyses of the mean differences in the ACFB of CD4 counts for patients who completed 4, 6, 8, 10, and 12 months of follow-up were not significantly different. However, among patients who had longer follow-up, the differences in CD4 counts between groups became significant at month 12 of the study ($78 \pm 72$ for the frequent group vs. $38 \pm 51$ for the infrequent group; $P = .04$).

**Longitudinal changes in HIV RNA level and CD4 cell count.** The mean change from baseline in HIV RNA level in the intent-to-treat analysis of the 2 strategy groups is shown in the top panel of figure 1. An early and persistent difference in virus load suppression between the groups was evident after month 2, and this was statistically significant from month 2 through month 8 of the study.

Changes from baseline in CD4 cell count are shown in the bottom panel of figure 1. The 2 groups had similar progressive increases in CD4 cell counts, reaching 75 cells/mm$^3$ in the infrequent group and 91 cells/mm$^3$ in the frequent group by month 8. Although differences were not statistically significant, by months 10 and 12, CD4 cell count changes began to separate, and the difference between groups approached significance. For example, at month 10 the frequent group had an increase of 123 cells/mm$^3$, whereas the infrequent group had an increase of only 73 cells/mm$^3$ ($P = .09$).

Figure 2 shows the proportion of patients with HIV RNA levels below the limit of detection (<400 copies/mL), according to study month, for the strategy groups. The overall proportion of patients who achieved undetectable virus loads was low (40%), even though most of the population had not received protease inhibitors prior to the start of the study. This probably reflected the long duration of prior nucleoside reverse transcriptase therapy (especially prior treatment with lamivudine). By month 4, 40% of patients in the frequent group had undetectable HIV RNA, compared with 17% in the infrequent group ($P = .002$). A statistically significant difference between the groups was also seen at month 8; in intervening months, inferiority of the frequent monitoring strategy was seen. Patients in the frequent group had undetectable virus loads a mean
Changes in antiretroviral regimens. The median number of changes to antiretroviral regimens per year was similar for the 2 groups (3.8 for the infrequent group vs. 3.3 for the frequent group; \( P = .3 \)), but the median time to initiation of new regimens was shorter for the frequent group than for the infrequent group (table 2). Patients in the infrequent group initiated the first change in therapy a median of 12 days after baseline, compared with 0 days for patients in the frequent group (\( P = .4 \)). By the third change in therapy, the times were significantly different: 129 days for the frequent group and 168 days for the infrequent group (\( P = .05 \)). Thus, the initial differences (at month 2) in HIV RNA levels between groups could have been due to an earlier first change in therapy in the frequent group, whereas the persistent difference in viral suppression may be due to earlier second and third regimen changes, which were initiated because of the results of more-frequent HIV RNA monitoring.

We examined the use of protease inhibitors in the study as a surrogate measure of the intensity of antiretroviral therapy. The median time to first protease inhibitor use was longer in the infrequent group (2 days, vs. 0 days in the frequent group; \( P = .006 \)), and the proportion of time spent on protease inhibitors was less in the infrequent group (0.88, vs. 0.98 in the frequent group; \( P = .03 \)). The proportion of time receiving protease inhibitors, but not the time to use of the first protease inhibitor, was a significant predictor of viral suppression. To assess the effect of later introduction of and less time receiving protease inhibitors, we modeled the ACFB in HIV RNA levels using both treatment variables and strategy group as a variable: table 3 shows univariate and multivariate models. Although timing and use of protease inhibitors variably affected viral suppression, strategy group was always a significant and independent predictor of virus load reduction, after the effects of protease inhibitor use were accounted for. Thus, the differences in viral suppression between groups were not due to less vigorous pursuit of effective regimens.

AIDS-defining clinical end points and survival. After a median of 10.8 months of follow-up and on the basis of the results of the interim analysis, all HIV RNA results were unblinded for the infrequent group, and patients were followed for a median of 25.3 months for occurrence of AIDS-defining clinical end points or death. Thirty-two new or recurrent AIDS-defining end points or deaths occurred. The Kaplan-Meier estimate of the mean time to a new AIDS event was not significantly longer for the frequent group (704 days, vs. 673 days for the frequent group; \( P = .3 \)), but fewer deaths occurred in the frequent group (5 deaths, vs. 8 deaths in the infrequent group; figure 3). The Kaplan-Meier estimated time to death showed a trend in favor of frequent monitoring (771 days, vs. 741 days for the infrequent group; \( P = .1 \)). However, this study did not have enough power to detect differences in clinical end points.

Adherence. An additional objective of the study was to evaluate whether frequent feedback concerning HIV RNA values would improve patient adherence and thereby contribute
Table 3. Univariate and multivariate models of HIV RNA suppression, according to strategy group and the timing and duration of protease inhibitor (PI) use.

<table>
<thead>
<tr>
<th>Variable (coefficient)</th>
<th>Univariate modela</th>
<th>P</th>
<th>Multivariate modelb</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACFB in HIV RNA levels</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Strategy group</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frequent monitoring</td>
<td>−0.92</td>
<td>.0002</td>
<td>−0.90</td>
<td>.001</td>
</tr>
<tr>
<td>Infrequent monitoring</td>
<td>−0.46</td>
<td>—</td>
<td>−0.48</td>
<td>—</td>
</tr>
<tr>
<td>Time to first PI use (b)</td>
<td>−0.006</td>
<td>.2</td>
<td>0.006</td>
<td>.4</td>
</tr>
<tr>
<td>Proportion of time receiving PIs (b)</td>
<td>2.9</td>
<td>.03</td>
<td>3.2</td>
<td>.1</td>
</tr>
<tr>
<td>Percentage of study period with undetectable levels of HIV RNAc</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Strategy group</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frequent monitoring</td>
<td>30.3</td>
<td>.002</td>
<td>30.0</td>
<td>.006</td>
</tr>
<tr>
<td>Infrequent monitoring</td>
<td>17.1</td>
<td>—</td>
<td>17.6</td>
<td>—</td>
</tr>
<tr>
<td>Time to first PI use (b)</td>
<td>−0.04</td>
<td>.2</td>
<td>0.08</td>
<td>.05</td>
</tr>
<tr>
<td>Proportion of time receiving PIs (b)</td>
<td>24</td>
<td>.001</td>
<td>36</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

a Univariate mean (group) or regression coefficient $\beta$ for the effect of variable on area about the change from baseline (ACFB) in HIV RNA level, or proportion of time undetectable.

b Multivariate (adjusted) mean or regression coefficient for the effect of variable on the ACFB in HIV RNA or proportion of time undetectable.

c The limit of detection was <400 copies/mL.

To improved virological outcomes. Patients were classified into 4 groups according to percentage adherence to antiretroviral medication in the previous 4 weeks on the basis of responses to self-administered questionnaires distributed at baseline, month 2, and month 6 (the groups were as follows: <80% adherence, 80%–95%, 95%–99%, and 100%) [24]. The responses to the questionnaires were kept blinded to the patients’ primary providers, to improve the level of candor. At baseline, the distribution of patients with differing degrees of self-reported adherence was well balanced in the 2 strategy groups. During the study, adherence improved overall, but the frequent group did not have better adherence than the other group (data not shown). However, as previously reported, better adherence was associated with improved HIV RNA suppression [24]. Thus, the greater virological suppression seen in the frequent group was not due to greater reported adherence to antiretroviral medications.

DISCUSSION

Although the monitoring of HIV RNA levels during therapy has become the standard of care for HIV-infected patients, this is the first study to prospectively evaluate the use of this test in the management of unrestricted antiretroviral therapy. Frequent monitoring of HIV RNA levels (every 2 months) with use of a PCR-based assay resulted in better treatment management, as measured by statistically significant improvements in HIV virus load suppression, compared with infrequent monitoring (twice yearly). Differences between the groups with respect to CD4 cell counts and survival did not reach statistical significance but showed trends that favor more frequent monitoring. Although this study did not determine the optimal frequency for determining HIV RNA levels, it does provide direct evidence that measurement only at baseline and twice yearly is too infrequent. Whether monitoring of HIV RNA levels every 3 or 4 months, as is recommended in published consensus statements [8, 21, 22], would have produced results similar to those for the group who were monitored every 2 months cannot be answered by the evidence from this trial. The current guidelines also recommend virus load measurement 2–8 weeks after a change in therapy, which was not routinely done for the infrequent group. This study also demon-

Figure 3. Kaplan-Meier plot of time to death during the randomized and extended follow-up portions of the study.
strates that clinical strategy studies can evaluate new monitoring technologies that are designed to improve management of HIV infection.

The early difference in HIV RNA reduction between the groups was unexpected, since for both groups there was access to baseline HIV RNA values, and they might be expected to perform similarly in early follow-up. It is possible that some factor unrelated to therapeutic monitoring favored the frequent group over the infrequent group. For example, more effective treatment decisions based on conscious or unconscious prejudice in favor of the frequent group could have improved the virological outcomes for those patients. In fact, we noted that initial adjustments of therapy were earlier in the frequent group, despite the fact that both groups received feedback on the baseline plasma HIV RNA levels. Delays in changing treatment in the infrequent group may have contributed to the differences between the groups that emerged after 2 months. However, we believe that this early effect is unlikely to account for the persisting advantages of frequent monitoring, for several reasons. First, the physician-investigators were treating patients directly under their care for whom they were highly motivated to provide the best therapy. Second, they had time to “catch up” and, in fact, made similar numbers of treatment changes in both groups, which suggests that they were trying to do so. Finally, although earlier use of protease inhibitors in the frequent group could have led to early differences, both the time to protease inhibitor use and the duration of use did not nullify the advantage of frequent monitoring on viral suppression, as demonstrated by the multivariate models.

By design, this study was not blinded for either physicians or patient participants. Patients were intentionally given access to their CD4 and virological data in easily understood graphic form to maximize its impact on their behavior. We hypothesized that more frequent feedback on the virological consequences of nonadherence might motivate patients to improve adherence to their therapy, but we found that it did not. Similar levels of self-reported adherence were found in the 2 strategy groups, suggesting that patient behavior was not affected by this information. As we have reported [24], better adherence improved viral suppression but did not explain differences between the strategy groups.

The primary analysis of this trial used an area-based measure of viral suppression, the ACFB in HIV RNA levels. Area-based measures offer several advantages over measures based on changes after a specified interval. First, they account for all of the changes in virus load that occur during follow-up. For patients in whom consistent suppression of virus load is not maintained and who have several changes in antiretroviral regimen, the ACFB captures all of the dynamic variation in HIV RNA levels during the study. Second, area-based measures have been shown to be better predictors of clinical outcome. In a study by Kim et al., [25] the ACFB in HIV RNA levels was a stronger predictor of time to clinical progression than change from baseline at fixed weeks, after baseline variables were accounted for. Finally, the ACFB of HIV RNA levels was determined to be the most powerful statistical measure of virological outcome in a comparison with 3 other measures in an analysis of data from this trial [26]. The ACFB may be the preferred analytic tool for virological outcome in clinical trials in which treatment may be changed multiple times, such as trials designed to evaluate the benefit of HIV-resistance testing.

Better outcomes in the frequent group may have been due to earlier detection of loss of virological control and to more-rapid treatment adjustments that prevented the development of antiretroviral resistance. In fact, we found significant differences in the time to the third change of regimen and trends in favor of subsequent regimens in the frequent group. Results of several studies of protease inhibitor failure have shown that the virus load at the time of switching is a strong predictor of subsequent virological success [27, 28]. In addition, not all patients failing potent antiretroviral regimens exhibit resistance at the time of relapse [29, 30]. Therefore, frequent monitoring of HIV RNA levels, perhaps as often as every 2 months, may be necessary to detect loss of virological suppression and adjust therapy before subinhibitory regimens select for high-level, cross-resistant strains of HIV.

### THE CALIFORNIA COLLABORATIVE TREATMENT GROUP (CCTG) 570 TEAM

The team participants were as follows: Joseph Toerner, M.D.; Craig Ballard, Pharm.D.; Judy Schnack, F.N.P.; and Gary Pfeffer,
N.P. (University of California San Diego); Gary Uyekawa, P.A.-C.; and DeAnn Diamond (University of Southern California); Bobi Keenan, A.C.R.N.; Marcia Alcouloumre, M.D.; and Winnie Huang, M.D. (University of California Irvine); Stan Desinski, M.D., and Carol Kane, R.N. (Santa Clara Valley Medical Center); Connie Kapeluck, R.N.; Mario Guerrero, M.D.; and Sally Kruger, M.S. (Harbor-University of California Los Angeles Medical Center); and Edward Seefried, R.N.; Andrew Rigby; and Nancy Fisk (University of California San Diego Treatment Center Data and Biostatistical Unit).

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APPENDIX

The area about the change from baseline (ACFB) is derived with the following formula:

$$ACFB = (t_n - t_0)Y_0 - \sum_{i=1}^{n}(t_i - t_{i-1})(Y_i - Y_{i-1}) .$$

The normalized weight of ACFB for a subject is derived with the following formula:

$$W = \left(\frac{t_i}{t_0}\right)\left[\left(\frac{t_n}{t_0} - \frac{t_i}{t_0} + \frac{t_{i-1}}{t_0}\right)^2\right] + \sum_{i=1}^{n}\left(\frac{t_i - t_{i-1}}{4}\right) ,$$

where $i = 0,1,2,\ldots, n$; $k$ is the number of baseline samples taken; $t_0$ is the baseline time; $t_i$ is the times of the sample measures; $t_f$ is the follow-up time for a subject; $t$ is the total duration of the study; $Y_i$ is the mean of 2 baseline sample values; and $Y_i$ is the sample value at time $t_i$.

References


