HIV-1 Viral Dynamics Studies in the Setting of Clinical Trials—A Window of Opportunity

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(See the article by Kuritzkes et al., on pages 1169–76.)

Interventional studies incorporating mathematical modeling of changes in HIV-1 RNA level during therapy with antiretroviral drugs have provided insights into HIV-1 pathogenesis [1, 2]; estimation of parameters that characterize rates of viral production and clearance, infected cell life spans, and phases of the viral replication cycle [3–5]; and means of determining the relative efficacies of single-agent and combination antiviral therapy [6, 7]. After pharmacological and biological lags, the rate at which HIV-1 RNA levels decrease in patient plasma after the initiation of treatment is a reflection of the net decay of the cells producing viral particles. This process occurs in phases—the first is rapid and reflects the short half-life of virus-producing activated CD4+ T cells, and the second phase is much longer and reflects a composite of the loss of longer lived cells of various types. Making the assumption that the life spans of various HIV-1–infected cells are relatively constant in comparable patients (i.e., matched for CD4+ T cell counts and HIV-1 RNA levels) and not affected by current therapies, then differences in HIV-1 RNA decay become a function of the efficiency with which the applied intervention prevents de novo infection of susceptible cells and subsequent virion production. Under these assumptions, comparing the first-phase and, to a lesser degree, the second-phase plasma HIV-1 RNA decay rates provides a means of determining the relative efficacies of various treatment regimens [6–9].

In this issue of the Journal, Kuritzkes et al. [10] present findings of a viral dynamic substudy of AIDS Clinical Trials Group (ACTG) 5095, a well-known, previously published study that established the superiority of efavirenz (EFV)–based combination therapy given with twice-daily fixed-dose combination zidovudine/lamivudine or zidovudine/lamivudine/abacavir over triple-nucleoside therapy containing zidovudine or zidovudine/lamivudine/abacavir given twice daily [11]. Subsequent reports showed that no difference could be demonstrated between the 3-drug and 4-drug EFV regimens [12].

The virological substudy was designed to compare first- and second-phase decay rates among the 3 treatment regimens and to explore potential differences in decay characteristics between men and women within treatment groups. Sex differences in HIV-1 RNA levels have been well documented: women are more likely to receive a diagnosis of AIDS at a lower HIV-1 RNA level, which suggests the possibility of differences in virus/cell dynamics.

Sixty-four subjects enrolled in the study, and no significant differences in baseline CD4+ T cell counts or HIV-1 RNA levels were noted among the patient groups, nor did these differ from those seen in the parent study. Careful attention to adherence to prescribed therapy and clinic visits was critical; nonadherent patients were not included in the data analysis and, when possible, were appropriately replaced. Plasma HIV-1 RNA levels at baseline; days 2, 7, and 10; and weeks 2, 4, and 8 were fitted to a 2-phase (biexponential) decay model using a nonlinear mixed-effects approach that incorporated multiple imputation to randomly impute HIV-1 RNA values censored to <50 copies/mL.

Observed median first- and second-phase plasma HIV-1 RNA decay rates were steeper in the group treated with the 3-drug EFV regimen (first phase, −0.67/day; second phase, −0.055/day), compared with that in patients treated with triple-nucleoside therapy (first phase, −0.56/day [P = .02]; second phase, −0.04/day [P = .09]). Those observed for patients receiv-
ing the 4-drug regimen were intermediate. When separate biexponential models were fitted for each treatment group separately, nearly identical values were obtained for the population mean estimates of the first- and second-phase decay as shown in figure 2 of Kuritzkes et al. Fitting of the group treated with 4-drug regimen was not possible because of variability in on-treatment data—a result of less-than-ideal adherence.

Changes in HIV-1 RNA levels from baseline to day 10 and day 56 mirrored the differences in decay rates. Statistically significant smaller changes were seen in the triple nucleoside–treated patients than in those given 3-drug EFV-based treatment. Similar differences were seen at day 10 in the group that received the 4-drug EFV regimen, although not at day 56, because it is more likely that issues such as tolerance and adherence arise over the long term. Whether the superiority of the 3-drug EFV-containing regimen in rapidly decreasing HIV-1 RNA levels is a function of antiviral activity or of superior distribution to areas where infected and susceptible cells comingle is unknown. It is noteworthy that differences between treatments were more pronounced in patients with higher baseline viral levels. Because HIV-1 RNA levels reflect the numbers of infected cells, it is logical that a higher viral burden will require more effective suppression to result in comparable reductions in HIV-1 RNA levels.

The issue of potential sex differences was addressed. Within treatment groups, there were no differences in first- or second-phase decay rates or changes in HIV-1 RNA levels at days 10 and 56 from baseline. Stated simply, virus/cell dynamics do not appear to be different between men and women when this interventional approach is used.

Taken together, the results show that mathematical modeling of real-world data can be linked to clinical trial outcomes. The triple-nucleoside arm of ACTG 5095 was stopped after 28–32 weeks by the Data Safety Monitoring Committee because of an unacceptable degree of virologic failure. When viral dynamic analyses were used, these differences were discernible by day 10 if participants were closely monitored for adherence to their treatment regimens. Departures from the prescribed treatment schedule may well affect first-phase slopes; however, when studies are done carefully, as demonstrated in the article by Kuritzkes et al., true differences in antiviral activity can be discerned. This raises the intriguing question—can early analyses of HIV-1 RNA decay data in very controlled clinical trials prevent the undesired prolongation of inferior treatment arms? This is of great importance when the consequence of prolonged inadequate therapy is drug resistance. Before this can be answered, additional viral dynamic substudies should be performed, correlating HIV-1 RNA decay values with additional clinical trial results and always realizing the limitations of such an approach because of the need for 100% adherence to the treatment regimens being studied.

It is important to note that long-term treatment success was not predicted by these early changes in HIV-1 RNA levels. It has become clear that inherent antiviral activity is only one factor among many to determine treatment outcome. Adherence, tolerability, and perhaps additional factors, as yet unidentified, converge and affect long-term outcomes. It is clear that the “classic” clinical trial model cannot be replaced by viral dynamic substudies—however, they may be useful in identifying less than ideal treatment arms, particularly as new agents directed against new targets are tested. It is possible that these data shed light on the possibility that current clinical trial design in HIV-1 therapeutics might be enhanced and made safer for the participants.

References