Presenting Plasma HIV RNA Level and Rate of CD4 T-Cell Decline

Geoffrey S. Gottlieb; Stephen E. Hawes; David C. Nickle; et al.


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Presenting Plasma HIV RNA Level and Rate of CD4 T-Cell Decline

To the Editor: The study by Dr Rodriguez and colleagues\(^1\) concludes that presenting human immunodeficiency virus (HIV) plasma RNA viral load only minimally predicts the rate of CD4 cell decline in individuals with HIV infection and hypothesizes that a significant (>90%) amount of HIV disease progression and pathogenesis is due to factors other than viral load. This is further discussed in the accompanying editorial by Drs Henry, Tebas, and Lane.\(^2\) The results are portrayed as casting doubt on the utility of an early viral load measurement to predict disease outcome in individuals. However, these results actually highlight the interindividual variability of the association between 2 surrogate markers. With further investigation, the results may indeed impugn the reliability of early CD4 T-cell loss trajectory estimates, but this study does not address either (1) the reliability of RNA viral load measurements for predicting the critical outcome of the development of clinical AIDS or death or (2) the utility of CD4 cell measurements for predicting AIDS.

In addition, this study does not distinguish between HIV type 1 (HIV-1) and HIV type 2 (HIV-2) infection; only HIV-1 levels were investigated. It did not consider the large amount of data linking the marked differences in plasma RNA viral load levels between HIV-1 and HIV-2 infection with the different natural histories of these 2 types of HIV infection in humans.\(^3,4\) The attenuated course of HIV-2 infection has been directly correlated with its low viral loads, typically less than 1000 copies/mL and below the limit of detection of most assays in up to 25% of antiretroviral therapy–naive individuals.\(^5\) The rate of HIV-2 progression to the real outcomes of interest of clinical disease and death, as well as the surrogate marker of CD4 cell decline, have both been directly correlated with plasma HIV-2 levels.\(^4,5\) In addition, although at the cohort level HIV-2–infected individuals tend to have rates of CD4 cell decline at approximately one quarter that of individuals infected with HIV-1 (4% vs 16% per year), when normalized by viral load level, the rates of CD4 cell decline in both HIV-1 and HIV-2 infection are remarkably similar (approximately 4% per year log\(_{10}\) viral load).\(^5\)

These data suggest, but do not prove, that the level of HIV replication, irrespective of HIV type, directly leads to AIDS pathogenesis. Rodriguez et al argue that high simian immunodeficiency virus viral loads in their natural nonhuman primate hosts do not lead to either CD4 cell depletion or disease progression, and that by extension this observation also applies to HIV in humans. However, it is more relevant that the comparatively low HIV-2 viral loads in humans only slowly, if ever, lead to the same disease processes as HIV-1. Although the detailed mechanisms of AIDS pathogenesis remain to be elucidated, studies of both HIV-1 and HIV-2 infection suggest that, at least in humans, it is directly linked to the level of viral replication.

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To the Editor: In their study, Dr Rodriguez and colleagues\(^1\) challenge the long-held view that baseline plasma HIV-1 RNA level is the best predictor of the rate of CD4 cell decline among untreated HIV-infected individuals, initially put forward by Mellors et al in 1997.\(^2\) There are several methodological issues that may have contributed to this controversy.

Intraindividual variability of CD4 cell counts and plasma HIV-1 RNA levels is quite substantial.\(^3\) As a result, the signal-to-noise ratio associated with this measurement may have obscured an existing relationship over a relatively short follow-up time. Furthermore, the limits quantification of commercially available plasma HIV-1 RNA assays has evolved

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since 1996. For example, in British Columbia, plasma HIV-1 RNA measurements were obtained based on the Roche HIV-1 monitor standard assay from June 1996 to February 2000, and since March 2000 plasma HIV-1 RNA measurements have been based on the Roche COBAS HIV-1 monitor ultrasensitive assay version 1.5 (Roche Diagnostics, Indianapolis, Ind). Thus, the upper and lower limits of these assays ranged over time from 500-1 million to 50-100,000 copies/mL. As such, this may contribute to a poor model fit and to measurement biases.

A similar problem arises from the virtual truncation of CD4 cell count (at the lower end of the spectrum) due to the CD4 cutoff associated with the initiation of highly active antiretroviral therapy, which is primarily driven by CD4 cell count levels. Tobit models,5 commonly used in econometrics and health services research, may alleviate these truncation issues. Under the Tobit model, it is assumed that the plasma HIV-1 RNA level measurements come from a mixture of distributions, in which each part of this mixture is assumed to come from a specific probability distribution.

Finally, the 2-stage random effects formulation should ideally be carried out as proposed by Diggle et al5 or Fitzmaurice et al6. The first stage of this model includes only time-varying covariates, and a decision is made about which parameters should be random and which covariance structure should be assumed based on the nature of the data. In the second stage of this model, the slope estimated in the first stage should then be regressed on the nonvarying covariates. Averages or medians of measurements over time should generally not be used when handling longitudinal data. If the data are summarized, the correlation that exists between measurements is compromised and the model produces a biased estimate of parameters and covariances.3,6

Based on these concerns, we feel that it is premature to conclude that baseline plasma HIV-1 RNA level is a poor predictor of the rate of CD4 cell decline among untreated HIV-infected individuals.

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In Reply: Dr Gottlieb and colleagues and Dr Lima and colleagues suggest that the results of our study may simply represent variability in the measurement of HIV RNA and CD4 T-cell count. We recognize that there is significant imprecision in these assays and we provided an adjustment for this additional source of variability, after which a large proportion of the person-to-person variation in rate of CD4 cell loss remained to be explained. As Gottlieb et al indicate, our study was not designed to address the relationship of viral replication with time to occurrence of AIDS or death, and we make no claims to that effect. Indeed, more precise and prolonged measurements of both viral replication and immune competence, were they available, would likely reveal a tighter association, indicating a greater role of the virus in driving immune response than suggested by our analysis. This possibility, however, does not contradict our results, which are based on those measurements commonly used in the clinic.

Gottlieb et al posit that HIV-2 infection constitutes evidence that the level of HIV replication is the predominant determinant of HIV disease progression. An alternative interpretation is that HIV-2 infection represents a natural experiment that mimics the lower stratum of our HIV RNA distribution, untreated individuals who maintain low levels of viremia and tend to experience a slower CD4 cell decline on average than those with higher viremia levels. At the individual level, however, many cases are likely not to conform to this group average, as has been reported.1,2 This ample spectrum of CD4 cell depletion rates parallels our own findings among HIV-1–infected persons with various levels of plasma viremia. Moreover, immune activation level is a strong correlate of CD4 cell count in both HIV-1– and HIV-2–infected patients despite widely disparate viremia levels.3 Thus, immune activation may be the most proximate mediator of CD4 cell depletion in both HIV-1 and HIV-2 infection.

The approach suggested by Lima et al of using a 2-step process for fitting the random-effects model corresponds to the approach used in our analysis. Lima et al also suggest that using Tobit modeling may have alleviated the caveat introduced by HIV RNA detection limits, but Tobit models are not primarily designed for the circumstances of our study, where the censored variable, HIV RNA, is one of the independent variables, not the dependent one. Of the 1289 participants in the study cohort, 109 had baseline CD4 cell counts of 200 cells/µL or less. Not only did the conclusions hold in that subset of participants, but they also did in the analysis of the Multicenter AIDS Cohort Study data set, which...
In Reply: Dr Gottlieb and colleagues raise important and valid points regarding the study by Dr Rodriguez and colleagues and our editorial. They correctly point out that the study focused exclusively on the relationship between plasma HIV-1 RNA levels and the decline in CD4 T-cell counts. They note that the lower viiremia levels seen with HIV-2 infection appear to be directly related to the difference in pathogenicity between HIV-1 and HIV-2, and that when adjusted for plasma viral load, a similar rate of CD4 T-cell decline is seen in patients infected with HIV-1 and HIV-2.

Our editorial was not intended to imply that HIV-1 or HIV-2 replication is not central to HIV pathogenesis or risk for disease progression: they are. We did intend to raise the issue of the role of plasma HIV RNA levels in the assessment of an HIV-positive individual’s rate of CD4 T-cell decline and spur interest in further studies examining factors that influence the rate of CD4 T-cell loss. When a clinician faces a patient with relatively early HIV infection and a high CD4 T-cell count, the clinician has to assess how rapidly the disease is going to progress and monitor how fast the individual patient will reach a threshold that puts him or her at increased risk for clinical events (a low CD4 T-cell count). Fortunately, the immediate goal of treatment of HIV in that situation is not the prevention of AIDS-defining morbidity or mortality, but rather avoiding a level of immunodeficiency that would put the patient at future clinical risk.

The study by Rodriguez et al does raise a practical issue regarding whether monitoring patients with a test that is relatively expensive (and not easily obtained for HIV-2) helps to predict or define when to initiate antiretroviral therapy prior to the development of any associated clinical disease. Their results suggest that for an individual asymptomatic HIV-1–infected patient, the plasma HIV RNA level may be unreliable in predicting the rate of CD4 T-cell decline and when to start antiretroviral therapy based on a CD4 T-cell threshold, and therefore the test may be of limited clinical utility in that situation. This study does not question the utility of monitoring viral loads once therapy is started or the critical and central role HIV plays in the pathogenesis of this disease. We would like to see further studies assessing how to determine in a cost-effective way when to start antiretroviral therapy for asymptomatic HIV-1– and HIV-2–infected persons.

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Systolic Blood Pressure and Outcomes in Patients Hospitalized With Acute Heart Failure

To the Editor: In their cohort study of outcomes in patients hospitalized with acute heart failure, Dr Gheorghiade and colleagues showed that lower systolic blood pressure (SBP) at admission predicts worse outcomes in patients with both...