Effects of Virologic Rebound on CD4 Cell Counts

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A retrospective study was conducted to assess the effects of various degrees of virologic rebound on CD4 cell counts over time in human immunodeficiency virus–infected patients. We found that (1) the higher the degree of virologic rebound, the more rapid the decrease in CD4 cell counts over time, and (2) the magnitude of the virologic rebound was inversely correlated with the CD4 cell counts at the time of rebound.

The decrease in AIDS-related deaths and the decrease in the number of opportunistic infections that have been observed in recent years have been attributed to viral suppression achieved with the use of highly active antiretroviral therapy (HAART) [1]. However, Kaufmann et al. [2] reported that patients who adhere to HAART may have an increase in their CD4 cell counts despite having persistent viremia; this suggests that there is a disconnect between virologic and immunologic responses. This disconnect is surprising, because an association between virus load (VL), decrease in immunocompetence, and progression to AIDS has been well established [3]. Because up to 20%–30% of patients who receive HAART develop viral rebound within 2 years after reaching undetectable VLs [4], we sought to determine the relationship between the degree of virologic rebound and the changes in CD4 cell counts over time.

We conducted a retrospective cohort study of 497 HIV-infected patients who were seen at the HIV clinic of a single medical school (Eastern Virginia Medical School, Norfolk), to assess the effects of different degrees of viral rebound on CD4 cell counts. The study period (from early 1996 through March 1999) coincided with the introduction of HAART. The “control group” was defined as patients who had consecutive detectable VLs (after having had an initial undetectable VL), with “time zero” defined as the onset of virologic rebound (n = 134). The study group was stratified into 4 groups on the basis of the median HIV RNA level during virologic rebound. The 4 groups and their median HIV RNA levels were as follows: group 1 (n = 62), 401–10,000 copies/mL; group 2 (n = 31), 10,001–50,000 copies/mL; group 3 (n = 21), 50,001–100,000 copies/mL; and group 4 (n = 20), >100,000 copies/mL. The CD4 cell counts of the control group and the study groups were recorded during the 24-month study.

For the control group, “adequate data” was defined as at least 2 consecutive undetectable VLs; for the rebound groups, it was defined as 2 consecutive rebound VLs. Patients with inadequate laboratory data (n = 91), patients who never achieved undetectable VLs (n = 162), and patients who developed detectable VLs and then subsequently achieved undetectable VLs (n = 35) were excluded.

Methods. The US Food and Drug Administration–approved Amplicor HIV Monitor VL test (Roche), which has a lower limit of detection of 400 HIV RNA copies/mL, was used for VL measurements. Data were analyzed by use of the Generalized Estimating Equations approach to longitudinal data. The Generalized Estimating Equations approach is a semiparametric approach to the analysis of longitudinal data that requires assumption only about the mean and variance of the response variables [5]. The xtgee routine of Stata software, version 5 (Stata), was used for analysis. The Spearman rank order correlation was used to assess the relationship between baseline CD4 cell counts and the magnitude of viral rebound. Regression lines were calculated for the control group and for the individual rebound groups (figure 1).

Results. The average age of patients in the control group (57 men and 18 women) was 43 years. The average age of patients in the study group (107 men and 27 women) was 39 years. The median number of recorded CD4 cell counts and recorded VLs, respectively, for each group were as follows: for the control group, 4 (range, 2–12) and 4 (range, 2–11); for group 1, 4 (range, 2–9) and 4 (range, 2–9); for group 2, 6 (range, 2–8) and 5 (range, 2–10); for group 3, 5 (range, 2–11) and 5 (range, 3–17); and for group 4, 4 (range, 2–13) and 5 (range, 3–13).

Patients with sustained viral suppression (those in the control group) had a progressive increase in their CD4 cell counts over time (average increase, 3.2 CD4 cells/mL per month; 95% CI, 1.7–4.7). Patients in group 1 had no statistically significant
change in CD4 cell counts during the study period (average increase, 1 CD4 cell/mL per month; 95% CI, −1.5 to 3.0). Patients in groups 2–4 had a significant decrease in their CD4 cell counts over time, compared with the CD4 cell counts of patients in the control group ($P < .0001$) and those of patients in group 1 ($P < .05$). The decrease in CD4 cell counts over time was 1.7 CD4 cells/mL per month (95% CI, 1.3–4.7), 4.1 CD4 cells/mL per month (95% CI, 0.3–7.9), and 6.6 CD4 cells/mL per month (95% CI, 2.0–11.1) in groups 2, 3, and 4, respectively. In addition, there was a statistically significant difference in the baseline CD4 cell counts of patients in the control group, compared with those of patients in groups 2–4 ($P < .05$), and there was an inverse correlation between baseline CD4 cell counts and the magnitude of viral rebound ($r = −0.31; P < .01$).

**Discussion.** We conducted a retrospective study of patients who experienced virologic rebound, and we examined the effect of such rebounds on CD4 cell counts. Because studies by Mellors et al. [3] and others have shown a correlation between the VL and a subsequent decrease in CD4 cell counts and progression to AIDS, we stratified our patients into 4 groups according to the magnitude of virologic rebound. The data suggest that patients who develop a viral rebound of >10,000 HIV RNA copies/mL are at risk of having decreasing CD4 cell counts during the next 2 years. As the magnitude of the rebound increases from a median value of 10,001–50,000 HIV RNA copies/mL to 50,001–100,000 HIV RNA copies/mL, the rate of decrease in the CD4 cell count increases from 1.7 to 4.1 cells/mL per month, to 6.3 cells/mL per month. However, patients with a viral rebound of <10,000 copies/mL maintained their CD4 cell counts for 2 years.

Our study group of patients with virologic rebound was most similar to the group of patients with "transient undetectable viraemia" ($n = 21$) in the study of Kaufman et al. [2]. Rather than combining all patients with rebound of different magnitudes into a homogenous group, stratifying patient groups according to the median HIV RNA level during virologic rebound may provide additional information about the effects of rebound on CD4 cells. The CD4-VL “disconnect” that was reported by Kaufman et al. [3] may be more likely to occur in patients with low VLs and may be less likely to occur in patients with increasingly higher levels of viral rebound.

In addition, patients who had lower CD4 counts at baseline developed viral rebounds of greater magnitude. This would suggest that patients who have lower CD4 counts at the time of viral rebound may merit closer follow-up and/or a change in therapy earlier during the course of their disease. These conclusions need to be confirmed in prospective studies that include a larger number of patients and have a longer duration of follow-up.

**References**