Factors Influencing Increases in CD4 Cell Counts of HIV-Positive Persons Receiving Long-Term Highly Active Antiretroviral Therapy

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Background. Highly active antiretroviral therapy (HAART) results in an improvement in immunologic function. We sought to investigate the factors associated with increases in CD4 cell count among human immunodeficiency virus (HIV)–positive antiretroviral-naive patients starting HAART.

Methods. Five hundred ninety-six subjects were followed for a median of 2.5 years (interquartile range, 1.0–4.0 years). Factors associated with changes in CD4 cell counts in the first 3 months of HAART and from 3 months onwards were analyzed.

Results. After 6, 12, and 24 months of HAART, the median increases in CD4 cell counts were 114, 181, and 248 cells/mm3, respectively; 84%, 84%, and 80% of subjects had a virus load of <400 copies/mL during the same periods. White ethnicity, higher pre-HAART virus load, and lower pre-HAART CD4 and CD8 cell counts were associated with greater increases in CD4 cell counts during the first 3 months of HAART. From 3 months onward, a greater cumulative proportion of time spent with virus load <400 copies/mL was associated with a more favorable change in CD4 cell count (an average increase of 5.2 cells/mm3/year [95% confidence interval [CI], 3.8–6.7 cells/mm3/year] for each extra 10% cumulative time spent with a virus load <400 copies/mL) (P < .0001). For every 100 cells/mm3 higher in baseline CD4 cell count, the increase was 6 cells/mm3/year less (95% CI, 2–11 cells/mm3/year) (P = .02). Sex, risk group, age, and HAART regimen were not associated with increases in CD4 cell counts.

Conclusions. These findings emphasize the importance of maintaining virological suppression and suggest other factors that influence long-term CD4 cell response.

The benefits of highly active antiretroviral therapy (HAART) on mortality and morbidity in HIV-positive persons are well documented [1–3]. It is known that HAART results in an improvement in immunologic status, one feature of which is an increase in the CD4 cell count [4–8]. The rapid increases in CD4 cell count during the first few weeks after starting HAART are believed to be mainly a result of redistribution of cells stored in the lymphoreticular system [9]. It is followed by a prolonged period of less-rapid increase, which is thought to be, in large part, due to the generation of naive CD4 cells through cell division or from the thymus [10].

The factors that affect the extent of the increase in the CD4 cell count in patients receiving HAART have been studied. Some have reported that the baseline CD4 cell count influences the rate of immune reconstitution [11, 12], whereas others have found no evidence of such a link [13–15]. There is also some evidence that commencing HAART at a younger age may be associated with an improved immunologic response [16, 17]. In the present study, we sought to evaluate the effects of these and other possible related factors on the rate of immunologic reconstitution, as characterized by increases in the CD4 cell count, in previously naive subjects starting HAART regimens.
SUBJECTS AND METHODS

Patient population. All subjects included in the study were patients at the Ian Charleson Centre at the Royal Free Hospital, London. Information on these patients is collected prospectively as patients attend for care. The information is audited every 6–9 months by a trained research assistant who updates information on death, antiretroviral treatment administered, and all AIDS-defining illnesses from patient notes and cross-checks the information in the notes with that in the database. Laboratory data are transferred directly from the laboratories, in an electronic format. In accordance with UK regulations, the Royal Free HIV Hospital Database has ethical approval to be used without individual patient consent, because data are anonymized and only aggregate data are presented. However, for the past 2 years, we have been obtaining informed consent from persons in the clinic at their annual checkup visit to the Ian Charleson Day Centre.

For the purposes of the present study, HAART was defined as ≥3 antiretrovirals (irrespective of the classes of drugs received). All subjects included in the analyses were naïve to antiretroviral therapy at the time of starting HAART and were followed from that time forward. They were required to have a pre-HAART CD4 cell count measurement during the period between 6 months before and the day of starting treatment. For those with ≥1 measurement during this period, the one closest to the date of starting HAART was chosen. Furthermore, at least 1 CD4 cell count was required to have been taken within the first 3 months after starting HAART. Subjects were followed until the date of their final HIV load measurement.

Laboratory methods. CD4 cell counts were determined by standard flow-cytometry techniques, and plasma HIV-1 RNA was measured by a variety of commercially available methods. When first introduced in 1996, virus load monitoring was done with the AMPLICOR PCR HIV-1 MONITOR test 1.0 (Roche Diagnostics), which was later upgraded to the 1.5 version with the addition of non-B primers. More recently, the Cobas assay was used.

Statistical methods. Median increases in CD4 cell counts at different time points and changes made in antiretroviral regimens were calculated and summarized. We have shown previously that, among those who maintain a virus load of <500 copies/mL for prolonged periods while taking HAART, an initial, rapid linear pattern in the increase of CD4 cell counts during the first 3 months is followed by a less-rapid linear increase from this time point onward [6]. Other investigators have also noted a similar biphasic pattern in increases in CD4 cell counts while receiving HAART [10, 18]. Therefore, to investigate the factors associated with increases in CD4 cell counts, 2 models were fitted: a model examining factors associated with increases in CD4 cell counts during the first 3 months of HAART and a model examining factors associated with increases from 3 months onward. Plots of the median and mean increases in CD4 cell counts among subjects included in the present study confirmed the approximate assumptions of a linearly increasing CD4 cell count from 3 months onward. In both models, the following potential factors were investigated as being associated with increases in CD4 cell counts during HAART: sex, ethnicity (white vs. other), primary risk group (homosexual vs. other), pre-HAART CD4 cell count, pre-HAART CD8 cell count, pre-HAART virus load, initial treatment regimen (1 protease inhibitor and 2 nucleoside reverse-transcriptase inhibitors, 1 nonnucleoside reverse-transcriptase inhibitor and 2 nucleoside reverse-transcriptase inhibitors, and other), age at the time of starting HAART, and year of starting HAART (1996 and before vs. 1997 onward). Including year as a continuous variable did not alter the results presented here. Complete stopping of all antiretrovirals was not adjusted for in analyses because of its strong association with attaining a virus load of <400 copies/mL. However, sensitivity analyses excluding those subjects who stopped all antiretroviral therapy at any time did not alter the findings presented here. Because we were interested in immunologic outcome regardless of treatment regimen, follow-up was not censored for changes in treatment.

The 3-month CD4 cell count was obtained by taking the CD4 cell count that occurred closest to 3 months after starting HAART, in the window from 1.5 to 4.5 months. After this, linear regression models were used to investigate factors associated with increases in the CD4 cell count between baseline and the time of this 3-month CD4 cell count.

Factors associated with increases in CD4 cell counts from 3 months onward were then investigated. For this analysis, the 3-month CD4 cell count was taken as the reference CD4 cell count, and the time at which this was measured was taken as the reference time. Changes in CD4 cell count and time were calculated from these references. We included in these analyses every CD4 cell count measured for each subject from the time of the 3-month CD4 cell count onward. The change between these CD4 cell counts and the 3-month CD4 cell count were modeled by use of mixed effects models [19]. Increases in CD4 cell counts from 3 months onward were assumed to be linear between virus load measurements. A random effects model fits an overall mean slope, but it assumes that each subject’s slope is effectively randomly sampled from a normal distribution of slopes. For this model, all factors potentially associated with increases in CD4 cell counts were included as interaction terms; that is, they were multiplied by the time parameter. This means that each factor was assumed to be associated with the rate of increase of CD4 cell count, rather than the absolute value per se. A further, time-updated covariate was also included: the percentage of time, from 3 months after starting HAART, that a subject had a virus load of <400 copies/mL. This variable lies...
between 0% (when a subject never achieved a virus load of <400 copies/mL after the 3-month time point) and 100% (when a subject maintained a virus load of <400 copies/mL continuously from 3 months after starting HAART until the time point of interest). This percentage is updated with every new virus load measurement, and the percentage is assumed to remain the same for the period until the next virus load measurement is taken. The overall underlying increase in CD4 cell count per year for reference subjects who (1) started HAART from 1997 onward, (2) never achieved a virus load of <400 copies/mL, and (3) had a pre-HAART CD4 cell count of 200 cells/mm³ was calculated, and this was used to compare the factors associated with different rates of increase in CD4 cell count. We assessed the goodness of fit of both this model and the linear regression model by visual examination of the residuals and found the fit of both models to be good.

RESULTS

Patient population. Of 642 previously antiretroviral-naive subjects starting HAART at the Royal Free Hospital, information on baseline CD4 cell count was missing from the database for 46. Thus, 596 persons met our entry criteria and were included in these analyses. Their pretherapy characteristics are described in table 1. Three hundred thirty-four (56%) had a homosexual risk for infection, 443 (74%) were male, and 378 (63%) were of white ethnicity. The median times between starting HAART and the baseline CD4 cell count and virus load determinations were 15 days (range, 0–186 days) and 21 days (range, 0–186 days), respectively. The median pre-HAART CD4 cell count and virus load were 194 cells/mm³ (interquartile range [IQR], 75–314 cells/mm³) and 5.3 log₁₀ copies/mL (IQR, 4.8–5.7 log₁₀ copies/mL), respectively. The median length of follow-up was 2.5 years (range, 1.0–4.0 years). Of those included in the study, 13 (2.1%) died and 517 (86.7%) have been followed until the beginning of January 2003, the cutoff date for this analysis. Therefore, the rate of loss to follow-up for this cohort was relatively low.

Overall increases in CD4 cell counts and changes made in HAART regimens. There were many changes made to HAART regimens among those subjects who continued to be followed during the study period. Of the 202 subjects with an observation after 36 months of HAART, only 40 (20%) were still receiving their initial regimen (table 2). The number of subjects stopping all antiretrovirals was low: at 6, 12, 24, and 36 months of HAART, the percentages of those who were followed at these time points and had currently stopped all antiretrovirals were 8%, 9%, 9%, and 10%, respectively (table 2).

In general, the response to HAART was good (table 2). After 6 months of HAART, the median increase from baseline CD4 cell count was 114 cells/mm³ (IQR, 51–199 cells/mm³). Of the 333 (84%) of 397 currently had virus loads of <400 copies/mL. After 12, 24, and 36 months of HAART, the median increases in CD4 cell count were 181, 248, and 326 cells/mm³, respectively, and 84%, 80%,
and 93% of the cohort had virus loads of <400 copies/mL during the same time periods.

Factors associated with increases in CD4 cell counts during the first 3 months of HAART. The factors associated with increases in CD4 cell counts during the first 3 months of HAART are shown in table 3. In univariable analyses, the short-term CD4 cell response to HAART was found to be greater among those with lower pre-HAART CD4 cell counts, those of white ethnicity, those with lower pre-HAART CD8 cell counts, and those with higher pre-HAART virus loads. In a multivariable analysis, only ethnicity, pre-HAART virus loads, and pre-HAART CD8 cell counts were found to be associated with increases in CD4 cell counts during the first 3 months of HAART. Table 3 shows that, for a subject of nonwhite ethnicity with a baseline virus load of 5 log_{10} copies/mL and a pretherapy CD8 cell count of 800 cells/mm^3, the average increase in CD4 cell count after 3 months of HAART was 87 cells/mm^3 (95% confidence interval [CI], 67–106 cells/mm^3). Those of white ethnicity, on average, had an additional increase in their CD4 cell count of 37 cells/mm^3 (95% CI, 12–62 cells/mm^3; P = .002) at 3 months, and every 100 cells/mm^3 in higher pretherapy CD8 cell count was associated with an increase of 2 cells/mm^3 smaller after 3 months of HAART (95% CI, 1–3 cells/mm^3; P = .002). Every 1 log higher pre-HAART virus load was associated with an increase of 29 cells/mm^3 higher (95% CI, 13–46 cells/mm^3; P = .0006) after 3 months of HAART.

Factors associated with increases in CD4 cell counts from 3 months of HAART onward. The results of analyses assessing the factors associated with increases in CD4 cell counts from 3 months onward are shown in table 4. In univariable models, a lower pre-HAART CD4 cell count, a virus load of <400 copies/mL, and starting HAART from 1997 onward were all found to be associated with greater monthly increases in CD4 cell count. In a multivariable model, the average annual increase (from 3 months onward) in CD4 cell count for someone who had a pre-HAART CD4 cell count of 200 cells/mm^3, who never achieved virus suppression to <400 copies/mL, and who started HAART from 1997 onward was 60 cells/mm^3 (95% CI, 46–73 cells/mm^3; P < .0001). This is shown as the underlying increase in table 4. Furthermore, for every 100 cells higher in pretherapy CD4 cell count, a subject’s annual increase would be smaller by 6 cells/mm^3 (95% CI, 2–11 cells/mm^3). Those starting HAART in 1996 and before had a smaller yearly increase, by 84 cells/mm^3 (95% CI, 48–120 cells/mm^3; P < .0001). As the cumulative time spent with a virus load of <400 copies/mL increased by 10%, there was an average additional increase in CD4 cell count of 5.1 cells/mm^3/year (95% CI, 3.7–6.6 cells/mm^3/year). For example, a subject who had maintained a virus load of <400 copies/mL for 50% of the period of follow-up would have an average annual increase of 5 × 5.1 = 26 cells/mm^3 greater than would a subject who has never achieved a virus load of <400 copies/mL (i.e., the percentage of time with a virus load of <400 copies/mL is 0). A subject who had achieved a virus load of <400 copies/mL by 3 months of HAART and then maintained a virus load of <400 copies/mL from that time onward would have an average yearly increase of 10 × 5.1 = 51 cells/mm^3 greater than a subject who has never achieved a virus load of <400 copies/mL. Because this variable is a time-updated factor, it can change for each person each time his or her virus load is measured, and, so, the modeled slope of the CD4 cell count may change in line with this.

Figure 1 shows the average increases in CD4 cell counts from 3 months after starting HAART for 2 hypothetical subjects. Because the effects of pre-HAART CD4 cell count and pre-HAART CD8 cell count on increases in CD4 cell counts were small, both subjects were assumed to have a pre-HAART CD4 cell count of 200 cells/mm^3, and, to make the results clinically relevant, they were assumed to have started HAART from 1997 onward. Subject A was assumed to have maintained a virus load of <400 copies/mL throughout the entire follow-up period. Subject B maintained a virus load of <400 copies/mL for the first 9 months of follow-up, and, thus, for this period, the percentage of time that the subject had had a virus load of <400 copies/mL is 100%. However, after 9 months of HAART, subject B experienced a virus load rebound, and, from this time point onward, the virus load was >400 copies/mL. Thus, after 12 months of HAART, the percentage of time subject B had had a virus load of <400 copies/mL was 75% (9/12 months); so the CD4 cell slope changed by an additional 38 cells/mm^3/year. At 12 months, subject B again had a virus load of >400 copies/mL, and, so, the cumulative percentage of time that the subject had maintained a virus load of <400 copies/mL at the end of this period was 60% (9/15 months), resulting in a further change in slope. At 18 months, the cumulative percentage of

### Table 2. Response to highly active antiretroviral therapy (HAART).

<table>
<thead>
<tr>
<th>Response</th>
<th>Time point after beginning HAART</th>
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<tbody>
<tr>
<td></td>
<td>6 months (n = 397)</td>
</tr>
<tr>
<td>Increase in CD4 cell count, median (IQR), cells/mm^3</td>
<td>114 (51–199)</td>
</tr>
<tr>
<td>Virus load of &lt;400 copies/mL, no. (%)</td>
<td>333 (84)</td>
</tr>
<tr>
<td>Change in original HAART regimen, no. (%)</td>
<td>143 (36)</td>
</tr>
<tr>
<td>Discontinued all antiretrovirals, no. (%)</td>
<td>31 (8)</td>
</tr>
</tbody>
</table>
The expected increase in CD4 cell count would be 153 (87 + 37 + 29) cells/mm³. CI, confidence interval; NNRTI, nonnucleoside reverse-transcriptase inhibitor; NRTI, nucleoside reverse-transcriptase inhibitor; PI, protease inhibitor.

If this person had a pre-HAART virus load of 6 log₁₀ copies/mL, their additional increase in CD4 cell count after 3 months of HAART for persons with this baseline factor above the underlying increase.

Ethnicity with a pre-HAART virus load of 5 log₁₀ copies/mL. The parameter estimates indicate the expected additional increase in CD4 cell count after 3 months of HAART for persons with this baseline factor above the underlying increase.

The results of the present study agree with those of several others that have shown that maintaining virological suppression results in greater increases in CD4 cell counts in the long term [12, 15, 21, 22]. To include a period of follow up of >4 years, we used a cutoff of 400 copies/mL, because this was the cutoff that was used historically for many of our virus load assays. However, the aim of HAART currently is to suppress viremia to <50 or even <10 copies/mL, and a patient who achieves a virus load of <50 copies/mL may have a much improved CD4 cell response, compared with that of a patient who has a virus load of 50–400 copies/mL [13].

Calendar year was also found to be associated with changes in CD4 cell count, with those starting HAART before 1996 having smaller increases than those starting HAART from 1997 onward. There are several potential factors that could possibly explain this. First, adherence could be assumed to have improved; as the importance of adherence has become established, awareness of ways of improving it among those receiving HAART has increased [23, 24]. However, it would be expected that any impact of improved adherence would be reflected in greater proportions of patients achieving virus loads.

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of <400 copies/mL [25], and, thus, the residual effect may be a reflection of the relatively cruder way in which we have characterized subjects’ virus loads. The introduction of new antiretrovirals, such as efavirenz and boosted protease inhibitors used as part of first-line HAART regimens, and better management of toxicities may also contribute to improved response to HAART in later calendar years.

Higher pre-HAART CD4 cell counts were found to be associated with smaller long-term increases in CD4 cell counts during HAART, which may reflect a greater scope for improvement among those with lower pre-HAART CD4 cell counts. However, although these factors were statistically significant, this effect was of a small magnitude, and, so, the clinical implications of this finding may be limited. There is conflicting evidence on this point, with some [17, 26], but not all [12, 13], studies finding those with higher baseline CD4 cell counts having a better response to HAART. However, it is possible that the true effect of pre-HAART CD4 cell count may have been diluted because of regression to the mean [26]. However, when calculating the pre-HAART CD4 cell count as the mean of the last 2 pre-HAART CD4 cell counts (which should reduce any effect of regression to the mean), we found results similar to those presented here.

We did not find any association between any of the demographic factors and increases in CD4 cell counts from 3 months onward. Certainly, other studies have found a lack of association between sex [27], ethnicity [20], risk group [28], and immunologic response to HAART, although some have found a relationship between younger age and immunologic response [16, 29]. Others have found a relationship between sex [30], current intravenous drug use [31], and clinical progression among those receiving HAART. It is possible that any effect of these factors on CD4 cell response to HAART is mediated through suppression of the virus load. However, when the mult-

### Table 4. Factors associated with CD4 cell response to highly active antiretroviral therapy from 3 months onward.

<table>
<thead>
<tr>
<th>Factor</th>
<th>Univariable analysis</th>
<th>Multivariable analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Increase in CD4 cell count per year (95% CI)</td>
<td>Increase in CD4 cell count per year (95% CI)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>P</td>
</tr>
<tr>
<td>Underlying CD4 cell increase, a cells/mm³/year</td>
<td>94 (85 to 103)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Pre-HAART CD4 cell count, per 100 cells/mm³ higher</td>
<td>−8 (−13 to −3.3)</td>
<td>.004</td>
</tr>
<tr>
<td>Pre-HAART virus load, per 1 log₁₀ copies higher</td>
<td>11 (−1 to 24)</td>
<td>.1</td>
</tr>
<tr>
<td>Proportion of time since 3 months with a virus load of &lt;400 copies/mL, per 10% higher</td>
<td>5.2 (3.8 to 6.7)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>−2 (−16 to 12)</td>
<td>.7</td>
</tr>
<tr>
<td>Primary risk group</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Homosexual</td>
<td>−22 (−16 to 18)</td>
<td>.6</td>
</tr>
<tr>
<td>Other</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>−11 (−30 to 8)</td>
<td>.5</td>
</tr>
<tr>
<td>Other</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Age at starting HAART, per 10-year increase</td>
<td>8 (−3 to 19)</td>
<td>.2</td>
</tr>
<tr>
<td>Calendar year of starting HAART</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1996 and before</td>
<td>−108 (−144 to −72)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>1997 onward</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Initial HAART regimen</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PI plus 2 NRTIs</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>NNRTI plus 2 NRTIs</td>
<td>−5 (−24 to 15)</td>
<td>.7</td>
</tr>
<tr>
<td>Other</td>
<td>26 (0.03 to 52)</td>
<td>.02</td>
</tr>
<tr>
<td>Pre-HAART CD8 cell count, per 100 cells/mm³ higher</td>
<td>−0.3 (−1.1 to 0.5)</td>
<td>1.0</td>
</tr>
</tbody>
</table>

**NOTE.** Parameter estimates were calculated by use of linear regression models. All models include the underlying CD4 cell increase term. Parameter estimates are in comparison with the reference category. CI, confidence interval; NNRTI, nonnucleoside reverse-transcriptase inhibitor; NRTI, nucleoside reverse-transcriptase inhibitor; PI, protease inhibitor.

a In multivariable analysis, for a subject with a pre-HAART CD4 cell count of 200 cells/mm³ who started HAART in 1997 and has never achieved a virus load of <400 copies/mL, their expected monthly increase in CD4 cell count would be cells/mm³/year.

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Figure 1. Average increases in CD4 cell counts for 2 hypothetical patients taking HAART, beginning at 3 months after starting HAART. A, Subject taking HAART from 1999 onward with a baseline CD4 cell count of 200 cells/mm$^3$, who maintained a virus load of $<400$ copies/mL for the entire period of interest. B, Subject taking HAART from 1997 onward with a baseline CD4 cell count of 200 cells/mm$^3$. This subject had a virus load measurement every 3 months and maintained a virus load of $<400$ copies/mL until 9 months, after which the virus load was $>400$ copies/mL.

tivariable analysis was repeated with the exclusion of virus load suppression, none of these demographic factors became clinically or statistically significantly associated with increases in CD4 cells.

Our analyses considered changes in only 1 marker of immune function and did not examine others, such as the level of immune activation and CD8 cell count (except at baseline). Neither did we take into account the naive or memory phenotype of the CD4 T cells and the changes in HIV-specific CD4 and CD8 T cell responses in these subjects over time [32–35]. This information is not routinely collected in our database. We do collect information on CD4 cell percentage, and, when analyses were repeated with use of this outcome, similar results were obtained (data not shown).

The present analysis may be influenced by the presence of selective follow-up, with those who died during the course of the study or those who were less adherent no longer attending the clinic. However, although informative censoring potentially could influence the estimate of the overall increase in CD4 cell count, it is less clear what, if any, impact this informative censoring would have on the association between cofactors and the CD4 cell response to HAART. Furthermore, given the low rate of loss to follow-up seen in the present study, we hope that our results have not been adversely affected by this potential bias.

Other factors that we have not been able to measure in the present study could possibly be associated with increases in CD4 cell counts. For example, adherence [36], cytomegalovirus status [37], weight, treatment changes and interruptions, stage of infection (Centers for Disease Control and Prevention category), host genetic factors, and HIV subtype [38] could all be investigated. However, because these data have not been collected in the past on the entire cohort or are not collected at all in our database, we were unable to study their influence on immune reconstitution. Furthermore, some studies have found that those coinfected with hepatitis C virus tend to have lower CD4 cell counts while taking HAART [39] and a greater risk of clinical progression [40], although not all investigators have agreed on this [41, 42]. Unfortunately, our cohort has a low prevalence of hepatitis C virus infection (8%) and injection drug users (4%), and, so, our clinic may not be the most appropriate setting in which to answer this question. Furthermore, our model may be insufficient to address the CD4 cell count slope once all antiretrovirals have been discontinued.

We used a novel approach to modeling changes in CD4 cell count, which allows changes in CD4 cell count slope as the cumulative percentage of time with changes in virus load suppression. We believe that this represents an improvement on fitting a model involving 1 CD4 cell count slope/person, but we recognize that our approach still has limitations and may not closely fit changes in CD4 cell numbers in some situations. For example, if a person stops all antiretrovirals, our model does not capture the rapid decline in CD4 cells that ensues. The disadvantage of fitting a model with more parameters is that it does not provide a simple means of summarizing the effects of potential covariates on increase in CD4 cell counts.

In summary, we have investigated factors associated with increases in CD4 cell counts among those undergoing HAART, both in the short term (up to 3 months) and in the longer term. Our study has followed a complete clinic population for $\geq 4$ years, and we have also investigated the joint effect of a large number of factors on increases in CD4 cell counts, allowing us to investigate the effect of each variable after adjusting for the others. There was a sustained increase in the CD4 cell response to HAART, with a median increase after 3 years of HAART of $\sim 300$ cells/mm$^3$. The ability to maintain a virus load of $<400$ copies/mL and start of HAART after 1997 were both associated with greater increases in CD4 cell counts. Pre-HAART CD4 cell counts were associated with long-term increases in CD4 cell counts during HAART, but the effect was of a small magnitude. Demographic factors were not found to
be associated with increases in CD4 cell counts in the long term. These analyses suggest that, if virus suppression can be maintained, a similar long-term response to HAART should be observed among all HIV-positive persons, from the point of view of increases in CD4 cell counts.

References


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