

Incomplete Peripheral CD4⁺ Cell Count Restoration in HIV-Infected Patients Receiving Long-Term Antiretroviral Treatment

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(See the editorial commentary by Julg and Walker on pages 795–7)

Background. Although antiretroviral therapy has the ability to fully restore a normal CD4⁺ cell count (>500 cells/mm³) in most patients, it is not yet clear whether all patients can achieve normalization of their CD4⁺ cell count, in part because no study has followed up patients for >7 years.

Methods. Three hundred sixty-six patients from 5 clinical cohorts who maintained a plasma human immunodeficiency virus (HIV) RNA level ≤1000 copies/mL for at least 4 years after initiation of antiretroviral therapy were included. Changes in CD4⁺ cell count were evaluated using mixed-effects modeling, spline-smoothing regression, and Kaplan-Meier techniques.

Results. The majority (83%) of the patients were men. The median CD4⁺ cell count at the time of therapy initiation was 201 cells/mm³ (interquartile range, 72–344 cells/mm³), and the median age was 47 years. The median follow-up period was 7.5 years (interquartile range, 5.5–9.7 years). CD4⁺ cell counts continued to increase throughout the follow-up period, albeit slowly after year 4. Although almost all patients (95%) who started therapy with a CD4⁺ cell count ≥300 cells/mm³ were able to attain a CD4⁺ cell count ≥500 cells/mm³, 44% of patients who started therapy with a CD4⁺ cell count <100 cells/mm³ and 25% of patients who started therapy with a CD4⁺ cell count of 100–200 cells/mm³ were unable to achieve a CD4⁺ cell count >500 cells/mm³ over a mean duration of follow-up of 7.5 years; many did not reach this threshold by year 10. Twenty-four percent of individuals with a CD4⁺ cell count <500 cells/mm³ at year 4 had evidence of a CD4⁺ cell count plateau after year 4. The frequency of detectable viremia (“blips”) after year 4 was not associated with the magnitude of the CD4⁺ cell count change.

Conclusions. A substantial proportion of patients who delay therapy until their CD4⁺ cell count decreases to <200 cells/mm³ do not achieve a normal CD4⁺ cell count, even after a decade of otherwise effective antiretroviral therapy. Although the majority of patients have evidence of slow increases in their CD4⁺ cell count over time, many do not. These individuals may have an elevated risk of non-AIDS-related morbidity and mortality.

The vast majority of patients who achieve and maintain an undetectable plasma HIV RNA level while receiving HAART exhibit sustained increases in their peripheral CD4⁺ cell count [1]. Most patients exhibit a rapid increase in the peripheral CD4⁺ cell count during the first

8–12 weeks of therapy. This is often followed by a more gradual increase until a normal CD4⁺ cell count is achieved [2, 3]. There exists, however, significant patient-to-patient heterogeneity with regard to peripheral CD4⁺ cell count outcomes; some patients apparently reach a plateau before normalization of their CD4⁺ cell count [4–8], although this phenomenon remains controversial [9, 10].

There is no clear consensus with regard to how to best define immunological success or failure in the context of durable treatment-associated viral suppression [1, 11]. Several studies have focused on rates of CD4⁺ cell count increases per year and have generally found that CD4⁺ cell counts continue to increase as long as

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Table 1. Demographic and pre-HAART characteristics of the 366 patients who initiated HAART and maintained viral load suppression for at least 48 months.

Characteristic	Value
Originating cohort	
UCSF Options	14 (4)
UCSF SCOPE	58 (16)
University of Alabama	170 (46)
Case Western Reserve University	43 (12)
University of Washington	81 (22)
Male sex	304 (83)
Age, median years (IQR)	47 (41–52)
Ethnicity	
White	223 (61)
Black	107 (30)
Other	36 (9)
Baseline CD4 ⁺ cell count	
Missing data	16 (4)
≤100 cells/mm ³	101 (28)
101–200 cells/mm ³	72 (20)
201–300 cells/mm ³	67 (18)
301–400 cells/mm ³	50 (14)
>400 cells/mm ³	60 (16)
Duration of observation, by baseline CD4 ⁺ cell count, median years (IQR)	
≤100 cells/mm ³	7.8 (5.8–9.9)
101–200 cells/mm ³	7.9 (6.2–9.8)
201–300 cells/mm ³	6.2 (5.2–9.3)
301–400 cells/mm ³	7.0 (5.7–10.3)
>400 cells/mm ³	6.7 (5.3–9.2)
Baseline viral load, median log ₁₀ copies/mL (IQR)	4.4 (3.7–5.1)
Baseline HAART regimen	
Unboosted PI	222 (61)
Boosted PI	22 (6)
NNRTI	86 (24)
PI and NNRTI	16 (4)
Triple NRTI	19 (5)
Unknown	1 (<1)
Antiretroviral therapy experience at HAART initiation	
Yes	154 (42)
None	185 (51)
Unknown	27 (7)
Year of HAART initiation	
1994	1 (0.27)
1995	1 (0.27)
1996	90 (25)
1997	89 (24)
1998	42 (11)
1999	29 (8)
2000	43 (12)
2001	27 (7)
2002	29 (8)
2003	14 (4)
2004	1 (0.27)
Hepatitis C virus coinfection	43 (12)

NOTE. Data are no. (%) of patients, unless otherwise indicated. NRTI, nucleoside reverse-transcriptase inhibitor; NNRTI, nonnucleoside reverse-transcriptase inhibitor; PI, protease inhibitor; SCOPE, Study of the Consequences of Protease Inhibitor Era; UCSF, University of California, San Francisco.

the CD4⁺ cell counts remain lower than normal levels, although the rate of increase decreases after several years [10]. One limitation of these approaches is that they report the mean values in the population. Other studies have reported the proportion of patients who experience an increase in CD4⁺ cell count to the normal range. These studies have invariably found that a significant proportion of individuals have a persistently low CD4⁺ cell count, at least throughout the 3–7 years of observation [5, 6, 8, 10, 12].

There is a growing appreciation that a persistently low CD4⁺ cell count during treatment is associated with increased risk of both AIDS- and non-AIDS-related events (e.g., cardiovascular disease, liver disease, and cancer) [13–19]. Importantly, the clinical risk associated with lower CD4⁺ cell counts during therapy is evident across the entire CD4⁺ T cell range, with a patient's overall prognosis approaching that of an HIV-negative individual only if CD4⁺ cell counts are consistently maintained at >500 cells/mm³ [18]. For these reasons, the recent Department of Health and Human Services guidelines suggest that a goal of therapy is to increase CD4⁺ cell counts to the normal range [11].

Because of the clinical significance of CD4⁺ cell counts during therapy and the lack of clarity with regard to CD4⁺ cell count increases during long-term therapy, we analyzed long-term changes in CD4⁺ cell count in a cohort of individuals who were selected on the basis of maintenance of an undetectable or low viral load. Because, in our previous studies, we did not see any evidence of a CD4⁺ cell count plateau during the first 4 years of therapy [9], we identified all patients who maintained undetectable or low viral loads for at least 4 years. In our primary analysis, we focused on outcomes after year 4 and in a secondary analysis. In our secondary analysis, we considered all data from after the initiation of therapy.

PATIENTS AND METHODS

Patients. Five clinic-based sites were used to assemble the cohort. The University of California, San Francisco, Options cohort consists of individuals referred from the San Francisco area with suspected or confirmed primary HIV infection or early HIV infection. The University of California, San Francisco, Study of the Consequences of Protease Inhibitor Era cohort is a clinic-based cohort of chronically infected individuals. The Case Western Reserve Cohort in Cleveland, Ohio, includes all patients who receive care at the Case Western Reserve University hospitals. The University of Alabama at Birmingham cohort consists of all patients receiving care at the University of Alabama at Birmingham HIV (1917) Clinic. The University of Washington HIV cohort is the cohort from an ongoing observational study that was initiated in 1995 to observe patients receiving care at the University of Washington Harborview Medical Center HIV Clinic (Seattle).

From these cohorts, we selected all patients who initiated their first HAART regimen and achieved viral suppression, defined as having achieved at least 2 consecutive plasma HIV RNA levels <1000 copies/mL within the first 48 weeks of therapy and having maintained this degree of viral suppression (<1000 copies/mL) for at least 4 years. HAART was defined as treatment with ≥ 3 antiretroviral drugs, including a protease inhibitor, a nonnucleoside reverse-transcriptase inhibitor, or abacavir. Patients were excluded if they used hydroxyurea, IL-2, IFN- α , or the combination of tenofovir and didanosine, because these are known to affect CD4⁺ cell count increases. We also excluded any patient with >1 year of missing data during the first 48-month period. Patients who modified their HAART regimens were not censored if plasma HIV RNA levels remained <1000 copies/mL.

Our primary analysis focused on outcomes after the visit at month 48. Observations after this study baseline were censored at any time when the plasma HIV RNA level increased to >1000 copies/mL after month 48 (for any reason) or when a patient was known to have initiated therapy with IFN- α , IL-2, hydroxyurea, or the combination of tenofovir with didanosine. Patients were also censored when they became lost to follow-up or if they had no plasma HIV RNA testing performed for ≥ 1 year.

Statistical analysis. Changes in CD4⁺ cell count were evaluated using several methods. We used linear mixed-effects modeling to examine longitudinal changes in the square-root of the CD4⁺ cell count. We also used linear mixed-effects regression to determine the association between the square-root of the CD4⁺ cell count and the following factors: baseline CD4⁺ cell count, CD4⁺ cell count at year 4, age, hepatitis C virus

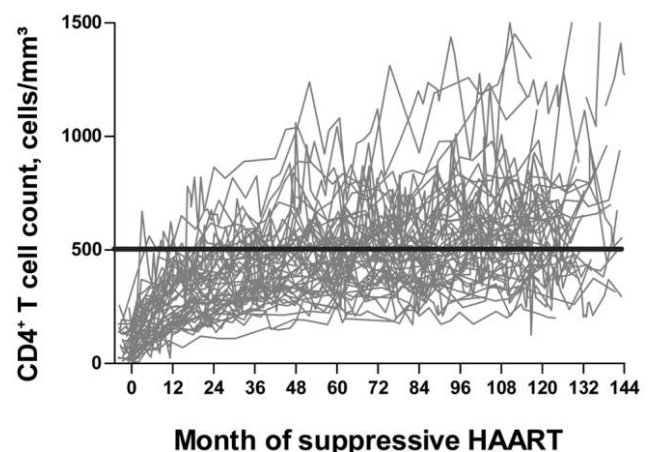


Figure 1. Peripheral CD4⁺ cell counts in patients who had maintained viral suppression for 10 continuous years. Only those who had a pretherapy CD4⁺ cell count <200 cells/mm³ are shown ($n = 48$). A significant subset of individuals appeared to have their CD4⁺ cell counts plateau below normal levels (defined here as 500 cells/mm³).

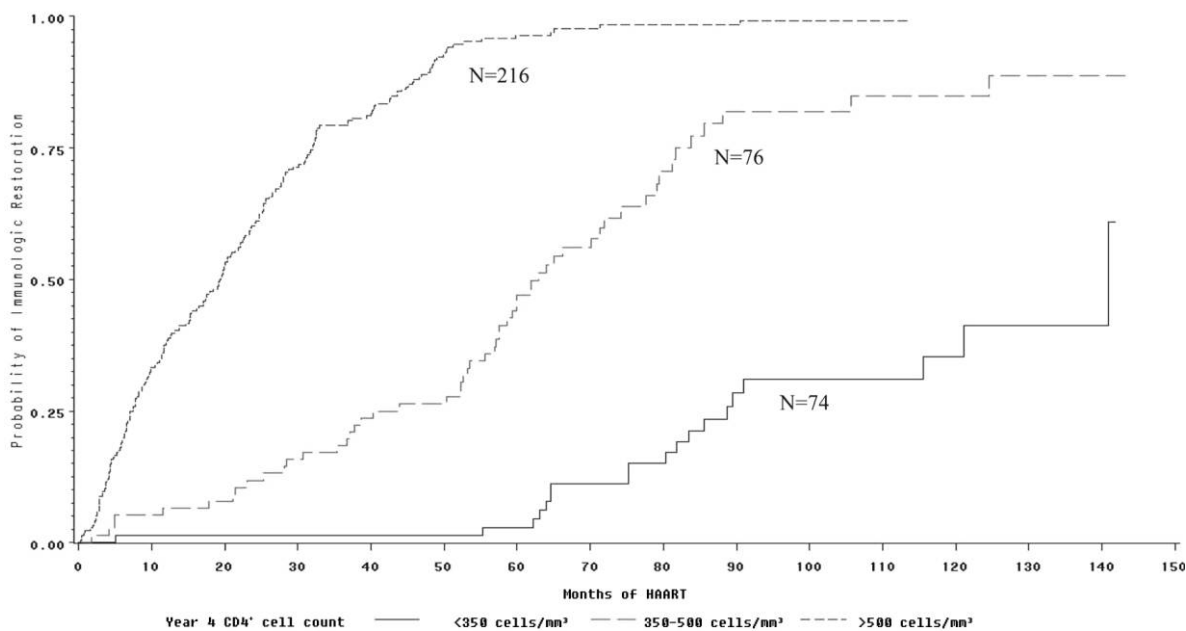


Figure 2. The time from initiation of HAART to achievement of a CD4⁺ cell count >500 cells/mm³, estimated using Kaplan-Meier techniques. The cohort was selected on the basis of having achieved and maintained a viral load <1000 copies/mL for at least 4 years. Patients were stratified on the basis of their CD4⁺ cell counts at year 4 (74 had a CD4⁺ cell count <350 cells/mm³, 76 had a CD4⁺ cell count of 350–500 cells/mm³, and 216 had a CD4⁺ cell count >500 cells/mm³). The time from initiation of HAART to achievement of a CD4⁺ cell count >500 cells/mm³ was significantly different among the strata ($P < .001$, by the log-rank test).

coinfection, nadir CD4⁺ cell count, use of a boosted protease inhibitor, year of HAART initiation, timing of initial response to therapy, pre-HAART nucleoside analogue exposure, and the proportion of visits with detectable viremia (“blips”). The magnitude of blips was assessed by multiplying the plasma HIV RNA level (\log_{10} transformed) by the indicator (0 or 1 for absence or presence of detectable viremia, respectively). For clarity, CD4⁺ cell counts were back transformed into the native scale in the text.

Because of potential nonlinearity over time, a spline-smoothing regression model was fit to the data for all time points. This flexible model allows for change-points (knots) to be placed at different time points. A piecewise linear model with a change-point before year 4 was determined to have the best fit. This model has only 1 knot (before year 4) that was linear both before and after the knot. We then constructed several piecewise linear models with breakpoints at each year of HAART to determine the change in slope with each successive year of HAART. The model was implemented using R, version 2.6.

The Kaplan-Meier method was used to determine the effects of baseline CD4⁺ cell count on time until immunological recovery. Quintiles were formed on the basis of CD4⁺ cell counts before initiation of HAART. The primary end point was the time to immunological restoration, defined as 2 successive CD4⁺ cell counts >500 cells/mm³. Strata were compared using

the log-rank test. Analyses were conducted using R, version 2.6, and SAS, version 9.1 (SAS Institute).

RESULTS

Patient characteristics. A total of 366 patients who achieved and maintained a viral load <1000 copies/mL for at least 4 years were identified and included in this analysis. The majority (83%) of patients were men (table 1). The median age at the time of HAART initiation was 47 years. The median CD4⁺ cell count before initiation of HAART was 201 cells/mm³ (interquartile range [IQR], 72–344 cells/mm³), and the median HIV RNA level before initiation HAART was 4.47 \log_{10} copies/mL (IQR, 3.74–5.11 \log_{10} copies/mL). The median CD4⁺ cell count at year 4 of HAART was 560 cells/mm³ (IQR, 390–776 cells/mm³). The majority (71%) of patients initiated HAART with a protease inhibitor–based regimen. Approximately one-half (51%) of the cohort was known to be treatment naive at the time of initiation of their first HAART regimen. Twelve percent of the population was hepatitis C virus seropositive.

The median duration of follow-up after the initiation of HAART was 7.5 years (IQR, 5.5–9.7 years). Eighty-one patients (22%) experienced >10 years of HAART-mediated viral suppression. There was a median of 32 observations per person (range, 7–125 observations per person).

Risk of not achieving a normal CD4⁺ cell count after year

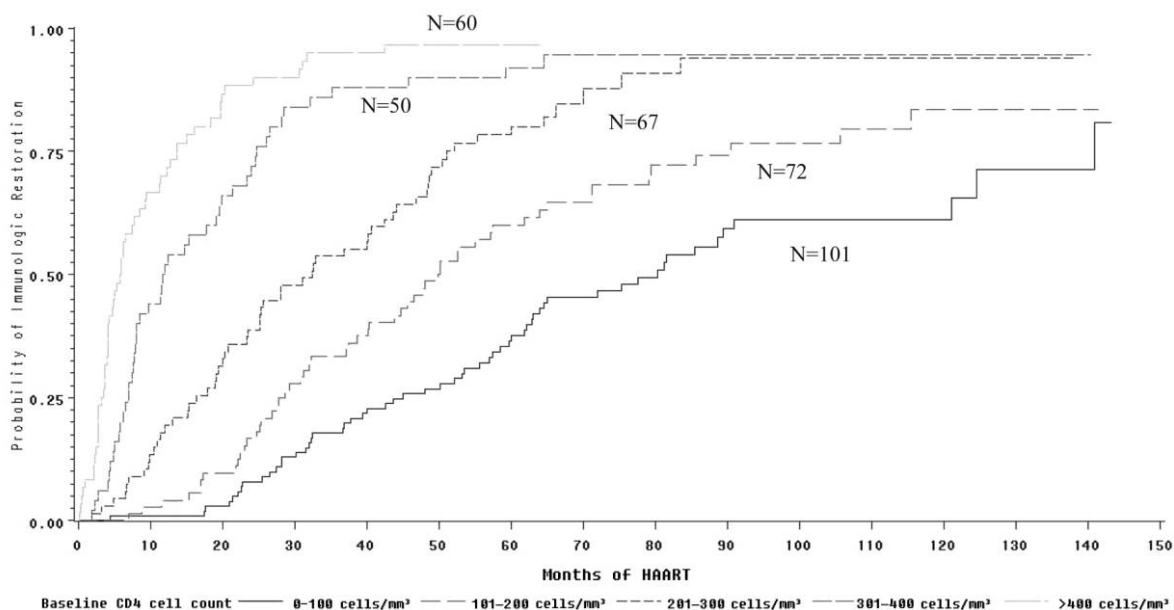


Figure 3. The time from HAART initiation to achievement of a CD4⁺ count >500 cells/mm³, estimated using Kaplan-Meier techniques. Patients were stratified on the basis of their CD4⁺ cell counts before initiation of therapy (101, 72, 67, 50, and 60 patients had CD4⁺ cell counts of ≤100, 101–200, 201–300, 301–400, and >400 cells/mm³, respectively). The time from HAART initiation to achievement of a CD4⁺ cell count >500 cells/mm³ was significantly different among the strata ($P < .001$, by the log-rank test).

4 of HAART. A total of 151 patients (41%) had a CD4⁺ cell count <500 cells/mm³ at year 4. Among those 151 individuals, 61 (40%) eventually had a confirmed increase in their CD4⁺ cell count to >500 cells/mm³, and the remainder had persistently low CD4⁺ cell counts; many patients had CD4⁺ cell counts that remained below this threshold through 10 years of observation (e.g., CD4⁺ cell count outcomes in all 48 patient who began therapy with a CD4⁺ cell count <200 cells/mm³ and who had at least 10 years of observation) (figure 1). As expected, the median time until a confirmed CD4⁺ cell count >500 cells/mm³ after year 4 was significantly different when patients were stratified by their CD4⁺ cell count at year 4 ($P < .001$) (figure 2).

Once patients achieved a normal CD4⁺ cell count, it usually remained normal. Only 2 individuals had a confirmed increase in their CD4⁺ cell count to >500 cells/mm³, followed by a sustained decrease to <500 cells/mm³.

CD4⁺ cell count slopes after year 4 of HAART. The overall mean change in CD4⁺ cell count after year 4 was 17 cells/mm³ per year (95% CI, 11–21 cells/mm³ per year). The rate was higher among those with a CD4⁺ cell count <350 cells/mm³ at year 4 (mean change, 21 cells/mm³ per year; 95% CI, 12–31 cells/mm³ per year) than it was among those with a CD4⁺ cell count of 350–499 cells/mm³ at year 4 (mean change, 17 cells/mm³ per year; 95% CI, 6–28 cells/mm³ per year) and among those with a CD4⁺ cell count >500 cells/mm³ at year 4 (mean change, 11 cells/mm³ per year; 95% CI, 3–17 cells/mm³ per

year; $P = .001$). Using linear mixed-effects models, we found that ~19% of individuals with a CD4⁺ cell count <350 cells/mm³ at year 4 and ~27% of patients with CD4⁺ cell counts of 350–500 cells/mm³ had a CD4⁺ cell count slope that was not significantly different from zero after year 4.

CD4⁺ cell count outcomes based on pretherapy characteristics. We also analyzed all data from the pre-HAART baseline through the end of observation, although it should be emphasized that the cohort was conditioned on having achieved durable viral suppression for the first 4 years of observation. The median change in CD4⁺ cell count during the first 4 years was comparable across the pre-HAART CD4⁺ cell count strata, as we have reported elsewhere [9]. The median time until a confirmed CD4⁺ cell count >500 cells/mm³ was different among the pre-HAART CD4⁺ cell count strata ($P < .001$, by the log-rank test). The estimated median duration from pre-HAART baseline to achievement of a normal CD4⁺ cell count was 6 months (95% CI, 4–9 months), 12 months (95% CI, 9–20 months), 32 months (95% CI, 24–44 months), 50 months (95% CI, 40–62 months), and 80 months (95% CI, 63–91 months) in those with a pretherapy CD4⁺ cell count of >400 cells/mm³, 301–400 cells/mm³, 201–300 cells/mm³, 101–200 cells/mm³, and ≤100 cells/mm³, respectively (figure 3). Although almost all patients (95%) who started HAART with a CD4⁺ cell count >300 cells/mm³ were able to attain a CD4⁺ cell count >500 cells/mm³, 44% of patients who started HAART with a CD4⁺ cell count <100 cells/mm³ and 25% who started HAART with

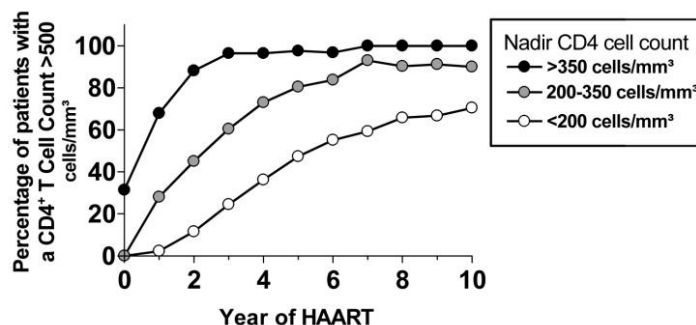


Figure 4. The percentage of patients with a CD4⁺ cell count in the normal range (>500 cells/mm³) over time, stratified by CD4⁺ cell count before initiation of therapy. Patients were censored after year 4 when plasma HIV RNA levels increased to >1000 copies/mL for any reason.

a CD4⁺ cell count of 100–200 cells/mm³ did not achieve a CD4⁺ cell count >500 cells/mm³ over a mean follow-up period of 7 years. Many did not achieve this level after 10 years of HAART (figure 4).

Factors associated with changes in CD4⁺ cell count after 4 years of HAART. In the mixed-effects analysis, we found that the mean change in CD4⁺ cell count after 4 years of observation was higher in those with lower pretherapy nadir CD4⁺ cell counts (21, 23, 18, 5, and 2 cells/mm³ for patients with a pretherapy CD4⁺ cell count of ≤100, 101–200, 201–300, 301–400, and >400 cells/mm³, respectively). We also examined other factors that might be associated with changes in CD4⁺ cell count after year 4 of therapy. In multivariate analysis, age was the only factor consistently associated with CD4⁺ cell count increases; younger patients had greater increases than did the older patients ($P = .009$). Hepatitis C virus coinfection, sex, and pre-HAART nucleoside analogue exposure were not statistically significant predictors of CD4⁺ cell count increases during this period.

We used an expansive definition of virological success because of the lack of certainty regarding low-level viremia for long-term outcomes. The proportion of visits at which virus was detectable (“blips”) was strongly associated with CD4⁺ cell count changes before year 4 ($P < .001$). There was, however, no association after year 4 ($P = .85$). There was a trend suggesting that the magnitude of the blip (rather than the frequency) was important, because higher-magnitude blips were associated with less robust CD4⁺ cell count increases (after year 4; $P = .07$).

A total of 16 patients had persistent low-level viremia (defined as having at least 50% of all viral loads after year 4 detectable but <1000 copies/mL). The median pre-HAART CD4⁺ cell count in these patients was 293 cells/mm³ (IQR, 184–429 cells/mm³). During a median follow-up period of 6 years (IQR, 5–7 years), 14 of these 16 patients achieved a normal CD4⁺ cell count.

DISCUSSION

With >25 antiretroviral drugs from at least 6 therapeutic classes now available, it is likely that the vast majority of patients who are able to access and adhere to combination therapy will achieve durable viral suppression. Because effective therapy can dramatically reduce the risk of the classically defined AIDS complications, the primary limitation of current therapeutic strategies may be the inability to fully restore immunocompetence. Failure to restore a normal peripheral CD4⁺ cell count is associated with an increased risk of morbidity and mortality associated with conditions not previously thought to be AIDS related, including cardiovascular disease, fatal liver disease, and cancer. As we report here and as has been described elsewhere [4–6, 10], the vast majority of patients who have virological response to therapy exhibit sustained increases in their peripheral CD4⁺ cell count, with most individuals achieving a normal CD4⁺ cell count. However, a significant subset of individuals clearly do not achieve the desired outcome, even after up to 10 years of treatment-mediated viral suppression. This appears to be particularly true among those individuals who delay therapy until their peripheral CD4⁺ cell count decreases to <200 cells/mm³, which is commonly done in both resource-rich and resource-poor regions [8, 20, 21].

Most published reports have focused on the mean change in CD4⁺ cell count over a period of 3–7 years. Although such information is clearly important, it does not provide clarity with regard to whether there is a small subset of individuals who experience prolonged immunological “failure,” which might be defined as reaching a plateau before CD4⁺ cell count normalization occurs. The situation may be analogous to viral load responses. Because most patients do well virologically, the focus is inevitably on the small proportion of failures rather than on the average response. Perhaps the most important observation from our current study is that there is a clear, albeit small, subset of individuals who do not experience normalization of their peripheral CD4⁺ cell count after 10 years of

therapy. The risk of a suboptimal immunological response depends on the pretherapy nadir CD4⁺ cell count, age, and the degree of viral suppression, as has been seen by other researchers [1]. Whether such patients who do not achieve immunologic response will experience normalization of their CD4⁺ cell count with time is unclear, but it seems unlikely, because we could not detect strong evidence of ongoing increases in CD4⁺ cell count after year 7 among those who had yet to achieve a normal CD4⁺ cell count.

The mechanisms underlying poor immunological outcomes during therapy are not clear. In the context of untreated HIV infection, immune activation—as measured by coexpression of CD38 and HLA-DR on T cells—is a strong and independent predictor of CD4⁺ cell loss and disease progression [22, 23]. This appears also to be true in the context of effective therapy [24, 25]. Other factors, such as thymic dysfunction [26], loss of gut mucosal integrity [27], T cell proliferation defects [28, 29], irreversible changes to the lymphoid infrastructure [30], and/or persistent viral replication [31, 32], may be involved. Careful biological assessment of those individuals with persistently low CD4⁺ cell counts during therapy is ongoing.

There are several limitations to this study that deserve mention. First, inclusion in the study was limited to patients who were able to maintain HIV RNA levels <1000 copies/mL for 4 years; thus, generalizability of results is limited to patients who achieve this degree of viral suppression. Second, the level of detection for the viral load assays used in clinical practice decreased over time, thus complicating our blip analysis. The fact that blips were more strongly associated with CD4⁺ cell count increases during the first 4 years of treatment than during the rest of the study period may reflect the fact that only high-level blips (HIV RNA level, >400 copies/mL) were detectable during that time. Third, we used an expansive definition for viral suppression, allowing patients to remain in the analysis if their plasma HIV RNA levels remained <1000 copies/mL. This was done because of the lack of certainty regarding the clinical significance of intermittent viremia [33]. In multivariable analysis, the frequency of blips had no impact on CD4⁺ cell count changes (after year 4), although the changing performance characteristics of the viral load assays may have influenced these findings. Only a small number of patients had persistent low-level viremia at each visit, and the outcomes in these patients were not appreciably different from those in the entire cohort. Fourth, many patients initiated therapy with an unboosted protease inhibitor, which is no longer considered to be the standard of care. It is unlikely, however, that the type of regimen used had a dramatic impact on outcomes, because patients were selected on the basis of viral load, and the level of residual viremia (among those with undetectable plasma HIV RNA levels) does not vary by regimen type [34].

In conclusion, patients who delay therapy until their CD4⁺

cell count decreases to <200 cells/mm³ may not achieve a normal CD4⁺ cell count, even after >10 years of otherwise effective therapy. A clear subset of individuals who do not achieve a normal CD4⁺ cell count by year 4 exhibit evidence of a plateau and may not be able to achieve a normal CD4⁺ cell count without other interventions. These individuals likely remain at risk for developing significant non-AIDS-related events [13]—an issue that we were not powered to address in this study. Depending on the mechanism for these suboptimal immunological outcomes, novel immune-based therapeutic approaches may be necessary to restore immunocompetence in these individuals.

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Potential conflicts of interest. All authors: no conflicts.

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