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

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Abstract

Background—Although antiretroviral therapy has the ability to fully restore a normal $CD4^+$ cell count (>500 cells/mm^3) 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/mm^3 (interquartile range, 72−344 cells/mm^3), 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/mm^3 were able to attain a $CD4^+$ cell count ≥500 cells/mm^3, 44% of patients who started therapy with a $CD4^+$ cell count <100 cells/mm^3 and 25% of patients who started therapy with a $CD4^+$ cell count of 100 −200 cells/mm^3 were unable to achieve a $CD4^+$ cell count >500 cells/mm^3 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/mm^3 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/mm^3 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

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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 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/mm^3 [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 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/mm^3. 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/mm^3 (interquartile range [IQR], 72−344 cells/mm^3), 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/mm^3 (IQR, 390−776 cells/mm^3). 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 4 of HAART

A total of 151 patients (41%) had a $CD4^+$ cell count <500 cells/mm^3 at year 4. Among those 151 individuals, 61 (40%) eventually had a confirmed increase in their $CD4^+$ cell count to >500 cells/mm^3, 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/mm^3 and who had at least 10 years of observation) (figure 1). As expected, the median time until a confirmed $CD4^+$ cell count >500 cells/mm^3 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/mm^3, followed by a sustained decrease to <500 cells/mm^3.

$CD4^+$ cell count slopes after year 4 of HAART

The overall mean change in $CD4^+$ cell count after year 4 was 17 cells/mm^3 per year (95% CI, 11−21 cells/mm^3 per year). The rate was higher among those with a $CD4^+$ cell count <350 cells/mm^3 at year 4 (mean change, 21 cells/mm^3 per year; 95% CI, 12−31 cells/mm^3 per year) than it was among those with a $CD4^+$ cell count of 350−499 cells/mm^3 at year 4 (mean change, 17 cells/mm^3 per year; 95% CI, 6−28 cells/mm^3 per year) and among those with a $CD4^+$ cell count >500 cells/mm^3 at year 4 (mean change, 11 cells/mm^3 per year; 95% CI, 3−17 cells/mm^3 per year; $P = .001$). Using linear mixed-effects models, we found that ~19% of individuals with a $CD4^+$ cell count <350 cells/mm^3 at year 4 and ~27% of patients with $CD4^+$ cell counts of 350−500 cells/mm^3 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/mm^3 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/mm^3, 301−400 cells/mm^3, 201−300 cells/mm^3, 101−200 cells/mm^3, and ≤100 cells/mm^3, respectively (figure

3). Although almost all patients (95%) who started HAART with a $CD4^+$ cell count >300 cells/mm^3 were able to attain a $CD4^+$ cell count >500 cells/mm^3, 44% of patients who started HAART with a $CD4^+$ cell count <100 cells/mm^3 and 25% who started HAART with a $CD4^+$ cell count of 100−200 cells/mm^3 did not achieve a $CD4^+$ cell count >500 cells/mm^3 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/mm^3 for patients with a pretherapy $CD4^+$ cell count of ≤100, 101−200, 201−300, 301−400, and >400 cells/mm^3, 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/mm^3 (IQR, 184−429 cells/mm^3). 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/mm^3, 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 pro-tease 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/mm^3 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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References

1. Battegay M, Nuesch R, Hirschel B, Kaufmann GR. Immunological recovery and antiretroviral therapy in HIV-1 infection. Lancet Infect Dis 2006;6:280–7. [PubMed: 16631548]
2. Pakker NG, Notermans DW, de Boer RJ, et al. Biphasic kinetics of peripheral blood T cells after triple combination therapy in HIV-1 infection: a composite of redistribution and proliferation. Nat Med 1998;4:208–14. [PubMed: 9461195]
3. Bucy RP, Hockett RD, Derdeyn CA, et al. Initial increase in blood $CD4^+$ lymphocytes after HIV antiretroviral therapy reflects redistribution from lymphoid tissues. J Clin Invest 1999;103:1391–8. [PubMed: 10330421]
4. Garcia F, de Lazzari E, Plana M, et al. Long-term $CD4^+$ T-cell response to highly active antiretroviral therapy according to baseline $CD4^+$ T-cell count. J Acquir Immune Defic Syndr 2004;36:702–13. [PubMed: 15167289]
5. Moore RD, Keruly JC. $CD4^+$ cell count 6 years after commencement of highly active antiretroviral therapy in persons with sustained virologic suppression. Clin Infect Dis 2007;44:441–6. [PubMed: 17205456]
6. Kaufmann GR, Perrin L, Pantaleo G, et al. CD4 T-lymphocyte recovery in individuals with advanced HIV-1 infection receiving potent antiretroviral therapy for 4 years: the Swiss HIV Cohort Study. Arch Intern Med 2003;163:2187–95. [PubMed: 14557216]
7. Tarwater PM, Margolick JB, Jin J, et al. Increase and plateau of CD4 T-cell counts in the 3 1/2 years after initiation of potent antiretroviral therapy. J Acquir Immune Defic Syndr 2001;27:168–75. [PubMed: 11404539]
8. Gras L, Kesselring AM, Griffin JT, et al. CD4 cell counts of 800 cells/mm^3 or greater after 7 years of highly active antiretroviral therapy are feasible in most patients starting with 350 cells/mm^3 or greater. J Acquir Immune Defic Syndr 2007;45:183–92. [PubMed: 17414934]
9. Hunt PW, Deeks SG, Rodriguez B, et al. Continued CD4 cell count increases in HIV-infected adults experiencing 4 years of viral suppression on antiretroviral therapy. AIDS 2003;17:1907–15. [PubMed: 12960823]
10. Mocroft A, Phillips AN, Gatell J, et al. Normalisation of CD4 counts in patients with HIV-1 infection and maximum virological suppression who are taking combination antiretroviral therapy: an observational cohort study. Lancet 2007;370:407–13. [PubMed: 17659333]
11. Panel on Antiretroviral Guidelines for Adult and Adolescents.. Guidelines for the use of antiretroviral agents in HIV-infected adults and adolescents.; Department of Health and Human Services. Dec 12007 [16 December 2007]. p. 1-143.Available at: http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf.
12. Le Moing V, Thiebaut R, Chene G, et al. Long-term evolution of CD4 count in patients with a plasma HIV RNA persistently <500 copies/mL during treatment with antiretroviral drugs. HIV Med 2007;8:156–63. [PubMed: 17461859]
13. Baker JV, Peng G, Rapkin J, et al. $CD4^+$ count and risk of non-AIDS diseases following initial treatment for HIV infection. AIDS 2008;22:841–8. [PubMed: 18427202]
14. El-Sadr WM, Lundgren JD, Neaton JD, et al. $CD4^+$ count–guided interruption of antiretroviral treatment. N Engl J Med 2006;355:2283–96. [PubMed: 17135583]
15. Weber R, Sabin CA, Friis-Moller N, et al. Liver-related deaths in persons infected with the human immunodeficiency virus: the D:A:D study. Arch Intern Med 2006;166:1632–41. [PubMed: 16908797]

16. Gutierrez F, Padilla S, Masia M, et al. Clinical outcome of HIV-infected patients with sustained virologic response to antiretroviral therapy: long-term follow-up of a multicenter cohort. PLoS ONE 2006;1:e89. [PubMed: 17183720]

17. Moore DM, Hogg RS, Chan K, Tyndall M, Yip B, Montaner JS. Disease progression in patients with virological suppression in response to HAART is associated with the degree of immunological response. AIDS 2006;20:371–7. [PubMed: 16439870]

18. Lewden C, Chene G, Morlat P, et al. Agence Nationale de Recherches sur le Sida et les Hepatites Virales (ANRS) CO8 APROCO–COPILOTE Study Group; Agence Nationale de Recherches sur le Sida et les Hepatites Virales (ANRS) CO3 AQUITAINE Study Group. HIV-infected adults with a CD4 cell count greater than 500 cells/mm^3 on long-term combination antiretroviral therapy reach same mortality rates as the general population. J Acquir Immune Defic Syndr 2007;46:72–7. [PubMed: 17621240]

19. Kaufmann GR, Furrer H, Ledergerber B, et al. Characteristics, determinants, and clinical relevance of CD4 T cell recovery to <500 cells/μL in HIV type 1–infected individuals receiving potent antiretroviral therapy. Clin Infect Dis 2005;41:361–72. [PubMed: 16007534]

20. Dybul M, Bolan R, Condoluci D, et al. Evaluation of initial $CD4^+$ cell counts in individuals with newly diagnosed human immunodeficiency virus infection, by sex and race, in urban settings. J Infect Dis 2002;185:1818–21. [PubMed: 12085332]

21. Braitstein P, Brinkhof MW, Dabis F, et al. Mortality of HIV-1–infected patients in the first year of antiretroviral therapy: comparison between low-income and high-income countries. Lancet 2006;367:817–24. [PubMed: 16530575]

22. Liu Z, Cumberland WG, Hultin LE, Kaplan AH, Detels R, Giorgi JV. $CD8^+$ T-lymphocyte activation in HIV-1 disease reflects an aspect of pathogenesis distinct from viral burden and immunodeficiency. J Acquir Immune Defic Syndr Hum Retrovirol 1998;18:332–40. [PubMed: 9704938]

23. Deeks SG, Kitchen CM, Liu L, et al. Immune activation set point during early HIV infection predicts subsequent $CD4^+$ T-cell changes independent of viral load. Blood 2004;104:942–7. [PubMed: 15117761]

24. Hunt PW, Martin JN, Sinclair E, et al. T cell activation is associated with lower $CD4^+$ cell gains in human immunodeficiency virus–infected patients with sustained viral suppression during antiretroviral therapy. J Infect Dis 2003;187:1534–43. [PubMed: 12721933]

25. Valdez H, Connick E, Smith KY, et al. Limited immune restoration after 3 years' suppression of HIV-1 replication in patients with moderately advanced disease. AIDS 2002;16:1859–66. [PubMed: 12351945]

26. Teixeira L, Valdez H, McCune JM, et al. Poor CD4 T cell restoration after suppression of HIV-1 replication may reflect lower thymic function. AIDS 2001;15:1749–56. [PubMed: 11579235]

27. Brenchley JM, Price DA, Schacker TW, et al. Microbial translocation is a cause of systemic immune activation in chronic HIV infection. Nat Med 2006;12:1365–71. [PubMed: 17115046]

28. Benito JM, Lopez M, Lozano S, Gonzalez-Lahoz J, Soriano V. Down-regulation of interleukin-7 receptor (CD127) in HIV infection is associated with T cell activation and is a main factor influencing restoration of $CD4^+$ cells after antiretroviral therapy. J Infect Dis 2008;198:1466–73. [PubMed: 18847371]

29. Marziali M, De Santis W, Carello R, et al. T-cell homeostasis alteration in HIV-1 infected subjects with low CD4 T-cell count despite undetectable virus load during HAART. AIDS 2006;20:2033–41. [PubMed: 17053349]

30. Schacker TW, Nguyen PL, Martinez E, et al. Persistent abnormalities in lymphoid tissues of human immunodeficiency virus–infected patients successfully treated with highly active antiretroviral therapy. J Infect Dis 2002;186:1092–7. [PubMed: 12355359]

31. Havlir DV, Strain MC, Clerici M, et al. Productive infection maintains a dynamic steady state of residual viremia in human immunodeficiency virus type 1–infected persons treated with suppressive antiretroviral therapy for five years. J Virol 2003;77:11212–9. [PubMed: 14512569]

32. Ostrowski SR, Katzenstein TL, Thim PT, Pedersen BK, Gerstoft J, Ullum H. Low-level viremia and proviral DNA impede immune reconstitution in HIV-1–infected patients receiving highly active antiretroviral therapy. J Infect Dis 2005;191:348–57. [PubMed: 15633093]

33. Nettles RE, Kieffer TL, Kwon P, et al. Intermittent HIV-1 viremia (Blips) and drug resistance in patients receiving HAART. JAMA 2005;293:817–29. [PubMed: 15713771]

34. Maldarelli F, Palmer S, King MS, et al. ART suppresses plasma HIV-1 RNA to a stable set point predicted by pretherapy viremia. PLoS Pathog 2007;3:e46. [PubMed: 17411338]

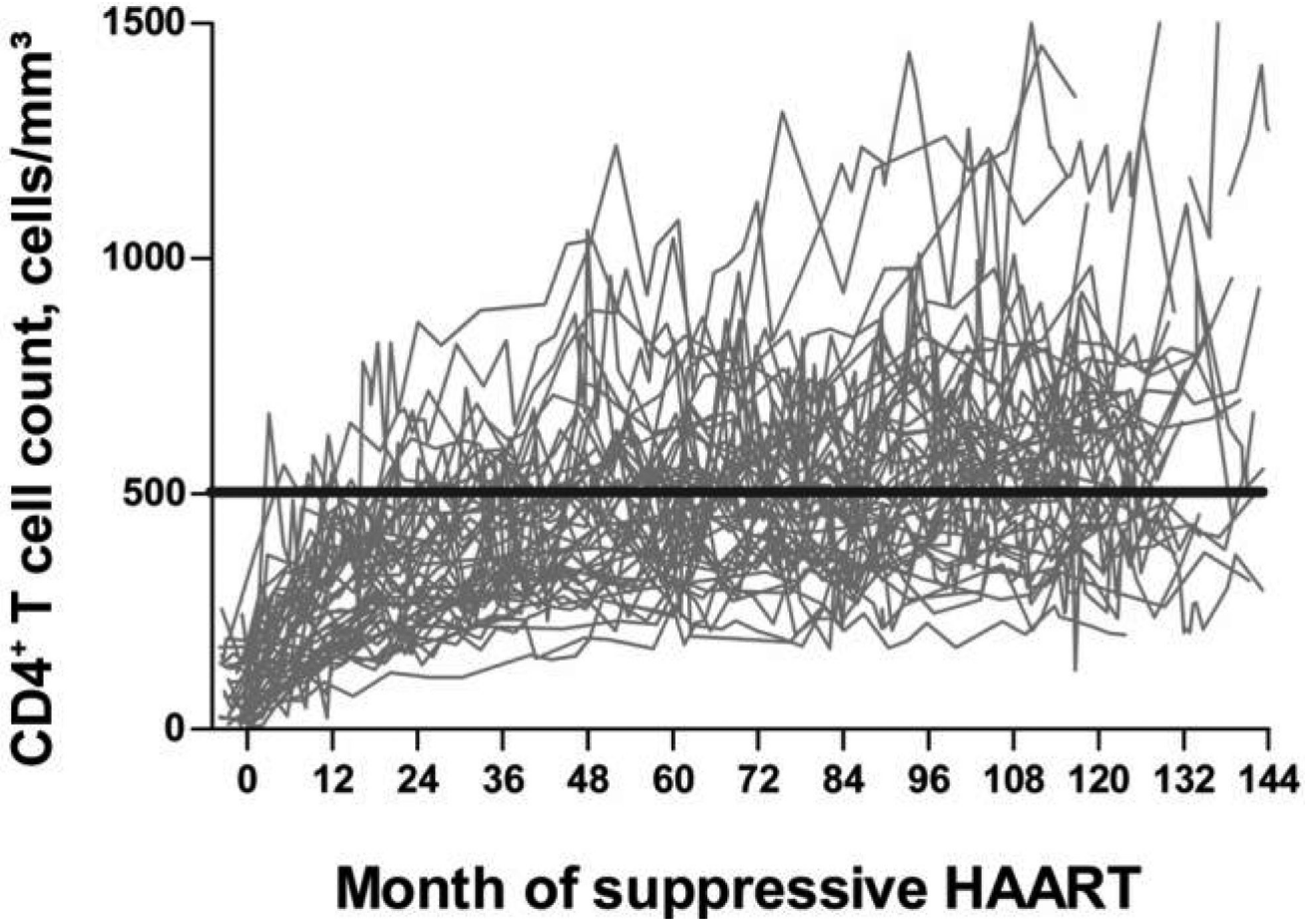

Figure 1.

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/mm^3 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/mm^3).

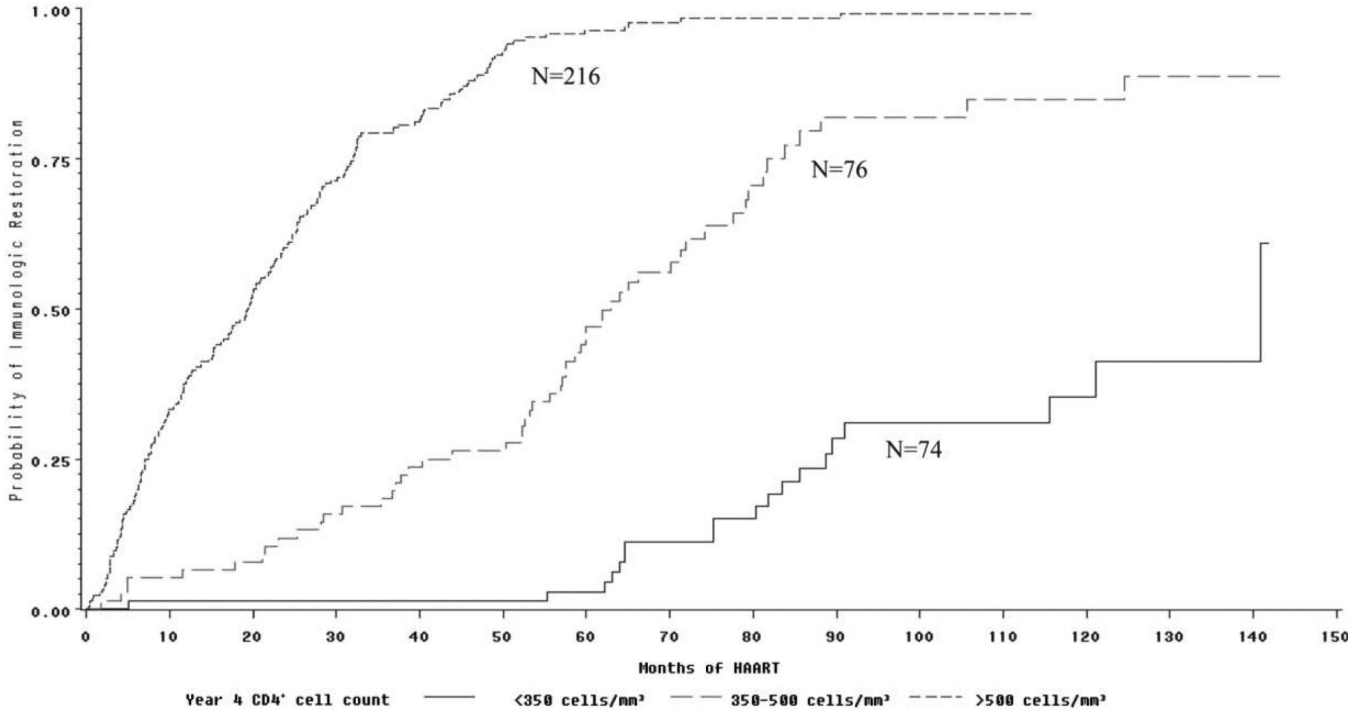

Figure 2.

The time from initiation of HAART to achievement of a $CD4^+$ cell count >500 cells/mm^3, 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/mm^3, 76 had a $CD4^+$ cell count of 350–500 cells/mm^3, and 216 had a $CD4^+$ cell count >500 cells/mm^3). The time from initiation of HAART to achievement of a $CD4^+$ cell count >500 cells/mm^3 was significantly different among the strata ($P < .001$, by the log-rank test).

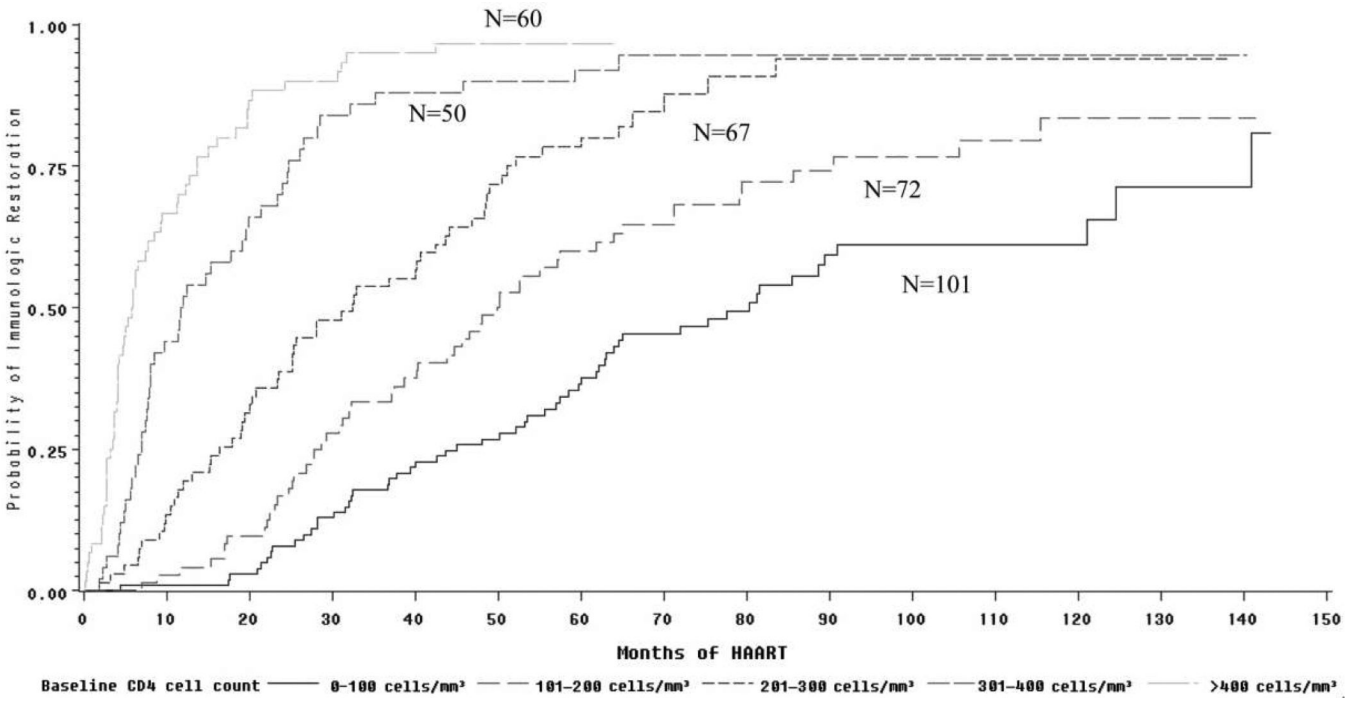

Figure 3.

The time from HAART initiation to achievement of a $CD4^+$ count >500 cells/mm^3, 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/mm^3, respectively). The time from HAART initiation to achievement of a $CD4^+$ cell count >500 cells/mm^3 was significantly different among the strata ($P < .001$, by the log-rank test).

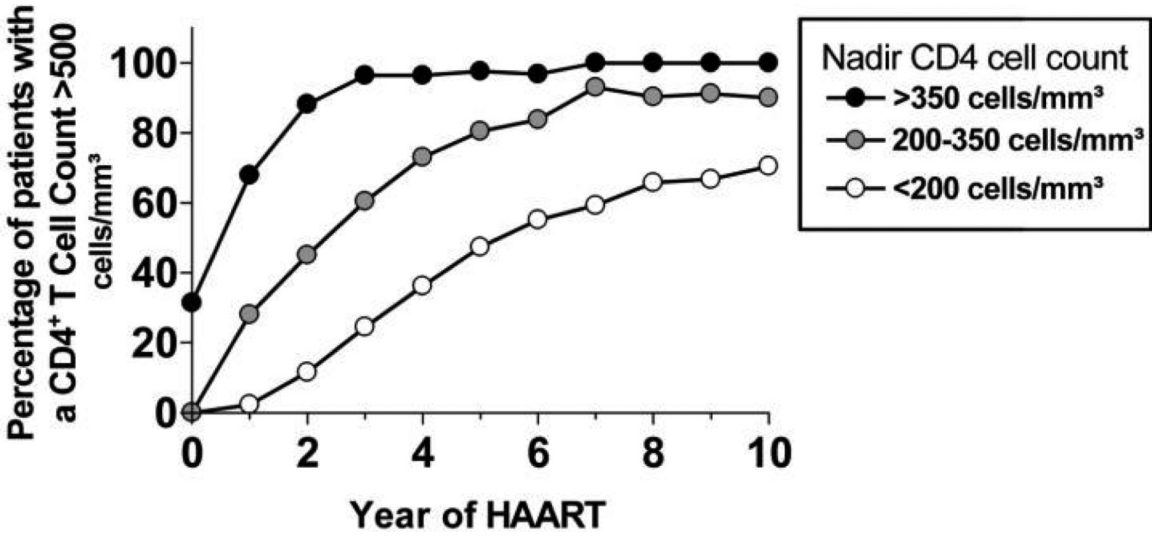

Figure 4.

The percentage of patients with a $CD4^+$ cell count in the normal range (>500 cells/mm^3) 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.

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)

Characteristic	Value
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.