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Modeling CD4+ Cell Count Increase Over a Six-Year Period in HIV-1–Infected Patients on Highly Active Antiretroviral Therapy in Senegal

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Abstract. To assess the extents and determinants of long-term CD4 cell increases after initiation of antiretroviral therapy (ART), changes in CD4 cell counts were analyzed in a cohort of HIV-1–infected Senegalese using a mixed-effects model. After a median follow-up of 54 months, an average of 483 CD4 cells/mm^3 (95% confidence interval [CI] = 331; 680) was reached. The average asymptote level was ~421 cells/mm^3 (95% CI = 390; 454) in patients with < 200 cells/mm^3 at baseline and ~500 cells/mm^3 in patients with > 200 cells/mm^3. The independent predictors of long-term CD4 cell reconstitution were the baseline CD4 cell count and the monthly average viral load over the entire follow-up. This good long-term immune reconstitution, optimal in subjects with low average viral loads and > 200 CD4 cells/mm^3 at baseline, argues in favor of the earliest possible access to ART and underlines the importance of strict compliance with the treatment.

INTRODUCTION

Highly active antiretroviral therapies (HAART) have considerably changed the clinical outcomes of patients living with HIV/AIDS in both developed and developing countries.[1–3] However, in developing countries, because of programmatic issues, the access of people living with HIV/AIDS to antiretroviral treatment occurs usually at an advanced disease stage with severe immunodeficiency.[4,5] This leads to a high early mortality rate after HAART initiation, although the long-term clinical outcome in survivors remains good.[3,5,6] In addition to its short-term impact on mortality, an advanced disease stage may also affect long-term immune recovery under HAART.

Generally, after HAART initiation, patients experience a rise in CD4 cell count. Early dynamics of CD4 cell reconstitution is usually made up of two phases.[7–16] The early phase is typically characterized by a high rate of CD4 cell increase and corresponds to a redistribution of trapped T cells.[7,8,14,17] In patients with low CD4 cell counts at baseline, this rate of increase is at least similar to the one seen in patients with much higher CD4 cell counts at baseline.[4,18,19] The second phase, a few months after HAART initiation, is characterized by a slower rate of CD4 cell increase and corresponds to an expansion of naive CD4 cells.[7–9,14,16] A few years later, that increase slows down significantly[12,19] or settles to a plateau.[20–22]

The consequences of severe immunodeficiency on long-term immune recovery have been the subject of intense controversy. Indeed, in patients with advanced AIDS, several authors reported a lack of CD4 cell increase and an impaired CD4 cell functional response,[12,19,20,22–24] whereas others reported a delayed CD4 cell increase regardless of the level of initial immunodeficiency.[25,26] These conflicting results may have resulted from confounders such as age, viral load, or follow-up duration.

Actually, several studies have shown that optimal CD4 cell reconstitution was seen in patients with constantly undetectable viral loads.[18,21,27] The viral load should be taken into account in the analysis of long-term immune reconstitution. Other factors associated with the viral load but inconstantly mentioned in the literature are age,[11,19,22,25,28] sex,[11] and HAART regimen.[29] Moreover, in Africa, frequent co-infections might affect the survival of HIV-1 patients.[30]

This study analyzes the long-term increase in CD4 cell count after HAART initiation in a cohort of adult Senegalese patients. This cohort was part of the Senegalese antiretroviral drug access initiative (ISAARV) that started in 1998 and was one of the first such programs in Africa.[5,31] This study considered mainly the viral load, the extent of immunodeficiency at baseline, and other baseline cofactors such as age, sex, and body mass index. The study focused on two issues: does the long-term immunologic response after HAART initiation depend on the extent of the previous immunodeficiency and what are the independent determinants of the long-term increase in CD4 cell count after HAART initiation?

MATERIALS AND METHODS

Patients. From August 1998 to April 2002, 404 HIV-1–infected patients ≥ 15 years of age were enrolled in ISAARV (Dakar) and included in this observational study. Data were censored as of September 2007.

After initial clinical examination and laboratory tests, those patients had to undergo clinical examinations at least every 2 months and laboratory tests at least every 6 months thereafter. Of the 404 patients, 346 had complete data at baseline (age, sex, viral load, CD4 cell count, CDC AIDS stage), and at least one additional CD4 cell count and one additional viral load measurement were included in the analyses, irrespective of their follow-up durations. Finally, because laboratory tests were very sparse during the last months of follow-up, only the results of the first 72 months were analyzed.

The initial ART regimen was a triple drug combination: two nucleoside reverse transcriptase inhibitors (NRTI) + a non-nucleoside reverse transcriptase inhibitor (NNRTI) or a protease inhibitor (PI), except for 18 patients who received only

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two NRTIs until May 2000. HAART was provided for free starting from December 2003.

This research received ethical clearance from the National Ethic Committee of Senegal, and all patients gave their written informed consent.

Laboratory tests. The CD4 cell counts were obtained using the FACSCount System (Becton Dickinson, San Jose, CA). The plasma viral loads were determined using either Bayer bDNA HIV-1 Quantiplex assay, version 2.0 or 3.0 (Bayer Diagnostics, Tarrytown, NY) or Amplicor HIV-1 Monitor assay, version 1.5 or 2.0 (Roche Molecular Systems, Belleville, NJ). Detectability thresholds were 500 copies/mL for Bayer and 50 copies/mL for Roche. The threshold of 500 copies/mL was used for the analysis. All tests were carried out at Dakar, Senegal, and the laboratories were involved in an external quality assessment.

Statistical analysis. *General approach.* The study distinguished three categories of CD4 cell counts at baseline: < 100, 100–199, and ≥ 200 cells/mm^3. The medians of the CD4 cell counts computed over successive 6-month periods were plotted against time.

The evolution of the CD4 cell count over time was estimated using a mixed-effects model.[32,33] In such a model, each estimated coefficient is made up of two components: 1) a fixed effect that represents the average value of the coefficient in the cohort and 2) a random effect that represents the individual deviation from that cohort average.

Long-term immune response. This called for a mechanistic model that represents the hypothetical dynamics of CD4 cells after HAART initiation as already established by previous studies. The model provides parameters with genuine clinical significance and allows testing the effects of the baseline covariates (age, sex, etc.) and of the viral load.

Specifically, modeling the increase in CD4 cells during the first 6 years after HAART initiation used an asymptotic regression model; i.e., a non-linear function of time with a final horizontal asymptote. In this model, the asymptote represents the predicted CD4 cell level after apparent stabilization. That level may be either a return to a normal CD4 cell level in response to antiretroviral therapy or a persistence at a subnormal level in case of impaired immune reconstitution.

The model included four parameters: the asymptote ($Asym$), the baseline value (C_0), the logarithm of the initial rate of increase ($lrc1$), and the change in that rate after 6 months ($lrc2$)[34,35]:

$$\sqrt{CD4} \propto Asym + (C_0 - Asym) \times \exp\left[-\exp(lrc1) \times t + lrc2 \times (t-6)_+\right]$$

A piecewise log-linear component was used to distinguish the immune response during the first 6 months from that response thereafter. In other words, the rate parameter is "$-\exp(lrc1) \times t$" before 6 months and becomes "$-\exp(lrc1) \times t + lrc2 \times (t - 6)$" after 6 months.

Square root–transformed CD4 cell counts were used to approximate a normal distribution; however, to facilitate interpretation, the results were expressed back in the original scale (i.e., number of CD4 cells/mm^3) whenever possible. The delta method was used to compute the 95% confidence intervals (CIs) in the original scale.

Sex, age, CD4 cell count (> 200 versus ≤ 200 cells/mm^3), and AIDS clinical stage at inclusion were considered as potential predictors of the long-term CD4 cell count. Virologic success was defined as a viral load of < 500 copies/mL. The relationship between the viral load and the long-term CD4 asymptote was analyzed through three variables: the time to virologic success, the monthly average viral load over the entire follow-up, and the proportion of the remaining follow-up time spent with viral suppression starting from detection of that suppression (this variable was assigned value zero in patients who never achieved viral suppression). An interaction term between the parameter for the long-term CD4 cell count (Asym) and the vital status of the patient at the end of follow-up was introduced. Therefore, the long-term CD4 cell count was estimated for patients who survived. The covariates were entered in the model one at a time and their significance was assessed using the likelihood ratio test for nested models. The latter models were estimated using the maximum likelihood and their goodness-of-fit assessed with graphical tools.[34]

To assess the goodness-of-fit of the asymptotic model, we also modeled the CD4 cell response in three subsets defined by their baseline CD4 cell counts (< 100, 100–200, and > 200 cells/mm^3) with mixed-effects polynomial regression models of time. The order of the polynomial of time was chosen high enough (fourth order) to give a good fit to the CD4 cell count.

The open-source statistical package R (library nlme[34]) was used for all statistical analyses (available at: http://www.r-project.org).

RESULTS

Cohort characteristics. Patients' characteristics at baseline are given in Table 1. The median follow-up time with information on the CD4 cell count was 54 months (interquartile range [IQR] = 42–66). During follow-up, 56 patients died (16%) so the median CD4 cell counts available for each patient fell to seven (IQR = 5–9). Moreover, as of September 2007, 80 (23%) patients were censored, and 22 (9%) were lost to follow-up (Figure 1).

Among the 346 patients, 13 began with a dual ART regimen (3.75%), and 141 had a PI (41%). During follow-up, 162 patients had at least one change in their ART (47.09%), the maximum being five changes.

Viral markers of HIV disease. Nearly 91% of the subjects achieved a virologic success in a median time of 6 months (IQR = 6–12). As shown in Figure 2, the probability of achieving an undetectable viral load increased steeply over the first 24 months but moderately thereafter. The multivariate analysis showed that older ages and higher baseline CD4 cell counts were associated with an increased probability of virologic

TABLE 1
Baseline characteristics of the 346 HIV-1–infected patients under HAART, Senegal, 1998–2007

Characteristic	Value at baseline
Age, median [IQR] (years)	37 [31–43]
Female sex	192 (55%)
CD4 cell count (cells/mm^3)	
< 100	135 (39%)
100–200	99 (29%)
> 200	112 (32%)
Viral load, median [IQR] ($\log_{10}$ copies/mL)	5.17 [4.65–5.57]
AIDS clinical stage	
CDC A or B	157 (46%)
CDC C	188 (54%)

IQR = interquartile range.

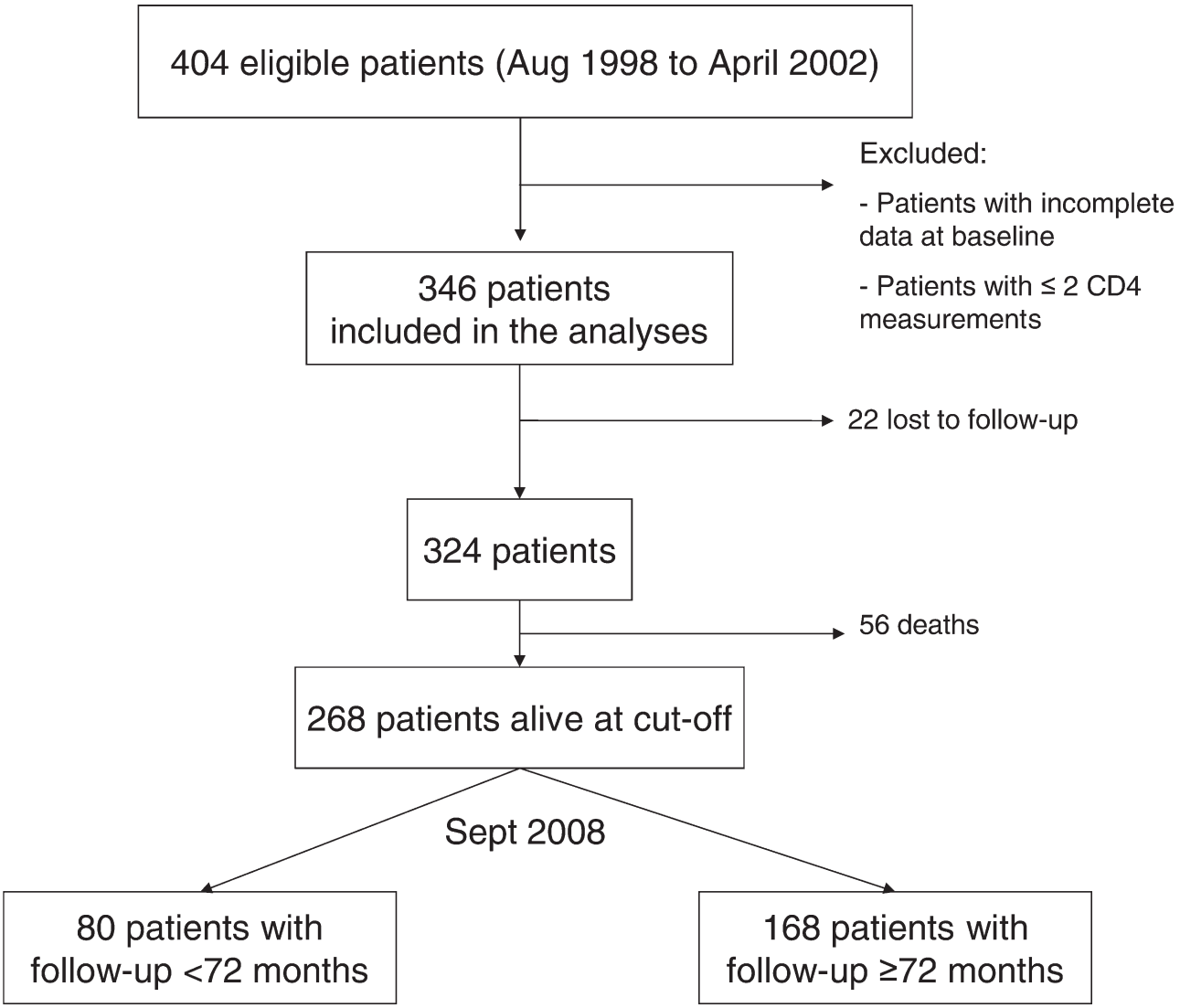

FIGURE 1. Description of the population studied—Initiative Sénégalaise d'Accès aux Antirétroviraux, 1998–2007.

success (relative risks: 1.14 [95% CI = 1.01; 1.29] by 10-year increment and 1.01 [95% CI = 1.01; 1.11] by 50 CD4 cells/mm^3, respectively). The correlation coefficient between the time to virologic success and the monthly average viral load over entire follow-up was 0.48 (95% CI = 0.4; 0.56). During the study period, 68% of the viral load measurements were < 500 copies/mL, and 61% of the study population remained < 500 copies/mL at all visits after achieving a first undetectable viral load.

Immune reconstitution. A plot of the median CD4 cell counts of the three groups defined according to the CD4 cell count at baseline is shown in Figure 3. That median increased from 139 cells/mm^3 (IQR = 59–226) at baseline to 483 cells/mm^3 (IQR = 331–680) at 72 months. The median changes in CD4 cell counts between baseline and the last measurement for the three CD4 groups are summarized in Table 2.

The final asymptotic model without covariates had a modeled average baseline CD4 cell level of 137 CD4 cells/mm^3 (95% CI = 124; 150). The rate of increase in CD4 cells (using the square root of the CD4 cell counts) during the first 6 months was 0.078 per month (95% CI = 0.069; 0.088); it showed a significant change afterward (–0.02, 95% CI = –0.01;–0.04]) until an asymptote around 453 CD4 cells/mm^3 (95% CI = 425; 482). Random effects were permitted for the intercept and the asymptote but were not necessary for the log of the rate of increase. The between-subject variation in the asymptote was quite large (the SD of the square root of the number of CD4 cells per cubic millimeter was 5.14 [95% CI = 4.70; 5.61), leading to a 95% prediction interval for the asymptote of 98–1,067. For each group defined according to the CD4 cell count at baseline, the curves of a polynomial model and of the fitted mean responses with the asymptotic model are displayed and show similar patterns (Figure 3).

In a second step, we assessed the associations between the covariates and the between-subject variation in the asymptote level (Table 3). In univariate analyses, the CD4 cell count at baseline, the time to first virologic success, and the monthly average viral load over entire follow-up were significantly associated with the level of the asymptote. There was also a borderline effect of sex on the asymptote level. The average asymptote level of the group with a baseline CD4 cell count < 200 cells/mm^3 and who survived was 421 CD4 cells/mm^3

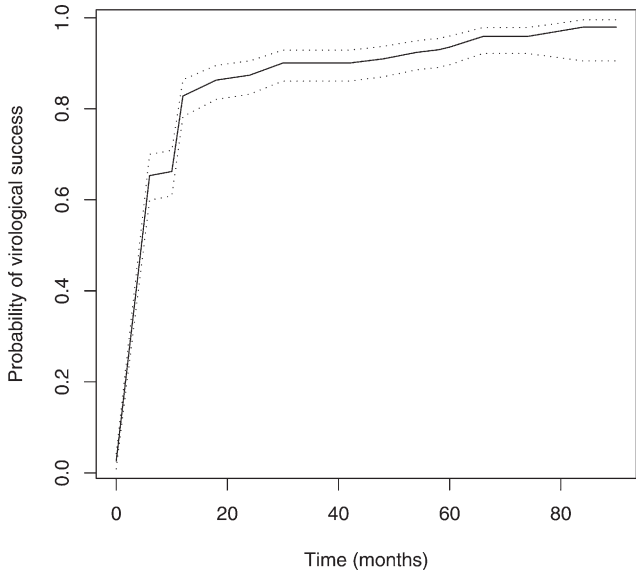

FIGURE 2. Non-parametric estimation of the probability (and 95% confidence interval) of achieving an undetectable viral load along time in 346 HIV-infected patients under HAART, Senegal, 1998–2007.

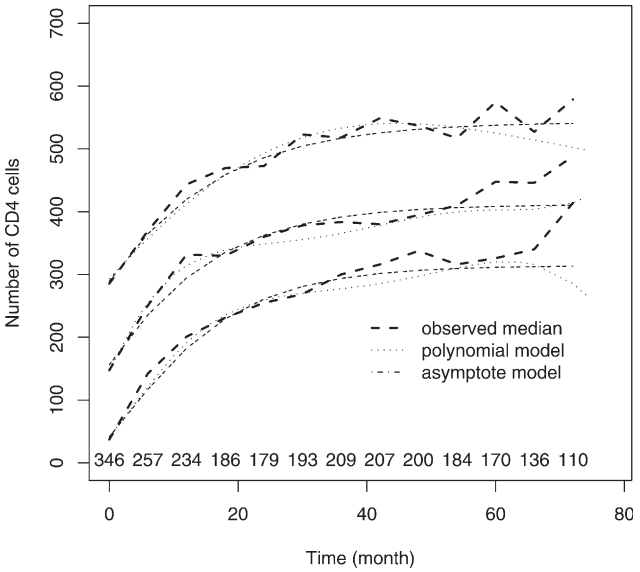

FIGURE 3. Median CD4 cell counts after HAART initiation in groups defined by their counts at baseline (< 100 lower curves, 100–200 median curves, and > 200 cells/mm^3 upper curves). Thick dashes represent the observed medians, thin dashes the asymptotic models, and dots represent the polynomial models. Figures at the bottom of the frame are the number of contributors to each measurement.

(95% CI = 390; 454). Approximately one quarter of the patients starting with a CD4 cell count < 200 cells/mm^3 reached a CD4 cell count of 600 cells/mm^3, and ~15% reached a CD4 cell count of 700 cells/mm^3.The asymptote level of the group with a baseline CD4 cell count > 200 cells/mm^3 was higher (mean level, 519 CD4/mm^3; 95% CI = 474; 564).

In multivariate analyses, patients with baseline CD4 cell counts > 200 cells/mm^3 had, on average, a 1.15-fold higher long-term CD4-cell level (95% CI = 1.02; 1.44) in comparison with patients with < 200 CD4 cells/mm^3. Each increase of 1 $\log_{10}$ of the monthly average viral load over the entire follow-up was associated with a 1.3-fold decrease of the CD4 cell asymptote level (95% CI = 1.03; 1.56). The average asymptote level of patients who started with < 200 CD4 cells/mm^3, maintained a good virologic suppression, and survived was 734 CD4/mm^3 (95% CI = 647; 822). A subject starting with > 200 CD4 cells/mm^3 and maintaining a good virologic suppression would reach an average CD4 cell count of ~828 cells/mm^3 (734; 923), which is a normal level.

The sensitivity of our results was analyzed to assess the influence of the sparseness of the measurements during the last months of follow-up and the influence of the CD4 cell value in patients who died. Results are given in relative rate of change in the value of the estimated coefficient. Using a follow-up duration ranging from 54 to 72 months, the amplitudes of the variations in the coefficients of the multivariate model were < 10%. Excluding from the analyses all the patients who died led to < 10% changes in those coefficients.

TABLE 2

Median observed CD4 cell counts at baseline, last measurement before 72 months, and difference between baseline and last measurement according to different categories of CD4 cell numbers at baseline

CD4 cell count at baseline	Number of observations (loss to follow-up/ death)	Median (IQR) difference (cells/mm^3)	Median CD4 at baseline (cells/mm^3)	Median CD4 at last measurement (cells/mm^3)
< 50 cells/mm^3	78 (7/16)	175.5 (65; 395)	21.5	208
50–100 cells/mm^3	57 (6/13)	132 (52; 321)	74	219
100–200 cells/mm^3	99 (7/19)	203 (95; 338)	148	344
> 200 cells/mm^3	112 (12/9)	144 (17; 308)	259	455

IQR = interquartile range.

DISCUSSION

This study outlined the effects of the baseline CD4 cell count and of the viral load on long-term immunologic reconstitution after HAART initiation in a low-resource setting. It used a mechanistic model based on a simplification of the biologic process under study (CD4 immune reconstitution). The model allowed a specific analysis of the main features of CD4 cell dynamics and was independent of the data structure.

These results confirm the place of the viral markers of HIV disease as a determinant of long-term immunologic reconstitution as already found by others in industrialized countries.[7,11,18,20,21,25,27] Several studies took into account a so-called "virologic response" to explain immune reconstitution but the definition of that "response" was not always the same.[11,12,15,21,25,27] In this study, the virologic response was considered under three aspects: the monthly average viral load over the entire follow-up, the proportion of time with viral suppression after achieving undetectability, and the time to first virus undetectability. Using these variables as surrogates of the virologic response avoids relying on a particular time point or on an arbitrary cut-off. In our results, only the monthly average viral load was independently associated with long-term CD4 cell reconstitution. This indicates a stronger association of the long-term immune response with the virologic failure than with the time to virologic success and also that the extent of the virologic rebound is also a key variable.

Among patients' characteristics measured at baseline, only the CD4 cell count was an independent predictor of long-term immune reconstitution. It is important to emphasize that we could not conclude whether, after 72 months of follow-up, patients with low CD4 cell counts at baseline reached the same

Table 3
Change in position of the asymptote CD4 cell count after HAART according to its long-term predictors

Predictors of long-term CD4 cell count asymptote	Univariate analyses		Multivariate analyses*	
	Change in square roots of predicted CD4 cell asymptote	Changes in predicted CD4 cell asymptote (cells/mm^3)	Change in square roots of predicted CD4 cell asymptote	Changes in predicted CD4 cell asymptote (cells/mm^3)
Age at baseline (per year)	+0.02 [−0.05;0 .08]	+0.7 [−32; 33]†	–	–
Gender (female vs. male)	+0.93 [−0.21; 2.08]	+38 [−2; 100]	–	–
CDC stage (A/B vs. C)	−0.01 [−0.65; 0.49]	−3 [−24; 18]	–	–
Baseline CD4 cell count (> 200 vs. ≤ 200 cells/mm^3)	+2.24 [1.05; 3.42]	+97 [61; 132]	+1.95 [0.88; 3.02]	+112 [84; 140]
Mean viral load (per unit increase in $\log_{10}$ copies/mL)	−2.39 [−2.91; −1.87]	−150 [−175; −125]	−3.13 [−3.71; −2.56]	−163 [−188; −138]
Time to the undetectable viral load (per month)	−0.1 [−0.13; −0.06]	−121 [−144; −98]	–	–
Proportion of the remaining follow-up with viral suppression‡	4.54 [3.01; 6.07]	179 [157; 201]	–	–

Univariate and multivariate analysis using a non-linear mixed-effects model, 346 HIV-1–infected patients under HAART, Senegal, 1998–2007.
* Only significant predictors were kept into the final model.
† Confidence intervals computed using the Delta method (potentially inaccurate because of approximation).
‡ Proportion of the remaining follow-up time spent with viral suppression starting from detection of that suppression (this variable was assigned value zero in patients who never achieved viral suppression).

level as patients with much higher counts. Only studies with longer follow-ups may provide that answer, but the most interesting result is that patients with < 200 CD4 cells/mm^3 needed significantly more time to reach the same CD4 levels than patients with higher CD4 cell counts before HAART initiation (the estimated asymptote is lower in the former patients) even though several studies have shown that the initial rates of increase in CD4 in the former patients could be higher.[13,14,27]

There was a borderline interaction between long-term CD4 cell count and sex that faded out when the viral load and the baseline CD4 cell count were included in the model. Contrary to other studies, we did not find a significant association between long-term immune reconstitution and age at inclusion, although the median age at baseline in the Senegalese cohort was lower than in many European or American cohorts.[11,19,22,25,28] However, age was found to be associated to the virologic response. In another study, Etard and others[36] did not find a significant association between age and adherence. Further exploration of this association should be done.

As reported in numerous other studies, we found there was a two-stage increase of the CD4 cell count,[8,11,13–16,18,27] but no significant differences before 12 months in the rate of CD4 cell increase according to AIDS stage, age, or CD4 cell count at baseline. Our study considered only one specific aspect of the immune function, the change in the number of CD4 cells, but did not take into account the proportion of naive CD4 or memory CD4 cells. Our results should be completed by studies on other immune reconstitution markers because the functions of the newly produced CD4 cells may be impaired.[7,14,18]

Subjects who died shortly after HAART initiation are likely to have had very low CD4 cell counts and different CD4 dynamics than those of surviving patients. The model used in this analysis accommodated this by stratification of the vital status of the patients. Therefore, long-term CD4 cell count level was estimated for a population who survived long enough. Moreover, excluding the patients who died of the analysis, we found that our results were not sensitive to the extreme values in the patients who died (change in point estimates < 10%). We also found that the number of CD4 cell measurements during the last months of follow-up had no impact on the positive results obtained.

This study presents several strengths and limitations. Despite its limited size, the study cohort boasts a long follow-up and few were lost to follow-up. There were missing data because some patients were included too late to achieve the 72 months of follow-up, but these data were missing completely at random, which did not bias the results. However, the departure from the horizontal asymptote of the empirical mean CD4 cell count after 60 months of follow-up may also suggest a "not completely at random" dropout mechanism.[33] In such a case, patients with low CD4 cells are more prone to dropout, leading to an apparent trend in the mean response. Diggle and others[33] have already shown that, if the dropout depends on past but not on future measurements, it can be ignored for likelihood-based inference. In other words, curves issued from a polynomial model or an asymptotic model give the mean response corrected for dropout. A simple polynomial random effects model fitted to the square root–transformed CD4 cell counts would be compatible with a plateau after 60 months. However, a slow increase for some subset of patients cannot be excluded, and longer follow-ups as in other observational studies are still needed to complete these results.

In summary, despite a great non-negligible initial immune reconstitution and even after 72 months on HAART, patients with the most advanced disease were still unable to reach the same CD4 cell counts as patients with a milder disease. These results argue strongly in favor of the earliest possible access to HAART and a sustained virologic suppression through strict compliance with the treatment.

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