ORIGINAL ARTICLE

Enhanced CD4+ T-Cell Recovery with Earlier HIV-1 Antiretroviral Therapy

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ABSTRACT

BACKGROUND

The relationship between the timing of the initiation of antiretroviral therapy (ART) after infection with human immunodeficiency virus type 1 (HIV-1) and the recovery of CD4+ T-cell counts is unknown.

METHODS

In a prospective, observational cohort of persons with acute or early HIV-1 infection, we determined the trajectory of CD4+ counts over a 48-month period in partially overlapping study sets: study set 1 included 384 participants during the time window in which they were not receiving ART and study set 2 included 213 participants who received ART soon after study entry or sometime thereafter and had a suppressed plasma HIV viral load. We investigated the likelihood and rate of CD4+ T-cell recovery to 900 or more cells per cubic millimeter within 48 months while the participants were receiving viral-load–suppressive ART.

RESULTS

Among the participants who were not receiving ART, CD4+ counts increased spontaneously, soon after HIV-1 infection, from the level at study entry (median, 495 cells per cubic millimeter; interquartile range, 383 to 622), reached a peak value (median, 763 cells per cubic millimeter; interquartile range, 573 to 987) within approximately 4 months after the estimated date of infection, and declined progressively thereafter. Recovery of CD4+ counts to 900 or more cells per cubic millimeter was seen in approximately 64% of the participants who initiated ART earlier (≤4 months after the estimated date of HIV infection) as compared with approximately 34% of participants who initiated ART later (>4 months) ($P<0.001$). After adjustment for whether ART was initiated when the CD4+ count was 500 or more cells per cubic millimeter or less than 500 cells per cubic millimeter, the likelihood that the count would increase to 900 or more cells per cubic millimeter was lower by 65% (odds ratio, 0.35), and the rate of recovery was slower by 56% (rate ratio, 0.44), if ART was initiated later rather than earlier. There was no association between the plasma HIV RNA level at the time of initiation of ART and CD4+ T-cell recovery.

CONCLUSIONS

A transient, spontaneous restoration of CD4+ T-cell counts occurs in the 4-month time window after HIV-1 infection. Initiation of ART during this period is associated with an enhanced likelihood of recovery of CD4+ counts. (Funded by the National Institute of Allergy and Infectious Diseases and others.)

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Human immunodeficiency virus type 1 (HIV-1) infection is characterized by a rapid and profound loss of peripheral-blood CD4+ T cells, followed by a spontaneous but transient recovery in CD4+ T-cell counts, the extent and duration of which are poorly defined.[1,2] After this transient increase, there is a progressive decline in CD4+ counts.[1,2] Observation of this triphasic trajectory of CD4+ counts raised the possibility that after acute infection there may be a narrow "restorative time window" wherein the immune system could be strategically poised for recovery and that the likelihood and rate of recovery may be augmented by earlier initiation of potent antiretroviral therapy (ART).

To test this hypothesis, we evaluated a large, well-characterized cohort of HIV-1–infected persons who received ART during acute or early infection. We determined whether starting ART earlier (i.e., within the proposed restorative time window), as compared with later (i.e., after the restorative time window), enhanced the likelihood and rate of restoration of CD4+ counts to normal levels among participants who started ART before the count had reached 500 cells per cubic millimeter and among those who started ART after this CD4+ threshold had been reached. A CD4+ count of 500 per cubic millimeter is a threshold that is frequently used to prompt the initiation of ART.[3-5] However, the range of CD4+ counts that are currently considered to be normal is quite wide (500 to 1500 cells per cubic millimeter),[6-8] with the result that many treated persons may be inappropriately categorized as having a normal CD4+ count. To identify the range of normal CD4+ counts to target during ART, we reviewed the published literature on CD4+ counts in HIV-uninfected persons.

Methods

Study Participants

We evaluated 468 HIV-1–infected persons from the San Diego Primary Infection cohort, recruited between June 1996 and June 2010,[9] for whom an estimated date of infection could be calculated with the use of a series of well-defined stepwise rules that characterize stages of infection on the basis of serologic and virologic criteria (see Table S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org). This algorithm was indexed to the staging algorithm for primary HIV-1 infection reported by Fiebig et al.[10] Approximately 98% of the participants were infected with HIV-1 subtype B. Participants were divided into two partially overlapping study sets according to the inclusion criteria shown in Figure 1. Study set 1 comprised participants who had not previously received ART and who did not receive ART for a period of time after entry into the cohort (384 participants), whereas study set 2 comprised those who commenced ART soon after study entry or at some time shortly thereafter (213 participants). In study set 1, a total of 136 participants did not receive ART for the entire 48-month observation period, whereas 248 eventually received ART; of these, 176 met the inclusion criteria for crossover to study set 2. Thus, the cohort of study set 2 was derived from two sources: those who crossed over from study set 1 (176 participants) and those who started to receive ART very soon after entry into the cohort (median, 9 days; interquartile range, 4 to 15) and did not meet the criteria for study set 1 (37 participants). The 176 participants who crossed over to study set 2 received ART a median of 5.2 months (interquartile range, 3.1 to 12.5) after the estimated date of infection. As a group, the 213 participants in study set 2 commenced ART, on average, 4.9 months (interquartile range, 2.8 to 10.6) after the estimated date of infection. The goals of categorizing the participants in this way were to define the trajectory of CD4+ counts during the proximal stages of untreated HIV disease (study set 1) and to investigate the effect of the timing of ART relative to the estimated date of infection on the likelihood and rate of recovery of CD4+ T-cell counts (study set 2).

Study Definitions

The CD4+ T-cell peak was defined as the highest CD4+ count recorded after infection in participants who were not receiving ART. The interval between the estimated date of infection and the peak CD4+ count in participants who were not receiving therapy (study set 1) was designated as the restorative time window and was derived mathematically (by calculation of the median and interquartile range of the interval between the date of the highest CD4+ count recorded after study entry and the estimated date of infection) and by inspection of the trajectory of CD4+ T-cell counts. Earlier ART was defined as the initiation of ART within the restorative time window, and

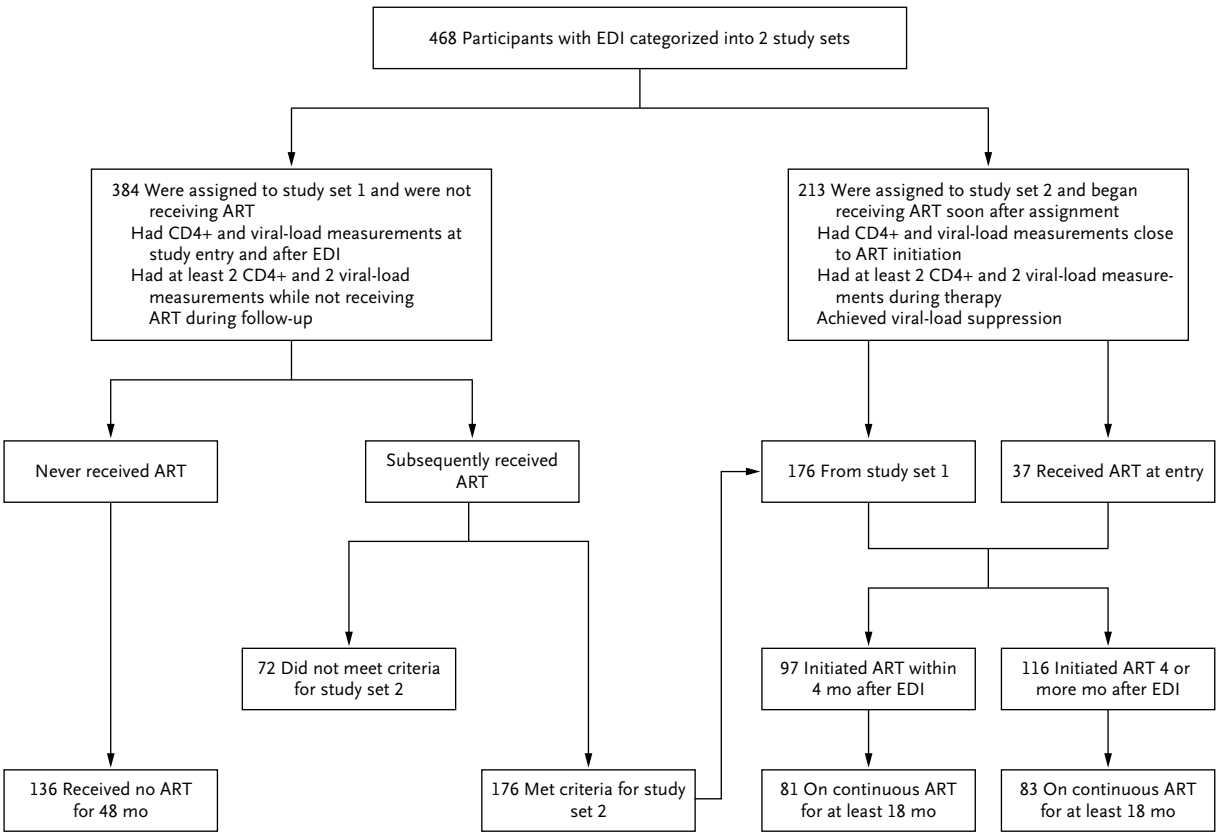


Figure 1. Study Sets and Inclusion Criteria.

A total of 468 participants with human immunodeficiency virus type 1 (HIV-1) infection for whom an estimated date of infection (EDI) could be calculated were stratified into two partially overlapping study sets according to the inclusion criteria indicated and as described in the Methods section. A total of 384 participants met the inclusion criteria for study set 1. Data from this study set were used to compute the trajectories of CD4+ counts and viral load after infection with HIV-1. A total of 248 participants assigned to study set 1 subsequently started ART; 176 of these participants met the inclusion criteria for study set 2, which comprised these 176 participants, along with an additional 37 participants who received ART soon after entry (precluding their inclusion in study set 1). Data from study set 2 were used to determine the relationship between the timing of the initiation of ART after infection with HIV-1 and the recovery of CD4+ T-cell counts. Study set 2 was further stratified according to whether participants initiated ART earlier or later: 97 participants in study set 2 initiated ART earlier (≤4 months after the EDI) and 116 initiated ART later (>4 months after the EDI); 164 participants received ART for a minimum of 18 months.

later ART as the initiation of ART after the restorative time window. Viral-load suppression was defined as the documentation of at least two consecutive undetectable plasma HIV viral loads (<75 copies per milliliter), measured at least 14 days apart, during receipt of ART. The CD4+ count and viral load before ART were the measurements obtained on the day of the initiation of ART or on the day closest to the day of treatment initiation (interquartile range, 0 to 12 days before initiation of ART). Higher CD4+ counts before ART were defined as counts of 500 or more cells per cubic millimeter, and lower CD4+ counts before ART as counts of less than 500 cells per cubic millimeter. To define normal CD4+ counts, we searched the Medline database for all studies in which CD4+ counts were reported for HIV-uninfected European Americans or African Americans (with the absence of infection confirmed or presumed), reflecting the racial and ethnic composition of our study cohort (Table S2 in the Supplementary Appendix). On the basis of the results of this search (see below), the CD4+ end point designated as primary CD4+ T-cell recovery was attainment of at least one CD4+ count that was 900 or more cells per cubic millimeter dur-

ing receipt of ART, and the end point designated as secondary CD4+ T-cell recovery was attainment of at least one CD4+ count that was 800 or more cells per cubic millimeter during receipt of ART.

STATISTICAL ANALYSIS

Square root and logarithmic (base 10) transformations were applied to normalize the distributions of CD4+ and viral-load data, respectively. CD4+ counts and viral-load trajectories (with 95% pointwise confidence bands) in study sets 1 and 2 were derived with the use of nonlinear generalized estimating equations. Follow-up times were prespecified in study set 1 as 48 months from the estimated date of infection or until participants began to receive ART, and in study set 2 as 48 months from the date of ART initiation, until discontinuation of ART or loss to follow-up, or until loss of viral-load suppression. Kaplan–Meier plots, Cox proportional-hazards models (for computing the rate ratios), logistic-regression models, linear mixed-effects models with a random intercept and slope, chi-square tests, Wilcoxon–Mann–Whitney tests, and Wilcoxon signed rank-sum tests were used when appropriate. A detailed description of the statistical methods is provided in the Supplementary Appendix.

RESULTS

STUDY SETS

A total of 468 persons with HIV-1 infection were included in the two partially overlapping study sets (Fig. 1). Most of the participants were European American men (Table 1). Approximately 80% of the participants reported symptoms consistent with an acute retroviral syndrome[11] around the time of their estimated date of infection. Participants entered the study at a median of 10 weeks after the estimated date of infection (Table 1). The proportion of participants presenting within each of the laboratory-defined stages of primary HIV-1 infection[10,12] varied (Table S1 in the Supplementary Appendix). The median age of the participants at the estimated date of infection was 33 years (interquartile range, 27 to 40), and the median age at the initiation of ART was 35 years (interquartile range, 29 to 42) (Table 1).

CD4+ COUNT AND VIRAL-LOAD TRAJECTORY BEFORE ART

Inspection of the trajectory of CD4+ counts among participants who were not receiving ART (study set 1) indicated that the CD4+ count peaked approximately 4 months after the estimated date of infection (Fig. 2A). This interval closely matched the calculated median interval from the estimated date of infection to the peak CD4+ count (3.5 months; interquartile range, 2.6 to 5.2) (Table 1). Given the convergence of these two values, the 4-month interval from the estimated date of infection to the peak CD4+ count was designated as the restorative time window. The median CD4+ count at study entry and the median peak count were 495 cells per cubic millimeter (interquartile range, 383 to 622) and 763 cells per cubic millimeter (interquartile range, 573 to 987), respectively (Table 1). After peaking, CD4+ counts declined progressively, returning to levels approximating those observed at study entry within about 12 to 14 months (Table 1 and Fig. 2A). In parallel with these changes in the CD4+ count, the viral load declined precipitously, reaching a nadir within 4 months, and did not change appreciably thereafter (Fig. S1A in the Supplementary Appendix).

CD4+ COUNT AND VIRAL-LOAD TRAJECTORY DURING ART

Among participants who started ART (study set 2), the median CD4+ count before treatment initiation was 451 cells per cubic millimeter and the median viral load was 4.95 $\log_{10}$ copies per milliliter (Table 1). ART was associated with a rapid gain of approximately 200 CD4+ T cells and then a slower, sustained increase (Fig. 2B), with a concomitant decline in the viral load to undetectable levels (Fig. S1B in the Supplementary Appendix).

Before the initiation of ART, CD4+ counts were spontaneously increasing in participants who started ART earlier (≤4 months after the estimated date of HIV infection) and were declining among those who started ART later (>4 months) (Fig. 2C and 2D). The median time from the estimated date of infection to the initiation of ART was approximately 7 months shorter in the earlier-ART group than in the later-ART group (2.8 months [interquartile range, 1.1 to 3.2] vs. 9.6 months [interquartile range, 5.6 to 16.6]) (Table 1). Despite this modest difference, CD4+ counts increased more quickly among those starting ART earlier, irrespective of whether ART was initiated when the CD4+ counts were higher or lower (Fig. 2C and 2D).

Among participants in the earlier-ART group who had higher CD4+ counts before the initiation

Table 1. Characteristics of Study Participants in Study Sets 1 and 2.*

Variable	Total	ART Initiated ≤4 Mo after EDI	ART Initiated >4 Mo after EDI	P Value†
Study set 1‡				
No. of participants	384			
Male sex — no. (%)	373 (97.1)			
European American — no. (%)	299 (77.9)			
Age at EDI — yr				
Median	33			
Interquartile range	27–40			
Time from EDI to study entry — wk§				
Median	10.0			
Interquartile range	8.4–13.2			
Duration of follow-up without treatment — mo				
Median	7.7			
Interquartile range	3.5–21.6			
Viral load at study entry — $\log_{10}$ copies/ml				
Median	4.92			
Interquartile range	4.12–5.61			
CD4+ count at study entry — cells/mm^3				
Median	495			
Interquartile range	383–622			
Time from EDI to peak CD4+ count — mo¶				
Median	3.5			
Interquartile range	2.6–5.2			
CD4+ count at peak — cells/mm^3				
Median	763			
Interquartile range	573–987			
Difference between CD4+ count at peak and at study entry — cells/mm^3				<0.001
Median	234			
Interquartile range	95–437			
Study set 2‖				
No. of participants	213	97	116	
Male sex — no. (%)	202 (94.8)	93 (95.9)	109 (94.0)	0.53
European American — no. (%)	172 (80.8)	87 (89.7)	85 (73.3)	0.01
Age at EDI — yr				0.08
Median	35	36	34	
Interquartile range	29–41	30–42	27–41	
Age at initiation of ART — yr				0.25
Median	35	36	35	
Interquartile range	29–42	31–42	28–42	
Time from EDI to study entry — wk				<0.001
Median	10.0	10.0	12.7	
Interquartile range	8.0–13.6	2.2–10.0	10.0–19.0	

Table 1. (Continued.)

Variable	Total	ART Initiated ≤4 Mo after EDI	ART Initiated >4 Mo after EDI	P Value†
CD4+ count at initiation of ART — cells/mm³				<0.001
Median	451	504	386	
Interquartile range	336–612	378–720	281–554	
Viral load at initiation of ART — $\log_{10}$ copies/ml				<0.001
Median	4.95	5.20	4.82	
Interquartile range	4.55–5.48	4.67–5.82	4.45–5.23	
Time from EDI to initiation of ART — mo				<0.001
Median	4.9	2.8	9.6	
Interquartile range	2.8–10.6	1.1–3.2	5.6–16.6	
Length of time receiving ART — mo				0.001
Median	33.8	41.5	29.4	
Interquartile range	19.8–48.0	23.0–48.0	15.9–44.7	
Time from initiation of ART to suppression of viral load — mo**				0.44
Median	3.9	4.0	3.7	
Interquartile range	2.3–5.6	2.3–5.7	2.4–5.4	
Time from initiation of ART to first CD4+ count of ≥900 — mo				0.002
Median	6.8	3.8	15.2	
Interquartile range	1.9–18.6	1.6–12.8	6.3–22.2	
Time from initiation of ART to first CD4+ count of ≥800 — mo				0.01
Median	4.1	2.7	7.6	
Interquartile range	0.9–15.4	0.5–12.1	1.9–16.9	
Attainment of CD4+ count ≥900 cells/mm³ within 48 mo after ART initiation — no. (%)	101 (47.4)	62 (63.9)	39 (33.6)	<0.001
Attainment of CD4+ count ≥800 cells/mm³ within 48 mo after ART initiation — no. (%)	126 (59.2)	75 (77.3)	51 (44.0)	<0.001

* ART denotes antiretroviral therapy, and EDI estimated date of infection.
† The P values were calculated with the use of a Wilcoxon–Mann–Whitney test or chi-square test, with the exception of the P values for the difference between peak CD4+ count and CD4+ count at study entry, which were calculated with the use of a Wilcoxon signed-rank test.
‡ In study set 1, a total of 3715 measurements of CD4+ counts and 3884 measurements of viral load were analyzed; the median number of measurements of CD4+ counts per participant was 7 (interquartile range, 4 to 13), with a range of 3 to 44, and the median number of measurements of viral load was 7 (interquartile range, 5 to 14), with a range of 3 to 44. The median time between consecutive measurements of CD4+ counts per participant was 20 days (interquartile range, 7 to 31).
§ The time from the EDI to study entry was defined as the interval between the EDI and the date of the first measurement of the CD4+ count or viral load, whichever was performed first, at study entry.
¶ The time from the EDI to the peak CD4+ count was defined as the time from the EDI to the date at which the highest CD4+ count (peak count) was recorded among participants who were not receiving ART.
‖ In study set 2, a total of 4027 measurements of CD4+ T-cell counts and 4179 measurements of viral load were analyzed; the median number of measurements of CD4+ counts per participant was 16 (interquartile range, 9 to 26), with a range of 3 to 56, and the median number of measurements of viral load was 16 (interquartile range, 10 to 27), with a range of 3 to 59. The median time between consecutive measurements of CD4+ counts per participant was 56 days (interquartile range, 36 to 65).
** The time to suppression of the viral load was defined as the time to the first of at least two consecutive undetectable viral-load measurements after the initiation of ART, measured at least 14 days apart.

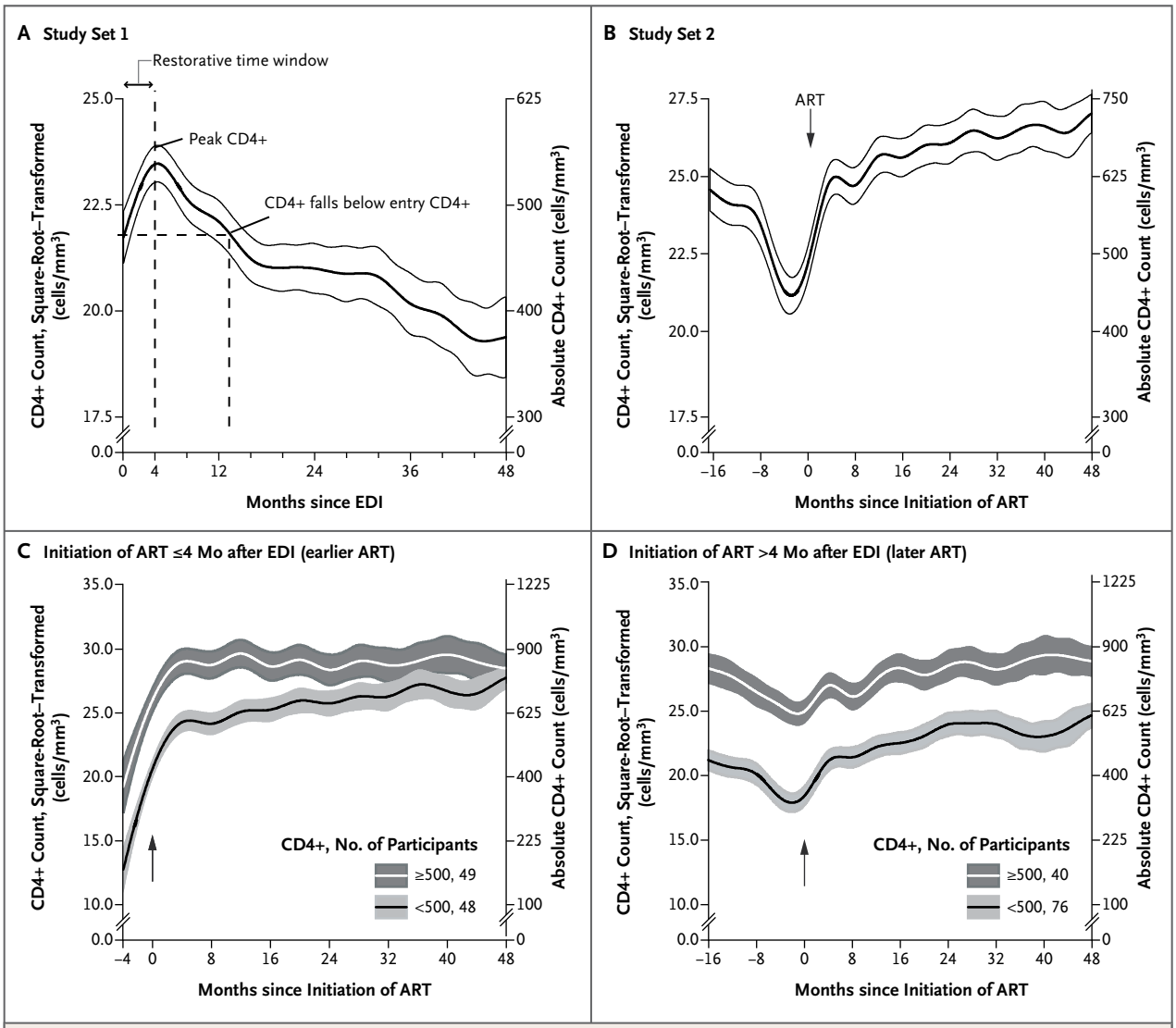


Figure 2. Trajectories of CD4+ T-Cell Counts before and after Initiation of ART.

Shown are trajectories of CD4+ counts with 95% pointwise confidence bands, modeled with the use of nonlinear generalized estimating equations. The y axes in all panels show the square root–transformed CD4+ counts (left) and the corresponding absolute counts (right). Panel A shows the cohort-level trajectory of CD4+ counts after the EDI among HIV-infected participants during the time they were not receiving ART, for a maximum of 48 months after the EDI (study set 1). Panel B shows the cohort-level trajectory among participants assigned to study set 2, computed from a maximum of 16 months before the initiation of ART to the time of initiation of ART (at arrow) and from the time of initiation of ART ahead to a maximum of 48 months. Panels C and D show the trajectories among participants in study set 2 according to whether they initiated ART earlier (≤4 months after the EDI) (Panel C) or later (>4 months after the EDI) (Panel D) and according to whether the CD4+ count at the time of initiation of ART was lower (<500 cells per cubic millimeter) or higher (≥500 cells per cubic millimeter). For Panels C and D, the differences between the study groups in the least-squares mean CD4+ counts from the time of initiation of ART were calculated with the use of linear mixed-effects models adjusted for age, sex, race, viral load at the time of the initiation of ART, and length of follow-up after the initiation of ART; the between-group difference in the absolute CD4+ T-cell counts was 232 cells per cubic millimeter (95% CI, 169 to 296) among participants who initiated ART 4 months or less after the EDI (Panel C) and 273 cells per cubic millimeter (95% CI, 219 to 327) among those who initiated ART more than 4 months after the EDI (Panel D) ($P<0.001$ for both comparisons).

of therapy, the trajectory of CD4+ counts crested at approximately 900 cells per cubic millimeter at approximately 4 months after the initiation of ART and then plateaued (Fig. 2C). In contrast, the trajectories of the CD4+ counts in the three other patient subgroups approached 800 to 900 cells per

cubic millimeter more slowly (Fig. 2C and 2D) or — in the case of participants who started ART more than 4 months after the estimated date of infection and had lower CD4+ counts before the initiation of ART — not reaching these values during the study period (Fig. 2D). The viral-load trajectories while participants were receiving ART were similar in the earlier-ART group and the later-ART group, both among participants who had higher CD4+ counts and among those who had lower CD4+ counts before the initiation of ART (Fig. S1C and S1D in the Supplementary Appendix). The trajectories of CD4+ counts while participants were receiving ART were also similar among those in whom the viral load at the time of initiation of ART was above the cohort median and those in whom the viral load was below the cohort median.

RECOVERY OF CD4+ T-CELL COUNTS

A review of data from 16,126 persons in 25 studies who were confirmed or presumed to be uninfected with HIV revealed that the weighted mean CD4+ count was 1014 cells per cubic millimeter (95% confidence interval [CI], 1008 to 1019), the median of the reported mean CD4+ counts was 952 cells per cubic millimeter (interquartile range, 840 to 1036), and the range of the reported means was 771 to 1109 cells per cubic millimeter (Table S2 in the Supplementary Appendix). We surmised that since the median CD4+ counts in HIV-infected participants at study entry and at the time of initiation of ART were, on average, approximately half those of HIV-uninfected persons (Table 1), this degree of CD4+ T-cell loss may have precluded recovery to 1000 cells per cubic millimeter in most participants. In addition, because the trajectories of the CD4+ counts in three of the four patient subgroups converged toward 800 to 900 cells per cubic millimeter (Fig. 2C and 2D), we selected two CD4+ values that approximated the lower tails of the CD4+ count distribution in HIV-uninfected persons to represent the primary and secondary end points of CD4+ T-cell recovery (≥900 cells per cubic millimeter and ≥800 cells per cubic millimeter, respectively).

A total of 47.4% of all participants met the criteria for the primary end point of CD4+ T-cell recovery, and 59.2% met the criteria for the secondary end point of recovery, with the frequency significantly higher among participants who started ART earlier than among those who started ART later (Table 1). In participants who met the criteria for these recovery end points, CD4+ counts remained higher, on average, by approximately 300 cells per cubic millimeter than the counts in participants who did not meet the criteria for these end points (Fig. S2 in the Supplementary Appendix). In univariate analyses, the variables that positively influenced the likelihood and rate of attainment of the end points for CD4+ T-cell recovery were white race, a shorter interval from the estimated date of infection to the initiation of ART, and a higher CD4+ count before the initiation of ART (Table 2, and Table S3 in the Supplementary Appendix). A longer duration of ART increased the likelihood of meeting the criteria for primary or secondary CD4+ T-cell recovery, but it did not increase the rate of recovery (Table 2).

INDEPENDENT EFFECTS OF THE TIMING OF ART ON CD4+ T-CELL RECOVERY

Initiation of ART when the CD4+ count was less than 500 cells per cubic millimeter, as compared with treatment initiation when the CD4+ count was 500 cells per cubic millimeter or higher, was associated with a likelihood of primary or secondary CD4+ T-cell recovery that was reduced by approximately 90% and a rate of recovery that was slower by approximately 80%, independently of whether ART was commenced earlier or later (model 1 in Table 2). However, a shorter interval between the estimated date of infection and the initiation of ART promoted CD4+ T-cell recovery, after adjustment for the CD4+ count (higher vs. lower) before ART, race, and duration of ART (models 2 and 3 in Table 2). For example, each additional month that elapsed from the estimated date of infection to the initiation of ART was independently associated with a likelihood of primary CD4+ T-cell recovery that was reduced by 10% (adjusted odds ratio, 0.90; 95% CI, 0.85 to 0.96) and a rate of recovery that was slower by 8% (adjusted rate ratio, 0.92; 95% CI, 0.88 to 0.96) (model 2 in Table 2). Similarly, among participants commencing ART later as compared with those commencing ART earlier, the odds of primary CD4+ T-cell recovery were lower by 65% (adjusted odds ratio, 0.35; 95% CI, 0.17 to 0.71) and the rate was slower by 56% (adjusted rate ratio, 0.44; 95% CI, 0.29 to 0.67) (model 3 in Table 2).

The median interval between the measurement of consecutive CD4+ counts ranged from 50 to 61 days in the four groups of participants stratified according to the timing of the initiation of ART (earlier vs. later) and the CD4+ count

Table 2. Likelihood and Rate of Primary or Secondary CD4+ T-Cell Recovery within 48 Months after Initiation of ART in Study Set 2.*

Predictive Factor	Primary CD4+ T-Cell Recovery				Secondary CD4+ T-Cell Recovery			
	Odds Ratio (95% CI)	P Value	Rate Ratio (95% CI)	P Value	Odds Ratio (95% CI)	P Value	Rate Ratio (95% CI)	P Value
Univariate models								
Time from EDI to ART initiation — each increase of 1 mo	0.89 (0.85–0.94)	<0.001	0.92 (0.88–0.96)	<0.001	0.92 (0.89–0.96)	<0.001	0.94 (0.91–0.97)	<0.001
Time from EDI to ART initiation — >4 mo vs. ≤4 mo	0.29 (0.16–0.50)	<0.001	0.42 (0.28–0.63)	<0.001	0.23 (0.13–0.42)	<0.001	0.42 (0.29–0.60)	<0.001
Viral load at ART initiation — each increase of 1 $\log_{10}$ copy/ml	1.26 (0.88–1.82)	0.21	1.15 (0.87–1.51)	0.33	1.35 (0.93–1.96)	0.12	1.14 (0.89–1.45)	0.29
CD4+ at ART initiation — each increase of 100 cells/mm^3	2.04 (1.66–2.51)	<0.001	1.47 (1.36–1.59)	<0.001	2.32 (1.81–2.97)	<0.001	1.50 (1.40–1.61)	<0.001
CD4+ at ART initiation — <500 vs. ≥500 cells/mm^3	0.08 (0.04–0.16)	<0.001	0.17 (0.11–0.27)	<0.001	0.06 (0.03–0.13)	<0.001	0.17 (0.11–0.24)	<0.001
Duration of therapy — each increase of 1 mo	1.04 (1.02–1.06)	<0.001	1.00 (0.99–1.02)	0.62	1.04 (1.02–1.06)	<0.001	1.00 (0.99–1.02)	0.72
Multivariate models†								
Model 1: CD4+ count — <500 vs. ≥500 cells/mm^3 at ART initiation	0.07 (0.04–0.15)	<0.001	0.17 (0.11–0.26)	<0.001	0.05 (0.02–0.12)	<0.001	0.16 (0.11–0.23)	<0.001
Model 2: Time from EDI to ART initiation — each increase of 1 mo	0.90 (0.85–0.96)	0.001	0.92 (0.88–0.96)	<0.001	0.94 (0.90–0.99)	0.01	0.95 (0.92–0.98)	0.001
Model 3: Time from EDI to ART initiation — >4 mo vs. ≤4 mo	0.35 (0.17–0.71)	0.004	0.44 (0.29–0.67)	<0.001	0.26 (0.12–0.55)	<0.001	0.46 (0.31–0.68)	<0.001
Model 4: Initiation of ART ≤4 mo, >4–12 mo, or >12 mo after EDI								
>4–12 mo vs. ≤4 mo	0.48 (0.21–1.06)	0.07	0.52 (0.33–0.83)	0.007	0.29 (0.13–0.67)	0.004	0.50 (0.32–0.77)	0.002
>12 mo vs. ≤4 mo	0.21 (0.08–0.55)	0.002	0.32 (0.17–0.61)	<0.001	0.23 (0.09–0.58)	0.002	0.41 (0.24–0.70)	0.001
Model 5: Initiation of ART ≤4 mo, >4–12 mo, or >12 mo after EDI with CD4+ at ART initiation ≥500 cells/mm^3								
>4–12 mo vs. ≤4 mo	0.74 (0.18–2.94)	0.66	0.55 (0.32–0.96)	0.04	0.39 (0.06–2.67)	0.34	0.56 (0.32–0.97)	0.04
>12 vs. ≤4 mo	0.17 (0.04–0.71)	0.02	0.31 (0.14–0.69)	0.004	0.20 (0.03–1.43)	0.11	0.47 (0.23–0.94)	0.03
Model 6: Initiation of ART ≤4 mo, >4–12 mo, or >12 mo after EDI with CD4+ at ART initiation <500 cells/mm^3								
>4–12 mo vs. ≤4 mo	0.26 (0.13–1.02)	0.05	0.41 (0.17–0.99)	0.05	0.26 (0.10–0.68)	0.006	0.30 (0.16–0.70)	0.003
>12 mo vs. ≤4 mo	0.27 (0.08–0.94)	0.04	0.34 (0.11–1.02)	0.05	0.24 (0.09–0.70)	0.009	0.33 (0.14–0.77)	0.01

* Study set 2 comprised 213 participants who were receiving ART. Primary CD4+ T-cell recovery was defined as attainment of at least one CD4+ count of 900 or more cells per cubic millimeter within 48 months after initiation of ART; secondary CD4+ T-cell recovery was defined as attainment of at least one CD4+ count of 800 or more cells per cubic millimeter within 48 months after initiation of ART. Logistic regression and Cox proportional-hazard models were used to compute the odds ratios and rate ratios, respectively.

† All multivariate models were adjusted for race and length of time receiving ART, in months; models 2, 3, and 4 were also adjusted for the CD4+ count (<500 per cubic millimeter vs. ≥500 per cubic millimeter) at the time of initiation of ART, whereas model 1 was also adjusted for whether ART was initiated earlier (≤4 months after the EDI) versus later (>4 months after the EDI).

(higher vs. lower) at the time of treatment initiation (Table S4 in the Supplementary Appendix). To address the possibility that differences in CD4+ T-cell recovery were the result of differences in the frequency at which CD4+ counts were measured, we looked at recovery patterns among participants in these four patient groups, stratified according to the frequency of measurement (more frequent vs. less frequent); this analysis showed that the patterns were similar (Table S4 in the Supplementary Appendix). To address the possibility of confounding due to variation in the duration of ART, we included treatment duration in the multivariate models (Table 2). Furthermore, similar results were obtained when the analyses were restricted to the 164 participants who received ART for a minimum of 18 months (Fig. 1, and Table S5 in the Supplementary Appendix).

TIME-DEPENDENT MODEL OF CD4+ RECOVERY

Among participants who were not receiving ART, the time windows of 0 to 4 months, more than 4 months to 12 months, and more than 12 months after the estimated date of infection correspond, respectively, to the times when CD4+ counts were increasing spontaneously, declining from peak levels, and falling lower than the level at study entry (Fig. 2A and Fig. 3A). To determine the relevance of these temporal landmarks to immune recovery, we calculated the odds and rates of CD4+ T-cell recovery in the six patient groups according to the time window in which ART was initiated and according to whether participants had a higher CD4+ count before ART (groups 1, 2, and 3) or a lower CD4+ count before ART (groups 4, 5, and 6) (Fig. 3A).

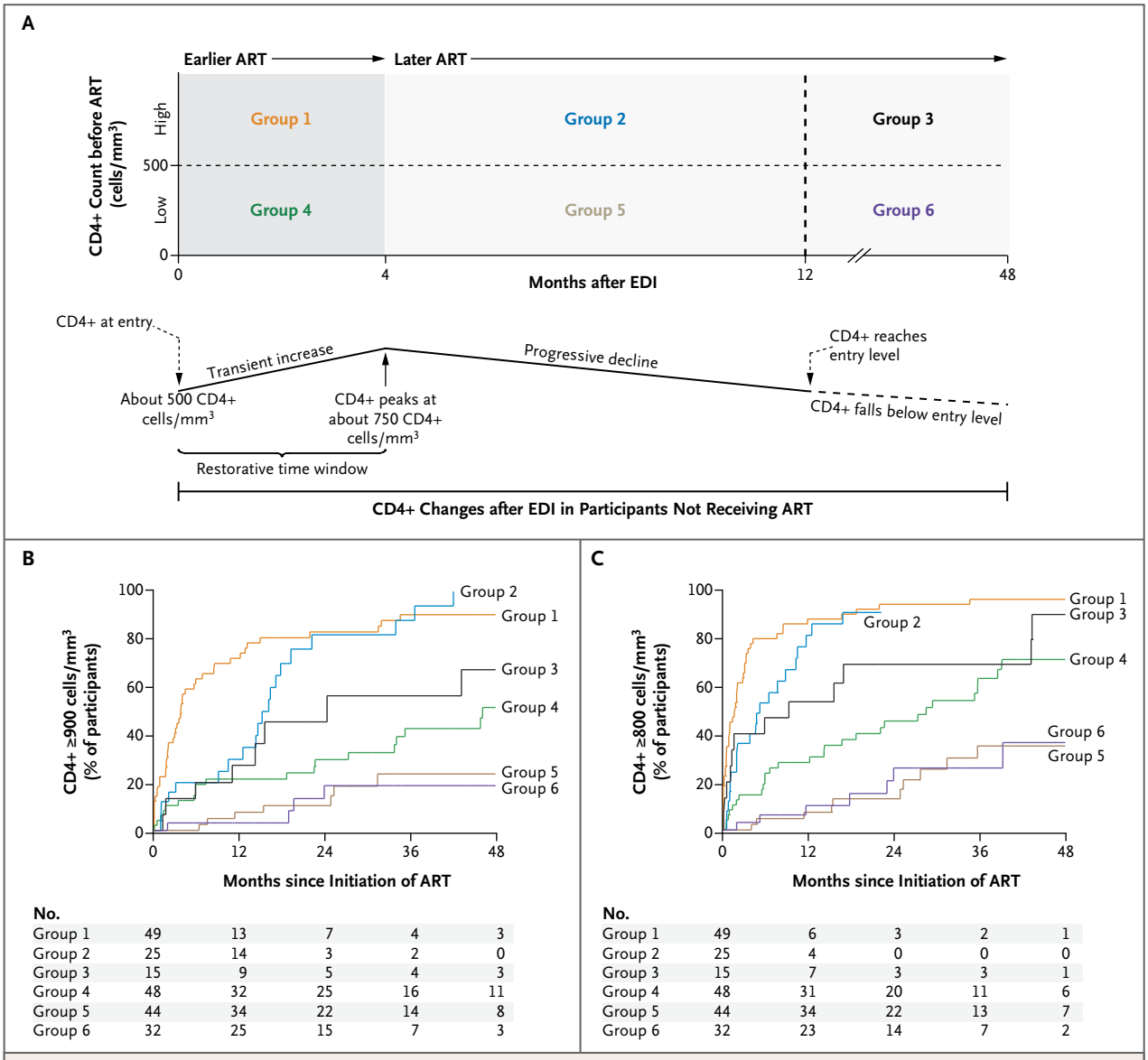
There was a stepwise reduction in the likelihood and rate of CD4+ T-cell recovery among participants starting ART between 4 and 12 months or more than 12 months after the estimated date of infection, as compared with participants starting ART 4 months or less after the estimated date of infection (model 4 in Table 2). However, among participants starting ART 4 months or less after the estimated date of infection, the initiation of treatment sooner after the estimated date of infection as compared with later did not further accelerate rates of CD4+ T-cell recovery (Fig. S3 in the Supplementary Appendix).

Among participants starting ART with a higher CD4+ count, there was a hierarchical trend in the likelihood and rate of meeting the criteria for the end point of primary or secondary CD4+ T-cell recovery, with the greatest likelihood and fastest rate observed among participants starting ART 4 months or less after the estimated date of infection (group 1), an intermediate likelihood and rate among participants starting ART between 4 and 12 months after the estimated date of infection (group 2), and the least likelihood and slowest rate among participants starting ART more than 12 months after the estimated date of infection (group 3) (Fig. 3B and 3C and model 5 in Table 2). In contrast, this trend was not observed among patients starting ART with a lower CD4+ count; participants with a lower CD4+ count who did not start ART until either 4 to 12 months (group 5) or more than 12 months (group 6) after the estimated date of infection had a similar likelihood and rate of CD4+ T-cell recovery — which were lower in both groups than in the group that started ART earlier (group 4) (Fig. 3B and 3C and model 6 in Table 2). Among participants starting ART at a lower CD4+ count (<500 cells per cubic millimeter), the rate of attaining a count of 500 or more cells per cubic millimeter while receiving ART was fastest in group 4, intermediate in group 5, and slowest in group 6 (Fig. S4A in the Supplementary Appendix).

The proportion of participants who met the criteria for at least secondary CD4+ T-cell recovery was highest in groups 1 and 2, intermediate in groups 3 and 4, and lowest in groups 5 and 6 (Fig. S4B in the Supplementary Appendix), a pattern that was consistent with the differential rates of CD4+ recovery in the six patient groups shown in Figures 3B and 3C. In addition, the proportion of participants who had a CD4+ count of less than 500 cells per cubic millimeter while receiving viral-load–suppressive ART ranged from less than 10% in groups 1 and 2 to more than 25% in groups 5 and 6 (Fig. S4B in the Supplementary Appendix).

DISCUSSION

There are two main findings in this study. First, the 4-month and 12-month time points after the estimated date of infection represent key inflection points in the trajectory of CD4+ counts; it is possible that these time points demarcate immunologically relevant intervals in the natural trajectory of CD4+ counts after acute HIV infection. The participants in this observational co-



B

No.					
Group 1	49	13	7	4	3
Group 2	25	14	3	2	0
Group 3	15	9	5	4	3
Group 4	48	32	25	16	11
Group 5	44	34	22	14	8
Group 6	32	25	15	7	3

C

No.					
Group 1	49	6	3	2	1
Group 2	25	4	0	0	0
Group 3	15	7	3	3	1
Group 4	48	31	20	11	6
Group 5	44	34	22	13	7
Group 6	32	23	14	7	2

Figure 3. Rate of Recovery of CD4+ T-Cell Counts after Initiation of ART, According to Timing of Initiation of ART and CD4+ T-Cell Count at Initiation of ART.

Panel A shows the classification of participants into six groups according to whether they initiated ART when their CD4+ cell count was higher (≥500 cells per cubic millimeter) or lower (<500 cells per cubic millimeter) and whether they initiated ART during the time window of 0 to 4 months after the EDI, between 4 and 12 months after the EDI, or more than 12 months after the EDI. The line schema beneath the boxes shows the changes in CD4+ counts that occurred during these time windows among participants who were not receiving ART. Panels B and C are Kaplan–Meier plots of the proportion of participants in the six groups who had at least one CD4+ count of 900 or more cells per cubic millimeter (Panel B) or 800 or more cells per cubic millimeter (Panel C) while they were receiving ART. In Panel B, the rate ratio for meeting the criterion of 900 cells per cubic millimeter (the primary end point) was 0.55 (95% CI, 0.32 to 0.96) in the comparison of group 2 with group 1 (the reference group) and 0.31 (95% CI, 0.14 to 0.69) in the comparison of group 3 with group 1.

hort entered the study a median of 10 weeks after the estimated date of infection and had an average initial CD4+ count that was approximately half the median CD4+ count in HIV-negative persons (in whom the count is approximately 900 to 1000 cells per cubic millimeter). We observed that during the first 4 months after the estimated date of infection, there was a spontaneous increase of

approximately 250 CD4+ cells per cubic millimeter relative to counts obtained close to the estimated date of infection. The magnitude of this spontaneous CD4+ T-cell recovery was similar to the relative gains observed in our study participants who were receiving viral-load–suppressive ART. We designated this interval of 4 months after infection as the restorative time window. However, this recovery was transient, and after closure of this window, CD4+ counts declined progressively, returning to study-entry levels (approximately 500 cells per cubic millimeter) by about 12 months after the estimated date of infection. Thus, the interval from infection to the CD4+ count threshold commonly used to prompt the initiation of ART (<500 cells per cubic millimeter)[3-5] is fairly short, an observation that is in accord with a recent study involving 18,495 HIV-infected persons who were not receiving ART.[13]

Second, participants who initiated ART 4 months or less after the estimated date of infection had the highest likelihood and the fastest rate of primary and secondary recovery of CD4+ counts (defined as attainment of at least one CD4+ count of 900 or 800 cells per cubic millimeter, respectively), participants who initiated ART more than 4 months to 12 months after the estimated date of infection had an intermediate likelihood and rate of recovery, and participants who initiated ART more than 12 months after the estimated date of infection had the least likelihood and the slowest rate of recovery. However, even among participants who started ART earlier, those who initiated ART with lower CD4+ counts, as compared with those who initiated ART with higher CD4+ counts, had a reduced likelihood and rate of CD4+ T-cell recovery. This is reflective of our finding that initiation of ART at lower CD4+ counts, as compared with higher CD4+ counts, is in itself associated with a likelihood of CD4+ T-cell recovery that is reduced by about 90% and with a slower rate of recovery. These findings underscore the dual effect on CD4+ T-cell recovery of the timing of ART and of the CD4+ count at the initiation of ART.

Starting ART soon after infection is likely to attenuate factors that are known to impair immune recovery (e.g., microbial translocation, immune activation,[14] and lymphoid-tissue damage),[14-20] promote development of HIV-specific T-helper responses, and limit the establishment and expansion of latent HIV reservoirs.[21-25] Attainment of CD4+ T-cell recovery may have two benefits. Foremost, CD4+ T-cells play a central role in the maintenance of lymphoid-tissue structure, which is necessary for their own homeostasis and reconstitution.[26] Consequently, enhanced CD4+ T-cell recovery with earlier initiation of ART may be associated with the rapid resolution of HIV-induced damage of lymphoid-tissue structure, a critical determinant of immune recovery.[19,20] This is mirrored by our observation that each additional month after the estimated date of infection that elapsed before ART was initiated was associated, on average, with about a 10% reduction in the likelihood of CD4+ T-cell recovery and a 10% slower rate of recovery. In addition, among patients receiving viral-load–suppressive ART, there is an inverse relationship between higher CD4+ counts during ART and the risk of complications not related to the acquired immunodeficiency syndrome (AIDS),[27,28] the risk of AIDS, and the risk of death.[29,30]

Our study has some limitations. First, we could not directly assess whether earlier ART reduces clinical progression. Second, this was not a randomized clinical trial; the participants were offered open-label ART, and they made the choice to initiate treatment. Therefore, the participants who received ART may not be representative of the larger population of persons with acute or early HIV infection. Third, most of the participants in our study were men; hence, any sex-specific differences in the pathogenesis of HIV infection[31] that may affect CD4+ T-cell recovery could not be ascertained.

In summary, after an acute decline, CD4+ T-cell counts have a transient spontaneous recovery. The initiation of ART within this early restorative time window, when the host immune system is poised for recovery, greatly accelerates the pace and augments the extent of CD4+ T-cell recovery. Even a fairly short deferral of ART after closure of this time window may come at the expense of compromised CD4+ T-cell recovery, irrespective of the CD4+ count at the time of treatment initiation. Further studies are needed to determine whether starting ART within the restorative time window promotes strategies that are designed to reduce latent HIV reservoirs.

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