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The Benefit of Immediate Compared to Deferred ART on CD4+ Cell Count Recovery in Early HIV Infection

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Abstract

Objective: To assess the impact of immediate versus deferred antiretroviral therapy (ART) on CD4+ recovery among individuals early in HIV infection.

Design: Using serologic markers of early infection together with self-reported dates of infection and HIV diagnosis, ART-naïve participants who were randomized to immediate versus deferred ART in the Strategic Timing of Antiretroviral Treatment (START) trial were classified into subgroups of duration of HIV infection at baseline. CD4+ cell count recovery over follow-up according to duration of HIV infection was investigated.

Methods: Three subgroups were defined: 1) infected 6 months (n=373); 2) infected 6–24 months (n=2,634); and 3) infected > 24 months (n=1,605). Follow-up CD4+, CD8+, and CD4:CD8 ratio for the immediate and deferred ART groups were compared by subgroup using linear models. For the deferred ART group, decline to CD4+ <350 cells/μL or AIDS according to infection duration was compared using time-to-event methods.

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Results: Follow-up CD4+ count differences (immediate minus deferred) were greater for those recently infected (+231 cells/ μ L) compared to the two other subgroups (202 and 171 cells/ μ L; $p < 0.001$). CD4:CD8 ratio treatment differences varied significantly ($p < 0.001$) according to duration of infection. In the deferred ART group, decline to CD4+ < 350 cells/ μ L or AIDS was greater among those recently infected (16.1 versus 13.2 and 10.5 per 100 person years for those infected 6–24 and > 24 months; $p = 0.002$).

Conclusions: In this randomized comparison of immediate versus deferred ART, the CD4+ cell count difference was greatest for those recently infected with HIV, emphasizing the importance of immediate ART initiation.

Keywords

HIV; START; antiretroviral therapy; CD4 recovery; early infection

Background:

The results of the Strategic Timing of Antiretroviral Treatment (START) trial demonstrated that among HIV-positive participants with a CD4+ count > 500 cells/ μ L initiating antiretroviral treatment (ART) immediately resulted in lower rates of a composite outcome of AIDS events, serious non-AIDS events, or death compared to waiting until an individual's CD4+ count dropped to 350 cells/ μ L.[1] The relative clinical benefit of immediate compared to deferred ART was consistent for a number of baseline subgroups.[1] Immediate minus deferred ART absolute risk differences for the primary composite outcome were greater for older participants, those with a lower CD4:CD8 ratio, and for those with a higher baseline viral load.[2]

One subgroup of interest which has not been considered in START until now is duration of HIV infection at the time of randomization. While the study is not powered to investigate clinical outcomes across subgroups of infection duration, CD4+ levels can be evaluated. Previous studies have demonstrated that the viral reservoir is diminished for individuals treated during the acute phase of HIV[3] and early after seroconversion.[4] Also, in observational cohort studies, greater CD4+ cell count recovery has been reported for participants who initiate ART closer in time to acquiring HIV infection.[5,6,7,8,9]

In this paper, we take advantage of the randomized design of START to assess whether differences in follow-up CD4+ and CD8+ cell counts between the immediate and deferred ART groups vary by estimated duration of infection. To carry out this subgroup analysis, stored baseline specimens were tested using a multi-assay algorithm (MAA) which had been previously used to estimate population level incidence of HIV.[10,11] This assay was used in combination with self-reported data on date of infection and date of diagnosis to identify 373 participants in START who were recently infected with HIV (< 6 months before randomization).[12] We compared differences between the immediate and deferred ART group in CD4+ and CD8+ counts and the CD4:CD8 ratio for these recently infected participants with those who had been infected for a longer period of time.

Methods:

Study Participants

The START trial randomized 4,684 HIV+ adults with CD4+ counts >500 cells/ μ L to immediate or deferred initiation of antiretroviral treatment (ART). Individuals in the deferred ART group were to initiate ART when their CD4+ count declined to 350 cells/ μ L or they developed AIDS. Participants had to have two CD4 counts >500 cells/ μ L at least 2 weeks apart within the 60 days prior to randomization.[1] All participants provided informed consent to participate in the trial, and additional consent for storage of specimens for future research was also obtained.

At study entry, in addition to demographic characteristics, CD4+ count, CD8+ count, and HIV RNA level were measured, and the date the participant was first diagnosed with HIV as documented in the participant's record was recorded, and, if known, the date the participant believed they were first infected with HIV was also recorded. As previously described, stored baseline plasma samples were tested using a multi assay algorithm (MAA), which incorporates both serologic and non-serologic markers of recent infection in order to identify participants who were recently infected at the time of randomization. [12]

For the current study, we classified participants in the START trial into three groups based on their estimated duration of infection at baseline: Group 1 was considered infected for < 6 months based on the MAA or self-reported date of infection; Group 2 was considered infected for 6 to 24 months if i) the MAA for the participant failed to confirm more recent infection, the infection date was unknown, and the diagnosis date was < 6 months before randomization, or ii) their HIV diagnosis date was 6 to 24 months before randomization; and, Group 3 was considered infected for > 24 months if their HIV diagnosis date was > 24 months before randomization.

Statistical analysis

Baseline characteristics were compared between groups using chi-square tests for proportions and Wilcoxon rank sum tests for medians. Longitudinal regression with repeated measures analyses were used to compare CD4+ count, CD8+ count, and CD4:CD8 ratio levels during follow-up between the immediate and deferred ART groups among Groups 1–3, adjusting for baseline levels. Treatment differences (immediate minus deferred) for the three duration of infection groups were compared with 2 degree of freedom (df) interaction tests. In our previous report that compared self-reported date of infection with the MAA for START participants, we showed that participants recently infected were younger and had higher baseline viral load levels compared to those who were not recently infected.[12] Based on this and the finding that absolute risk differences in the START composite primary endpoint varied by age and viral load,² for CD4+ cell count and the CD4:CD8 ratio we also carried out analyses to assess 3-way interactions between treatment group, duration of infection group, and age and viral load. Two-way interactions between treatment group and age and viral load were assessed to determine treatment differences irrespective of duration of infection.

Selected analyses were also carried out within START treatment groups. In the deferred group, the rate of decline to CD4+ <350 cells/ μ L (censored at last CD4 measurement) or AIDS (threshold for initiating ART; censored at last known alive date) was compared among the 3 groups using proportional hazards regression analysis, with and without censoring for ART initiation. Hazard ratios (HRs) adjusted for age, gender, race, geographic location, CD4+ cell count, and HIV RNA level at entry are cited with 95% confidence intervals. In the immediate ART group, the 3 groups were compared for virologic suppression (HIV RNA $\leq$ 200 copies/mL) at 1, 4 and 8 months following randomization using separate adjusted logistic regression models for each time point with baseline covariates corresponding to age, gender, race, geographic location, CD4+ cell count, and HIV RNA level. For this analysis, we restricted the cohort to immediate ART group participants who initiated ART within one week of randomization.

Statistical analyses were performed using SAS, version 9.3 (SAS Institute, Cary, NC). All p-values cited are 2-sided and not adjusted for multiple comparisons.

Results:

Group 1 includes 373 participants (167 participants who self-reported being infected in the 6 months prior to enrollment and 206 participants who did not know the duration of their infection, but who were diagnosed with HIV in the 6 months before randomization and were also classified as recently infected by the MAA).[12] Groups 2 and 3 include 2,634 and 1,605 participants, respectively. Seventy-two participants who would have been classifiable in either Groups 1 or 2 did not have a baseline sample available for MAA testing and are excluded from this analysis.

Baseline Characteristics According to Estimated Duration of Infection at Randomization

At entry, individuals in the recently infected group (Group 1) were younger than those in Groups 2 and 3 (31 vs 34 vs 40 years, $p < 0.001$) and more likely to be MSM (75% vs 59% vs 44%, $p < 0.001$). Group 1 also had a higher median baseline HIV RNA and a smaller percentage of participants with viral load < 3000 copies/mL than the other two groups (27199 vs 13553 vs 9744 copies/mL; $p < 0.001$) and (11.5% vs 23.6% vs 29.8%; $p < 0.001$), a moderately higher baseline CD4+ count (660 vs 654 vs 644 cells/ μ L; $p = 0.007$), a moderately lower baseline CD8+ count (1018 vs 1031 vs 1070 cells/ μ L; $p = 0.003$), and a higher CD4:CD8 ratio (0.70 vs 0.67 vs 0.63; $p < 0.001$) (Table 1). Among participants who reported their presumed date of HIV infection (overall 40%), the median time from infection to randomization for Groups 1, 2 and 3 were 4.8, 14.3 and 58.0 months, respectively.

Treatment Differences in Use of Antiretroviral Therapy

In Group 1, ART was used for 95% of follow-up time in the immediate ART group and 33% of follow-up time in the deferred ART group; for Group 2, these percentages were 95% and 30%; and for Group 3, the percentages were 93% and 26%.

Treatment Differences in CD4+ and CD8+ Cell Counts and the CD4:CD8 Ratio

As previously reported, over an average follow-up period of 3 years, the mean CD4+ cell count was 194 cells/ μ L higher in the immediate compared to the deferred ART group.¹ The average follow-up CD4+ difference between the immediate and deferred ART groups varied significantly according to estimated duration of HIV infection (231 vs 202 and 172 cells/ μ L; $p < 0.001$ for interaction). The mean CD4+ counts increased over follow-up in the immediate arm for all 3 subgroups, with the greatest increase in the recent infection group (188, 171 and 151 respectively, for Groups 1, 2 and 3; $p = 0.002$) (Figure 1). For the deferred ART group, the average CD4+ count declined over follow-up by 42, 31, and 21 cells/ μ L for Groups 1, 2 and 3, respectively ($p = 0.18$) (Figure 1).

The mean CD4:CD8 ratio difference (immediate-deferred) over follow-up also varied according to estimated duration of infection at entry (0.52 vs 0.40 vs 0.34; $p < 0.001$ for interaction) (Figure 2). The mean CD4:CD8 ratio increased over follow-up for all 3 subgroups in the immediate ART group, and the increase varied according to duration of infection at entry ($p < 0.001$). For the CD4:CD8 ratio in the deferred ART group, there was little change from baseline and the differences among the three subgroups did not vary significantly ($p = 0.57$).

The mean CD8+ difference (immediate minus deferred) did not vary significantly over follow-up according to estimated duration of infection ($p = 0.33$ for interaction) (Supplemental Figure 1).

Treatment Differences in CD4+ and CD4:CD8 Ratio by HIV RNA Level and Age

The mean follow-up CD4+ count and the CD4:CD8 ratio were greater in the immediate vs. deferred ART groups among those with higher baseline HIV RNA levels (Figures 3A and 3C; HIV-RNA x treatment interactions $p = < 0.001$ for both CD4+ count and CD4:CD8 ratio). These trends did not differ by duration of infection group (3-way interaction $p = 0.39$ and $p = 0.34$). For example, treatment differences in CD4+ count between Groups 1 and 3 were 46, 31, and 45 cells/ μ L for the three baseline viral load strata. For CD4:CD8 ratio these Group 1 versus Group 3 mean differences were 0.09, 0.20, and 0.20 for the three viral load strata. Similarly, differences in mean CD4+ count and CD4:CD8 ratio differences between treatment groups for the three duration of infection groups did not vary by age (Figures 3B and 3D; 3-way interactions $p = 0.71$ and $p = 0.19$).

Rate of CD4+ Decline to <350 cells/ μ L or AIDS in the Deferred ART Group

In the deferred ART group, the rate of CD4+ decline to <350 cells/ μ L or development of AIDS was greater among those recently infected compared to those who were not recently infected (Figure 4A). Rates per 100 person years were 15.6, 12.7, and 10.5 for Groups 1, 2, and 3, respectively ($p = 0.002$). HRs adjusted for age, gender, race, geographic location, CD4+ cell count, and HIV RNA level at entry for Group 1 versus 3 and for Group 2 versus Group 3 were 1.38 (95% CI: 1.03 to 1.84) and 1.26 (95% CI: 1.06 to 1.49), respectively (p -value for corresponding 2df likelihood ratio test < 0.001). A stronger trend ($p < 0.001$) was observed when follow-up was censored at ART initiation (Figure 4B). Adjusted HRs for Group 1 versus 3 and for Group 2 versus Group 3 were 1.52 (95% CI: 1.14–2.05) and 1.36

(95% CI: 1.14–1.63). The median (25th, 75th percentile) CD4+ count at ART initiation for Groups 1, 2 and 3 were 386 (300, 509), 399 (316, 551), and 440 (335, 595) cells/ μ L, respectively.

Rates of CD4 decline to <350 cells/ μ L or development of AIDS within each infection group separately by gender and within subgroups defined by race/ethnicity and region of enrollment are presented in Supplemental Table 1. Predictors of CD4 decline to <350 cells/ μ L or development of AIDS within each of the infection groups are presented in Supplemental Table 2.

Virologic Suppression in the Immediate ART Group

Supplemental Table 3 compares the percent with virologic suppression at 1, 4 and 8 months in the immediate ART group by duration of infection group. At one month fewer participants in Group 1 had a viral load $\geq$ 200 copies/mL than in Groups 2 and 3 ($p < 0.001$ for unadjusted 2df test for difference among subgroups). By 4 and 8 months the percent with viral load $\geq$ 200 copies/mL was similar for the three subgroups defined by duration of HIV infection ($p = 0.10$ for at both visits for unadjusted 2df comparisons). When considering adjusted comparisons, the difference in suppression rates at Month 1 was no longer significant ($p = 0.07$) after including baseline viral load in the model.

Discussion

The primary purpose of this study was to determine whether differences in follow-up levels of CD4+ count between the immediate and deferred ART groups in START varied by estimated duration of HIV infection at the time of randomization. We found that the treatment difference in follow-up CD4+ count was greatest for those infected for less than 6 months at the time of randomization.

Since an early study in 16 individuals of the initiation of combination ART during primary HIV infection reported that CD4+ count increased to levels similar to those of HIV-negative controls and also appeared to prevent permanent loss of important subsets of CD4 T lymphocytes[13], several other larger observational studies have reported that an enhanced CD4+ count recovery was evident among participants who initiated ART closer to the time of seroconversion.[5,7,8,9] Findings for the immediate ART group in START are consistent with the findings of these studies but has the advantage of having an appropriate control group with which to compare the CD4+ changes during follow-up resulting from immediate ART. Further follow-up of this cohort is necessary to determine the implications of the CD4+ count differences between treatment groups we observed after an average of 3 years. Follow-up of START participants is ongoing and planned to continue through 2021.

The variable treatment difference in CD4+ count observed according to duration of infection is also generally consistent with a randomized trial of short-course ART in primary HIV infection. In the Short Pulse Anti-Retroviral Therapy at Seroconversion (SPARTAC) trial, 366 participants were randomized (1:1:1) to ART for 48 weeks, ART for 12 weeks, or no ART and followed for a median of 4.2 years for a composite primary endpoint of CD4+ < 350 cells/ μ L or initiation of ART. Median CD4+ count at entry was 559 cells/ μ L and the

median time from seroconversion at randomization was estimated as 12 weeks. A trend for a greater effect of 48 weeks of ART (followed by ART discontinuation) compared to no ART on the primary endpoint was found for those randomized sooner after seroconversion. Hazard ratios (48 weeks of ART versus no ART) for CD4+ < 350 cells/ μ L or initiation of ART were 0.41 for those randomized within 4 weeks of seroconversion, 0.65 for those randomized with 12 weeks and 1.28 for those randomized within 12 weeks ($p=0.09$ for trend).[14].

In our study, follow-up CD8+ differences between treatment groups did not differ by duration of infection, and as a consequence when the CD4:CD8 ratio was considered, a pattern similar to that seen for CD4+ count was observed. In a small study comparing CD4+ and CD8+ recovery following ART initiation in individuals with primary and chronic HIV infection, there was decline in CD8+ among those with primary infection similar to what we observed but an increase in those with chronic infection after one month. However, by 12 months, CD8+ had declined in both groups. Like our study, those with primary infection had much greater CD4+ count increases than those with chronic infection.[15].

Among the immediate ART group, the recently infected subgroup of participants tended to have a lower rate of virologic suppression at month 1 compared to those not recently infected. By month 4, however, rates of suppression were higher and comparable to the rates in the other two groups. This slower time to reach suppression is not surprising given the higher baseline viral load among those recently infected participants. Among participants in the deferred ART group, we observed a higher rate of CD4+ decline to < 350 cells/ μ L or progression to AIDS within the recently infected subgroup compared to those infected longer. This difference in rates could also be attributed to the higher viral load in the recent infection group. The study eligibility criteria may have also played a part. The study required two CD4+ cell counts above 500 cells/ μ L within 60 days before randomization and these criteria coupled with the likelihood that many sites may have had participants under care who could readily be screened and consented likely led to the enrollment of individuals with more stable CD4+ levels and lower viral load. This in turn led to slower rates of CD4+ decline following randomization among many participants in START, particularly those who have been infected longer.

There were some limitations to our study. As noted above, we cannot determine whether the greater CD4+ differences for the recent infection group as compared to the other two groups led to differences in clinical outcomes. This may not even be possible to establish with the planned follow-up through 2021. In addition, there is likely some misclassification of participants in the groups, particularly Groups 2 and 3 which are largely based on the date of diagnosis not date of infection or the MAA. While we can be fairly confident that the 3 subgroups differ substantially in duration of infection at randomization, the magnitude of the difference is uncertain because of misclassification and the large percentage of participants not knowing the date of infection. Finally, it is possible that duration of infection is a marker for another factor. While treatment is randomized in START, duration of infection is not. Those with recent infection differed from those with later infection in many respects.

In summary, the subgroup of recently infected individuals from the START trial constitutes the largest randomized study of immediate versus deferred ART for those with recent infection. If differences in CD4+ cell count and the CD4:CD8 ratio between the immediate and deferred groups for those with recent infection result in greater clinical benefit than those infected longer at randomization, then the overall benefit of immediate ART in START may be underestimated because the great majority of participants in START had been infected for longer than 6 months, with many longer than 2 years likely as a result of screening and eligibility criteria.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
Mean CD4+ cell counts (95% CI) over follow-up for the immediate and deferred ART groups by duration of HIV infection at randomization.

Figure 2.
Mean CD4:CD8 ratio (95% CI) over follow-up for the immediate and deferred ART groups by duration of HIV infection at randomization.

Figure 3.

Mean treatment differences (Immediate – Deferred) in CD4⁺ cell count (A and B) and CD4:CD8 ratio (C and D) within subgroups of baseline HIV-RNA (left column) and baseline age (right column) according to estimated duration of infection at randomization.

A) Kaplan-Meier plot for time to CD4+ < 350 cells/ μ L or the development of AIDS in the deferred ART group by duration of HIV infection at randomization. The threshold for initiating ART in the deferred ART group was reaching a CD4+ < 350 cells/ μ L or developing AIDS. B) Kaplan-Meier plot for time to CD4+ < 350 cells/ μ L or AIDS in the deferred ART group by duration of HIV infection at randomization, censored when participants initiated ART.

Table 1.

Baseline characteristics of START participants according to estimated duration of infection at randomization.

<i>No. Participants</i>	<i>373</i>	<i>2634</i>	<i>1605</i>	<i>4612</i>	<i>P-Value¹</i>
Demographics					
Age (years)					
<30	31 [25, 40]	34 [28, 42]	40 [33, 46]	36 [29, 44]	<0.001
30–49	168 (45.0)	880 (33.4)	248 (15.5)	1296 (28.1)	<0.001
50+	174 (46.7)	1500 (57.0)	1096 (68.3)	2270 (60.1)	
Gender (female)	31 (8.3)	254 (9.6)	261 (16.3)	546 (11.8)	
Race	41 (11.0)	637 (24.2)	562 (35.0)	1240 (26.9)	<0.001
Asian					<0.001
Black	52 (13.9)	201 (7.6)	130 (8.1)	383 (8.3)	
Latino/Hispanic	54 (14.5)	684 (26.0)	647 (40.3)	1385 (30.0)	
White	58 (15.5)	395 (15.0)	170 (10.6)	623 (13.5)	
Other	191 (51.2)	1254 (47.6)	618 (38.5)	2063 (44.7)	
Geographic Location	18 (4.8)	100 (3.8)	40 (2.5)	158 (3.4)	0.019
US/Europe/Australia (High)	167 (44.8)	1179 (44.7)	788 (49.1)	2134 (46.3)	
S America/Africa/Asia (Low-Mid)	206 (55.2)	1455 (55.2)	817 (50.9)	2478 (53.7)	
HIV History					
Likely mode of HIV infection					<0.001
Men who have sex with men (MSM)	281 (75.3)	1557 (59.1)	709 (44.2)	2547 (55.2)	
Heterosexual	69 (18.5)	940 (35.7)	751 (46.8)	1760 (38.2)	
Injection drug use	4 (1.1)	23 (0.9)	36 (2.2)	63 (1.4)	
Blood products/other/unknown	19 (5.1)	114 (4.4)	109 (6.8)	242 (5.2)	
Months between HIV diagnosis and randomization	2.6 [1.9, 3.4]	7.3 [3.6, 13.3]	51.6 [35.6, 80.2]	12.8 [4.5, 37.0]	<0.001
Unknown HIV infection date	206 (55.2)	1496 (56.8)	1052 (65.6)	2754 (59.7)	<0.001
Months between HIV infection and randomization ²	4.8 [4.0, 5.4]	14.3 [9.4, 23.2]	58.0 [40.9, 94.7]	19.5 [9.7, 44.2]	<0.001
Laboratory Results					
CD4 (cells/ μ L)	660 [585, 780]	654 [587, 773]	644 [579, 747]	651 [584, 764]	0.007

	Group 1 (< 6 months) Med [IQR], N (%)	Group 2 (6–24 months) Med [IQR], N (%)	Group 3 (> 24 months) Med [IQR], N (%)	Overall Med [IQR], N (%)	¹ P-Value
CD8 (cells/ μ L)	1018 [764, 1358]	1031 [768, 1368]	1070 [796, 1457]	1041 [776, 1400]	0.003
CD4:CD8 ratio	0.70 [0.50, 0.90]	0.67 [0.50, 0.92]	0.63 [0.45, 0.86]	0.66 [0.48, 0.89]	< 0.001
HIV RNA (copies/mL)	27199 [8140, 75431]	13553 [3330, 44103]	9744 [2176, 35769]	12683 [3041, 43100]	< 0.001
< 3000	43 (11.5)	621 (23.6)	476 (29.7)	1140 (24.8)	< 0.001
3000–49999	205 (55.0)	1419 (54.0)	838 (52.4)	2462 (53.5)	
50000+	125 (33.5)	590 (22.4)	286 (17.9)	1001 (21.7)	
Treatment Assignment					
Immediate	198 (53.1)	1318 (50.0)	777 (48.4)	2293 (49.7)	0.24
Deferred	175 (46.9)	1316 (50.0)	828 (51.6)	2319 (50.2)	

¹ Unadjusted p-value comparing the three groups. Wilcoxon rank sum test use to compare medians, and chi-square tests for percents.

² Of those with known HIV infection date: n = 1858 (Group 1 n = 167; Group 2 n = 1138; Group 3 n = 553)