Risk Factors for Low CD4+ Count Recovery Despite Viral Suppression Among Participants Initiating Antiretroviral Treatment With CD4+ Counts > 500 Cells/mm3: Findings From the Strategic Timing of AntiRetroviral Therapy (START) Trial

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Background: Low CD4+ recovery among HIV-positive individuals who achieve virologic suppression is common but has not been studied among individuals initiating treatment at CD4+ counts of >500 cells/mm3.

Setting: United States, Africa, Asia, Europe and Israel, Australia, Latin America.

Methods: Among participants randomized to immediate antiretroviral therapy (ART) in the Strategic Timing of AntiRetroviral Therapy trial, low CD4+ recovery was defined as a CD4+ increase of <50 cells/mm3 from baseline after 8 months despite viral load of ≤200 copies/mL. Risk factors for low recovery were investigated with logistic regression.

Results: Low CD4+ recovery was observed in 39.7% of participants. Male sex [odds ratio (OR), 1.53; $P = 0.007$], lower screening CD4+ cell counts (OR, 1.09 per 100 fewer cells/mm3; $P = 0.004$), higher baseline CD8+ cell counts (OR, 1.05 per 100 more cells/mm3; $P < 0.001$), and lower HIV RNA levels (OR, 1.93 per $\log_{10}$ decrease; $P < 0.001$) were associated with low CD4+ recovery. D-dimer had a quadratic association with low CD4+ recovery, with lowest odds occurring at 0.32 μg/mL. At lower HIV RNA levels, the odds of low CD4+ recovery were elevated across the levels of screening CD4+ count; but at higher HIV RNA levels, the odds of low CD4+ recovery were higher among those with lower vs. higher screening CD4+.

Conclusions: Low CD4+ recovery is frequent among participants starting ART at high CD4+ counts. Risk factors include male sex, lower screening CD4+ cell counts, higher CD8+ cell counts, and lower HIV RNA levels. More follow-up is required to determine the impact of low CD4+ recovery on clinical outcomes.

Key Words: antiretroviral therapy, CD4, HIV, immune response

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INTRODUCTION

In most HIV-positive patients treated with antiretroviral therapy (ART), viral suppression is achieved and CD4+ counts recover to > 500 cells/mm3.[1–7] The percentage of patients with a low CD4+ count recovery varies between 15% and 30% depending on the definition used and on the time period since the start of ART.[8–10] Among patients who initiate ART at low CD4+ counts, low CD4+ recovery after initiation of ART is associated with increased risk for AIDS, serious non-AIDS diseases, and death.[8,11–15] Several risk factors for the failure to show a substantial increase in CD4+ counts have been well characterized among patients who initiate ART at CD4+ levels of <500 cells/mm3. These risk

factors include older age, lower HIV RNA levels, hepatitis C coinfection, active hepatitis B coinfection, longer duration of HIV infection, and lower nadir CD4+ count.[8–11,16–19] Genetic factors have also been cited as possible links to low CD4+ recovery.[14,19–23] To our knowledge, the determinants of low CD4+ recovery after virologic suppression have not been studied specifically among patients who initiate ART at CD4+ counts of >500 cells/mm^3.

The goal of this investigation is to estimate the prevalence of low CD4+ count recovery despite virologic suppression after 8 months of ART among participants with HIV who initiate ART at a CD4+ count of >500 cells/mm^3 and to determine the predictors of low recovery, including pre-ART CD4+ cell count. This will be accomplished using participants randomized to the immediate ART treatment group in the Strategic Timing of AntiRetroviral Treatment (START) trial.[13] The number of clinical events in the immediate ART initiation group of the START trial was very low, so we did not have the power to evaluate the clinical implication of low CD4+ recovery.

METHODS

Design

The START trial was approved by the Institutional Review Board or ethics committee at each participating site, and written informed consent was obtained from all study participants. The study design and the baseline characteristics of participants in the START trial have been reported previously.[13,24,25] In the START trial, HIV-positive, ART-naive participants with CD4+ counts of >500 cells/mm^3 were randomized to immediate initiation of ART (n = 2325) or to deferred initiation until the CD4+ count declined to 350 cells/mm^3 or AIDS developed (n = 2359). ART regimens were selected by participants and their providers from a list of approved drug combinations derived from the guidelines of the Department of Health and Human Services.[26] Participants were required to have 2 CD4+ counts of >500 cells/mm^3 at least 2 weeks apart within 60 days before randomization. We refer to the first of these CD4+ counts as the screening CD4+ and the second as the baseline CD4+ count. In addition to CD4+ cell count, CD8+ cell count and HIV RNA level were measured locally before randomization and at 1 month, 4 months, and every 4 months of follow-up thereafter. Similar to Baker et al[11] and Florence et al,[16] low CD4+ recovery after ART initiation was defined as CD4+ increase of <50 cells/mm^3 8 months after randomization despite HIV RNA level of ≤200 copies/mL at 8 months; high recovery was defined as CD4+ increase of ≥50 cells/mm^3 among those with HIV RNA level of ≤200 copies/mL. Those who do not achieve large gains in CD4+ count after the initiation of ART have also been referred to as immunologic nonresponders.

Statistical Analysis

If change is measured from the baseline, the relationship of change in CD4+ count with baseline CD4+ count is influenced by measurement error and within-participant variability (ie, regression to the mean).[27,28] To reduce the effect of regression to the mean for studying the association of CD4+ count change (value at 8 months minus baseline value) with pre-ART CD4+ count, we used 2 methods. The first approach used the screening CD4+ count (the 1st of the 2 pre-ART counts), which was not used to calculate CD4+ count change, as the predictor of change in CD4+ count and of low CD4+ recovery. Based on the work by Ederer,[29] we assumed that if the correlation between baseline CD4+ count and 8-month CD4+ count was similar to the correlation between screening CD4+ count and 8-month CD4+ count, the effect of regression to the mean could be largely eliminated with this approach. The bias in estimating an association between an initial value and a change from that initial value arises in part due to mathematical coupling: the initial value is both the predictor and is part of the derived response, and this can create bias in the estimated association. This can be partially avoided using as a predictor a second "initial" value, provided that it was obtained in close temporal proximity to the initial value from which the change is measured. The second approach used a method proposed by Blomqvist[27,30] to estimate the association between "true" or "usual" pre-ART CD4+ cell count levels (with correction for measurement error and short-term intra-person variability) and the change in CD4+ count. The second approach has the advantage of not requiring 2 measurements of pre-ART CD4+ counts for assessing the change. However, it does require an estimate of the reliability coefficient (ratio of between person to total variability). In this investigation, the reliability coefficient was estimated by the correlation of the screening and baseline CD4+ counts.

Linear mixed effects models[31] were used to analyze CD4+ differences between groups over follow-up. Risk factors for low CD4+ count recovery were studied with logistic regression; odds ratios (ORs) and 95% confidence intervals (CIs) are cited. Because ORs are not good approximations of the relative risk when the outcome is common, relative risks from log-binomial and Poisson regression models are also cited. Univariable (ie, unadjusted) and multivariable (adjusted) analyses were carried out. As potential baseline (pre-ART) risk factors for low recovery, we considered age, sex, race (Asian, black, Hispanic, white/other), geographic location, treatment regimen, body mass index (BMI, kg/m^2), coinfection with hepatitis C, coinfection with hepatitis B, screening CD4+ count, baseline CD8+ count, HIV RNA level (copies/mL), baseline interleukin-6 (IL-6, pg/mL), baseline D-dimer (μg/mL), and the duration of time since HIV diagnosis. Geographic region was categorized as United States, Africa, Asia, Europe and Israel, Australia, or Latin America. The treatment regimen was categorized as non-nucleoside reverse transcriptase inhibitor (NNRTI) + 2 nucleoside reverse transcriptase inhibitors (NRTIs), protease inhibitor (PI) + 2 NRTIs, integrase inhibitor + 2 NRTIs, or other. The great majority of participants were prescribed Tenofovir and emtricitabine as the 2 NRTIs. Thus, further categorization of this class of drugs was not carried out (see Table 2, Supplemental Digital Content, http://links.lww.com/QAI/B275, in Ref. 13 for further details of the treatment regimens used in the START trial). The adjusted analysis

included all these variables. For variables with associations that changed between the univariable and multivariable models, we explored interactions among variables as possible explanations of the changes. For continuous predictors, we checked linearity against the logit function using empirical logit plots: for each continuous predictor, observations were grouped based on deciles of the predictor, and observed logits of the probability of low CD4$^+$ recovery were plotted against the mean values of the predictor within each decile. All analyses were done with SAS statistical software, versions 9.4 (SAS Institute, Cary, NC).

RESULTS

Study Cohort

Of the 2325 participants randomized to the immediate ART group of the START trial, 2063 started ART within 30 days of randomization; of these, 1983 had a CD4$^+$ count and HIV RNA level at the month 8 visit, and of these, 1884 (95%) had an HIV RNA level of ≤200 copies/mL at month 8. These 1884 patients comprise the cohort for this study.

Overall, for these 1884 participants, the mean (SD) screening, baseline, and 8-month CD4$^+$ cell counts were 709 (191), 694 (193), and 806 (261) cell/mm^3, respectively. The median (25th, 75th percentile) number of days between screening and baseline CD4$^+$ counts was 21 (16, 33) days. Correlations between screening and 8-month CD4$^+$ count and between baseline CD4$^+$ count and 8-month CD4$^+$ count were 0.51 and 0.50, respectively.

Prevalence of Low CD4$^+$ Count Recovery and Change in CD4$^+$ Count Over Follow-Up for Those With Low Versus High Recovery

Among the 1884 participants in the immediate ART group who had an HIV RNA level of ≤200 copies/mL 8 months after initiating ART, 748 (39.7%; 95% CI: 37.5% to 42.0%) had low CD4$^+$ recovery. The average change in CD4$^+$ count from baseline to 8 months was −93 cells/mm^3 (95% CI: −102 to −84) in low responders vs. +247 cells/mm^3 (95% CI: 236 to 258) in high responders. After an initial increase in CD4$^+$ cell count for low responders and a decrease in CD4$^+$ count for high responders between month 8 and month 12, which we attribute to regression to the mean, over 12–60 months of follow-up (median follow-up = 3.0 years, 25th and 75th percentiles are 2.3 and 4.1 years, respectively), the mean CD4$^+$ count was 228 cells/mm^3 higher in high responders than in low responders (95% CI: 207 to 249) controlling for baseline CD4$^+$, and CD4$^+$ counts increased more rapidly among high responders with an average increase of 3.3 cells/mm^3/mo (95% CI: 2.9 to 3.6) vs. 2.2 cells/mm^3/mo in low responders (95% CI: 1.8 to 2.7) (Fig. 1). Thirty-six months after initiating ART, only 17% of low responders had CD4$^+$ counts over 1000 cells/mm^3 compared with 37% of high responders ($P < 0.0001$ for difference).

Association of Pre-ART Screening and Baseline CD4$^+$ Count With Change in CD4$^+$ Count at 8 Months

Table 1 gives the estimates of slopes for the regression of change in CD4$^+$ cell count from baseline to 8 months on screening and baseline CD4$^+$ cell count levels. The slope is positive and not significant for screening CD4$^+$ cell count, indicating that for each 100 cell higher screening CD4$^+$ count, the change in CD4$^+$ count at 8 months was +2.1 cells/mm^3 greater. By contrast, as a result of regression to the mean, for baseline CD4$^+$ cell count, the slope is negatively biased at −32.5 cells/mm^3 (95% CI: −37.8 to −27.2; $P < 0.001$). The slope estimated with Blomqvist's method, which adjusts the baseline CD4$^+$ count for measurement error, is similar to the slope for the screening CD4$^+$ cell count: +1.7 cells/mm^3 (95% CI: −11.6 to +16.9; $P = 0.82$) for a 100 cell higher baseline CD4$^+$ count.

Similar to the results shown in Table 1, the univariate association between the percentage with a low CD4$^+$ response at 8 months and screening CD4$^+$ cell count shows no clear relationship ($P = 0.85$ for trend) (Fig. 2).

Univariable and Multivariable Predictors of Low CD4$^+$ Count Recovery

Table 1, Supplemental Digital Content, http://links.lww.com/QAI/B275, gives baseline characteristics for those with low and high recovery. Table 2 shows the results for univariable and multivariable logistic regression models for

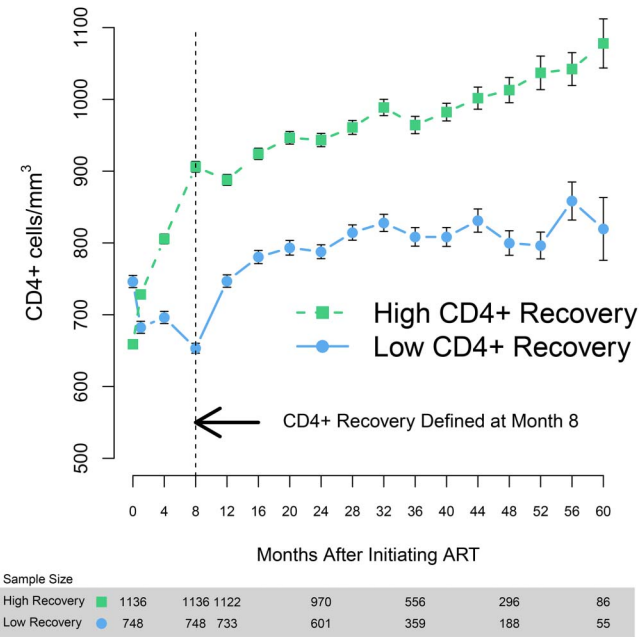

FIGURE 1. Mean CD4$^+$ counts (cells/mm^3 ± standard error of the mean) during follow-up for participants with high recovery (CD4$^+$ increase of ≥50 cells/mm^3 8 months after initiating ART) vs. those with low recovery (CD4$^+$ increase of <50 cells/mm^3 8 months after initiating ART). All participants had HIV RNA level of ≤200 copies/mL at month 8.

TABLE 1. Change in CD4+ Cell Count From Baseline to 8 Months Per 100 Cells/mm^3 Higher in Screening and Baseline CD4+ Count Levels

Predictor	Estimate	SE	95% CI	P
Screening CD4+ (cells/mm^3)	2.1	2.8	−3.4 to 7.7	0.45
Baseline CD4+ (cells/mm^3)	−32.5	2.7	−37.8 to −27.2	<0.001
Baseline CD4+ (Blomqvist estimator)	1.7	7.3	−11.6 to 16.9	0.82

baseline predictors of low CD4+ recovery. In multivariable analyses, male participants had significantly greater odds of low CD4+ recovery than female participants (OR, 1.53; $P = 0.007$), but the association was not significant in univariable analysis (OR, 0.93; $P = 0.47$). The striking difference in the effect of sex between univariable and multivariable models is explained by the confounding effect of HIV RNA—itself a strong predictor of CD4+ recovery—between female and male participants: the median (25th, 75th percentile) of $\log_{10}$ viral load was 3.81 (3.05, 4.36) for female participants and 4.26 (3.69, 4.70) for male participants.

In univariable analyses, black participants had significantly higher odds of low CD4+ recovery than white/other participants (OR, 1.51; $P < 0.001$), and Africans had higher odds of low recovery than participants in the United States (OR, 1.70; $P = 0.004$). In the multivariable model, the black race was no longer significant; the association remained significant when African participants were compared with participants in the United States (OR, 1.62; $P = 0.043$). The univariable OR for black vs. white/other was attenuated in the multivariable model because the model included both race and geographic region. In a multivariable model excluding geographic region but including all other variables (results not shown), the OR for black vs. white/other was 1.34 (95% CI: 1.00 to 1.78; $P = 0.047$).

In univariable analysis, participants treated with a PI + 2 NRTIs had lower odds of low CD4+ recovery compared with participants treated with NNRTI + 2 NRTIs (OR, 0.67; $P = 0.002$), but the effect was not significant in the multivariable model. The reduced association in the multivariable analysis is largely due to the adjustment for a geographic region. Participants in the 3 geographic areas with the lowest odds of low recovery (United States, Europe and Israel, and Australia) were significantly more likely to be treated with a PI + 2 NRTIs ($\chi^2_{15} = 222.5$; $P < 0.001$ for the test of homogeneity). Aside from race and treatment regimen, ORs for other covariates considered were not materially modified with the exclusion of geographic region from the multivariable model.

Higher baseline CD8+ was associated with increased odds of low CD4+ recovery in both univariable analysis (OR, 1.03 per 100 more cells/mm^3; $P < 0.001$) and multivariable analysis (OR, 1.05 per 100 more cells/mm^3; $P < 0.001$). Lower baseline HIV RNA level was associated with increased odds of low recovery in both univariable analysis (OR, 1.68; $P < 0.001$) and multivariable analysis (OR, 1.93; $P < 0.001$). Time since HIV diagnosis was weakly associated with the odds of low CD4+ recovery in univariable analysis (OR, 1.04 per 1-year longer; $P = 0.011$) but not in multivariable analysis (OR, 1.03; $P = 0.15$).

As previously described, screening CD4+ cell count was not associated with CD4+ change at 8 months. Similarly, in univariable analysis, screening CD4+ was not associated with the odds of low recovery ($P = 0.85$). However, in the multivariable model, lower screening CD4+ was associated with increased odds of low recovery (OR, 1.09 per 100 fewer cells/mm^3; $P = 0.004$). This was explored further and a significant interaction between screening CD4+ cell count and baseline HIV RNA level was found ($P = 0.005$ for interaction term from the logistic model when both screening CD4+ and baseline $\log_{10}$ HIV RNA were continuous predictors for low recovery). Figure 3 illustrates the interaction. Among those with lower baseline HIV RNA levels, the association between screening CD4+ count and low CD4+ recovery at 8 months was weaker (red bars). Similarly, we checked for interaction between baseline CD8+ cell count and baseline HIV RNA levels (see Figure 1, Supplemental Digital Content, http://links.lww.com/QAI/B275), but the effect of the interaction was not significant ($P = 0.62$).

In univariable and multivariable analyses, we included a quadratic term for D-dimer, because empirical logit plots suggested a possible quadratic association between D-dimer and the odds of low CD4+ recovery. Both analyses indicated a quadratic effect of D-dimer. From the univariable analysis, the estimated odds of low CD4+ recovery were lowest for D-dimer of 0.27 μg/mL (median D-dimer was 0.32 μg/mL); the odds of low CD4+ recovery for the 25th percentile (0.22 μg/mL) and the 75th percentile (0.50 μg/mL) of D-dimer vs. 0.27 μg/mL were 6.7% and 0.7% higher, respectively. From the multivariable analysis, the estimated odds of low CD4+ recovery were lowest for D-dimer of 0.32 μg/mL; the odds of

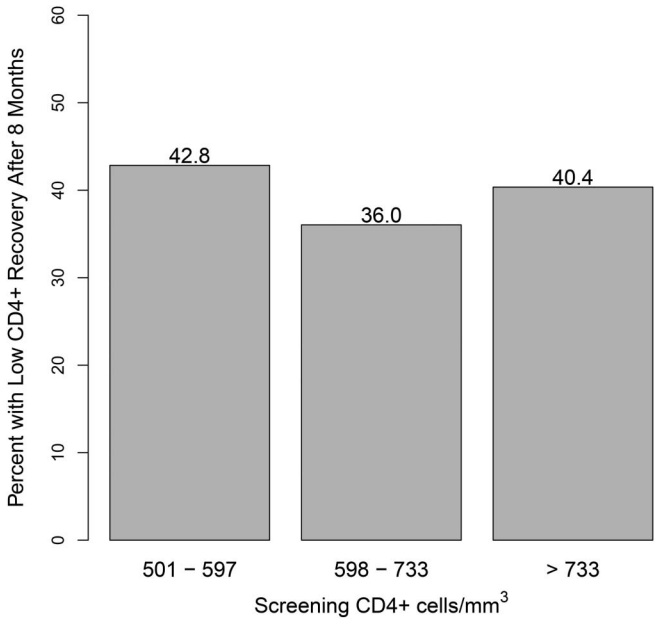

FIGURE 2. Percentage of participants with low CD4+ recovery after 8 months by tertiles of screening CD4+ (the 1st of 2 pre-ART CD4+ values).

TABLE 2. Univariable and Multivariable ORs for Low $CD4^+$ Recovery

	Univariable		Multivariable	
Risk Factor	**OR (95% CI)**	***P***	**OR (95% CI)**	***P***
Age, OR per 10 years higher	1.06 (0.97 to 1.16)	0.23	1.10 (0.98 to 1.24)	0.11
Female	1.00 (ref.)		1.00 (ref.)	
Male	0.93 (0.75 to 1.14)	0.47	1.53 (1.12 to 2.10)	0.007
Race				
White/other	1.00 (ref.)		1.00 (ref.)	
Asian	1.28 (0.89 to 1.83)	0.18	1.12 (0.33 to 3.78)	0.86
Black	1.51 (1.22 to 1.87)	<0.001	1.08 (0.73 to 1.59)	0.70
Hispanic	1.17 (0.88 to 1.55)	0.27	1.28 (0.90 to 1.81)	0.17
Geographic location				
United States	1.00 (ref.)		1.00 (ref.)	
Africa	1.70 (1.19 to 2.44)	0.004	1.62 (1.01 to 2.58)	0.043
Asia	1.26 (0.79 to 2.01)	0.33	1.27 (0.34 to 4.81)	0.72
Europe and Israel	1.02 (0.72 to 1.44)	0.92	1.03 (0.68 to 1.58)	0.88
Australia	1.09 (0.57 to 2.07)	0.80	1.09 (0.52 to 2.27)	0.82
Latin America	1.17 (0.82 to 1.67)	0.38	1.15 (0.75 to 1.76)	0.52
Treatment regimen				
NNRTI + 2 NRTIs	1.00 (ref.)		1.00 (ref.)	
Protease inhibitor + 2 NRTIs	0.67 (0.52 to 0.86)	0.002	0.78 (0.59 to 1.04)	0.09
Integrase inhibitor + 2 NRTIs	0.72 (0.44 to 1.17)	0.18	0.90 (0.52 to 1.56)	0.70
Other	2.80 (0.25 to 30.99)	0.40	1.52 (0.09 to 25.75)	0.77
Body mass index, OR per kg/m^2 higher	0.99 (0.98 to 1.01)	0.55	0.98 (0.96 to 1.00)	0.08
Hepatitis C coinfection	1.06 (0.64 to 1.75)	0.84	0.99 (0.55 to 1.76)	0.96
Hepatitis B coinfection	1.60 (0.95 to 2.72)	0.08	1.45 (0.79 to 2.67)	0.24
Screening $CD4^+$, OR per 100 fewer $cells/mm^3$	1.00 (0.95 to 1.04)	0.85	1.09 (1.03 to 1.15)	0.004
Baseline $CD8^+$, OR per 100 more $cells/mm^3$	1.03 (1.02 to 1.05)	<0.001	1.05 (1.03 to 1.07)	<0.001
Baseline HIV RNA copies/mL, OR per $\log_{10}$ lower	1.68 (1.50 to 1.87)	<0.001	1.93 (1.68 to 2.22)	<0.001
Baseline IL-6 pg/mL, OR per $\log_2$ higher	1.01 (0.91 to 1.12)	0.89	1.07 (0.95 to 1.20)	0.28
*Baseline $\log_2$ D-dimer μg/mL	1.25 (1.03 to 1.52)	0.021	1.27 (1.03 to 1.57)	0.028
*Baseline $(\log_2$ D-dimer $\mu g/mL)^2$	1.09 (1.02 to 1.17)	0.013	1.11 (1.03 to 1.19)	0.006
Time since HIV diagnosis, OR per 1 year higher	1.04 (1.01 to 1.07)	0.011	1.03 (0.99 to 1.06)	0.15

Low recovery: initial $CD4^+$ recovery of ≤50 $cells/mm^3$ 8 months after initiating ART; high recovery: initial $CD4^+$ recovery of >50 $cells/mm^3$ 8 months after initiating ART.
*Considering both linear and quadratic regression coefficients in the adjusted model, the OR associated with a doubling of D-dimer from 0.323 (median) to 0.646 is 1.003. In the model with adjustment for other covariates and only a linear term for D-dimer, this OR was 1.01.

low $CD4^+$ recovery for the 25th and 75th percentiles of D-dimer vs. 0.32 μg/mL were 11.5% and 0.2% higher, respectively, assuming fixed values of all other variables.

The empirical logit plots also suggested a possible quadratic effect of screening $CD4^+$ (this is also suggested by Fig. 2); a quadratic effect was found in univariable analysis (data not shown), but the association was no longer present after considering the interaction between screening $CD4^+$ and viral load.

The estimated relative risks for comparison with ORs are given in Table 2, Supplemental Digital Content, http://links.lww.com/QAI/B275. Relative risks are lower than the ORs, but risk factors for low recovery identified from these analyses are similar.

CONCLUSIONS

To our knowledge, this is the first study investigating the prevalence and risk factors for $CD4^+$ recovery specifically among individuals who initiate ART at $CD4^+$ counts of >500 $cells/mm^3$. We showed that low $CD4^+$ recovery after starting ART at $CD4^+$ counts of >500 $cells/mm^3$ is frequent despite virologic suppression, and the lower $CD4^+$ cell counts after ART initiation for those with low recovery compared with those with high recovery at 8 months persisted through 5 years of follow-up. Similar to other studies, we found that male sex,[32,33] lower screening $CD4^+$ cell count,[16,33,34] and lower baseline HIV RNA level[11,16,35] increased the odds of low $CD4^+$ recovery. We also found that race and/or geographic region may be an important predictor of poor $CD4^+$ recovery and could inform studies to identify potential genetic or environmental etiologies. The association with screening $CD4^+$ cell count was not large—for a 100 cell lower screening count, the odds of low response was increased by 9%. In addition, we found that the association with pre-ART screening $CD4^+$ count depends on the level of HIV RNA. Associations of low $CD4^+$ response with screening $CD4^+$ counts were weaker among those with low HIV RNA levels. This interaction and the lack of recognition of the impact of measurement error and within-person variability on studies of

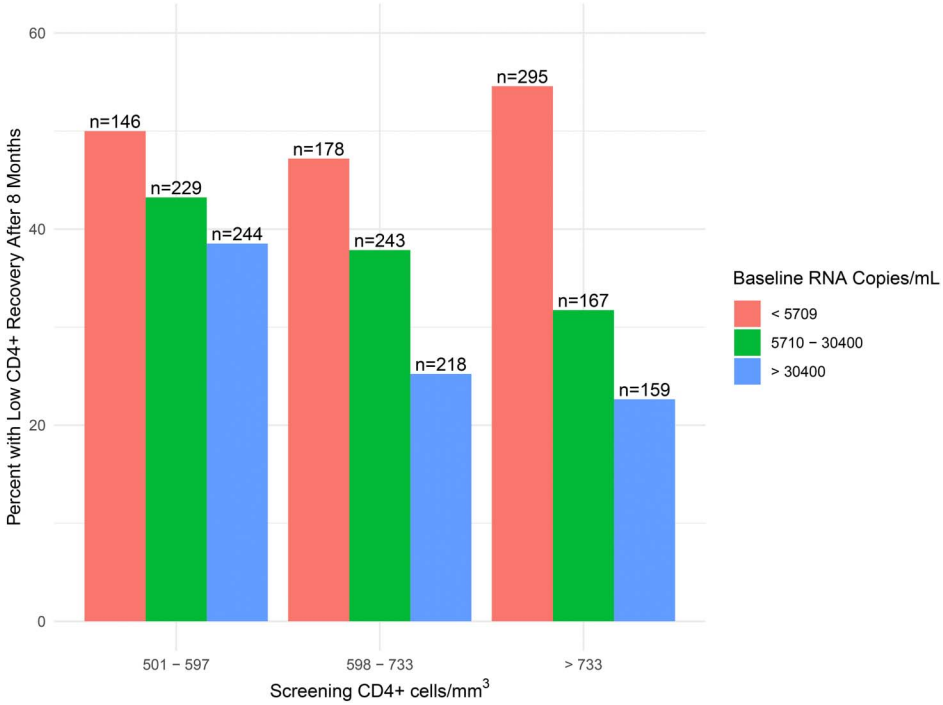

FIGURE 3. Percentage of participants with low CD4+ recovery after 8 months by tertiles of screening CD4+ (the 1st of 2 pre-ART CD4+ values) and baseline HIV RNA copies/mL. Samples sizes are indicated for each subgroup.

the association between change and initial value (discussed later) may explain differences among studies of low responders, some which identified low baseline or nadir CD4+ count with low CD4+ recovery and some which did not.

While perhaps counterintuitive, the finding that lower baseline HIV RNA levels increased the odds of low CD4+ recovery has been reported previously.[33] This effect may be due to previous innate suppression of HIV replication, such that lack of CD4+ decline may have already been achieved, blunting any additional increase. This is in line with the findings that HLA-Bw4 is associated with lower HIV RNA levels during natural history and blunted CD4+ response on cART.[19] One other possible explanation is that patients with lower HIV RNA levels at entry in the START trial had a much longer duration of untreated HIV infection when compared with those with higher HIV RNA levels. A widely held hypothesis is that HIV-associated damage from immune activation within lymphatic tissues leads to fibrosis that impairs T-cell homeostasis and immune recovery. Longer duration of untreated HIV infection may worsen the process of LN fibrosis and, in part, contribute to reduced CD4+ recovery during ART treatment.[36,37]

In contrast to most studies reporting age as a risk factor for low CD4+ recovery,[11,16,33–35,38,39] possibly due to thymic senescence, we did not find a strong association between older age and low CD4+ recovery. This may be because the great majority of participants in the START trial were aged less than 45 years.

Previous studies have not investigated inflammatory and coagulation markers such as IL-6 and D-dimer. We did not observe an association of IL-6 with low CD4+ count recovery; however, we found a curvilinear association of D-dimer with low recovery. We have previously reported that both markers are associated with HIV viral load at baselines.[40] With adjustment for HIV viral load and other factors, this association persisted.

In linear regression analysis, we demonstrated that screening and baseline CD4+ counts had different relationships with CD4+ change from baseline to 8 months. The inverse relationship with baseline CD4+ cell count can be explained by regression to the mean. When this association was corrected for measurement error and temporal variability,[27,30] the slope estimate was nearly identical with the slope for screening CD4+ count. This finding may be useful for other investigations that have only a single pre-treatment measurement.

In addition to having 2 pre-ART CD4+ cell counts to consider as predictors of low CD4+ response, other strengths of our study are the large sample size and the geographic and demographic diversity of the cohort. A limitation of our study is that we do not have sufficient follow-up data to investigate the clinical implications of low recovery due to the small number of events in the immediate ART initiation group of the START trial.[13] Longer follow-up is required. It may be that low CD4+ recovery among those who initiate ART at CD4+ counts of >500 cells do not have the same risk of morbidity and mortality as those who have low recovery after initiating ART at lower counts. Indeed, CD4+ counts below 500 are not uncommon in HIV-negative individuals.[41] Furthermore, we do not know the pre-HIV infection CD4+ values, and hence, the extent that "return" to health as a reason for the lack of relatively poorer improvement in CD4+ cell count is not possible to determine. This issue has been less of an issue in previous studies assessing the impact from ART in patients with lower nadir CD4+ counts, where it is more likely that there may have been an impact from the

HIV infection on the $CD4^+$ count. Based on this, it is noteworthy that screening $CD4^+$ count did not predict low $CD4^+$ count recovery for those with lowest HIV RNA levels. This suggests that there may be a subgroup for whom HIV does not affect $CD4^+$ count and who remained at their pre-HIV set-point when ART was initiated. Conversely, the reduced odds of low recovery for higher screening $CD4^+$ cell count in those with higher HIV RNA levels is not readily explainable this way. It is possible that these participants may have levels below their pre-HIV value and their reduced odds of low $CD4^+$ recovery would reflect variation in irrecoverable harm within the population from HIV. Overall, our results are supportive of this interpretation because a greater percentage of those with lower screening $CD4^+$ cell counts (and hence more injury from HIV) had low $CD4^+$ recovery. An alternative explanation is that the results (Fig. 3) merely reflect variation in the populations selected. It is also possible that factors not yet identified are associated with low recovery and risk of disease. These include host genetic factors,[9] and these, in turn, could influence the risk of clinical outcomes. Future host genetic analyses may elucidate this issue.

In summary, low $CD4^+$ recovery among HIV-positive patients is frequent even among those who initiate ART at $CD4^+$ levels of >500 cells/mm^3. The large number of participants with low recovery with early ART initiation suggests that there is much we do not know about the determinants of low recovery. The risk of morbidity and mortality among those who initiate ART at higher $CD4^+$ counts and have low $CD4^+$ recovery remains to be determined.

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