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Poor Initial CD4+ Recovery With Antiretroviral Therapy Prolongs Immune Depletion and Increases Risk for AIDS and Non-AIDS Diseases

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Abstract

Background—Low CD4+ increases risk for both AIDS- and non–AIDS-related morbidity and mortality. The magnitude of CD4+ recovery early after initial antiretroviral therapy (ART) is important in the ultimate duration of immune depletion.

Methods—We examined CD4+ recovery among 850 participants in the Community Program for Clinical Research on AIDS Flexible Initial Retrovirus Suppressive Therapies study with virologic suppression (ie, achieved an HIV RNA level <400 copies/mL) with 8 months of initial ART and determined subsequent risk for AIDS, non-AIDS diseases (non-AIDS cancers and cardiovascular, end-stage renal, and liver diseases), or death using Cox regression during a median 5-year follow-up.

Results—Mean pretreatment CD4+ was 221 cells/μL; 18% (n = 149) had a poor CD4+ recovery (<50 cells/μL) after 8 months of effective ART, resulting in lower CD4+ over 5 years. Older age (hazard ratio 1.34/10 yrs, $P = 0.003$) and lower screening HIV RNA (hazard ratio 0.65 per $\log_{10}$ copies/mL higher, $P = 0.001$), but not screening CD4+, were associated with a poor CD4+ recovery. After 8 months of effective ART, 30 patients experienced the composite outcome of AIDS, non-AIDS, or death among participants with a poor CD4+ recovery (rate = 5.8/100 person-years) and 74 patients among those with an adequate recovery (≥50 cells/μL; rate = 2.7/100 personyears) (adjusted hazard ratio = 2.24, $P < 0.001$). The risk of this composite outcome associated with a poor CD4+ recovery declined when ART was initiated at higher CD4+ counts ($P < 0.01$).

Conclusions—Impaired immune recovery, despite effective ART, results in longer time spent at low CD4+, thereby increasing risk for a broad category of HIV-related morbidity and mortality conditions.

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Keywords

CD4 recovery; immune reconstitution; AIDS; non-AIDS conditions; HIV disease progression; antiretroviral therapy; cardiovascular disease; liver disease; kidney disease; non–AIDS-defining malignancies

INTRODUCTION

Treatment of HIV infection with combination antiretroviral therapy (ART) suppresses viral replication, leading to recovery of CD4+ cells in most individuals,[1,2] accounting for large reductions in AIDS-related morbidity and mortality over the past decade.[3–5] Recent data from the Strategies for Management of Antiretroviral Therapy (SMART) study and observational cohorts indicate that the duration of time spent at low CD4+ levels is an important determinant of both AIDS and non-AIDS morbidity and mortality.[6–8] Thus, rapid CD4+ recovery immediately after initiation of ART is clinically important. Previous studies have reported that 15%–20% of HIV-infected patients initiating combination ART fail to achieve an adequate CD4+ cell rise (25–50 cells/μL) within 6 months of beginning ART, despite virologic suppression.[9,10] This poor immunologic response has been associated with increased risk for AIDS or death.[10]

We examined the risk associated with a poor "initial CD4+ recovery" with effective ART, in terms of both AIDS- and non–AIDS-related conditions—specifically common non- AIDS diseases consisting of atherosclerotic cardiovascular disease, end-stage renal disease, cirrosis, and non–AIDS-defining malignancies. We also examined predictors of a poor initial immune response and assessed the potential for long-term CD4+ recovery in these patients. The Flexible Initial Retrovirus Suppressive Therapies (FIRST) trial, conducted by the Terry Beirn Community Program for Clinical Research on AIDS, was well suited to study this relationship in that both fatal and severe nonfatal AIDS and non-AIDS events, along with CD4+ counts and HIV RNA levels, were collected in a standardized manner after initiation of ART.

METHODS

Design

We used follow-up data (median of 5 years) for participants in FIRST, which involved 80 research sites in the United States. The study design and primary results of FIRST have been reported.[11,12] Briefly, between 1999 and 2002, 1397 ART-naive HIV-infected participants were randomized equally to 1 of 3 ART strategies—nucleoside reverse transcriptase inhibitors plus protease inhibitors (PIs), nucleoside reverse transcriptase inhibitors plus a nonnucleoside reverse transcriptase inhibitor (NNRTI), or the use of a 3-class strategy (PI + NNRTI + nucleoside reverse transcriptase inhibitor). Clinical, immunologic, and virologic outcomes were ascertained. CD4+ counts were assessed at 2 time points before ART initiation; the screening value was first, and the baseline value was second. The median time between measures was 10 days (interquartile range 7–20). After randomization and initiation of ART, participants were seen at month 1, month 4, and every 4 months thereafter for data collection. At these visits, standardized clinical end point collection forms were completed, and CD4+ and HIV RNA levels (Roche Amplicor 1.0) were measured.

HIV RNA and CD4+ responses at month 8 are shown in Figure 1 for participants in FIRST. This study cohort was limited to the subset with evidence of "effective ART treatment," defined as HIV RNA <400 copies/mL at month 8. An 8-month time frame was chosen based on the visit schedule during FIRST, and it incorporates the period of rapid CD4+ recovery

immediately after ART initiation. The initial CD4+ recovery at month 8 was defined as "poor" if the change from baseline (the second CD4+ measurement before initiating ART) was <50 cells/μL and "adequate" if the recovery was ≥50 cells/μL. A threshold of 50 cells/μL was based on current guidelines defining immunologic failure as a CD4+ recovery <25–50 cells/μL during the first year of therapy, with most of this increase occurring within months of ART initiation.[13]

Outcomes

All new or recurrent AIDS events, deaths from any cause, malignancies, and nonfatal cardiovascular, renal, and liver disease events were collected during follow-up. Qualifying AIDS events included probable or confirmed cases defined by US Centers for Disease Control and Prevention AIDS criteria (1993),[14] adapted to include additional conditions related to immunodeficiency (footnote in Fig. 3). Non-AIDS disease events included fatal and nonfatal cardiovascular (myocardial infarction, stroke, coronary artery intervention, or death from chronic atherosclerotic cardiovascular disease); renal (end-stage renal disease or death from chronic kidney disease); liver (cirrhosis or death from liver failure); and non-AIDS cancers (all cancers excluding Kaposi sarcoma, lymphoma, and invasive cervical cancer). Structured case report forms were completed for AIDS and non-AIDS events. A Clinical Events Committee reviewed and adjudicated all AIDS and non-AIDS events.

Statistical Analysis

Logistic regression was used to examine associations between a poor initial CD4+ recovery and the following covariates: age, sex, race, screening CD4+ count (the first CD4+ measurement and not used to define a poor recovery) and HIV RNA level, prior AIDS event, and coinfection with hepatitis B or C. An odds ratio (OR) >1 implies that the covariate is associated with an increased risk for a poor CD4+ recovery at month 8. Using longitudinal regression analyses[15] adjusted for the same baseline covariates listed above, rates of change in CD4+ beginning at month 8 were estimated for those with and without an adequate initial CD4+ recovery.

To assess the relationship of pretreatment CD4+ count and CD4+ response at 8 months, screening CD4+ count was used as the predictor instead of baseline values to avoid a spurious association (ie, regression to the mean) that could result from assessing the association of baseline CD4+ count with change from baseline.[16] Cox's proportional hazards models were used to study the relationship of the initial CD4+ recovery and risk (after month 8) for AIDS, non-AIDS disease, or death adjusted for the same covariates used for logistic models. These outcomes did not vary by treatment group in FIRST; therefore, analyses are pooled over the 3 groups.[17] Findings are summarized with hazard ratios (HRs) and 95% confidence intervals (CIs), corresponding to risk of an event among participants with a poor initial CD4+ recovery compared with participants with an adequate recovery. Rates per 100 person-years are also cited. Analyses were performed using SAS (Version 8.2). All reported *P* values are 2 sided.

RESULTS

Patient Characteristics

The baseline characteristics of participants in FIRST have been reported.[12] Our cohort (effective ART at month 8, n = 850; Fig. 1) generally included participants whowere older (39 vs 37 years; $P < 0.001$), more commonly white race (32% vs 18%; $P < 0.001$), less likely intravenous drug use users (13% vs 18%; $P = 0.01$), and with higher mean baseline CD4+ counts (221 vs 196 cells/μL; $P = 0.02$) and lower mean baseline HIV RNA levels (5.0 vs 5.1 $\log_{10}$ copies/mL; $P = 0.05$), when compared with remaining FIRST participants (largely

those with HIV RNA levels ≥400 copies/mL at 8 months). Within our cohort, 12% had a CD4+ recovery <25 cells/μL, 18% had a CD4+ recovery <50 cells/μL, and 34% had a CD4+ recovery <100 cells/μL at 8 months. Of those assigned to a PI-based regimen, 61.6% were prescribed nelfinavir with 24.9% using a ritonavir-boosted PI. Efavirenz accounted for 60.4% of NNRTI use, and zidovudine was part of the ART regimen in 54.0%. The median follow-up was 60 months.

Predictors of a Poor Initial CD4+ Recovery

Table 1 presents a comparison of baseline characteristics by CD4+ recovery, along with results from multivariate logistic regression examining predictors of a poor initial CD4+ recovery, despite effective ART. Older age and lower HIV RNA levels before initiation of ART were associated with a poor CD4+ recovery at month 8. Screening CD4+ count was associated with a poor CD4+ recovery in univariate analyses (OR 1.10 per 100 cells/μL higher; 95% CI 1.02 to 1.19) but not in the multivariate models. However, baseline CD4+ count was associated with a poor CD4+ recovery in both univariate (OR 1.18; 95% CI 1.09 to 1.28) and multivariate (OR 1.16; 95% CI 1.05 to 1.27) models. Randomized ART strategy was not associated ($P = 0.54$ for comparison of 3 groups) with the initial CD4+ recovery (OR for PI vs NNRTI = 0.82; 95% CI 0.53 to 1.28; and OR for 3-class strategy vs NNRTI = 0.81; 95% CI 0.53 to 1.23) nor zidovudine prescribed at study entry (OR 1.33; 95% CI 0.93 to 1.90). While taking ART during follow-up, approximately 75% of participants reported 100% adherence to their regimen, with no difference between the poor and adequate recovery groups ($P = 0.61$). Furthermore, the HIV RNA response after 1 and 4 months of ART did not predict immune recovery. Among participants with a poor initial CD4+ recovery, HIV RNA was<400 copies/mL in 64% at month 1 and 83% at month 4, whereas for participants with an adequate CD4+ recovery the HIV RNA was <400 copies/mL in 45% at month 1 and 90% at month 4. Fifty-four percent of participants with poor CD4+ recovery had an HIV RNA level <400 copies/mL at 1 and 4 months and at 8 months compared with 42% of the patients with an adequate CD4+ recovery ($P = 0.007$).

CD4+ Recovery With Longer Follow-up

CD4+ recovery over the entire follow-up was examined to characterize the long-term immunologic consequences of a poor initial CD4+ recovery (Fig. 2). Mean CD4+ counts for participants with a poor and adequate recovery, respectively, were: 287 and 207 cells/μL at baseline ($P < 0.001$), 268 and 410 cells/μL at month 8 ($P < 0.001$), and 441 and 556 cells/μL after 5 years of follow-up ($P < 0.001$). The rate of CD4+ rise after month 8 was similar between the 2 groups (slope after a poor recovery = 27 cells per μL per year; slope after an adequate recovery = 27 cells per μL per year; $P = 0.99$). Over a median follow-up of 52 months after month 8, the percent of time spent at CD4+ counts <350 cells/μL was 50% for those with a poor initial CD4+ recovery and 34% among participants with an adequate initial CD4+ recovery. In addition, 46.2% of participants with a poor CD4+ recovery, and 63.3% with an adequate CD4+ recovery, achieved a CD4+ count ≥500 cells/μL at least twice during follow-up (at or after month 8; $P < 0.01$).

Morbidity and Mortality Subsequent to the Initial CD4+ Recovery

Among the 814 participants who had not experienced an event during the first 8 months, there were 16 participants with AIDS events, 8 with non-AIDS disease events, and 7 deaths from other causes among 143 participants with a poor initial CD4+ recovery and 33 AIDS events, 31 non-AIDS disease events, and 19 deaths from other causes among 671 with an adequate CD4+ recovery. There were 32 nonfatal and 17 fatal AIDS events overall, and the most common AIDS-related illnesses were esophageal or pulmonary candidiasis (n = 11), lymphoma (n = 8), and *Pneumocystis jirovecii* infection (n = 7). Among the fatal and

nonfatal non-AIDS diseases, there were 14 participants with cardiovascular, 6 with renal, 16 with non-AIDS cancers, and 5 with liver-related events.

Rates for the composite endpoint of AIDS, non-AIDS disease, or death were examined by the initial CD4+ recovery at 3 different cutoffs (25, 50, or 100 cells/μL; Fig. 3). Risk after month 8 was greater with a poor initial CD4+ recovery (<50 cells/μL) compared with an adequate recovery (≥50 cells/μL; adjusted HR = 2.24; 95% CI 1.44 to 3.49); this relationship was similar with a CD4+ cutoff of 25 cells/μL (HR 1.76; 95% CI 1.04 to 3.01) or 100 cells/μL (HR 1.59; 95% CI 1.06 to 2.36) at month 8. Approximately half of subsequent clinical events among those with a poor CD4+ recovery occurred during the first year (or 8–20 months after initiating ART). The adjusted risk associated with a poor CD4+ recovery, compared with an adequate recovery, was also estimated for components of the composite outcome: AIDS (HR 2.84; 95% CI 1.52 to 5.29), non-AIDS diseases (HR 1.57; 95% CI 0.73 to 3.39), and death from other causes (HR 1.36; 95% CI 0.58 to 3.19). The risk for AIDS is the strongest, though point estimates for non-AIDS events are in the same direction. Further, the most common non-AIDS events, cardiovascular (HR 1.31; 95% CI 0.35 to 4.87) and non–AIDS-defining malignancies (HR 2.09; 95% CI 0.67 to 6.51), suggest a similar potential for higher risk. The low numbers and more modest risk increase for non-AIDS events, compared with AIDS, account for the wider confidence bounds and nonsignificant risk estimates.

Risk Associated With a Poor Initial CD4+ Recovery Decreases With Earlier ART Initiation

Risk of the composite including AIDS, non-AIDS, or death after a poor, compared with an adequate, initial CD4+ recovery was examined by screening CD4+ levels (<100, 100–199, 200–349, ≥350 cells/μL) in Figure 4. The risk associated with a poor initial CD4+ recovery declines when ART is started at higher CD4+ counts ($P < 0.01$ for interaction). In addition, rates of the composite outcome were higher when follow-up CD4+ counts were <350 cells/μL (6.4/100 person-years; 95% CI 4.9 to 7.9) as compared with ≥350 cells/μL (1.5/100 person-years; 95% CI 1.0 to 2.0).

DISCUSSION

ART treatment strategies that minimize time spent at lower CD4+ levels are important in reducing risk for HIV-related morbidity and mortality, including both AIDS and non-AIDS diseases. We examined the association of initial CD4+ recovery after 8 months of effective ART (HIV RNA <400 copies/mL) and risk for a composite of AIDS, common non- AIDS disease events, or death among 850 previously ART-naive HIV-infected participants during a 5-year median follow-up. A poor initial CD4+ recovery (<50 cells/μL), despite effective ART, was associated with increased risk for this composite outcome. Lower pretreatment CD4+ counts did not alter the likelihood of a poor initial CD4+ recovery, but the consequences of a poor CD4+ recovery on subsequent morbidity and mortality were greater when ART was initiated at lower CD4+ counts. This is likely due to the prolonged duration of low CD4+ counts for participants with a poor initial CD4+ recovery—32% more time spent with CD4+ counts <350 cells/μL compared with those with an adequate initial CD4+ recovery (≥50 cells/μL).

The degree of HIV-related immune depletion is now recognized as an important contributor to risk for many non-AIDS diseases and traditional AIDS events. In the D:A:D study, rates of liver-related mortality and all non-AIDS causes of death decrease at higher CD4+ levels.[8] Previous analyses using follow-up data from FIRST demonstrated that risk for cardiovascular, renal, liver, and non-AIDS cancer events was independently associated with latest CD4+ levels.[18] This study adds to these observations and indicates that the duration of

time spent at lower CD4+ levels after the initiation of ART contributes to risk for both AIDS and non-AIDS diseases.

The first phase of immune recovery after initiation of ART is characterized by a redistribution of both naive and memory CD4+ cells from lymphatic tissues, whereas the subsequent gradual CD4+ recovery over time is primarily naive CD4+ cells.[19] Lymphatic tissues are the major viral reservoirs during HIV infection, and the majority of infected cells are T cells.[20,21] Higher HIV RNA levels may therefore be associated with greater numbers of CD4+ T cells being sequestered within lymphatic tissues, resulting in a greater redistribution of cells after ART-associated viral suppression. Indeed, higher pretreatment HIV RNA levels are consistently associated with greater CD4+ cell recovery after starting ART.[22–25] In addition, thymus output during sustained HIV replication is important for repopulating naive CD4+ cells in lymphatic tissues, consistent with research showing that age is an important determinant of both early- and late-immune recovery after ART.[22,26–28] Our results agree with other studies that younger age and higher pretreatment HIV RNA level are associated with a better CD4+ cell recovery with effective ART.[22,24,27,28]

The clinical importance of achieving specific CD4+ count thresholds after initiation of ART has received increasing attention in recent years. A threshold of 500 cells/μL is often used to define a normal CD4+ count because this represents the lower limit of the normal range in HIV-negative adults,[29–31] though a goal of 800 cells/μL has also been suggested as this represents the mean CD4+ count among HIV-negative adults.[32] Symptomatic HIV-related events (Centers for Disease Control and Prevention category B and C events) may be more frequent among individuals who fail to achieve CD4+ counts >500 cells/μL, though previous risk assessments have been limited by the low number of events overall at these CD4+ levels.[30] An observational multicenter study showed that mortality rates among 2435 HIV-infected patients with a CD4+ count >500 cells/μL were the same as for the general population after 6 years of ART use.[33] Furthermore, the notion that CD4+ levels >500 cells/μL are normal is consistent with the observation from the EuroSIDA study that the rate of CD4+ recovery with ART slows once levels >500 cells/μL are achieved.[34] The ability to achieve normal CD4+ counts is reflected in the degree of early recovery.[30] Indeed, in this study, participants with a poor, compared with an adequate, initial CD4+ recovery were less likely to achieve a CD4+ count >500 cells/μL and spent more time at CD4+ counts <350 cells/μL.

CD4+ recovery was not predicted by the pretreatment CD4+ count among participants in this study. This is in contrast to a previous study, where patients with a baseline CD4+ count <200 cells/μL were less likely to have poor recovery, defined as an increase <25 cells/μL at 6 months, than patients with baseline CD4 + ≥200 cells/μL.[10] Our use of screening CD4+ count as a predictor, versus the baseline measure used to define change, reduces the effects of regression to the mean and this may explain the difference. Because of the within-patient variability of CD4+ count, even when there is no relationship between baseline level and change from baseline, a spurious negative correlation is induced. This can largely be circumvented by using a previous measurement (eg, screening in our case) as the predictor variable instead of the baseline value used for measuring change.[16,35,36]

In summary, a potential benefit associated with earlier initiation of ART, and the one not previously emphasized, may be avoiding the risk associated with a poor CD4 recovery and the consequent greater time spent at lower CD4+ levels associated with both AIDS and non-AIDS diseases. Further, a poor CD4 recovery can be expected in 15%–20% of patients irrespective of CD4+ level at the time of initiation of ART. Additional research is needed examining reasons for a poor CD4+ recovery and to study immune-modulating interventions that increase CD4+ responses in these patients.

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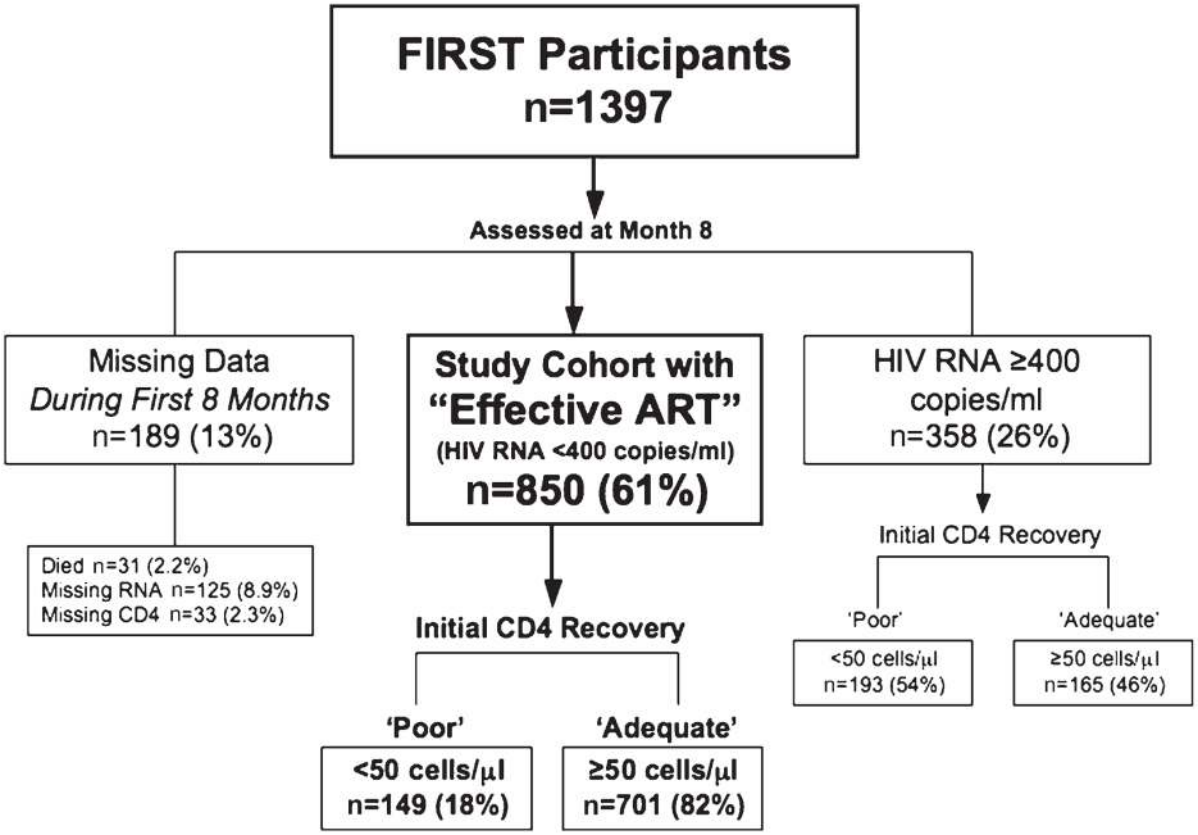

FIGURE 1.
CD4+ and HIV RNA response in FIRST study participants assessed at month 8.

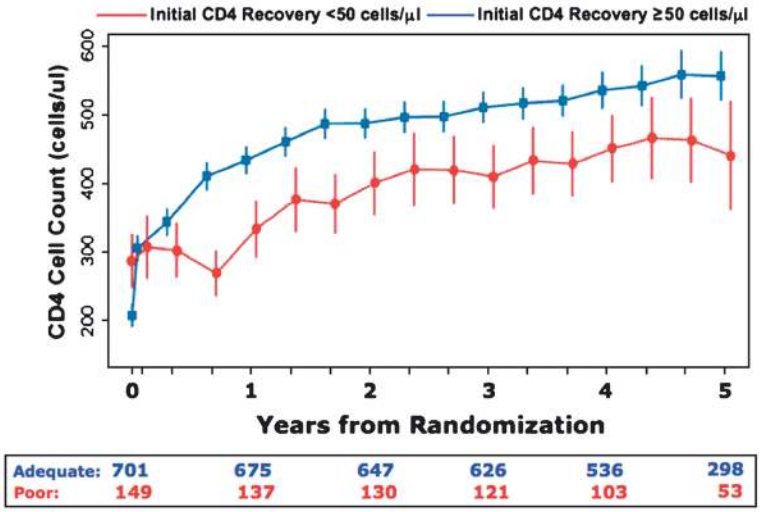

FIGURE 2.

CD4+ count over time stratified by initial CD4+ recovery with ART. Mean CD4+ count (with 95% CI) is plotted over 5 years of follow-up among FIRST participants with virologic suppression (HIV RNA <400 copies/mL) after 8 months of initial ART and stratified by a poor (<50 cells/μL rise) or adequate (≥50 cells/μL rise) CD4+ recovery at month 8. The numbers of participants at each time point are listed below.

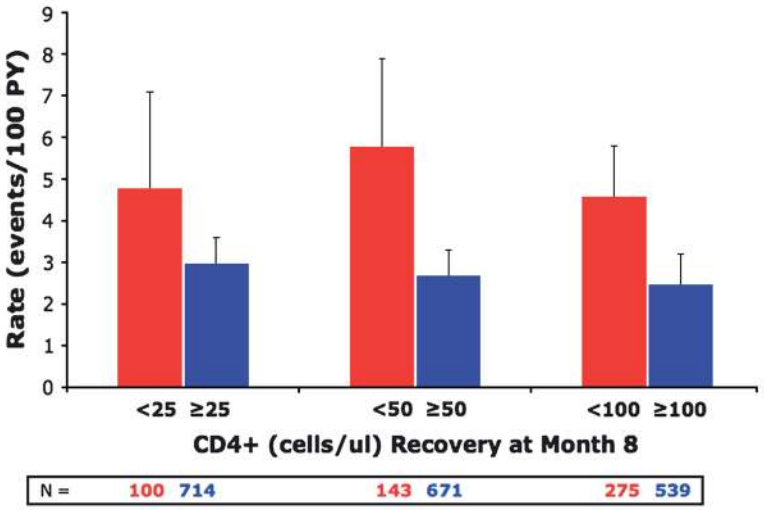

FIGURE 3.

Incidence of AIDS, non-AIDS disease, or death based on initial CD4+ recovery. Rate per 100 person-years (with 95% CI) of morbidity and mortality (defined as AIDS, non-AIDS diseases, or death) after 8 months of effective ART is plotted. Data are presented by CD4+ count recovery using 3 cutoffs: 25, 50, and 100 cells/μL. The relative higher morbidity and mortality among those with less initial CD4+ recovery is consistent across all 3 cutoffs. The numbers of participants from each category are also listed. "AIDS Criteria" were adapted from 1993 Centers for Disease Control and Prevention AIDS criteria to include additional conditions: invasive aspergillosis, bartonellosis, Chaga disease (American trypanosomiasis) of the central nervous system, disseminated herpes zoster, visceral leishmaniasis (kala-azar), Hodgkin lymphoma, non-Hodgkin lymphoma (all cell types), chronic intestinal microsporidiosis (>1 month), nocardiosis, extrapulmonary *Penicillium marneffei*, extrapulmonary *Pneumocystis jirovecii*, and *Rhodococcus equi* disease. Non-AIDS events include cardiovascular, renal, and liver disease and non–AIDS-defining malignancies.

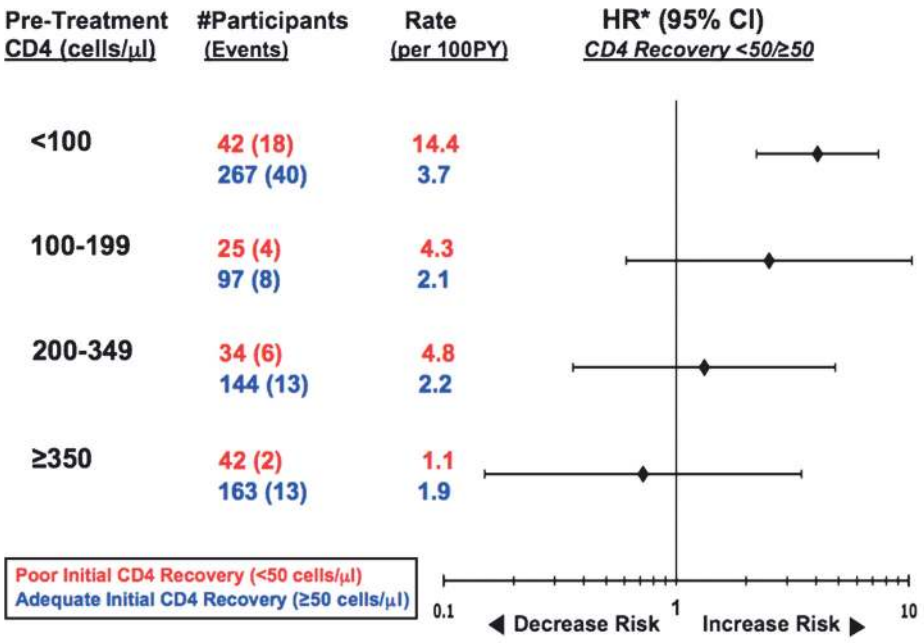

FIGURE 4.

Risk of AIDS, non-AIDS, or death stratified by pretreatment CD4+ count. The risk of morbidity and mortality (defined as AIDS, non-AIDS disease, or death) after 8 months of effective ART is presented and stratified by pretreatment screening CD4+ count. The numbers of participants, events, and rates per 100 person-years are provided. A poor CD4+ recovery (<50 cells/μL) at 8 months leads to higher rates of subsequent morbidity and mortality overall, compared with participants with an adequate CD4+ recovery (≥50 cells/μL), though this risk declines when ART is started at higher CD4+ counts. This is reflected in the decreasing HR estimates of risk for morbidity and mortality after a poor CD4+ cell recovery, with reference to an adequate recovery, as pretreatment CD4+ count increases. *HRs were adjusted for age, gender, race/ethnicity, coinfection with hepatitis B or C, prior AIDS event, randomized ART treatment strategy, and screening CD4+ and RNA level.

TABLE 1

Predictors of a Poor Initial CD4 Recovery (<50 Cells/μL) Despite 8 Months of Effective ART (HIV RNA <400 Copies/mL)

	Initial CD4+ Recovery				
	<50 cells/μL (n = 149)	**≥50 cells/μL (n = 701)**	**Diff. (*P*)‡**	**Adjusted OR* (95% CI)**	***P***
Age (mean) OR/10 yrs older	41.0	38.7	2.3 (0.01)	1.34 (1.11 to 1.62)	0.003
Gender (% female)	20.8	20.1	0.7 (0.85)	1.00 (0.63 to 1.60)	1.00
Race (% nonwhite)	65.8	68.6	−2.8 (0.50)	0.80 (0.54 to 1.21)	0.29
Hepatitis B/C (%)	26.8	23.3	3.5 (0.36)	1.09 (0.71 to 1.65)	0.70
Prior AIDS (%)†	30.9	36.9	−6.0 (0.16)	0.94 (0.61 to 1.44)	0.78
Screening CD4+ count (mean cells/μL) OR per 100 cells/μL higher	255	211	44 (0.02)	1.04 (0.94 to 1.15)	0.46
Screening RNA (mean log10 copies/mL) OR per log10 copies/mL higher	4.7	5.0	−0.30 (≤0.001)	0.65 (0.51, 0.83)	0.001

*Adjusted for all the predictors listed and randomized strategy groups.

†Includes patients with a clinical AIDS event before initiation of ART, excluding CD4 <200 cells/μL as sole criteria.

‡Diff, difference.