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Elevated CD8 Counts During HAART are Associated with HIV Virologic Treatment Failure

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Abstract

Objective—To evaluate whether elevated CD8 counts are associated with increased risk of virologic treatment failure in HIV-infected individuals.

Design—Retrospective cohort study.

Methods—U.S. Military HIV Natural History Study participants who initiated HAART in 1996–2008, had 6- and 12-month post-HAART HIV RNA <400 c/ml, ≥2 subsequent HIV viral loads and a baseline CD8 count were eligible (n=817). Baseline was 12 months after HAART

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start, virologic failure was defined as confirmed HIV RNA ≥ 400 c/ml, and CD8 counts ≥ 1200 cells/mm³ were considered elevated. Cox models were used to examine the effect of baseline and time-updated CD8 counts on virologic failure.

Results—There were 216 failures for a rate of 5.6 per 100 person-years (95% confidence interval [CI] 4.9-6.4). Among those initiating HAART in 2000-2008, participants with elevated baseline CD8 counts had significantly greater risk of virologic failure compared to those with baseline CD8 counts ≤ 600 cells/mm³ (hazard ratio [HR] = 2.68, 95% CI 1.13 – 6.35). Participants with elevated CD8 counts at $>20\%$ of prior 6-month follow-up visits had greater risk of failure at the current visit than those who did not (HR = 1.53, 95% CI 1.14 - 2.06). Those with CD8 counts that increased after HAART start had greater risk of failure than those with CD8 counts that decreased or remained the same (HR = 1.59, 95% CI 1.19 – 2.13).

Conclusions—Initial or serial elevated CD8 counts while on HAART or an increase in CD8 counts from HAART initiation may be early warnings for future treatment failure.

Keywords

Human immunodeficiency virus; CD8 count; antiretroviral therapy; HIV viral load suppression; HIV virologic failure

INTRODUCTION

Despite substantial reductions in mortality and morbidity among HIV-infected persons receiving highly active antiretroviral therapy (HAART), there continue to be individuals for whom therapy fails to suppress viral replication [1]. To characterize and better understand those who do not respond to HAART, numerous predictors for virologic treatment failure have been proposed. Studies focusing on initial virologic response have found younger age, African American race, poor adherence to treatment, missed visits, lower baseline CD4 counts and higher baseline HIV RNA levels were associated with initial virologic treatment failure [2-9].

Virologic failure is a concern not only when monitoring the initial response to therapy, but also once viral suppression on therapy has been established. At approximately 2 years after initial suppression, cumulative rates of virologic failure can range from 20 to 40% [4, 8, 10-12]. In addition to many of the same predictors found for initial failure to suppress HIV RNA after starting HAART, factors associated with post-suppression virologic failure include prior antiretroviral (ART) exposure, date of HAART start, duration of viral suppression, oral lesions, and change in treatment or prior treatment failure [6-7, 10-15]. A recently reported scoring algorithm to predict virologic failure following suppression included a subset of the risk factors listed previously [14]. Although the rates of virologic failure predicted by the algorithm were very close to the observed rates, some settings may not have the capacity to identify all of these factors and there are likely other predictive factors not yet identified.

One potential predictor that is readily available in most clinical settings, yet has not often been included in previous studies of virologic failure, is the total CD8 cell count. The relationship between CD8 response and HIV outcomes is incompletely understood, but appears to be multi-faceted. The CD8 response can be viewed in 3 different contexts: HIV-specific CD8 cells, the activation of CD8 subsets, and the total CD8 count. Associations with HIV outcomes vary by the type of CD8 response being considered.

Up to 20% of circulating CD8 cells in those with untreated chronic HIV infection are HIV-specific [16]. HIV-specific CD8 cells play an important role in the control of HIV viremia.

Depletion of the CD8-specific response results in loss of virologic control in animal models of HIV [17], and in humans, CD8 cells have been shown to suppress HIV replication through both cytolytic and non-cytolytic mechanisms [18-22]. A soluble factor involved in the non-cytolytic antiviral response has been elaborated from CD8 cells from long-term survivors with asymptomatic chronic HIV infection [23] and better clinical outcomes have been noted with increased anti-HIV CD8 cell activity [24-29].

However, a hyperdynamic or over-stimulated CD8 immune response, reflected by activation of CD8 subsets as well as elevated total CD8 counts, may accelerate immune dysfunction and certain disease processes. Current evidence suggests a correlation between CD4 loss and hyperdynamic CD8 response [16,30], although CD4 losses may also occur via alternate mechanisms [31]. The expression of some CD8 subsets, particularly CD38+CD8+, has been linked to HIV disease progression [32-35]. Multiple studies have assessed the relationship between activation of CD8 subsets and response to HAART [36-40]. Motivated by the need to find markers for virological treatment failure in resource-limited settings lacking routine viral load capability, several studies have investigated the potential use of CD38 expression [38-40]. While significant correlations between increased CD38 expression and virologic failure were observed, poor sensitivity and specificity of this marker precluded wider application.

Many studies have demonstrated widespread elevation of total CD8 cell counts in untreated HIV infection [16,30,41] and some have reported a decrease in CD8 cells upon HAART initiation [42]. Observed increases in circulating CD8 cells in HIV positive individuals have been attributed to declines in CD4 cells and subsequent CD8 compensation known as “blind T-cell homeostasis” [43]. Some early studies conducted before HAART became available showed significant associations between elevated baseline total CD8 counts and progression to AIDS [44-46] while others failed to find such associations with AIDS [47] or CD4 outcomes [48]. In light of these conflicting results and as a greater understanding of the complexity of the CD8 response evolved, more studies focused on CD8 subsets. Thus, few studies have evaluated total CD8 counts in the context of virologic response to HAART.

If elevated total CD8 counts were a pathologic (hyperdynamic) as opposed to a benign (blind T-cell homeostasis) process, the elevated CD8 count could be a potential marker for adverse events, such as virologic treatment failure. This concept has not yet been adequately explored. In this study we examine whether elevated total CD8 counts are predictive of virologic treatment failure. Because adherence has been shown to be an important factor in viral response, we focused on individuals who demonstrated initial viral suppression and therefore may be more compliant with therapy.

METHODS

Study Population

Study participants were enrolled in the U.S. Military HIV Natural History Study (NHS), an ongoing multisite prospective cohort study of consenting HIV-infected Department of Defense beneficiaries [49-50]. Since its inception in 1986, the NHS has enrolled over 5000 participants. Medical history information and routine laboratory measures including CD4 cell counts, CD8 cell counts, and HIV RNA levels were collected at semi-annual study visits. The central Infectious Diseases Institutional Review Board approved this study.

Inclusion Criteria

This study selected NHS participants who initiated HAART between 1996 and 2008 and demonstrated initial viral suppression (defined below). Further inclusion criteria required at least two HIV RNA measures following viral suppression, and availability of a baseline

CD8 cell count (Figure 1). Comparisons between the 817 included and the 1559 participants excluded due to lack of viral suppression, insufficient follow-up data or lack of CD8 count at baseline showed that the included group was more often Caucasian, initiated HAART in more recent calendar years (2000-2008 vs. 1996-1999), had a shorter time from HIV diagnosis to HAART initiation, and were generally healthier at HAART start (greater CD4 counts, lower HIV RNA levels). A lower percentage of those included used ART prior to HAART and a lower percentage had any clinical AIDS events prior to HAART compared to the excluded participants. Classes of drugs used in the first HAART regimen also differed significantly by inclusion/exclusion group, reflecting the era in which HAART was initiated. In addition, participants included in the analysis had significantly higher CD8 counts at HAART start compared to those who were excluded (difference in medians = 35 cells/mm³, $p=0.02$).

Definitions

Viral suppression (VS) was defined as both the 6- and 12-month post-HAART HIV RNA levels < 400 copies/ml; this was the limit of detection for early assays and we opted to standardize VS across time periods. Because participants were not at risk for virologic failure in this study until they demonstrated VS, baseline was defined as 12 months following HAART initiation. Virologic failure (VF) was defined as a confirmed HIV RNA measurement ≥ 400 copies/ml with the date of VF defined as the date of the first HIV RNA level ≥ 400 copies/ml after VS. CD8 counts ≥ 1200 cells/mm³, the upper limit of normal according to clinical laboratory reference values [51], were considered elevated. HAART was defined as previously described [9]. ART refers to regimens not defined as HAART and typically indicated mono or dual-therapy with nucleoside reverse transcriptase inhibitors. Variables defined at the time of HAART start used the latest value occurring in a window of 6 months prior to HAART initiation. Baseline variables were those measured closest to the baseline date (± 3 months).

Statistical Methods

CD4 cell counts, CD8 cell counts and HIV RNA levels nearest to each 6-month anniversary (± 3 months) from HAART initiation were selected for analysis. Follow-up data were censored at the last 6-month HIV RNA measurement prior to 3 consecutive missing HIV RNA values. Baseline group comparisons used chi-square tests for categorical variables and Wilcoxon two-sample tests for continuous variables. Incidence rates of VF were calculated per 100 person-years (pyrs) of follow-up with exact Poisson 95% confidence intervals (CI). Kaplan-Meier curves were used to estimate the cumulative proportion of participants remaining free of VF during follow-up both overall and by era in which HAART was initiated. Cox proportional hazards models were used to estimate associations between CD8 counts and risk of VF. Separate models were used to examine effects of baseline and current CD8 counts. Baseline CD8 counts were categorized using quartiles at HAART start.

CD8 counts measured during analysis time were parameterized using two different time-updated CD8 covariates, each examined in separate models. The first time-updated covariate calculated the proportion of previous visits (starting at baseline) with elevated CD8 counts. Because CD8 counts were infrequently elevated, choices for the parameterization of this time-updated covariate were limited. Therefore the proportion was categorized according to the upper quartile to compare those with > 20% of prior visits with elevated CD8 counts to those with $\leq 20\%$ of prior visits with elevated CD8 counts. The second time-updated CD8 covariate described change in CD8 counts from HAART initiation to each lagged visit and was categorized as an increase, decrease or stay the same, or pattern unknown due to missing data. All time-updated values were carried forward no further than 18 months, after which they were set to missing.

Initial models were stratified by era in which HAART was initiated (1996-1999 vs. 2000-2008), allowing a separate baseline hazard for each era while estimating a common CD8 effect. These eras were chosen a-priori to reflect differences in HIV treatment and care in the first few years after HAART became available and thereafter. Additional models included an interaction between HAART start era and CD8 count, to estimate separate hazard ratios (HR) for CD8 count by HAART start era. Adjustment variables considered for inclusion in multivariate models included baseline age, gender, race, ART prior to HAART, clinical AIDS events prior to baseline, years from HIV diagnosis to baseline, HIV RNA at HAART start, and CD4 cell count. In general, final multivariate models excluded covariates that were neither significant ($p < 0.05$) nor impacted the CD8 estimate by more than 20%. However, because of potential co-linearity between CD8 and CD4 counts, models were constructed with and without CD4 counts included. Two sensitivity analyses were conducted: 1) time-updated values were carried no further than 12 months and 2) a percent increase greater than reported assay variability [52] was modeled rather than an absolute increase in CD8 counts. SAS software, version 9.2 (SAS Institute) was used for all analyses.

RESULTS

Baseline Characteristics

Of the 817 eligible participants, 445 (54%) initiated HAART between 1996 and 1999 while 372 (46%) initiated HAART between 2000 and 2008. Baseline participant characteristics by era in which HAART was initiated and overall are shown in Table 1. Those starting HAART in the more recent era were significantly younger, less likely Caucasian, had a lower CD4 count and a higher HIV RNA level at HAART start, and a lower baseline CD8 count than those starting HAART in the 3 years after it became available in 1996. In addition, the more recent HAART era group had a significantly shorter time from HIV diagnosis to baseline, lower proportions of participants using ART before HAART and lower proportions with any clinical AIDS events prior to baseline. Classes of drugs used in the initial HAART regimen also varied according to HAART start era.

CD8 counts decreased significantly from HAART initiation to baseline (one year later) by a median of 61 cells/mm³ (95% CI: 45 to 87 cells/mm³ decrease). Greater decreases were observed among those initiating HAART in 2000-2008 (median decrease of 109 cells/mm³, 95% CI: 72 to 167 cells/mm³ decrease) compared to those initiating HAART in 1996-1999 (median decrease of 32 cells/mm³, 95% CI: 1 to 55 cells/mm³ decrease, $p < 0.001$).

Rates of VF

Participants were followed for a median of 4 years (interquartile range [IQR]: 2-7 years). At 2 years after confirmed viral suppression, Kaplan-Meier estimates of VF were 12% (95% CI 10%, 15%) overall, 15% (95% CI 12%, 18%) among those initiating HAART in 1996-1999 and 9% (95% CI 6%, 13%) among those initiating HAART in 2000-2008. During the entire follow-up period, a total of 216 participants had a VF, giving a rate of 5.6 per 100 pyrs (95% CI: 4.9 - 6.4). VF rates varied by both era in which HAART was initiated and baseline CD8 count (Figure 2). Rates were higher among those initiating HAART in 1996-1999 compared to those initiating HAART in 2000-2008 (unadjusted HR = 2.68, 95% CI 1.90 - 3.78). Among those initiating HAART in 1996-1999, VF rates among categories of baseline CD8 count were similar. In contrast, VF rates were highest for elevated baseline CD8 counts among those initiating HAART in 2000-2008.

Baseline CD8 count and risk of VF

Corresponding to the patterns observed in VF rates, the relationship between baseline CD8 count and risk of VF varied by HAART era (Table 2). Among those initiating HAART in

1996-1999 baseline CD8 count was not significantly associated with risk of VF, but among those initiating HAART in 2000-2008, participants with an elevated (≥ 1200 cells/mm³) baseline CD8 count had significantly greater risk of VF compared to those with a baseline CD8 count of 600 cells/mm³ or lower (adjusted HR = 2.68, 95% CI 1.13 – 6.35). Recent HAART era participants with baseline CD8 counts in the middle categories (601-849, 850-1199 cells/mm³) were not at significantly greater risk of VF compared to those with a baseline CD8 count of ≤ 600 cells/mm³ (Table 2).

Current CD8 count and risk of VF

Of the 216 participants with VF, 67 (31%) had elevated CD8 counts at more than 20% of visits prior to the VF. In comparison, 121 (20%) of the 601 participants without a VF had elevated CD8 counts at more than 20% of visits prior to their censoring date. In accordance with this observation, Cox models including a time-updated CD8 covariate showed that participants with > 20% of prior 6-month visits with elevated CD8 counts had greater risk of VF than those with $\leq 20\%$ of prior visits with elevated CD8 counts (adjusted HR = 1.53, 95% CI 1.14 – 2.06, Table 3). This increased risk associated with elevated CD8 counts was greater among those initiating HAART in 2000-2008 (adjusted HR = 2.70, 95% CI 1.42 – 5.13) than in those initiating HAART in 1996-1999 (adjusted HR = 1.34, 95% CI 0.96 – 1.86), although this difference was marginally significant ($p=0.06$ for interaction).

For those with VF, CD8 counts increased from HAART start to the visit immediately preceding the VF by a median of 51 cells/mm³ (IQR: -237 to +241 cells/mm³), while for those without a VF, CD8 counts decreased from HAART start to the visit prior to censoring by a median of 108 cells/mm³ (IQR: -382 to +102 cells/mm³). In Cox models increases in CD8 count from HAART start were significantly associated with VF when compared to CD8 counts that decreased or remained the same (adjusted HR = 1.59, 95% CI 1.19 – 2.13, Table 3). This comparison did not vary significantly by HAART start era ($p=0.68$ for interaction). In sensitivity analysis, those with a > 4% increase in CD8 counts also had significantly greater risk of VF compared to those with $\leq 4\%$ increases (adjusted HR = 1.71, 95% CI 1.28 – 2.28). All adjusted CD8 model estimates were similar when CD4 was not included in the multivariate model and when time-updated values were carried forward for only 12 months (data not shown).

DISCUSSION

In a cohort of HIV-infected military beneficiaries who demonstrated initial viral suppression after initiation of HAART, we found that elevated total CD8 counts were associated with greater risk of future virologic failure. This association persisted using three separate evaluations of CD8 counts: one measured at the time of confirmed initial viral suppression (defined as 12 months post-HAART in this study), and two different metrics for CD8 measured after initial viral suppression: proportion of prior visits with elevation and change in CD8 counts from HAART start.

Few studies have explored the total CD8 count as a potential predictor for virologic treatment failure. One study found no significant association between total CD8 count and categories of suppressed viral replication versus continuing viral replication [40]. However this study was cross-sectional and thus not designed to capture cumulative effects of total CD8 counts. In our study we used time-updated covariates to relate the cumulative history of elevated CD8 counts (from the time of initial suppression) to the probability of future virologic failure. We found that baseline and serial elevation in the total CD8 count as well as an increase in CD8 counts from HAART start to the current visit was associated with increased risk of virologic failure. Possible explanations for these associations include the adverse effects of a hyperdynamic or over-stimulated immune response which may be

reflected in the total CD8 count. Alternatively, elevated CD8 cells may have resulted from low-level viremia, which is associated with increased risk of virologic failure [53]. In addition, coinfections may have been responsible for both elevated CD8 counts and increased risk of failure, although this is temporally less plausible.

For both CD8 count measured at the time of initial viral suppression and CD8 count measured during follow-up (when evaluating the proportion of CD8 counts that were elevated), we found stronger associations with virologic failure when HAART was initiated in the more recent era of 2000-2008, rather than 1996-1999. This retrospective study was not designed to address the basis for this differential effect, but some explanations are consistent with our data. First, the effect may relate to duration of HIV infection at the time of HAART initiation. The 2000-2008 HAART group had been infected with HIV for a much shorter time compared to those initiating HAART in 1996-1999. A recent study showed a sharper decline in CD8 counts after initiation of HAART among those with early versus chronic HIV infection [54]. In the first year following HAART, we also observed a steeper CD8 count decline for the recent HAART era group with early HAART initiation compared to the 1996-1999 group that had been infected longer before starting HAART. Immune system recovery may be greater for treatment initiated earlier in the course of infection; poor response among those initiating treatment later in the course of HIV infection may obscure a relationship between elevated CD8 counts and VF. A second possible explanation relates to toxicity of HAART regimens prescribed in the 1990s. Higher rates of virologic failure among those initiating HAART in 1996-1999 may more often be linked to toxicity-related discontinuation of therapy, rather than intermittent noncompliance. In this scenario, low-level viremia leading to elevated CD8 counts and VF may be less plausible.

This study had several limitations. The participants in this analysis were a select group that showed initial response to HAART by having < 400 copies/mL of HIV RNA at both 6 and 12 months after initiation. This group differed significantly from the excluded participants in many respects, including CD8 counts at HAART start. However, the purpose of these selection criteria was to identify and restrict the analysis to participants who were more likely adherent to treatment; data regarding adherence was not available for the entire study period so selection was used to attempt to control for the important role of this variable in virologic treatment failure. A second limitation is that our categorization of the proportion of previous visits with elevated CD8 counts was fairly arbitrary. However, additional evidence for the effect of elevated CD8 levels on virologic treatment failure was found using baseline CD8 counts and using the change in CD8 counts from HAART start to each visit. Confirmation of these findings in a larger cohort is advisable.

The rate of virologic failure observed in this study (5.6 per 100 pyrs overall or 12% at 2 years) was lower than what has been reported in earlier years [4,8,10-12]. However, rates of treatment failure in general have been decreasing in recent years [55-57] and a more current estimate of virologic failure [58] was closer to what we have observed in our cohort which includes participants initiating HAART as late as 2008. Despite this decline in failure rates, virologic failure remains an important concern when monitoring HIV-infected patients on lifelong treatment. Thus, clinically relevant tools that are readily available to predict treatment failure are needed. In this study we have highlighted the potential of the total CD8 count as one such tool. While the CD8 count alone may not have adequate sensitivity to predict virologic failure, its use in combination with the battery of existing predictors for virologic failure could make a significant contribution to prediction algorithms. Because some of the other suggested predictors involved characteristics not common in our study (prior virologic failure, suboptimal adherence, or suppression less than 12 months), an elevated CD8 count may be one of the few indicators of future virologic failure among virally suppressed individuals who may not otherwise be viewed as high risk for failure. By

identifying those patients at increased risk of virologic failure, targeted efforts to confirm treatment adherence or increase the frequency of monitoring could be implemented with the goal of preventing virologic failure among those who are currently maintaining viral suppression.

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Figure 1.
Flowchart of NHS participants included in the analysis. Exclusions are shown on the right.

Figure 2. Rates of VF per 100 person-years by baseline CD8 count and era in which HAART was initiated.

Table 1

Baseline Characteristics Overall and by Era of HAART Initiation

Baseline Characteristic*	Total	HAART Initiated in 1996-1999	HAART Initiated in 2000-2008	p-value
Number of Participants	817	445	372	
Median age, yrs (IQR)	36 (30 - 41)	36 (31 - 41)	35 (29 - 41)	0.008
Male (N, %)	751 (92%)	403 (91%)	348 (94%)	0.12
Race (N, %)				0.04
Caucasian	387 (47%)	225 (51%)	162 (44%)	
African American	327 (40%)	174 (39%)	153 (41%)	
Other	103 (13%)	46 (10%)	57 (15%)	
Median CD4 at HAART start** (IQR), cells/mm ³	357 (256 - 477)	395 (261 - 517)	323 (244 - 431)	<.001
Median CD4 at baseline (IQR), cells/mm ³	531 (390 - 703)	547 (403 - 746)	520 (386 - 667)	0.053
Median HIV RNA at HAART start** (IQR), log ₁₀ copies/ml	4.4 (3.6 - 4.9)	4.2 (3.4 - 4.9)	4.6 (4.1 - 5.0)	<.001
Median CD8 count at HAART start* (IQR), cells/mm ³	859 (605 - 1209)	817 (601 - 1183)	914 (609 - 1227)	0.051
Median CD8 count at baseline (IQR), cells/mm ³	761 (569 - 1016)	789 (603 - 1034)	738 (548 - 974)	0.03
Median years from HIV diagnosis to baseline (IQR)	2.2 (1.2 - 6.1)	3.3 (1.2 - 8.2)	1.7 (1.2 - 3.7)	<.001
Any ART prior to HAART start (N, %)	272 (33%)	232 (52%)	40 (11%)	<.001
Any clinical AIDS events prior to baseline (N,%)	51 (6%)	36 (8%)	15 (4%)	0.02
Class of Drugs used in 1st HAART regimen (N,%)				<.001
PI, NRTI	423 (52%)	354 (80%)	69 (19%)	
NNRTI, NRTI	312 (38%)	58 (13%)	254 (68%)	
NRTI only	51 (6%)	7 (2%)	44 (12%)	
PI, NNRTI, NRTI	31 (4%)	26 (6%)	5 (1%)	

* HAART: highly active antiretroviral therapy, ART: non-HAART antiretroviral therapy, PI: protease inhibitor, NRTI: nucleoside reverse transcriptase inhibitor, NNRTI: non-nucleoside reverse transcriptase inhibitor

** Missing data comprised less than 10% of total

Table 2 Adjusted Baseline CD8 Count Model Estimates for Time to Virologic Failure by HAART Era¹

	Era in Which HAART was Initiated			
	1996-1999		2000-2008	
Baseline CD8 Count	Adjusted HR ² (95% CI)	p-value	Adjusted HR ² (95% CI)	p-value
≤ 600	1.00 (Reference)		1.00 (Reference)	
601-849	0.76 (0.50 - 1.15)	0.20	1.01 (0.41 - 2.49)	0.98
850-1199	1.00 (0.65 - 1.54)	0.99	1.21 (0.51 - 2.88)	0.66
≥ 1200 (elevated)	1.19 (0.75 - 1.89)	0.46	2.68 (1.13 - 6.35)	0.03

¹ HAART: highly active antiretroviral therapy² Adjusted for age, previous ART, baseline CD4 count, HAART start era, and the interaction between HAART start era and baseline CD8 count

Table 3

Unadjusted and Adjusted Model Estimates for Time to Virologic Failure

Covariate ¹	Unadjusted HR (95% CI)	P-value	Adjusted HR ² (95% CI)	P-value	Adjusted HR ³ (95% CI)	P-value
Proportion of CD8 counts that are elevated⁴						
≤ 0.2	1.00 (Reference)		1.00 (Reference)			
> 0.2	1.44 (1.08 - 1.93)	0.01	1.53 (1.14 - 2.06)	0.005		
Change in CD8 count from HAART start to previous visit⁵						
Decrease or Stay the Same	1.00 (Reference)				1.00 (Reference)	
Increase	1.63 (1.22 - 2.17)	<.001			1.59 (1.19 - 2.13)	0.002
Unknown	1.65 (1.07 - 2.54)	0.02			1.55 (1.00 - 2.39)	0.048
Age at baseline (yrs)						
Per 5 years older	0.82 (0.75 - 0.89)	<.001	0.79 (0.72 - 0.86)	<.001	0.80 (0.73 - 0.88)	<.001
Gender						
Men	1.00 (Reference)					
Women	0.90 (0.56 - 1.46)	0.67				
Race						
Caucasian	1.00 (Reference)					
African American	1.06 (0.80 - 1.41)	0.68				
Other	1.31 (0.86 - 2.01)	0.21				
Current CD4 count						
Per 100 cell increase	1.03 (0.99 - 1.08)	0.18	1.03 (0.98 - 1.08)	0.27	1.03 (0.98 - 1.08)	0.22

Covariate ¹	Unadjusted HR (95% CI)	p- value	Adjusted HR ² (95% CI)	p- value	Adjusted HR ³ (95% CI)	p- value
HIV RNA at HAART start						
Per 1 log10 increase	0.90 (0.79 - 1.03)	0.13				
Years of HIV Infection⁶						
Per 1 year increase	1.01 (0.98 - 1.05)	0.48				
ART prior to HAART	1.49 (1.12 - 1.98)	0.006	1.63 (1.22 - 2.19)	0.001	1.63 (1.22 - 2.18)	0.001
Clinical AIDS event prior to Baseline	0.67 (0.37 - 1.20)	0.18				

¹ HAART: highly active antiretroviral therapy, ART: non-HAART antiretroviral therapy

² Adjusted for baseline age, previous ART before HAART, time-updated CD4 count and proportion of prior CD8 counts elevated

³ Adjusted for baseline age, previous ART before HAART, time-updated CD4 count and change in CD8 count from HAART start to previous visit

⁴ Using all 6-month CD8 measures prior to outcome event

⁵ Using only the CD8 count at HAART start and the CD8 count prior to outcome event

⁶ Years from documented HIV positive test to baseline