Acute HIV Infection and CD4/CD8 Ratio Normalization After Antiretroviral Therapy Initiation

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Background: We estimated the effect of initiating virologically suppressive antiretroviral therapy (ART) during acute HIV infection versus chronic HIV infection (AHI vs. CHI) on CD4/CD8 ratio normalization.

Setting: A prospective clinical cohort study.

Methods: We included patients initiating ART with AHI and CHI between 2000 and 2015 and compared time from ART initiation to the first normal CD4/CD8 ratio (defined as CD4/CD8 $\geq$1) using Kaplan–Meier curves and multivariable Cox proportional hazards models. Patient time was censored at virologic failure, lost to follow-up, or death. We also characterized CD4, CD8, and CD4/CD8 trajectories over the first 3 years of ART.

Results: The 1198 patients were 27% female and 60% African American, with a median age of 37 years (interquartile range 28–47) at ART initiation. The 83 AHI patients were more likely male, younger, and of white race, than CHI patients. After 2 years of suppressive ART, 70% of AHI patients achieved a normal CD4/CD8 ratio, compared to 6%–38% of CHI patients, with greater likelihood of normalization at higher baseline CD4 counts. Time to normalization was shortest among AHI patients, followed by CHI patients with higher baseline CD4. The adjusted hazard ratio for time to normalization for AHI patients compared to CHI patients with baseline CD4 >350 was 4.33 (95% CI: 3.16 to 5.93). Higher baseline CD4/CD8 ratio was also associated with time to normalization (adjusted hazard ratio 1.54; 1.46, 1.63, per 0.1 increase in ratio).

Conclusions: Initiating ART during AHI at higher baseline CD4 cell counts and CD4/CD8 ratios was associated with shorter time to CD4/CD8 ratio normalization.

Key Words: HIV, anti-HIV agents, CD4-CD8 ratio, inflammation, acute retroviral syndrome

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INTRODUCTION

Despite effective antiretroviral therapy (ART), persons living with HIV (PLWH), compared with HIV-uninfected persons, experience a higher incidence of non–AIDS-related morbidities, such as advanced cardiovascular disease and many types of malignancies.[1–4] The life expectancy of PLWH receiving ART is also persistently lower than that for HIV-uninfected populations in some regions of the world and for patients with poor immune response.[5–8] These differences likely have multiple causes including lifestyle factors, viral coinfections, as well as persistent immune dysfunction due to HIV.[9–12] Chronic immune activation and inflammation leading to immunosenescence are associated with morbidity and mortality, and biomarkers of activation and inflammation remain higher among PLWH after years on effective ART.[12–14] A CD4/CD8 ratio <1 is associated with biomarkers of activation and inflammation and is predictive of non–AIDS-related morbidity and mortality.[15–19] The CD4/CD8 ratio should therefore be considered as a potential marker for measuring the success of treatment strategies that limit persistent inflammation.

Initiating ART early in HIV infection improves clinical outcomes.[20] ART started during acute HIV infection (AHI) rapidly suppresses HIV replication and increases the recovery of CD4 cell counts, and may prevent persistent immune activation and inflammation.[21–24] However, few studies have investigated the evolution of CD4/CD8 ratios longitudinally in the clinical setting or examined CD4/CD8 ratios in patients initiating ART close to infection. We estimated the effect of initiating ART during AHI versus chronic HIV infection

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(CHI) on CD4/CD8 ratio recovery. We also characterized trajectories of CD4 cells, CD8 cells, and the CD4/CD8 ratio after ART initiation among both AHI and CHI patients.

METHODS

Study Population

Patients were drawn from the University of North Carolina (UNC) Center for AIDS Research HIV Clinical Cohort (UCHCC), a prospective clinical cohort of primary HIV care patients at UNC hospitals since 1996,[25] and from the Duke-UNC Acute HIV Cohort, which includes HIV-infected individuals referred to UNC or Duke Hospital with either a negative or indeterminate antibody test and reproducibly detectable HIV RNA, or a positive antibody test with seronegative documentation in the previous 30 days.[21] The AHI group included acute HIV cohort participants who initiated ART between January 1, 2000, and December 31, 2015, <120 days after estimated infection date, calculated as 14 days before acute retroviral syndrome onset (Fig. 1).[21] The CHI group included UCHCC participants with no record of acute retroviral syndrome who initiated ART in the same calendar period. UNC's Institutional Review Board approved this study, and patients provided written informed consent.

Outcomes

We examined time from ART initiation (baseline) to CD4/CD8 ratio normalization, defined as the first CD4/CD8 ratio ≥1. We chose this definition because a ratio <1 is associated with immune dysfunction markers[15] and for comparability with previous CD4/CD8 normalization studies. We compared all AHI patients to CHI patients categorized by CD4 count at baseline: <200, 200–350, and >350 cells/mm^3. Patients were censored at the earliest of: death; virologic failure, defined as the first of 2 consecutive viral loads ≥400 copies/mL at least 30 days apart 24 weeks after baseline; loss to follow-up, defined as 1 year after the last HIV clinic or laboratory visit); or administrative censoring on December 31, 2015. We examined trajectories of CD4 counts, CD8 counts, and CD4/CD8 ratios in 3-month intervals for 3 years after baseline, including the closest laboratory measurement within 45 days of each time point.

Statistical Analyses

Chi-square and Kruskal–Wallis tests compared AHI and CHI patients' baseline characteristics. We performed time-to-event analyses using Kaplan–Meier curves with log-rank tests, and Cox proportional hazards models to estimate hazard ratios (HRs) and 95% confidence intervals, adjusting for baseline CD4/CD8 ratio, sex, race/ethnicity, and age. Analyses were stratified by AHI and CHI categories as well as baseline CD4/CD8 ratios, using tertiles of AHI patients' baseline CD4/CD8 ratio distribution. Distributions of CD4 and CD8 cell counts and CD4/CD8 ratios were compared between groups using Wilcoxon rank–sum tests at months 0, 3, 9, 12, 24, and 36 after baseline, censoring patients after virologic failure.

In primary analyses, we excluded patients who were missing baseline CD4/CD8 ratio (n = 115), did not have any CD4/CD8 ratio measured during the study period (n = 57), and had a normal baseline ratio (n = 12 AHI patients and 38

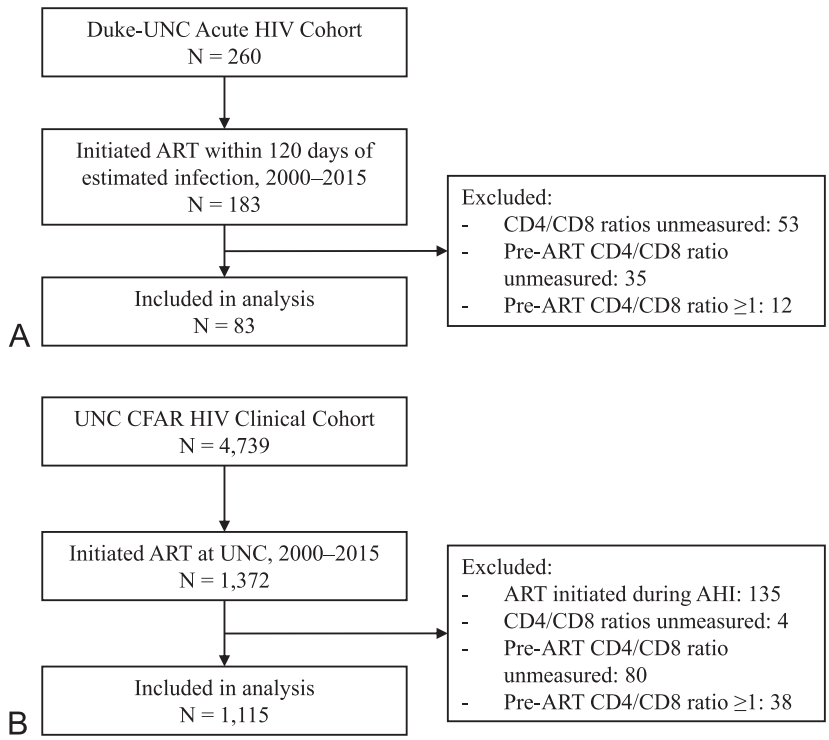

FIGURE 1. Flow diagram of patient inclusion and exclusion for AHI (A) and CHI (B).

CHI patients) (Fig. 1). In secondary analyses, we included patients with missing or normal baseline ratios. For patients with missing CD4 or CD4/CD8 ratio at baseline, we used multiple imputation with 50 imputations and a single Markov chain, based on AHI status, sex, race/ethnicity, age, MSM, and baseline $\log_{10}$ HIV RNA. *P* values were 2-sided and <0.05 was considered statistically significant. SAS software, version 9.4 (Cary, NC), was used for all analyses.

RESULTS

The 1198 included patients were 27% female, 60% African American, 26% white, and 14% Hispanic or other race/ethnicity, and they contributed a median follow-up time of 4.6 years [interquartile range (IQR) 1.8–8.3] and a total of 6606 person-years. At baseline, the median (IQR) age was 37 years (28, 47), calendar year 2007 (IQR 2003, 2011), CD4 count 234 cells/mm^3 (IQR 62–408), CD8 count 823 cells/mm^3 (IQR 510–1177), and CD4/CD8 ratio was 0.2 (IQR 0.1–0.4). The 83 AHI patients (7%) were younger and more likely to be male and white (all $P < 0.05$) (Table 1). Seventeen percent of patients were censored at lost to follow-up, 23% at virologic failure, and 6% at death, and these varied by AHI and CHI categories, with CHI patients with CD4 <200 having greater proportions of patients censored due to death and virologic failure. AHI patients had a median of 13 (IQR 8–23) available CD4/CD8 ratio measurements with a median interval of 2.5 months (IQR 0.9–3.4) between measurements. CHI patients had a median of 15 (IQR 7–26) CD4/CD8 ratio measurements with a median interval of 3.2 months (IQR 1.8–5.0) between measures. Among AHI patients, the median time from estimated infection date to ART initiation was 43 days (IQR 35–58).

Time to CD4/CD8 Normalization

One year after baseline, 62% of AHI patients who achieved and maintained virologic suppression had a normal CD4/CD8 ratio, in contrast to 23%, 13%, and 2% of CHI patients with baseline CD4 >350, 200–350, and <200, respectively (Fig. 2A, $P < 0.05$). After 2 years of ART and remaining suppressed, these percentages rose to 70% among AHI patients compared to 38%, 21%, and 6% for CHI patients with baseline CD4 >350, 200–350, and <200, respectively. The median time to CD4/CD8 normalization among AHI patients was 0.5 years, in contrast to 3.4 and 7.4 years among CHI patients with baseline CD4 >350 and 200–350, respectively. After 14.3 years of follow-up, <50% of CHI patients with baseline CD4 <200 had a normal ratio.

Further dividing patients into subgroups with baseline ratio <0.3, 0.3–0.5, and 0.5–1.0, consistent with overall results (Fig. 2A), we observed the most rapid CD4/CD8 normalization among AHI patients in all subgroups (Fig. 2B–D, all $P < 0.05$). Among both AHI and CHI patients, irrespective of baseline CD4, subgroups with higher baseline CD4/CD8 ratios had shorter times to normalization than those with lower baseline ratios (all $P < 0.05$). Comparing only CHI patients with baseline CD4 200–350 to CHI with CD4 >350, we

TABLE 1. Demographic and Clinical Characteristics of Patients Initiating Antiretroviral Therapy, 2000–2015, Stratified by Acute Versus Chronic HIV Infection and Baseline CD4 Cell Count

		Chronic HIV Infection			
Characteristic	**Acute HIV Infection (N = 83)**	**CD4 < 200 (N = 542)**	**CD4 200–350 (N = 232)**	**CD4 > 350 (N = 341)**	***P****
Sex, n (%)					<0.05
Male	75 (90)	399 (74)	165 (71)	241 (71)	
Female	8 (10)	143 (26)	67 (29)	100 (29)	
Race/ethnicity, n (%)					<0.05
African American	48 (58)	324 (60)	134 (58)	211 (62)	
White	28 (34)	130 (24)	58 (25)	98 (29)	
Hispanic, any race	7 (8)	15 (3)	2 (1)	5 (1)	
Other	0 (0)	73 (13)	38 (16)	27 (8)	
Calendar year, median (IQR)	2009 (2007–2012)	2005 (2002–2009)	2007 (2004–2011)	2010 (2007–2013)	<0.05
Age, median years (IQR)	26 (23–38)	40 (33–48)	38 (28–47)	30 (25–40)	<0.05
CD4 count, median cells/mm^3 (IQR)†	454 (338–587)	54 (17–122)	269 (239–307)	469 (403–590)	<0.05
CD8 count, median cells/mm^3 (IQR)†	1142 (829–1531)	549 (318–842)	884 (602–1187)	1064 (841–1435)	<0.05
CD4/CD8, median (IQR)†	0.4 (0.2–0.6)	0.1 (0.1–0.2)	0.3 (0.2–0.5)	0.5 (0.4–0.6)	<0.05
HIV RNA, median $\log_{10}$ copies/mL (IQR)†	5.2 (4.6–5.8)	5.3 (4.8–5.8)	4.6 (4.2–5.0)	4.3 (3.8–4.7)	<0.05
Follow-up time, total years	98	2119	679	736	
Censored, n (%)					
LTFU	14 (17)	98 (17)	49 (21)	53 (16)	
VF	5 (6)	161 (30)	43 (19)	61 (18)	
Death	0 (0)	60 (11)	8 (3)	1 (<1)	

*P value comparing acute and chronic groups using Kruskal–Wallis test for continuous variables and Pearson χ^2 test for categorical variables.
†Laboratory measurements are the closest available measure in the year preceding ART initiation.
LTFU, loss to follow-up; VF, virologic failure.

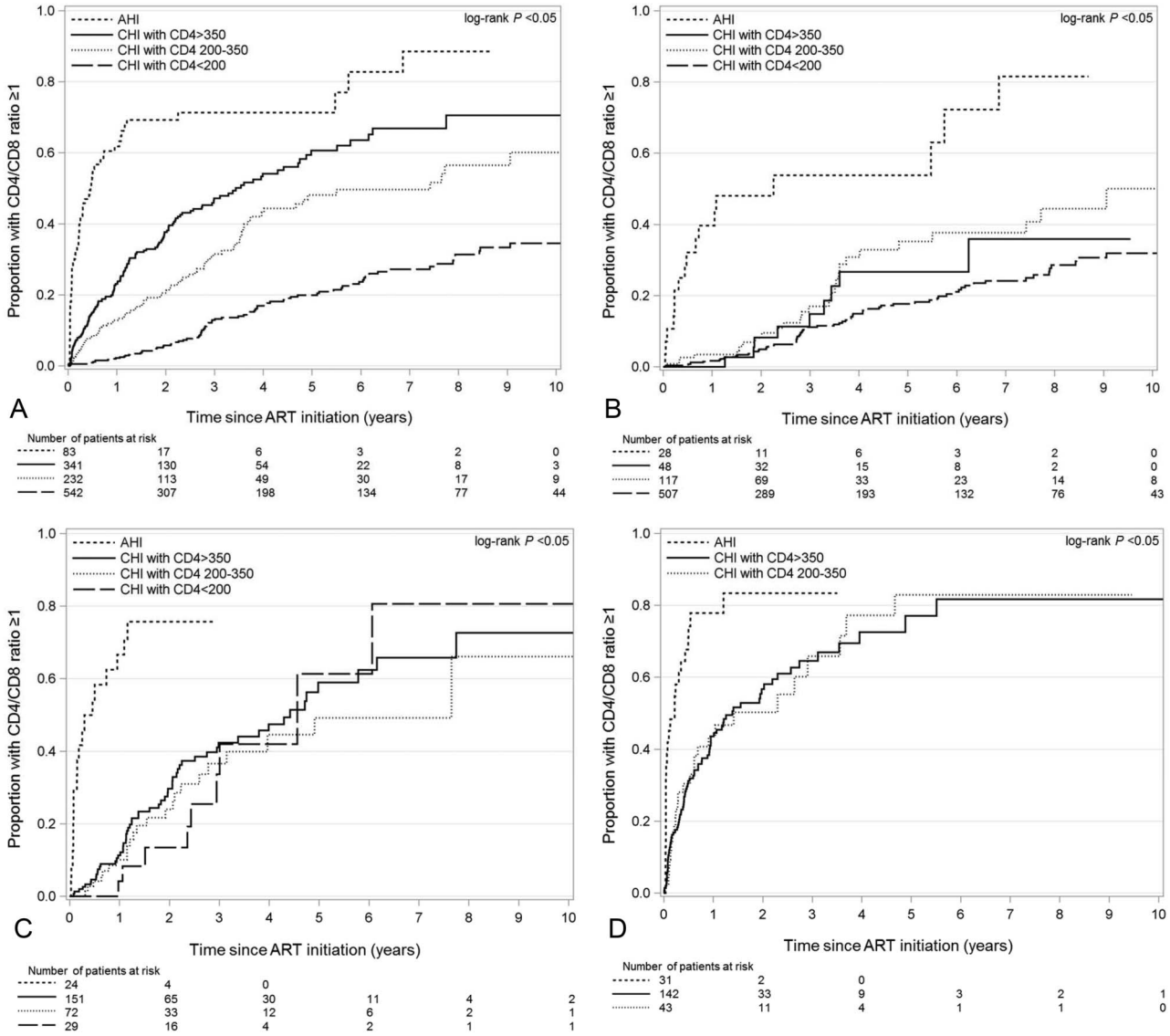

FIGURE 2. Time from ART initiation to CD4/CD8 ratio normalization stratified by AHI and CHI according to baseline CD4 cell count, 2000–2015. Among (A) all patients (n = 1198); and patients with a baseline CD4/CD8 ratio (B) <0.3 (n = 700); (C) 0.3–0.5 (n = 276); and (D) 0.5–1.0 (n = 222).

observed no difference in time to CD4/CD8 ratio normalization in ratio subgroup <0.3 (8% vs. 8% normalized after 2 years, respectively, $P = 0.53$), subgroup 0.3–0.5 (24% vs. 30%, $P = 0.36$), or subgroup 0.5–1.0 (50% vs. 57%, $P = 0.92$). In comparison to all CHI patients with baseline CD4 >200, CHI patients with CD4 <200 seemed to take longer to achieve a normal CD4/CD8 ratio in the subgroup with baseline ratio of <0.3 (5% vs. 8% normalized after 2 years, $P < 0.05$). We did not compare to patients with baseline CD4 <200 in other ratio subgroups because very few had a CD4/CD8 ratio 0.3–0.5 (n = 29, 5%) or 0.5–1.0 (n = 6, 1%).

Unadjusted Cox model results for time to normalization were consistent with Kaplan–Meier curves, with an HR comparing AHI patients to all combined CHI patients of 5.69 (95% CI: 4.30 to 7.53), and an HR comparing AHI patients to CHI with baseline CD4 >350 of 2.86 (95% CI: 2.1 to 3.87). Compared to CHI patients with baseline CD4 <200, the unadjusted HR was higher for CHI with higher CD4 counts and for AHI patients (Table 2). In models partially adjusted for age, sex, and race, HR estimates were similar. In fully adjusted models also including baseline CD4/CD8 ratio, baseline CD4 was not longer associated with time to normalization in CHI patients, but AHI still had an HR of 5.05 (95% CI: 3.36 to 7.59) compared to CHI with CD4 <200 (Table 2). In fully adjusted models, AHI had an HR of 4.43 (95% CI: 3.27 to 5.99) compared to all combined CHI, and an HR of 4.33 (95% CI: 3.16 to 5.93) compared to CHI with CD4 >350. Model estimates, both unadjusted and adjusted, stratified by baseline CD4/CD8 ratio showed similar differences in time to normalization between groups as did stratified Kaplan–Meier curves (Supplemental Digital Content Table, http://links.lww.com/QAI/B209).

TABLE 2. Unadjusted and Adjusted Hazard Ratios and 95% Confidence Intervals for Time to CD4/CD8 Ratio Normalization

	HR (95% Confidence Interval)		
Parameter	**Unadjusted**	**Partially Adjusted***	**Fully Adjusted†**
Category			
CHI with CD4 <200	1. (ref.)	1. (ref.)	1. (ref.)
CHI with CD4 200–350	2.58 (1.90 to 3.50)	2.61 (1.92 to 3.55)	1.14 (0.82 to 1.59)
CHI with CD4 >350	4.25 (3.25 to 5.56)	4.35 (3.30 to 5.75)	1.17 (0.84 to 1.63)
AHI	12.16 (8.70 to 16.99)	13.98 (9.80 to 19.93)	5.05 (3.36 to 7.59)
Age, per 10-yr increase	0.87 (0.79 to 0.95)	1.06 (0.96 to 1.16)	1.11 (1.01 to 1.21)
Race/ethnicity, non-Hispanic white vs. all others	1.07 (0.85 to 1.34)	0.98 (0.78 to 1.23)	0.92 (0.74 to 1.16)
Sex, male vs. female	0.79 (0.64 to 0.99)	0.72 (0.57 to 0.91)	0.82 (0.65 to 1.04)
CD4/CD8 ratio, per 0.1 increase	1.59 (1.52 to 1.67)	—	1.54 (1.46 to 1.63)

*Partially adjusted model includes all variables in table, measured at baseline, except CD4/CD8 ratio.

†Fully adjusted model includes all variables in table, measured at baseline.

Baseline CD4/CD8 ratio was predictive of time to normalization in all models, with a fully adjusted HR of 1.54 (95% CI: 1.46 to 1.63) per 0.1 ratio increase (Table 2). In both unadjusted and partially adjusted analyses, male sex was associated with a lower rate of normalization, but this was not statistically significant in the fully adjusted analyses that included both CHI CD4 categories and baseline CD4/CD8 ratio (HR 0.82, 95% CI: 0.65 to 1.04). A 10-year increase in age was associated with lower normalization rates in the unadjusted model (HR 0.87, 95% CI: 0.79 to 0.95), but higher normalization rates in the fully adjusted model (HR 1.11, 95% CI: 1.01 to 1.21). Race/ethnicity was not associated with time to normalization in unadjusted or adjusted analyses.

Sensitivity Analyses

In a sensitivity analysis also including patients with CD4/CD8 ratios ≥1 at baseline (n = 12 additional patients for AHI, n = 38 additional patients for CHI), after 2 years of ART and remaining suppressed, a total of 73% of AHI patients had a normal CD4/CD8 ratio, compared to 43%, 21%, and 6% for CHI with CD4 >350, 200–350, and <200, respectively. In another sensitivity analysis using imputation for missing baseline laboratory values, in the fully adjusted model, age was no longer associated with time to CD4/CD8 normalization (HR 1.06, 95% CI: 0.97 to 1.17), and CHI with CD4 >350 had a significantly shorter time to normal CD4/CD8 compared to CHI with CD4 <200 (HR 1.53, 95% CI: 1.09 to 2.14). Other associations remained unchanged. To explore whether natural CD4 and CD8 changes in AHI patients impacted CD4/CD8 normalization estimates, we conducted a subgroup analysis of patients without the

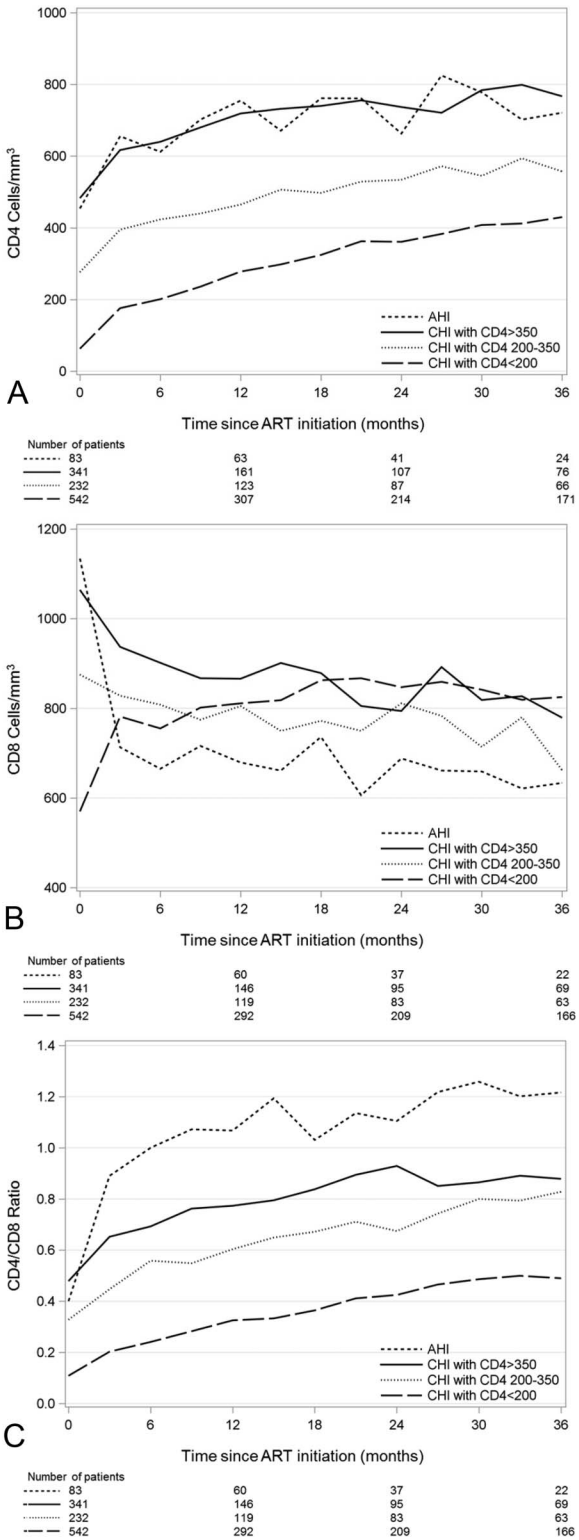

FIGURE 3. Median and IQRs of CD4 (A), CD8 (B), and CD4/CD8 ratio (C) among AHI and CHI patients after antiretroviral therapy initiation, 2000–2015.

outcome or censoring by 3 months after ART (n = 29 for AHI and n = 502 for CHI), using this time point as the new baseline. In fully adjusted models including CD4/CD8 ratio at 3 months, AHI patients had a normalization HR of 5.06 (95% CI: 3.21 to 7.97) compared to all CHI patients, and 2.34 (95% CI: 1.37 to 3.98) compared to CHI with CD4 >350. In an analysis censoring patients at a less strict definition of virologic failure (any HIV RNA ≥400 copies/mL after 90 days of ART), estimates were also similar to the main findings. In analyses including baseline CD8 count instead of baseline CD4/CD8 ratio in fully adjusted models, estimates were similar to partially adjusted analyses.

CD4, CD8, and CD4/CD8 Ratio Trajectories

Compared to CHI patients with baseline CD4 <200, the CD4 counts and CD4/CD8 ratios of AHI patients remained higher at every examined time point (Figs. 3A, C, all $P < 0.05$). AHI patients also had higher baseline CD8 counts than CHI with CD4 <200 but experienced a rapid drop in CD8 counts after starting ART and maintained levels lower than this CHI group after 2 years but not significantly lower after 3 years (Fig. 3B, $P < 0.05$ and $P = 0.06$, respectively). These changes were reflected in the CD4/CD8 ratio that quickly rose by 3 months after baseline among AHI patients, reaching a normal median 6 months after baseline. CHI patients with CD4 >350 had baseline CD4, CD8, and CD4/CD8 ratio comparable to AHI patients (median 483 vs. 454, 1064 vs. 1134, and 0.5 vs. 0.4, respectively). Three years after baseline, these CHI patients' CD4 cell counts increased to levels comparable to AHI counts (median 767 vs. 721, $P = 0.13$), but CD8 counts remained elevated (median 779 vs. 634, $P < 0.05$), and CD4/CD8 ratios were lower, although not with statistical significance (0.9 vs. 1.2, $P = 0.08$).

DISCUSSION

In this study, patients who initiated ART during AHI within 4 months of infection were more likely to achieve a normal CD4/CD8 ratio than patients who were chronically infected at ART start. Patients with AHI also had the shortest time to normalization when compared to CHI patients, regardless of CHI patients' CD4 counts and CD4/CD8 ratios at baseline. Among CHI patients, those with higher baseline CD4 and CD4/CD8 ratios fared better in time to normalization. However, even CHI patients with baseline CD4 counts >350 did not achieve normal CD4/CD8 ratio to the extent of AHI patients. After 3 years of therapy, CHI patients with baseline CD4 >350 reached CD4 counts comparable to those of AHI patients, but their CD8 counts remained elevated, whereas AHI patients experienced a rapid drop in CD8 cells in the first few months of ART.

Our findings on the impact of ART initiation very early in HIV infection on immune recovery are consistent with earlier observational studies showing that ART during acute or primary HIV leads to faster and higher rates of CD4/CD8 ratio recovery.[17,26–30] A primary HIV infection study also reported the dual role of rapid CD4 rise and CD8 drop in CD4/CD8 ratio normalization after ART initiation.[27] Although it is possible that a CD8 drop would occur naturally after early AHI, 2 studies of untreated AHI patients showed little to no decrease in CD8 counts and persistent CD8 elevation.[27,31] In addition, our sensitivity analyses adjusting for CD4/CD8 ratio 3 months after ART initiation were similar to the main results, suggesting that CD4/CD8 ratio recovery in AHI was more likely attributable to ART. There is variability in the literature, however, in the reported incidence of normalized ratios, with 2-year estimates ranging from approximately 30%–65%, which may be explained by different study definitions and approaches.[27,28,30] Acute/primary HIV has been variably defined using seroconversion dates, Fiebig staging, and retroviral syndrome, with treatment initiation windows ranging from 1 to 6 months. Normalized CD4/CD8 ratios have been defined using a threshold of 0.9, 1, or 1.2 and either 1 or 2 measurements. Some investigators excluded patients who had limited follow-up or never achieved viral suppression. One study used competing risk analysis, which did not censor patients after virologic failure or loss to follow-up and could have resulted in lower proportions.[30] Our study's strict definition of early treatment (<120 days of estimated infection, with a median of 43 days among AHI patients) may explain our 2-year ratio normalization of 70%.

In CHI patients, CD4/CD8 ratio recovery rates were low in our study as in previous works,[17,26,30,32–35] partly due to persistently elevated CD8 counts. Even CHI patients initiating ART with CD4 >350 attained normal CD4 counts after 3 years but not normal CD8 counts or CD4/CD8 ratios. These trends are consistent with other cohort studies,[27,36] and with a cross-sectional analysis showing that CD8, not CD4, differences drive CD4/CD8 ratio variability in patients with long-term suppression.[33] Earlier ART in CHI improves CD4 recovery,[24,37–39] but its impact on CD4/CD8 ratio normalization may be more nuanced. In our study, after stratifying or adjusting for pre-ART CD4/CD8 ratio, there was little difference in ratio normalization rates by CD4 count among CHI, but a higher CD4/CD8 ratio at baseline remained a significant predictor of normalization. One study reported that pre-ART CD4 counts and CD4/CD8 ratios were jointly predictive of ratio recovery in chronic patients, in models including both variables.[35] Other studies found both pre-ART CD4 and CD8 counts were predictive of CD4/CD8 ratio recovery but did not adjust for CD4/CD8 ratios.[30,32,33,35] Our analyses suggest that adjusting for CD4 and CD8 alone may not take into account the level of immune dysfunction at ART initiation because pre-ART CD4/CD8 ratio remained strongly predictive of ratio normalization. After established immune dysfunction as indicated by a low ratio, pre-ART CD4 count may have only a modest effect on CD4/CD8 ratio improvements, with slow and rare ratio recovery taking place as CD4 counts increase slowly over time, while CD8 counts remain persistently elevated. Furthermore, CD8 cell dynamics observed in our study (Fig. 3B) may generate hypotheses and warrant further research because CD8 trajectories seem to differ not only by AHI versus CHI status but also by baseline immunosuppression, in contrast to more parallel CD4 changes.

Few recent studies have examined demographic factors associated with CD4/CD8 ratio recovery during ART in either AHI or CHI. Some studies have reported better ratio recovery for female patients,[30,40,41] and one study for white patients.[40] We found a similar effect of female sex but no association with race. Younger age has generally been associated with better ratio recovery.[35,40–42] In our study, younger age was associated with shorter time to normalization in unadjusted analyses, but longer time to normalization after adjusting for baseline CD4/CD8 ratio. After imputing missing baseline ratios, there was no longer an association between age and ratio normalization. The age effect reversal, which has also been reported in one other study,[30] was unexpected given that younger age has been shown to lead to better CD4 restoration.[43–47] The reason for this discrepancy with previous work is not clear. One possible explanation is that restricting our analysis to patients with available baseline ratios introduced selection bias. Alternatively, the improved adherence typically observed among older patients,[48] when compared with younger patients with similar CD4/CD8 ratios, even with sustained suppression, may impact immune recovery. Unfortunately, we could not adjust for adherence in our analyses. It is also possible that CD4/CD8 ratio mediates the effect of age on immune recovery and thus, should not be included in models estimating this effect.

Patterns of different T-lymphocyte depletion and recovery in HIV infection are complex and only partially understood.[49] Timing of ART initiation can affect not only cell counts but also the relative frequency of naive and memory cells and the level of activation, which may play a role in CD4/CD8 ratio and immune recovery.[39,49–51] Previous research has shown that low CD4/CD8 ratios correlate with several markers of inflammation, immune activation, and immunosenescence.[16,17] It is possible that the CD4/CD8 ratio may be useful in capturing immune dysfunction that is not evident from isolated CD4 or CD8 counts. Some studies found that pre-ART CD4/CD8 ratios are more predictive of immune recovery,[41,42,52,53] or that combined CD4 and CD4/CD8 thresholds may provide better markers of complete immune restoration.[41,42,46] Patients who have persistently low CD4/CD8 ratios, even in the presence of normalized CD4 counts, may benefit from interventions to improve immune recovery or from more intensive care and disease management, although studies conflict regarding the prognostic value of the CD4/CD8 ratio.[17,18,32,35,36,54–56] There may also be implications for research on HIV cure strategies, considering the association of low CD4/CD8 ratios with reservoir size, viral persistence, and time to rebound in very early AHI.[57–59] Future studies will need to establish what definite role the CD4/CD8 ratio can play in routine clinical care, immunological interventions, and HIV cure research. In addition, CD4/CD8 ratio studies would benefit from determining what thresholds are most representative of immune recovery and of clinically relevant immune dysfunction, especially to determine correlates of response to immunological interventions.

One major strength of this study is the prospective follow-up of patients treated closely within observed seroconversion. In addition, we were able to compare acutely treated patients to chronic patients at various stages of immunosuppression, demonstrating that the role of AHI may go beyond CD4 count levels at ART initiation. This study also combines time-to-event analyses for CD4/CD8 ratio normalization with longitudinal examination of T-cell and ratio distributions, providing insight into immune system changes in addition to factors associated with immune recovery. In addition, CD4/CD8 ratio measurement frequency was very similar across groups, limiting the potential for bias. However, our results are limited by relatively small sample sizes, which reduced statistical power when stratifying patients according to both CD4 and CD4/CD8 ratio at baseline. Moreover, we were not able to adjust for additional variables that may affect immune activation such as coinfection with cytomegalovirus or tobacco smoking.[33,60,61] Finally, our study included patients from only one geographic area and may not be generalizable to other regions, although the UCHCC is representative of the southeastern US HIV epidemic.[25]

In summary, our study showed that initiating ART within a few weeks of HIV infection is associated with substantially higher rates and shorter time to CD4/CD8 ratio normalization, compared to patients initiating treatment with CHI. In addition, although initiating therapy with a higher CD4 count during CHI may lead to better CD4 recovery, it may not be associated with CD4/CD8 ratio normalization when CD8 counts are elevated and ratios are low at initiation. This work further underscores the importance of diagnosing and treating HIV early, because immune dysfunction caused by HIV disease progression, as measured by the CD4/CD8 ratio, may not be reversible for patients with longer delays.

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