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Impact of Latent *M. tuberculosis* Infection Treatment on Time to CD4/CD8 Recovery in Acute, Recent, and Chronic HIV Infection

Eduarda Grinsztejn, MD,[a] Sandra Wagner Cardoso, MD, PhD,[b] Luciane Velasque, PhD,[c] Brenda Hoagland, MD, PhD,[b] Desiree Gomes dos Santos, MD,[b] Carolina Coutinho, PhD,[b] Simone da Costa Cruz Silva, PhD,[b] Sandro Coutinho Nazer, BSc,[b] Ana Cristina Garcia Ferreira, MD, PhD,[d] Jessica Castilho, MD, MPH,[e] Beatriz Grinsztejn, MD, PhD,[b] and Valdilea G. Veloso, MD, PhD[b]

Introduction: In people living with HIV, active and latent tuberculosis (TB) coinfections are associated with immune activation that correlate with HIV progression and mortality. We investigated the effect of initiating antiretroviral therapy (ART) during acute (AHI), recent (RHI), or chronic HIV infection (CHI) on CD4/CD8 ratio normalization and associated factors, the impact of latent TB infection treatment, and prior/concomitant TB diagnosis at the time of ART initiation.

Methods: We included sex with men and transgender women individuals initiating ART with AHI, RHI and CHI between 2013 and 2019, from a prospective cohort in Brazil. We compared time from ART initiation to the first normal CD4/CD8 ratio (CD4/CD8 $\geq$1) using Kaplan–Meier curves and multivariable Cox proportional hazards models. Sociodemographic and clinical variables were explored. Variables with *P*-values $<$0.20 in univariable analyses were included in multivariable analyses.

Results: Five hundred fifty participants were included, 11.8% classified as AHI and 6.4% as RHI, 46.7% with CHI-CD4 cell counts $\geq$350 cells/mm^3 and 35.1% with CHI-CD4 cell counts $<$350 cells/mm^3. Time to normalization was shortest among AHI patients, followed by RHI and CHI individuals with higher baseline CD4. In the multivariable model, AHI was associated with a six-fold increased likelihood of achieving a CD4/CD8 ratio $\geq$1 (hazard ratio [HR]: 6.03; 95% confidence interval [CI]: 3.70 to 9.82; $P < 0.001$), RHI with HR: 4.47 (95% CI: 2.57 to 7.76; $P < 0.001$), and CHI CD4 $\geq$350 cells/mm^3 with HR: 1.87 (95% CI: 1.24 to 2.84; $P = 0.003$). Latent TB infection treatment was significantly associated with a higher likelihood of the outcome (HR: 1.79; 95% CI: 1.22 to 2.62; $P = 0.003$). Previous history or concomitant active TB at ART initiation was associated with a lower likelihood of the outcome (HR: 0.41; 95% CI: 0.16 to 1.02; $P = 0.054$).

Conclusions: Initiating ART early during AHI may offer an opportunity to mitigate immune damage. Efforts to implement HIV diagnosis and ART initiation during AHI are critical to amplify ART benefits.

Key Words: acute HIV infection, latent tuberculosis infection, antiretroviral therapy, immune reconstitution, Brazil

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INTRODUCTION

Life expectancy of people living with HIV (PLWH) receiving antiretroviral therapy (ART), especially those with poor immune response,[1,2] is lower than that of HIV-uninfected populations in some regions of the world. These differences are because of multiple causes including lifestyle factors, coinfections, time of ART initiation, and persistent immune dysfunction because of HIV.[3–5]

Although the risk of AIDS-related illness and opportunistic diseases decreases once CD4 cell counts have recovered to levels $\geq$350 cells/mm^3, the risk of non-AIDS morbidity persists.[6] Disruption of T-cell homeostasis by HIV induces CD4 depletion and CD8 expansion, resulting in an inverted CD4/CD8 ratio.[7] The CD4/CD8 T-cell ratio represents an important indicator of HIV disease severity and response to ART.[1] People with HIV (PWH) with persistent CD4/CD8 T-cell ratio inversion (defined as a ratio $<$1.0) exhibit elevated biomarkers of T-cell activation, exhaustion, and immunosenescence.[7–9] Low CD4/CD8 ratio in individuals on

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From the [a]Department of Hematology-Oncology, University Hospitals Seidman Cancer Center, Cleveland, OH; [b]Instituto de Pesquisa Clínica Evandro Chagas-Fiocruz, Rio de Janeiro, Brazil; [c]Departamento de Matemática e Estatística, Universidade Federal do Estado do Rio de Janeiro (UNIRIO), Rio de Janeiro, RJ, Brazil; [d]Fundação Oswaldo Cruz, Rio de Janeiro,Brazil; and [e]Vanderbilt University, Nashville, TN.

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Correspondence to: Beatriz Grinsztejn, MD,Av Brasil 4365 Manguinhos, Rio de Janeiro, RJ, Brazil (e-mail: gbeatriz@ini.fiocruz.br).

suppressive ART have been independently associated with persistently elevated markers of T-cell activation[8] and a CD4/CD8 ratio <1 is predictive of non–AIDS-related morbidity and mortality.[9–12]

Several studies assessing ART initiation during acute HIV infection (AHI) have suggested significant treatment benefits, such as reduction of viremia,[13] lower viral set point,[14] lower probability of transmission,[15] and a reduced number of infected cells limiting the size of the latent pool of HIV-infected CD4 cells.[16] Moreover, starting ART in the initial phase of infection may allow preservation of the immune system, increasing the recovery of CD4 cell counts, prevent persistent immune activation, inflammation, immunosenescence, and associated morbidity and mortality.[17] Notably, only 5.1%–38% of chronically infected patients achieve a CD4/CD8 ratio ≥1 after 2 years of ART initiation.[11,18,19]

The HIV epidemic in Brazil is concentrated among men who have sex with men (MSM) and transgender women (TGW), with a high proportion of them remaining unaware of their HIV status.[20] A recent national survey found that HIV prevalence was 18% among urban MSM, with 58% of the sample aged 18–24 years and 64% of black/Afro-Brazilian or mixed race.[21] Despite a universal public health system that provides access to comprehensive prevention and care services including HIV testing, laboratory monitoring, ART "treat all" policy,[22] pre and postexposure prophylaxis (PrEP/PEP), late treatment initiation is pervasive and persistent[23] in Brazil. In 2020, up to 27% of the PLWH who started ART had a CD4 count <200 cells/mm^3.[24]

Tuberculosis (TB) is the most frequent opportunistic infection among PLWH in low- and middle-income countries (LMIC) and remains the leading cause of HIV/AIDS-related mortality, accounting for an estimated 25% of deaths in this population.[25] TB-HIV coinfection has profound effects on the immune system. HIV is the most powerful known risk factor for progression of *Mycobacterium tuberculosis* infection to active TB and also increases the risk of latent TB infection (LTBI) reactivation exponentially, whereas TB[26] and LTBI[27] induce significant immune activation and inflammation that correlate with more rapid HIV disease progression. Immediate ART initiation even at high CD4 counts significantly reduces the risk of TB. Nevertheless, ART alone is insufficient to prevent TB.[28,29] LTBI treatment provides additive protection even at higher CD4 counts[30] and reduces mortality.[31,32]

We sought to investigate a cohort of cisgender MSM and TGW from Rio de Janeiro, Brazil, who initiated ART during AHI, recent HIV infection (RHI), and chronic HIV infection (CHI), and we estimated the time to CD4/CD8 ratio recovery and associated factors, including the impact of LTBI treatment and prior/concomitant TB diagnosis at time of ART initiation.

METHODS

Study Site

The Instituto Nacional de Infectologia Evandro Chagas (INI)-Fiocruz is the largest provider of primary, specialty, and tertiary care for individuals living with HIV/AIDS in Rio de Janeiro, Brazil. A longitudinal observational clinical database has been maintained since 1986 on all patients receiving HIV care at the institution. This robust cohort has been described elsewhere.[33–35] Data are updated regularly using outpatient and inpatient clinical documentation, including ART prescriptions (drugs, dates of use and doses) and laboratory testing results (syphilis test, HIV-1 RNA, CD4 and CD8 cell counts). Trained abstractors record the information onto standardized forms. Collected data were reviewed for accuracy through internal and external procedures.

Study Population and Definitions

Since August 2013, a prospective cohort of cisgender MSM and TGW with acute or recent HIV infection (PLWH) was launched.[36] We included all cisgender MSM and TGW participants diagnosed with acute or recent HIV infection between August 2013 and December 2019, and as a comparative group, all cisgender MSM and TGW participants with chronic HIV infection were enrolled in the INI clinical cohort during the same period.

Three study groups were defined based on timing of HIV infection: acute, recent, and chronic (AHI, RHI, and CHI, respectively). The AHI group included all individuals with HIV diagnosis categorized as Fiebig I-V,[37] defined as a negative result for a third-generation HIV rapid test followed by a reactive result for the HIV antigen/antibody combination assay, or a detectable HIV RNA on pooled testing subsequently confirmed with an individual HIV RNA test. The RHI group consisted of individuals with HIV diagnosis categorized as Fiebig VI, defined as a reactive HIV serology and a documented HIV-negative serology within the previous 6 months or a reactive western blot lacking p31 (pol) reactivity, and CHI referred to individuals enrolled in the cohort with chronic HIV infection who initiated ART during study period.

All participants with AHI or RHI were offered ART and initiated ART on the day of HIV diagnosis. For all chronically infected HIV individuals, timing of ART initiation was according to the Brazilian ART guidelines. Since December 2013, the Brazilian Ministry of Health recommends ART initiation immediately after HIV diagnosis, regardless of CD4 cell counts.[38] We offered all participants who tested positive for HIV linkage to care, specialized HIV care, and ART. All groups received standard of care first-line ART regimen based on Brazilian guidelines. Until January 2017, first-line ART consisted of a fixed-dose combination of tenofovir, lamivudine, and efavirenz, which was replaced by a preferred regimen with dolutegravir, tenofovir, and lamivudine since then.

Active TB diagnosis was defined as the presence of a positive culture specimen identified as *M. tuberculosis* (MTB) from sputum, lymph node, or any other sterile site or MTB identified in a sputum sample using a molecular test (The Amplified Mycobacterium Tuberculosis Direct Test [E-MTD; Gen-Probe, San Diego, CA] or Genotype MTBDR line probe assay [Hain Lifescience GmbH, Nehren, Germany]) or any clinical–radiological suspect case of lung or extrapulmonary disease in which the consulting physician decided to start TB

treatment[39,40] and/or was under TB treatment. Prior TB was defined as a past history of completed TB treatment before ART initiation.

Patients were tested for LTBI at cohort entry, before ART initiation. The Brazilian TB guidelines have changed throughout the period that this study was conducted. Initially, LTBI treatment was only indicated for those with a reactive purified protein derivative (PPD). In more recent years, LTBI treatment is indicated to any HIV+ individual with a CD4< 350 cells/mm3, regardless of a PPD or Interferon Gamma Release Assay result. For those with a CD4 cell count > 350, LTBI treatment is indicated if a PPD or Interferon Gamma Release Assay test is positive.[41]

Screening for TB is only indicated if a patient develops signs/symptoms that are compatible with TB, such as fever, weight lost, night sweats, and cough, among others. There is no routine testing for TB in the guidelines, unless signs/symptoms suggestive of TB are present.

For the present study, CHI individuals who had at least 1 available follow-up visit and 1 HIV- RNA and CD4/CD8 ratio result after ART initiation were considered eligible. For the AHI or RHI cohort, clinical visits were held at enrolment, after 1 and 3 months, and every 6 months thereafter. CD4, CD8 cell counts, and viral loads were obtained at baseline (within 30 days of diagnosis) and at every follow-up visit during the study period.

Study participants were censored at the earliest of death, virologic failure (defined as a viral load ≥1000 copies/mL at least 24 weeks postbaseline), achievement of CD4/CD8 ≥1, or administrative censoring on December 31, 2020, whichever occurred first.

Outcomes

The main outcome was time from ART initiation (baseline) to CD4/CD8 ratio normalization, defined as the first CD4/CD8 ratio ≥1.[42] We chose this definition because a ratio <1 is associated with immune dysfunction markers[9] and for comparability with earlier CD4/CD8 normalization studies. We compared patients with AHI and RHI or CHI by CD4 count at baseline: ≥350 and <350 cells/mm^3.

Statistical Methods

Descriptive statistics were calculated among patients by timing of the HIV infection group (AHI, RHI, or CHI), including median and interquartile range (IQR) for continuous measures and percentages for categorical measures. Between-groups comparisons were made using Kruskal–Wallis and χ^2 tests for continuous and categorical variables, respectively. The following variables were explored: age in years (continuous), race (white [reference category] vs black/mixed), gender (cisgender MSM [reference category] vs TGW), years of schooling (≥12 years [reference category] vs <12 years of education), active syphilis (no [reference category] vs yes), and chronic hepatitis B (no [reference category] vs yes) coinfections at enrolment. We create the variable "TB Status," which includes 3 categories: "Prior/active TB diagnosis and treatment," "LTBI treatment," and "No TB or LTBI treatment."

Kaplan–Meier plots and the log-rank test were used to analyze the time to CD4/CD8 ratio ≥1. Cox proportional hazards regression models were fitted to estimate predictors, relative hazards, and 95% confidence intervals of hazard of achieving CD4/CD8 ratio ≥1. Variables with P values <0.20 in univariable analysis were included in multivariable analyses, removing terms of least significance until a final model was reached. The final model includes only variables with P values ≤0.05. R software version 3.0.3[43] was used for all statistical analyses.

Ethical Considerations

This study was approved by the ethics committee of the Instituto Nacional de Infectologia Evandro Chagas (INI)-Fiocruz (CAAE: 36859614.8.0000.5262). All participants provided written informed consent.

RESULTS

Demographic and Clinical Characteristics

Between August 2013 and December 2019, a total of 605 cisgender MSM and TGW initiated care at INI. Of those, 55 were excluded because of missing data on the baseline CD4/CD8 ratio, all of them were chronically infected (Fig. 1). From the 550 participants included, 65 (11.8%) were classified as AHI, 35 (6.4%) as RHI, and 450 (81.8%) as CHI. Of patients with CHI, 257 (46.7%) had CD4 cell counts ≥350 and 193 (35.1%), <350 cells/mm^3. No AHI or RHI participants had a CD4 cell count <350. Of all participants, 79.2% were cisgender MSM, 20.8% TGW and 69.4% black and mixed race. The overall median age was 27.1 (IQR: 23.7–33.7). They contributed to a median follow-up time of 1.8 years (IQR 0.9–3.2) and a total of 1305 person-years. Of the 550 participants included, 33(6.0%) were censored because of virologic failure, 12 (2.2%) because of death, and 280 (50.9%) because of administrative censoring at the end of study follow-up. Overall, 24.1% of the study population had active syphilis at ART initiation, and this did not vary significantly among the study groups. Nine individuals used LTBI treatment in the AHI group, 7 in the RHI, 31 in the CHI with CD4 ≥350 cells/mm^3, and 20 in the CHI with CD4 <350 cells/mm^3. Overall, 53 (9.6%) individuals (all with chronic HIV) had prior/concomitant TB (25 cases classified as prior TB and 28 cases as active TB) at time of ART initiation (11 with CD4 ≥350 cells/mm^3; 42 with CD4 <350 cells/mm^3; Table 1).

ART Initiation, Viral Loads, CD4 and CD8 Counts

Among study participants with AHI and RHI, the median time from estimated diagnosis date to ART initiation differs between groups (P < 0.001), and was 3 days (IQR: 2–16) and 15 days (IQR: 6.5–46), respectively; whereas for CHI participants, it was 45 days for CD4 ≥350 (IQR:16–112) and CD4 <350 (IQR: 21–87) groups. The median CD4 count at enrollment was 582 cells/mm^3 (IQR: 399–845), 588.5 cells/

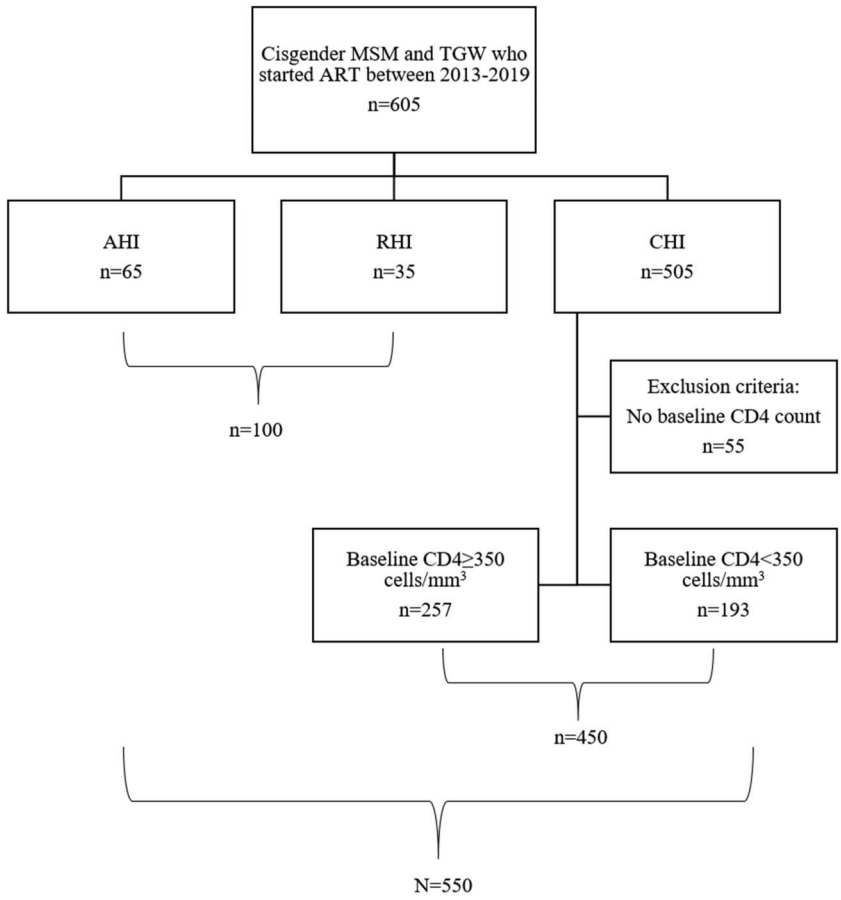

FIGURE 1. Flowchart for the selection of the study population. Total number of participants, and those included and excluded in each of the 3 study groups are shown.

mm^3 (IQR 439–679), 553 cells/mm^3 (IQR: 433–773), and 160 cells/mm^3 (IQR 71–255) for AHI, RHI, and CHI with baseline CD4 cell counts ≥350 and <350, respectively. The median CD4/CD8 ratio was 0.7 (IQR: 0.4–1.4), 0.53 (IQR: 0.3–0.7), 0.52 (IQR: 0.4–0.7), and 0.18 (IQR: 0.1–0.3) for individuals with AHI, RHI, and CHI with baseline CD4 cell counts ≥350 and <350, respectively. The median HIV viral load was 4.9 log10 copies/mL (IQR: 3.9–5.8), 4.6 log10 copies/mL (IQR: 3.8–5.4), 4.2 log10 copies/mL (IQR: 3.5–4.7), and 5.0 log10 copies/mL (IQR: 4.3–5.4) for AHI, RHI, and CHI with baseline CD4 cell counts ≥350 and <350, respectively. The ART regimen included a dual nucleoside reverse-transcriptase inhibitor (NRTI; tenofovir/lamivudine), combined with an integrase strand transfer inhibitor (INSTI) for 281 individuals (51.1%), an NNRTI for 195 individuals (35.5%), or a ritonavir-boosted protease inhibitor (PI) for 74 individuals (13.5%), respectively (Table 1).

Time to CD4/CD8 Ratio Normalization

We excluded for this analysis all enrolled participants that had a CD4/CD8 ratio ≥1 at baseline (n = 16 [24.6%] with AHI, 3 (8.6%) with RHI, 16 (6.2%) with CHI with CD4 ≥350 and 1 (0.5%) with CHI CD4 <350).

As shown in Figure 2, one-year from ART initiation, the probability of achieving CD4/CD8 normalization was 58% AHI patients and 53% of RHI compared with 20% and 8% of CHI patients with baseline CD4 ≥350 and CD4 <350, respectively. After 4 years of follow-up, the probability of achieving CD4/CD8 ratio ≥1 was 40% and 27% among CHI with baseline CD4 ≥350 and CD4 <350, respectively.

The median time to CD4/CD8 normalization among individuals with AHI and RHI was 5.7 (1.1–16.8) months and 7 (2.5–40.9) months, respectively. In contrast, the median time to CD4/CD8 normalization among individuals with CHI with baseline CD4 ≥350 was 20.8 months (12.7–37.3) (Table 1). At the end of the study period, less than 50% of individuals with CHI had achieved a CD4/CD8 ratio ≥1. Subgroups with higher baseline CD4/CD8 ratios had shorter times to normalization than those with lower baseline ratios ($P < 0.0001$; Fig. 2).

At the end of the follow-up period, the proportion of participants with Fiebig II, III, IV, V, and VI who achieved a CD4/CD8 ratio ≥1 was 100%, 60%, 85%, 67%, and 69%, respectively, with significant difference between groups ($P < 0.001$). Among those with CHI with CD4 cell counts ≥ and <350, it was 34% and 17%, respectively, also differing between groups ($P < 0.001$; Fig. 3).

Unadjusted Cox model results for likelihood of CD4/CD8 ratio normalization (Table 2) were consistent with Kaplan–Meier curves (Fig. 2), with a hazard ratio (HR) comparing AHI to CHI patients with baseline CD4 <350 of 6.97 (95% CI: 4.33 to 11.24; $P < 0.001$), RHI patients to CHI with baseline CD4<350 of 5.21

TABLE 1. Socio Demographic and Clinical Characteristics of Participants (N = 550) Initiating ART Stratified by Acute, Recent, or Chronic (CD4 Cell Counts ≥350, <350) HIV Infection, 2013–2019

	Total, N = 550	AHI, n=65 (11.8%)	Recent HIV Infection, n = 35 (6.4%)	Chronic HIV Infection, n = 450 (81.8%)		
	n (%)	n (%)	n (%)	CD4 ≥350 n = 257(46.7%)	CD4 <350 n = 193 (35.1%)	*P*
Characteristic				n (%)	n (%)	
Gender						0.0154*
Cisgender MSM	435/549 (79.2)	55/65 (84.6)	33/35 (94.3)	190/256 (74.2)	157/193 (81.3)	
TGW	114/549 (20.8)	10/65 (15.4)	2/35 (5.7)	66/256 (25.8)	36/193 (18.7)	
Age, years median (IQR)	27.1 (23.7–33.7)	27.2 (23.9–32.8)	27.7 (26.0–32.7)	25.4 (22.4–31.3)	30.1 (25.0–37.9)	<0.001†
Race/ethnicity						0.0122*
Black/mixed	374/539 (69.4)	38/65 (58.5)	22/33 (66.7)	194/255 (76.1)	122/187 (65.2)	
White	165/539 (30.6)	27/65 (41.5)	12/33 (36.4)	61/255 (23.9)	65/187 (34.8)	
Schooling						<0.001*
≥12 yrs	115/486 (23.7)	21/63 (33.3)	18/35 (51.4)	44/224 (19.6)	32/164 (19.5)	
<12 yrs	371/486 (76.3)	42/63 (66.7)	17/35 (48.6)	180/224 (80.4)	132/164 (80.5)	
Active syphilis‡	90/374 (24.1)	10/56 (17.9)	4/25 (16)	43/166 (25.9)	33/127 (26.0)	0.4516*
Chronic HBV‡	8/508 (1.6)	0/62 (0.0)	0/33 (0.0)	1/237 (0.4)	7/176 (4.0)	0.038*
ART regimen						<0.001*
INSTI	281/550 (51.1)	29/65 (44.6)	4/35 (11.4)	158/257 (61.5)	90/193 (46.6)	
PI	74/550 (13.5)	17/65 (26.2)	3/35 (8.6)	19/257 (7.4)	35/193 (18.1)	
NNRTI	195/550 (35.5)	19/65 (29.2)	28/35 (80.0)	80/257 (31.1)	68/193 (35.2)	
ART initiation, days median (IQR)	36 (10–83)	3 (2–16)	15 (6.5–46)	45 (16–112)	45 (21–87)	<0.001†
CD4 count cells/mm^3 median (IQR)	424 (237–633)	582 (399–845)	588.5 (439–679)	553 (433–773)	160 (71–255)	<0.001†
CD8 count cells/mm^3 median (IQR)	1043 (696.5–1473)	940 (545.5–1609)	1243 (814–1651.25)	1124.5 (895–1528.75)	912.5 (545.5–1207.6)	<0.001†
CD4/CD8 median (IQR)	0.41 (0.2–0.7)	0.7 (0.4–1.1)	0.53 (0.3–0.7)	0.52 (0.4–0.7)	0.18 (0.1–0.3)	<0.001†
Viral load $\log_{10}$copies/mL median (IQR)	4.5 (3.8–5.2)	4.9 (3.9–5.8)	4.6 (3.8–5.4)	4.2 (3.5–4.7)	5.0 (4.3–5.4)	<0.001†
Time to CD4/CD8 normalization, months (IQR)	20.1 (10.1–37.0)	5.7 (1.1–16.8)	7 (2.5–40.9)	20.8 (12.7–37.3)	25.3 (14.8–38.5)	<0.001†
TB status						<0.001*
Prior/active TB diagnosis/ treatment	53/550 (9.6)	0/65 (0.0)	0/35 (0.0)	11/257 (4.3)	42/193 (21.8)	
LTBI treatment	67/550 (12.7)	9/65 (13.8)	7/35(20.0)	31/257 (12.1)	20/193 (10.4)	
No TB or LTBI treatment	430/550 (78.2)	56/65 (86.2)	28/35 (80.0)	215/257 (83.7)	131/193 (67.9)	
Censored						
Deaths	12/550 (2.2)	0/65 (0.0)	1/35 (2.9)	0/257 (0.0)	11/193 (5.7)	
Viral load failure	33/550 (6.0)	7/65 (10.7)	3/35 (8.6)	15/257 (5.8)	8/193 (4.1)	
Administrative§	280/550 (50.9)					

*χ^2 test.
†Kruskal–Wallis test·
‡At baseline.
§Right-censoring because of the end of the study observation period, at December 31, 2020.
HBV, Hepatitis B; INSTI, integrase strand transfer inhibitor; IP, protease inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor.

(95% CI: 3.03 to 8.96; $P < 0.001$) and CHI with baseline CD4 ≥350 to CHI with baseline <350 of 2.05 (95% CI: 1.37 to 3.07; $P = 0.001$; Table 2).

In the multivariable model, compared with CHI with CD4 <350, AHI was associated with a seven-fold increased likelihood of CD4/CD8 ratio normalization (HR 7.18; 95% CI: 4.55 to 11.34; $P < 0.001$), followed by RHI (HR 4.99; 95% CI: 2.92 to 8.51; $P < 0.001$) and CHI with CD4 ≥350 cells/mm3 (HR 2.03; 95% CI: 1.35 to 3.05; $P = 0.001$). Overall, LTBI treatment was significantly associated with higher likelihood of CD4/CD8 ratio normalization (HR 1.57; 95% CI: 1.09 to 2.26; $P = 0.015$). Age, race/ethnicity, gender, schooling, viral load, prior/concomitant TB diagnosis/ treatment, and all other evaluated coinfections were not statistically associated with CD4/CD8 ratio normalization (Table 2).

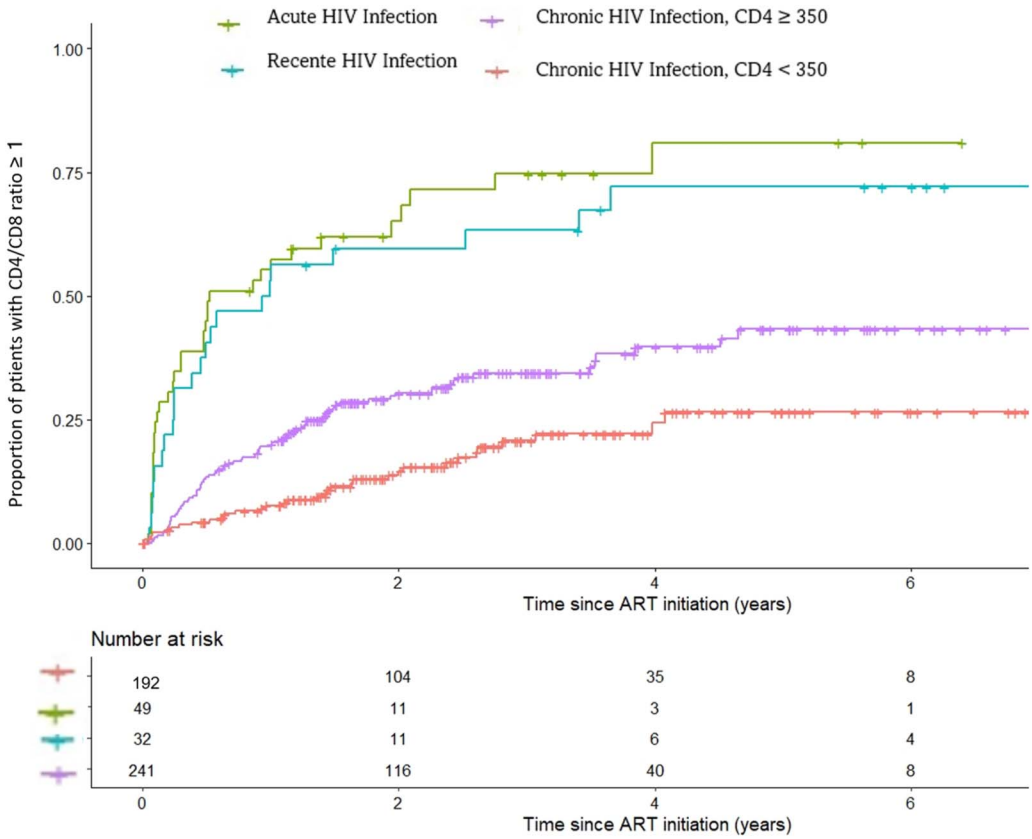

FIGURE 2. Kaplan–Meier curves. Time from ART initiation to CD4/CD8 ratio normalization stratified by acute, recent, and chronic HIV infection according to baseline CD4 cell count, 2013–2019.

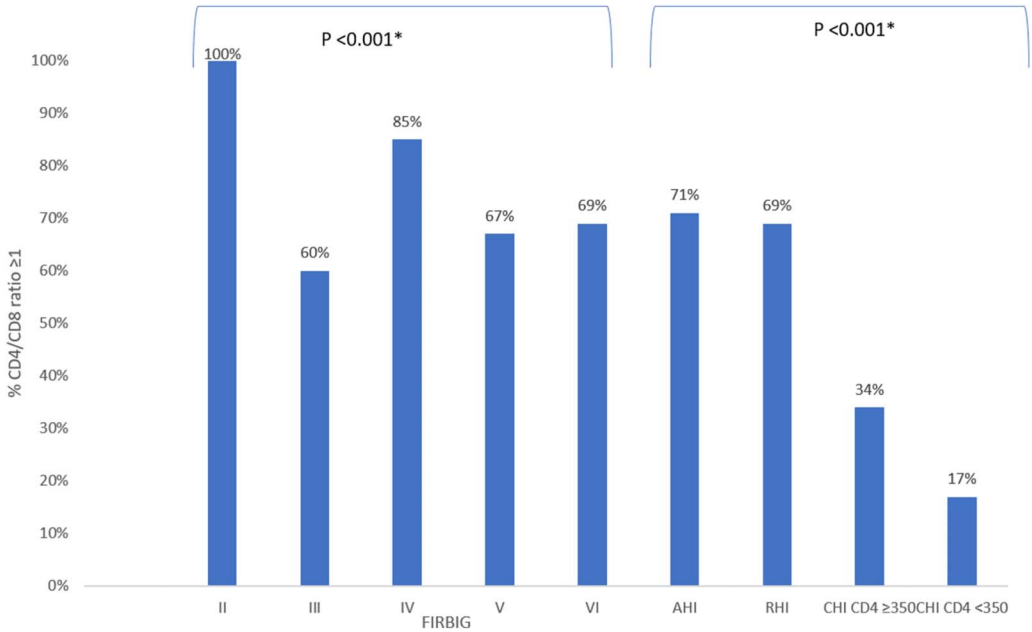

FIGURE 3. Proportion of patients who achieved CD4/CD8 ratio ≥ 1 by Fiebig stage and study group. The percentage of patients with a CD4/CD8 ration ≥1 is shown for Fiebig laboratory staging of early HIV infection and study groups. *χ^2 test.

TABLE 2. Hazard Ratios for time to CD4/CD8 Ratio Normalization

	Unadjusted HR		Adjusted HR	
Variable	**HR (CI 95%)**	***P***	**HR (CI 95%)**	***P***
HIV infection group				
CHI With CD4 <350	1 (ref.)		1 (ref.)	
CHI With CD4 ≥350	2.05 (1.37 to 3.07)	0.001	2.03 (1.35 to 3.05)	0.001
RHI	5.21 (3.03 to 8.96)	<0.001	4.99 (2.92 to 8.51)	<0.001
AHI	6.97 (4.33 to 11.24)	<0.001	7.18 (4.55 to 11.34)	<0.001
Age per 10-year increase (continuous)	0.87 (0.73 to 1.04)	0.123	—	
Race/ethnicity				
White	1 (ref)		—	
Black/Mixed	1.29 (0.96 to 1.77)	0.122	—	
Gender				
Cisgender MSM	1 (ref)		—	
TGW	1.06 (0.75 to 1.48)	0.753	—	
Schooling				
≥12 years	1 (ref)		—	
<12 years	1.14 (0.80 to 1.61)	0.475	—	
Viral load $\log_{10}$ copies/mL (continuous)	1.10 (0.97 to 1.26)	0.144	—	
Syphilis				
No	1 (ref)		—	
Yes	1.01 (0.68 to 1.50)	0.964	—	
Chronic HBV				
No	1(ref)		—	
Yes	0.77 (0.25 to 2.41)	0.653	—	
Status TB				
No diagnosis/treatment	1 (ref)		—	
Prior/Concomitant TB diagnosis/treatment	0.36 (0.18 to 0.70)	0.003	—	
LTBI treatment	1.60 (1.12 to 2.30)	0.010	1.57 (1.09 to 2.26)	0.015

DISCUSSION

In this longitudinal study, we found that cisgender MSM and TGW living with HIV (PLWH) who initiated ART during AHI and RHI were more likely to achieve CD4/CD8 ratio normalization compared with those who started ART during CHI with CD4 cell counts ≥350 and <350 cells/mm^3. Our results are the first in a large LMIC cohort of PLWH to show that ART initiation at early stages of HIV infection positively affect CD4/CD8 normalization, which has been associated with immune activation, senescence, and systemic inflammation.[44,45] Moreover, our results suggest that LTBI treatment was associated with the CD4/CD8 normalization, increasing 57% in the chance of recovery, whereas diagnosis and treatment of prior or concomitant active TB at time of ART initiation was associated with decreased likelihood for the study population, compared with the reference group (CHI with CD4 <350).

The baseline CD4/CD8 ratio was higher in AHI individuals, with 24.6% having a CD4/CD8 ratio ≥1 in this group compared with only 8.6% in the RHI group. However, both groups had CD4/CD8 ratios lower than those values reported for the Brazilian general population.[46] Similar results have been described from a Thai AHI cohort,[44] underscoring the rapidity of immune damage caused by HIV. The CD4/CD8 ratio has been proposed as a unique marker for immune dysfunction in HIV, because it reflects the CD4 cell count depletion and the activation and proliferation of CD8 T cells in HIV infection.[47]

Our results of higher likelihood of CD4/CD8 ratio normalization occurring in PLWH who initiate ART early in infection are consistent with similar studies from other settings. A substudy of the SPARTAC trial[48,49] showed a higher probability of CD4/CD8 ratio normalization when ART was initiated within 6 months of seroconversion. Data from a cohort in San Diego, USA revealed that very early ART within 40 days of the estimated date of infection in Fiebig I-II acutely infected patients was associated with a significant increase in CD4/CD8 ratio.[50] A 1-year longitudinal evaluation of 83 patients from North Carolina, USA starting ART within 120 days after the estimated date of infection also displayed a better reconstitution of CD4/CD8 ratio compared with chronically infected subjects.[19] In addition, more recent data from a large multisite cohort from Italy confirmed that early ART, defined as ART introduced within 3 months from AHI, has a beneficial effect on immune function recovery.[51] Conversely, in a single-center cohort study conducted in Bangkok between 2009 and 2020 of 483 AIH patients who began ART during Fiebig I-V, it was observed that early HIV disease dynamics predicted an unfavorable CD4/CD8 T-cell ratio recovery after ART, suggesting that adjunctive strategies should be considered to achieve immune normalization.[52]

Brazil was the first LMIC to adopt the "treat all" recommendation and to provide HIV pre-exposure prophylaxis (PrEP) for those with high HIV vulnerability free of charge through the national public health system. Yet, these interventions have been insufficient to halt the epidemic. In a study[53] conducted in Rio de Janeiro, Brazil, including 3000 cisgender MSM and TGW at a large HIV prevention and care service, the estimated annualized HIV incidence rate was 7.35% (6.65% for cisgender MSM and 9.16% for TGW). This unacceptably high incidence rate suggests that HIV continues to spread within these vulnerable populations in 1 of the largest urban areas of the country. These phases are characterized by very high levels of HIV-RNA load, greatly amplifying HIV transmission.[15,54] Rapid ART initiation during AHI and RHI represent a unique opportunity to reduce onward HIV transmission. Furthermore, long-lived reservoirs of virus are established early on, representing a major obstacle to achieving HIV eradication.[17]

We found that PLWH who received LTBI treatment were more likely to achieve CD4/CD8 ratio normalization after controlling for timing of ART relative to HIV infection. LTBI has been associated with elevated interferon-gamma levels, a pro-inflammatory cytokine that in part reflects lymphocyte activation.[55] In addition, T-cell activation, as measured by CD38 and HLA-DR expression on $CD4^+$ and $CD8^+$ T lymphocytes, has been found elevated in latent and active TB patients.[27] The TEMPRANO study[32] showed that 6-month LTBI treatment had a durable protective effect in reducing all-cause mortality in PLWH on ART, regardless of baseline CD4 levels. LTBI treatment and ART had an additive effect, with the maximal benefit in patients who had both therapies, which suggests that receiving both is a better option than receiving either therapy alone. In a recent meta-analysis,[56] PLWH on LTBI treatment with ART also tended to have a lower risk of death than PLWH receiving ART without LTBI treatment. Furthermore, results from the THRio study[30] showed a higher TB incidence among all patients without LTBI treatment, including those with high baseline CD4 counts with negative or unknown tuberculin skin test, indicating that patients receiving ART remain at high risk of TB. The independent and synergistic effects of ART and LTBI treatment transcends preventing TB occurrence, being critical to maximize ART-related immune recovery.

One major strength of our study was the prospective follow-up of patients treated closely within observed seroconversion. Notably, TB remains the leading cause of HIV-related morbidity and mortality in LMICs and we were able to investigate the effect of TB/LTBI on ART-related immune recovery.

However, our results are limited by relatively small sample sizes, single-center design, and exclusion of women living with HIV. The sample size limited our ability to compare the effect of TB/LTBI between groups, i.e. all cohort patients with active TB were chronically infected. The restriction of our analysis to patients with available baseline CD4/CD8 ratios may have introduced selection bias. Finally, we could not adjust for adherence in our analyses. The improved adherence typically observed among older PLWH when compared with younger PLWH with similar CD4/CD8 ratios,[57] even with sustained suppression, may affect immune recovery.

In summary, our study contributes to the knowledge that initiating ART early during AHI may offer an opportunity to mitigate immune damage. Efforts to implement HIV diagnosis and ART initiation during AHI are critical to amplify ART benefits. Larger studies are needed to further investigate the impact of LTBI treatment on ART-related immune recovery and clinical outcomes in LMIC.

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