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Permalink

<https://escholarship.org/uc/item/89x976q7>

Journal

The Journal of Infectious Diseases, 222(Supplement_1)

ISSN

0022-1899

Authors

Fichtenbaum, Carl J
Ribaldo, Heather J
Leon-Cruz, Jorge
et al.

Publication Date

2020-07-09

DOI

10.1093/infdis/jiaa259

Peer reviewed

Patterns of Antiretroviral Therapy Use and Immunologic Profiles at Enrollment in the REPRIEVE Trial

Carl J. Fichtenbaum,^{1,6} Heather J. Ribaldo,² Jorge Leon-Cruz,² Edgar T. Overton,³ Markella V. Zanni,⁴ Carlos D. Malvestutto,⁵ Judith A. Aberg,⁶ Emma M. Kileel,⁴ Kathleen V. Fitch,⁴ Marije Van Schalkwyk,⁷ Nagalingeswaran Kumarasamy,⁸ Esteban Martinez,⁹ Breno Riegel Santos,¹⁰ Yvetot Joseph,¹¹ Janet Lo,⁴ Sue Siminski,¹² Kathleen Melbourne,¹³ Craig A. Sponseller,¹⁴ Patrice Desvigne-Nickens,¹⁵ Gerald S. Bloomfield,¹⁶ Judith S. Currier,¹⁷ Udo Hoffmann,¹⁸ Pamela S. Douglas,¹⁹ and Steven K. Grinspoon⁴; on behalf of the REPRIEVE Investigators^a

¹Division of Infectious Diseases, University of Cincinnati College of Medicine, Cincinnati, Ohio, USA, ²Center for Biostatistics in AIDS Research, Harvard T.H. Chan School of Public Health, Boston, Massachusetts, USA, ³Division of Infectious Diseases, University of Alabama at Birmingham School of Medicine, Birmingham, Alabama, USA, ⁴Metabolism Unit, Massachusetts General Hospital and Harvard Medical School, Boston, Massachusetts, USA, ⁵Division of Infectious Diseases, Ohio State University Medical Center, Columbus, Ohio, USA, ⁶Department of Medicine, Icahn School of Medicine at Mount Sinai, New York, New York, USA, ⁷Family Centre for Research with Ubuntu, Division of Adult Infectious Diseases, Stellenbosch University and Tygerberg Hospital, Cape Town, South Africa, ⁸Infectious Diseases Medical Centre, Voluntary Health Services, Chennai, India, ⁹Hospital Clinic and University of Barcelona, Barcelona, Spain, ¹⁰Infectious Diseases Service, Hospital Nossa, Senhora da Conceição/GHC, Porto Alegre, Brazil, ¹¹Les Centres GHESKIO, Port-au-Prince, Haiti, ¹²Frontier Science and Technology Foundation, Amherst, Massachusetts, USA, ¹³HIV Medical Sciences, Gilead Sciences, Foster City, California, USA, ¹⁴Kowa Pharmaceuticals America, Montgomery, Alabama, USA, ¹⁵National Heart, Lung and Blood Institute, Baltimore, Maryland, USA, ¹⁶Department of Medicine, Duke Global Health Institute and Duke Clinical Research Institute, Duke University, Durham, North Carolina, USA, ¹⁷Division of Infectious Diseases, University of California-Los Angeles, Los Angeles, California, USA, ¹⁸Cardiac MR PET CT Program and Department of Radiology, Massachusetts General Hospital, Boston, Massachusetts, USA, and ¹⁹Duke University Medical Center, Durham, North Carolina, USA

Background. Patterns of antiretroviral therapy (ART) use and immunologic correlates vary globally, and contemporary trends are not well described.

Methods. The REPRIEVE trial (Randomized Trial to Prevent Vascular Events in HIV) enrolled persons with human immunodeficiency virus (HIV) who were aged 40–75 years, receiving ART, and had low-to-moderate cardiovascular disease risk. ART use was summarized within Global Burden of Disease (GBD) super-regions, with adjusted linear and logistic regression analyses examining associations with immune parameters and key demographics.

Results. A total of 7770 participants were enrolled, with a median age of 50 years (interquartile range, 45–55 years); 31% were female, 43% were black or African American, 15% were Asian, 56% had a body mass index >25 (calculated as weight in kilograms divided by height in meters squared), and 49% were current or former smokers. The median CD4 T-cell count was 620/μL (interquartile range, 447–826/ μ L), and the median duration of prior ART use, 9.5 years (5.3–14.8) years. The most common ART regimens were nucleoside/nucleotide reverse-transcriptase inhibitor (NRTI) plus nonnucleoside reverse-transcriptase inhibitor (43%), NRTI plus integrase strand transfer inhibitor (25%), and NRTI plus protease inhibitor (19%). Entry ART varied by GBD region, with shifts during the trial enrollment period. In adjusted analyses, entry CD4 cell count and CD4/CD8 ratio were associated with GBD region, sex, entry regimen, duration of ART, and nadir CD4 cell count; CD4 and CD8 cell counts were also associated with body mass index and smoking status.

Conclusions. There were substantial variations in ART use by geographic region and over time, likely reflecting the local availability of specific medications, changes in treatment guidelines and provider/patient preferences. The analyses of CD4 cell counts and CD4/CD8 ratios may provide valuable insights regarding immune correlates and outcomes in people living with HIV.

Clinical Trials Registration. NCT02344290.

Keywords. HIV; statins; pitavastatin calcium; antiretroviral therapy; CD4 cell count; CD4/CD8 ratio; REPRIEVE; cardiovascular disease.

Approximately 37 million people globally are living with human immunodeficiency virus (HIV) [1]. The success of antiretroviral therapy (ART) has resulted in longer survival for people with HIV (PWH) [2]. Worldwide, >24.5 million PWH are now

receiving ART [3]. The current era of ART has seen major shifts in ART availability and prescribing patterns, along with changes in key patient characteristics, including body mass index (BMI; calculated as weight in kilograms divided by height in meters squared). Moreover, the availability of new antiretrovirals is not uniform across worldwide regions, and relatively little is known regarding the changing patterns of ART use globally especially in the aging population. Finally, there is limited information on contemporary patterns of ART use and how such patterns relate to other factors like immune status.

The current analysis leveraged detailed data acquired on ART use and immune status across a global cohort of PWH. The

^aSee Acknowledgments for full list of REPRIEVE Investigators.

Correspondence: Carl J. Fichtenbaum, Division of Infectious Diseases, University of Cincinnati College of Medicine, 231 Albert Sabin Way, PO Box 670560, Cincinnati, OH 45267-0560 (fichtecj@ucmail.uc.edu).

The Journal of Infectious Diseases® 2020;222(S1):S8–19

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REPRIEVE trial (Randomized Trial to Prevent Vascular Events in HIV) was designed as the first large-scale, long-term randomized trial to assess a primary cardiovascular disease (CVD) prevention strategy among PWH, with low-to-moderate risk for CVD according to traditional risk factors, using statin therapy [4, 5]. The trial was initiated to address the reported increased CVD and CVD mortality rates among PWH, contemporaneous with overall improvements in AIDS-related complications and life expectancy [6–8]. The trial enrolled 7770 PWH across 5 continents between 2015 and 2019. The large size of the trial and diversity of the enrolled population allows for the opportunity to assess differences in HIV-specific elements, such as patterns of ART usage, as well as immunologic characteristics and correlates. Further context for REPRIEVE and methods on ascertainment of key data elements is provided in the introductory article within this supplement [9].

The aims of this analysis were to characterize patterns of ART use and immunologic characteristics over the 4-year period of enrollment in REPRIEVE and to examine indices of immunologic health in relation to key participant characteristics across regions. We hypothesized that there would be differences in the patterns of ART usage over time and that sociodemographic and potentially modifiable health factors would be associated with different immunologic profiles. Specifically, we investigated whether there were regional differences in CD4 and CD8 T-cell counts and how these might relate to other health parameters, demographics and patterns of ART use. Understanding how specific ART regimens affect CVD risk is particularly germane because clinical outcomes are being documented within REPRIEVE. Furthermore, it is the complex interplay between host characteristics, environmental exposures, the immune system, HIV, antiretrovirals, and other factors that affects CVD risk and the development of CVD. Information ensuing from these analyses will not only prove critical to contextualizing the longitudinal results of the REPRIEVE trial but will also help inform our understanding of changing patterns of ART use and correlates of immune function among PWH across the globe.

METHODS

Sites and Study Population

The REPRIEVE trial (NCT02344290) is a prospective, double-blind, randomized, placebo-controlled, multicenter, phase III efficacy study with 2 arms (pitavastatin calcium [4 mg/d] vs placebo), enrolling PWH currently taking ART [4, 5], at >100 sites in 12 countries. The primary entry criteria included PWH ≥ 40 and ≤ 75 years of age, taking any combination ART regimen for ≥ 6 months before study entry, with CD4 cell counts $>100/\mu\text{L}$ [4, 5].

At trial entry, information on medical history was ascertained, including cardiovascular risk history, physical examination, and medication history. Laboratory values were obtained as part of the trial screening and entry process or abstracted

from clinical care records (see supplementary methods in Grinspoon et al [9]).

Antiretroviral Regimen Definitions

Antiretroviral regimen histories were collected at entry to include estimates of total duration of ART exposure, duration of exposure to protease inhibitors (PIs), thymidine analogues, tenofovir disoproxil fumarate (TDF), and abacavir. The details of the current ART regimen at trial enrollment (including estimated start date) is reported as the entry regimen. For this analysis, entry regimen classes were categorized by use of nucleoside/nucleotide reverse-transcriptase inhibitors (NRTIs), nonnucleoside reverse-transcriptase inhibitors (NNRTIs), PIs, and integrase strand transfer inhibitors (INSTIs). For simplicity, boosting agents for PIs, such as ritonavir and cobicistat, are not described.

Statistical Analyses

Distributions of entry regimens are shown graphically, stratified according to the Global Burden of Disease (GBD) super-region [10] and within key demographic factors, including duration of current regimen, self-reported natal sex and race, and calendar date of enrollment. Distributions of immunologic parameters at study entry—CD4 cell counts, CD8 cell counts, and CD4/CD8 ratio (≥ 1.0 or <1.0)—are examined descriptively and by means of adjusted linear (CD4 and CD8 cell counts) and logistic regression (low CD4/CD8 ratio) analyses to evaluate associations with enrollment region, ART exposures, and key participant characteristics. Given the complex patterns of these covariates and their potential confounding and collinearity across and within enrollment regions, modeling was repeated in exploratory subgroup analyses by GBD region, natal sex, and total duration of prior ART exposure; targeted interaction tests were evaluated. Owing to collinearity between GBD region and race, multivariable analyses were adjusted only for race in the high-income regions. As a result of this parameterization, the reference comparator for enrollment region is high-income white race. Given the large sample size and high power to detect small effect sizes, formal statistical comparisons are limited to regression analyses, with inference based on very low type 1 error ($P < .001$) and clinically meaningful estimated effect sizes. Data analysis was conducted using SAS software, version 9.4 for UNIX (SAS Institute).

Ethics Statement

Each clinical research site obtained institutional review board/ethics committee approval and any other applicable regulatory entity approvals. Participants were provided with study information, including discussion of risks and benefits and were asked to sign the approved declaration of informed consent.

RESULTS

Study Population

From March 2015 through July 2019, a total of 7770 participants enrolled. The median age was 50 years (interquartile

range [IQR], 45–55 years). Thirty-one percent of participants were natal female, and 2% reported identifying on the transgender spectrum. The overall racial distribution of participants was 43% black or African-American, 35% white, 15% Asian, and 7% other races. In North America (Canada, United States, and Puerto Rico), 18% were Latino or Hispanic. The median CD4 cell count at entry was 620/ μ L (IQR, 447–826/ μ L). The HIV-1 RNA level was below local assay quantification limits in 87% of participants, and of the remaining 13%, 75% had viral loads \leq 200 copies/mL (See Grinspoon et al [9, table 1] for further description of the cohort).

ART Exposure

The median duration of prior oral ART exposure at REPRIEVE entry was 9.5 years (IQR, 5.3–15 years). Prior exposure to PIs was reported in 47% of participants (median 7.0 years; IQR, 3.6–11 years), to thymidine analogues in 49% (5.9 years; 3.0–9.9 years), and to TDF in 85% (5.5 years; 3.0–8.7 years) (Table 1).

Entry ART regimens included NRTIs plus NNRTIs (47%); NRTIs plus INSTIs (25%); and NRTIs plus PIs (with or without boosting agents) (19%); 6% and 3% of participants, respectively, were taking other NRTI-containing and NRTI-sparing regimens (these regimens primarily included either a PI or an NNRTI taken with an INSTI, with or without an NRTI). The median regimen duration at study entry was 2.3 years (IQR, 0.8–5.2 years); 10% of participants had been taking this regimen for $>$ 8.8 years (Table 1). The most commonly used agents in the NRTI class, were Lamivudine (3TC) or Efavirenz (EFV) in combination with TDF (in 61%), tenofovir alafenamide (TAF) (15%), or and abacavir (12%), respectively. In the NNRTI class, the most commonly used agents were efavirenz (68%), rilpivirine (16%), and nevirapine (13%). The most commonly used PIs were darunavir (44%), atazanavir (40% (with or without boosting agents), and lopinavir-ritonavir (15%). In the INSTI class, dolutegravir (DTG) (50%), elvitegravir (34%), and raltegravir (14%) were used most commonly.

There were important differences in entry regimen by enrollment region (Figure 1). In particular, there was greater regimen diversity among participants enrolled in the high-income region, followed by the Latin America and Caribbean region, with clear evolution of regimens over time that was less apparent in other regions (Figure 2). The use of INSTIs was almost exclusive to the high-income region, with DTG and elvitegravir the most common choices. The amount of raltegravir use waned over the enrollment period, with emerging use of bictegravir (Supplementary Figure 1A). Within the NRTI class, TDF use predominated across all regions (Supplementary Figure 2). TAF was used increasingly over the course of enrollment in the high-income region (Supplementary Figure 1B). There were stark differences in PI use across enrollment regions, with darunavir far more common in the high-income region, with some emerging use in Latin America and the Caribbean and

South Asia (India) (Figure 1D). Aazanavir was used across all regions and lopinavir/ritonavir predominated in sub-Saharan Africa. Efavirenz was the most commonly used NNRTI across all regions (Figure 1E). Rilpivirine use increased over the enrollment period in the high-income and Southeast Asia GBD super-regions (Supplementary Figure 3) and nevirapine was a common NNRTI choice in other regions.

Controlling for enrollment region, ART regimen at entry also varied by duration prior ART exposure, BMI and nadir CD4 cell count (Supplementary Figures 4–6). Given the current focus on INSTI use and its association with weight gain, the trend showing a higher percentage of INSTI-based regimens associated with higher BMI (Supplementary Figure 5) was examined further with stratification by duration of entry regimen. This analysis revealed the trend was strongest among those on their entry regimen for less than 1 year (Supplementary Figure 7). Because uptake of widespread INSTI use is relatively recent, it is noted that the numbers of participants on an INSTI regimen for $>$ 3 years at the time of REPRIEVE entry is very low, and no measure of precision is presented to allow any formal inference.

Immunologic Profiles

The median CD4 cell count at entry was 620/ μ L (IQR, 447–826/ μ L), the median CD8 cell count was 779/ μ L (564–1032/ μ L), and the median CD4/CD8 ratio was 0.81 (0.56–1.15) (Table 2). While overlapping across regions, the distributions of CD4 and CD8 cell counts were slightly higher in the high-income and Latin America and Caribbean regions. The CD4/CD8 ratios were highest among participants in Southeast and East Asia (Thailand), and lowest in South Asia and sub-Saharan Africa.

Sub-Saharan African enrollment, black or African American race (high-income region only), male natal sex, and NRTI-sparing or multiclass ART regimens were associated with lower CD4 cell counts. In contrast, enrollment from the Latin America and Caribbean region and current smoking were associated with higher CD4 cell counts. A positive association was noted between higher CD4 cell counts and longer ART exposure, higher BMI, and higher nadir CD4 cell counts across the distributions of these covariates (Figure 3). Sensitivity analyses restricted to those with HIV-1 RNA levels below the assay limit of quantification did not affect the results (data not shown).

The findings were also generally robust in analyses performed by enrollment region, natal sex, and duration of prior ART exposure (data not shown). Exceptions include the relationship between CD4 cell count and BMI that was not apparent in the Latin America and Caribbean region and the effect of nadir CD4 cell counts on current CD4 cell counts that was attenuated with increasing duration of prior ART exposure (Supplementary Figure 8). In further exploratory analyses, adjustment for white blood cell (WBC) counts at entry attenuated the CD4 cell count associations with BMI, sub-Saharan Africa and Latin America and Caribbean GBD enrollment, and

Table 1. Demographic and Cardiovascular Characteristics by Entry Antiretroviral Therapy^a

Characteristic	Participants, No. (%) ^b					
	Total (N = 7770)	NRTI + INSTI (n = 1978)	NRTI + NNRTI (n = 3676)	NRTI + PI (n = 1439)	NRTI Sparing (n = 199)	Other NRTI Containing (n = 476)
Demographic and Behavioral						
Age, median (IQR), y	50 (45–55)	51 (46–55)	49 (44–54)	50 (46–55)	51 (47–56)	51 (47–55)
Natal sex						
Male	5352 (69)	1563 (79)	2293 (62)	974 (68)	150 (75)	370 (78)
Female	2418 (31)	415 (21)	1383 (38)	465 (32)	49 (25)	106 (22)
Race ^c						
Black or African American	3378 (43)	786 (40)	1679 (46)	630 (44)	65 (33)	218 (46)
White	2701 (35)	1064 (54)	829 (23)	487 (34)	101 (51)	218 (46)
Asian	1139 (15)	24 (1)	893 (24)	193 (13)	20 (10)	9 (2)
Other	552 (7)	104 (5)	275 (7)	129 (9)	13 (7)	31 (7)
Ethnicity ^d						
Hispanic or Latino	698 (18)	302 (17)	188 (20)	117 (18)	23 (16)	68 (17)
Not Hispanic or Latino	3187 (81)	1472 (82)	743 (79)	532 (81)	115 (82)	324 (83)
Unknown	34 (1)	13 (1)	14 (1)	4 (1)	3 (2)	0 (0)
Smoking status						
Current	1933 (25)	586 (30)	764 (21)	378 (26)	52 (26)	153 (32)
Former	1906 (25)	606 (31)	752 (20)	352 (24)	54 (27)	140 (30)
Never	3923 (51)	784 (40)	2158 (59)	708 (49)	93 (47)	180 (38)
Substance use						
Current	152 (2)	52 (3)	52 (1)	34 (2)	6 (3)	8 (2)
Former	2277 (29)	958 (48)	592 (16)	431 (30)	83 (42)	213 (45)
Never	5333 (69)	967 (49)	3030 (82)	972 (68)	110 (55)	252 (53)
Cardiovascular and Metabolic						
BMI ^e						
<18.5	288 (4)	19 (1)	226 (6)	34 (2)	3 (2)	6 (1)
18.5–24.9	3115 (40)	613 (31)	1656 (45)	585 (41)	77 (39)	184 (39)
25–29.9	2664 (34)	755 (38)	1190 (32)	490 (34)	79 (40)	148 (31)
≥30	1696 (22)	586 (30)	603 (16)	329 (23)	40 (20)	138 (29)
HIV-Related Health Status						
Nadir CD4 T-cell count						
<50/ μ L	1406 (18)	352 (18)	513 (14)	307 (21)	57 (29)	176 (37)
50–199/ μ L	2386 (31)	490 (25)	1193 (32)	473 (33)	69 (35)	160 (34)
200–349/ μ L	2039 (26)	501 (25)	1031 (28)	397 (28)	33 (17)	77 (16)
≥350/ μ L	1677 (22)	541 (27)	834 (23)	224 (16)	33 (17)	45 (9)
Unknown	262 (3)	94 (5)	105 (3)	38 (3)	7 (4)	18 (4)
History of AIDS-defining event						
CD4 T-cell count, median (IQR), cells/ μ L	620 (447–826)	628 (456–845)	633 (468–832)	612 (422–820)	605 (447–834)	521 (348–720)
CD8 T-cell count median (IQR), cells/ μ L	779 (564–1032)	775 (555–1006)	750 (547–992)	838 (600–1129)	840 (601–1083)	886 (664–1112)
HIV-1 RNA level below LLQ						
<20 copies/mL	2819 (47)	1207 (64)	849 (37)	442 (38)	96 (51)	223 (50)
<40 copies/mL	2243 (37)	407 (22)	1131 (49)	528 (45)	56 (30)	121 (27)
<400 copies/mL	187 (3)	31 (2)	129 (6)	21 (2)	4 (2)	2 (<0.5)
≥LLQ	750 (13)	240 (13)	202 (9)	179 (15)	31 (17)	98 (22)
ART History						
Total ART use median (IQR)	9.6 (5.3–14.8)	9.0 (4.8–15.6)	8.3 (4.7–12.3)	11.0 (6.5–16.0)	17 (11–21)	16.0 (10.4–20.3)
Total ART use						
<5 y	1709 (22)	503 (25)	968 (26)	209 (15)	6 (3)	23 (5)
5–10 y	2305 (30)	556 (28)	1230 (33)	406 (28)	35 (18)	78 (16)
≥10 y	3754 (48)	918 (46)	1478 (40)	823 (57)	158 (79)	375 (79)
Unknown	2 (<0.5)	1 (<0.5)	0 (0)	1 (<0.5)	0 (0)	0 (0)
Protease exposure	3624 (47)	985 (50)	615 (17)	1400 (97)	192 (96)	430 (90)
Thymidine exposure	3799 (49)	601 (30)	1870 (51)	867 (60)	137 (69)	323 (68)
Abacavir exposure	1618 (21)	775 (39)	297 (8)	262 (18)	74 (37)	209 (44)
Tenofovir exposure	6572 (85)	1707 (86)	3035 (83)	1241 (86)	151 (76)	437 (92)
Duration of entry ART regimen, median (IQR), y	2.3 (0.8–5.2)	1.0 (0.5–1.9)	3.6 (1.7–6.8)	2.9 (0.9–6.2)	1.8 (0.7–4.6)	1.4 (0.6–3.8)

Abbreviations: ART, antiretroviral therapy; BMI, body mass index; HIV, human immunodeficiency virus; INSTI, integrase strand transfer inhibitor; IQR, interquartile range; LLQ, lower limit of quantification; NNRTI, nonnucleoside reverse-transcriptase inhibitor; NRTI, nucleoside/nucleotide reverse-transcriptase inhibitor; PI, protease inhibitor.

^aAll statistics are calculated based on participants with data collected. Missing data include smoking status (n = 8), substance use (n = 8), history of AIDS-defining event (n = 6), and HIV-1 RNA level below the LLQ (n = 1771). Two participants were missing an entry regimen at the time of analysis and are excluded from the total by entry regimen.

^bData represent no. (%) of participants unless otherwise specified.

^c“Other” race includes participants self-identifying as native or indigenous to the enrollment region, as >1 race (with no single race noted as predominant), or as of unknown race.

^dEthnicity presented according to National Institutes of Health definition for participants in the United States (including Puerto Rico) and Canada only.

^eBMI is calculated as weight in kilograms divided by height in meters squared.

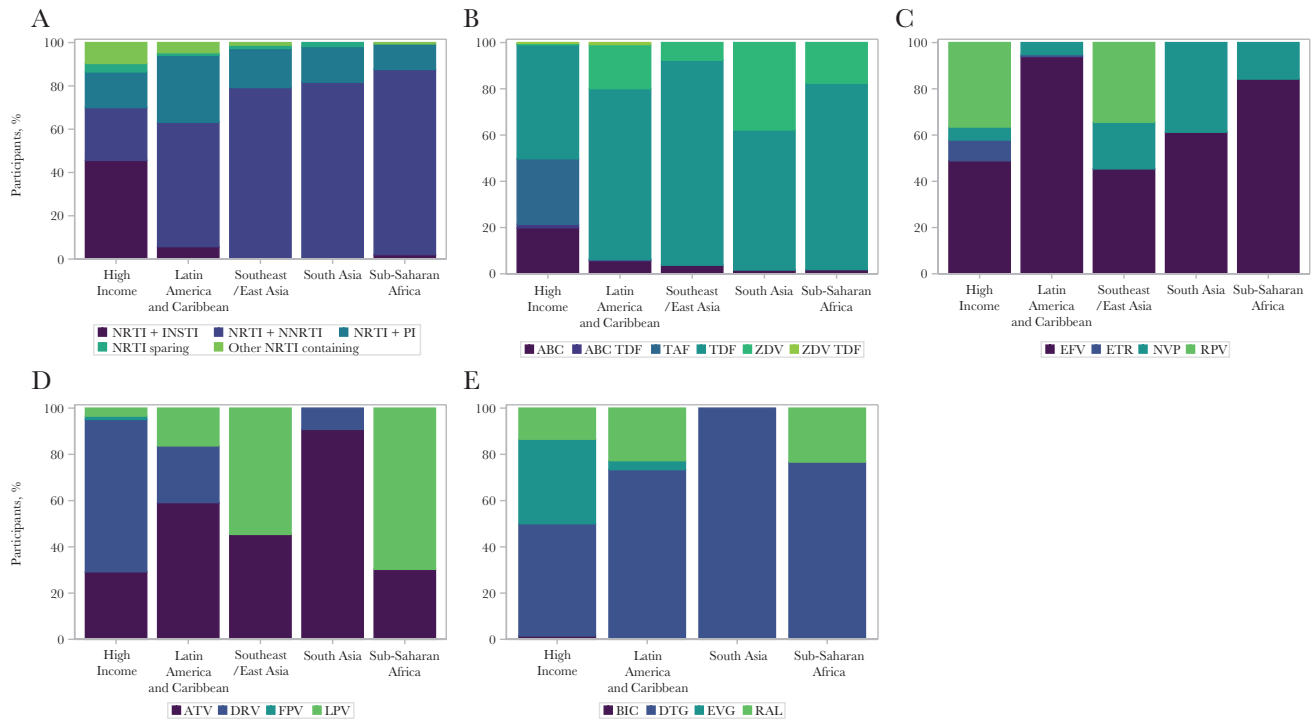


Figure 1. Class of entry regimen stratified by Global Burden of Disease region. Only regimens and agents with frequency >5 % of participants are shown. Abbreviations: ABC, abacavir; ATV, atazanavir; BIC, bictegravir; DRV, darunavir; DTG, dolutegravir; EFV, efavirenz; ETR, Etravirine; FPV, fos-ampronavir; INSTI, integrase strand transfer inhibitor; LPV, lopinavir; NNRTI, nonnucleoside reverse-transcriptase inhibitor; NRTI, nucleoside/nucleotide reverse-transcriptase inhibitor; NVP, nevirapine; PI, protease inhibitor; RAL, raltegravir; RPV, rilpivirine; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate; ZDV, zidovudine.

smoking status (Supplementary Figure 9 and Supplementary Table 2). The addition of WBC counts into the adjusted model of CD4 cell counts did not affect the significance of the relationship with CD4 cell count nadir or natal female sex. In analysis restricted to high-income GBD region enrollment, Latino/Hispanic ethnicity was not associated with higher CD4 cell counts (data not shown).

Marked differences in CD8 cell counts across enrollment regions and by entry ART regimen were apparent, and there was a positive association between BMI and CD8 cell counts. There was no association between CD8 cell counts and nadir CD4 cell count. Male natal sex (compared with female) and current smoking (compared with former and never smoking) were associated with a higher CD8 cell count (Figure 3B). These findings were all robust in exploratory subgroup analyses by enrollment region, natal sex, and prior ART duration, and sensitivity was restricted to participants with HIV-1 RNA levels below the assay limit of quantification (data not shown). Additional adjustment by WBC counts attenuated the positive associations of CD8 cell counts with BMI and smoking status (Supplementary Figure 9).

There were several notable associations with entry CD4/CD8 ratios. South Asia and sub-Saharan African enrollment regions were associated with a higher odds of having a low (<1.0) CD4/CD8 ratio (Figure 3C). Male natal sex, NRTI plus PI and other

entry regimens (ie, NRTI-sparing regimens, multiclass regimens), a shorter duration of total ART exposure, and a lower CD4 cell count nadir were associated with higher odds of a low CD4/CD8 ratio (Figure 3C). Again, these findings were robust in exploratory subgroup analyses performed by enrollment region, natal sex, and prior ART duration and sensitivity restricted to participants with HIV-1 RNA levels below the assay limit of quantification (data not shown).

DISCUSSION

The REPRIEVE trial provides an opportunity to investigate and compare patterns of contemporary use of ART and immunologic profiles evaluating associations with sociodemographic factors and select health characteristics across GBD super-regions, in a time of evolving patterns of global ART use from 2015 to 2019. The study population had extensive prior exposure to ART, with a median 9.5 years at the time of enrollment. The data demonstrate clear differences in the patterns of ART use by GBD regions with greater regimen variability in high-income regions along with more use of INSTIs and more NNRTI use in other GBD regions.

Furthermore, specific use of different antiretrovirals changed over the enrollment period with increased use of TAF, DTG, and rilpivirine and decreased use of atazanavir in the high-income GBD super-region. Changes in the use of specific antiretrovirals

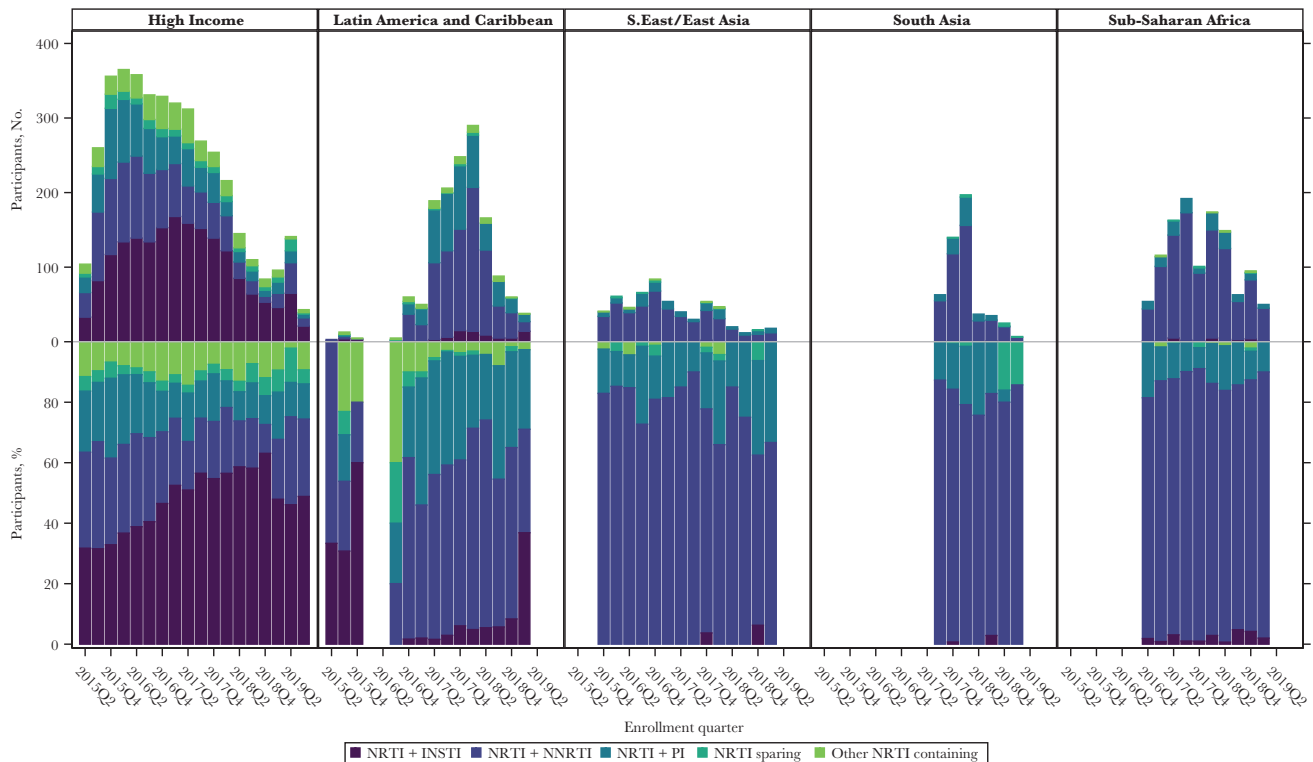


Figure 2. Changes in entry regimen class by time of enrollment. Top panels show the numbers of participants; lower panels, the percentages participants (calculated within each bar). Within each panel, enrollment quarter with a frequency <3 within a panel not shown. Abbreviations: INSTI, integrase strand transfer inhibitor; NNRTI, nonnucleoside reverse-transcriptase inhibitor; NRTI, nucleoside/nucleotide reverse-transcriptase inhibitor; PI, protease inhibitor; Q2, quarter 2; Q4, quarter 4.

were observed in select other GBD super-regions, such as an increase in DTG in Thailand and TAF in the Latin America and Caribbean region. Amidst this variability, the use of tenofovir prodrugs was consistent across all regions. Analyses of immunologic profiles showed entry CD4 cell count and CD4/CD8 ratio were associated with region of enrollment, natal sex, total duration of ART, and nadir CD4 cell count. CD4 cell count was also associated with BMI and smoking status. The immunologic findings were consistently observed across GBD regions and in subgroup analyses by region, sex, and total duration of ART exposure.

Data from REPRIEVE provide a valuable snapshot of regional and temporal differences in the global use of antiretrovirals. Although the observed patterns of ART use likely reflect the availability of specific agents across different regions, changes in practice guidelines, and preferences by providers and patients, there are few published reports, to our knowledge, of patterns of ART use across regions [11]. Studies of contemporaneous populations across multiple global regions in the current era of ART are lacking though there are reports of first- and second-line therapy use [12, 13].

Analysis of the immunologic profiles of study participants yielded several key insights. As expected, nadir CD4 cell count was associated with CD4 at entry with lower nadirs tracking with lower entry CD4 cell counts, even in the subpopulation

with extensive ART exposure. Higher CD4 cell counts were associated with female natal sex, longer exposure to ART, higher BMI, and current smoking across all regions. Higher CD4/CD8 ratios, a measure of immune reconstitution, were similarly associated with longer ART exposure, higher nadir CD4 cell counts, female natal sex, and higher BMI.

The addition of WBC counts to the adjusted models eliminated the association between CD4 cell counts and smoking. Similarly, there was no longer an association observed between CD4 cell counts with higher BMI and a higher CD4/CD8 ratio. We suspect that higher WBC counts correlate with more immune activation and may be more closely correlated than smoking, BMI and CD4/CD8 ratios. Indeed, we demonstrated that higher WBC counts are associated with higher CD4 and CD8 cell counts (Supplementary Table 2). There have been a number of observations in persons without HIV demonstrating higher leukocyte and CD4 cell counts associated with cigarette smoking [14–16]. The proinflammatory state induced by cigarette smoke is hypothesized to lead to both higher CD4 and higher CD8 cell counts.

Numerous studies have demonstrated that lower nadir CD4 cell counts are associated with incomplete recovery of CD4 cell counts in response to treatment with ART [17, 18]. Similarly, CD4 cell counts rise in a predictable manner over time with ART treatment [19–21]. There are a also number of studies

Table 2. Immunologic Outcomes by Global Burden of Disease Super-region

Outcome	Total (N = 7770)	High Income (n = 4096)	Latin America and Caribbean (n = 1423)	Southeast/East Asia (n = 590)	South Asia (n = 504)	Sub-Saharan Africa (n = 1157)
CD4 T-cell count, cells/μL						
All participants						
Median (IQR)	620 (447–826)	614 (446–835)	658 (482–865)	626 (476–784)	591 (378–758)	598 (433–802)
10th to 90th percentile range	309–1050	305–1070	339–1091	341–977	257–998	307–1010
ART exposure <5 y						
Median (IQR)	590 (401–801)	587 (400–793)	629 (439–847)	536 (333–691)	542 (296–746)	579 (403–796)
10th to 90th percentile range	262–1039	249–1022	310–1064	181–815	194–952	270–1038
ART exposure 5–10 y						
Median (IQR)	614 (448–834)	621 (456–859)	649 (472–849)	573 (400–714)	591 (395–750)	587 (436–788)
10th to 90th percentile range	319–1052	313–1096	366–1089	311–905	265–997	328–989
ART exposure ≥10 y						
Median (IQR)	637 (470–834)	623 (454–832)	692 (523–909)	666 (513–812)	640 (433–788)	618 (449–821)
10th to 90th percentile range	329–1053	319–1060	355–1126	396–1015	281–1024	328–1007
CD8 T-cell count, cells/μL						
All participants						
Median (IQR)	779 (564–1032)	788 (546–1002)	838 (601–1112)	679 (505–879)	891 (647–1244)	772 (583–1016)
10th to 90th percentile range	427–1362	405–1304	468–1458	396–1101	483–1581	453–1352
ART exposure <5 y						
Median (IQR)	794 (571–1066)	743 (526–983)	847 (612–1136)	617 (473–809)	879 (626–1270)	803 (598–1042)
10th to 90th percentile range	439–1404	402–1286	487–1489	324–1024	463–1664	456–1379
ART exposure 5–10 y						
Median (IQR)	770 (565–1003)	729 (532–933)	797 (586–1041)	699 (530–858)	925 (644–1267)	807 (599–1055)
10th to 90th percentile range	425–1337	402–1252	434–1392	385–1089	515–1564	477–1357
ART exposure ≥10 y						
Median (IQR)	777 (562–1030)	786 (561–1050)	868 (615–1133)	679 (504–882)	880 (683–1186)	739 (564–960)
10th to 90th percentile range	426–1361	406–1355	469–1479	404–1120	488–1528	449–1302
CD4/CD8 ratio						
All participants						
Median (IQR)	0.81 (0.56–1.15)	0.85 (0.56–1.20)	0.81 (0.54–1.15)	0.91 (0.68–1.22)	0.63 (0.44–0.89)	0.78 (0.55–1.06)
10th to 90th percentile range	0.36–1.53	0.37–1.63	0.34–1.57	0.52–1.52	0.29–1.15	0.37–1.37
Ratio <1, no. (%)	4214 (65)	1841 (62)	928 (66)	330 (57)	353 (62)	762 (70)
ART exposure <5 y						
Median (IQR)	0.76 (0.47–1.10)	0.84 (0.49–1.17)	0.78 (0.46–1.12)	0.78 (0.56–1.19)	0.57 (0.34–0.80)	0.74 (0.50–1.04)
10th to 90th percentile range	0.30–1.53	0.31–1.67	0.28–1.52	0.38–1.41	0.24–1.10	0.32–1.40
Ratio <1, no. (%)	1004 (68)	299 (62)	331 (68)	30 (58)	106 (64)	238 (73)
ART exposure 5–10 y						
Median (IQR)	0.81 (0.56–1.14)	0.89 (0.61–1.24)	0.82 (0.58–1.21)	0.84 (0.61–1.13)	0.63 (0.46–0.91)	0.73 (0.53–1.03)
10th to 90th percentile range	0.39–1.55	0.41–1.75	0.41–1.59	0.43–1.32	0.29–1.13	0.39–1.28
Ratio <1, no. (%)	1259 (66)	468 (59)	291 (64)	81 (69)	146 (81)	273 (74)
ART exposure ≥10 y						
Median (IQR)	0.84 (0.59–1.17)	0.83 (0.55–1.20)	0.83 (0.58–1.12)	0.94 (0.71–1.25)	0.72 (0.52–0.94)	0.84 (0.61–1.12)
10th to 90th percentile range	0.40–1.53	0.38–1.58	0.37–1.57	0.57–1.60	0.34–1.23	0.44–1.40
Ratio <1, no. (%)	1949 (63)	1072 (63)	306 (66)	219 (54)	101 (80)	251 (64)

Abbreviations: ART, antiretroviral therapy; IQR, interquartile range.

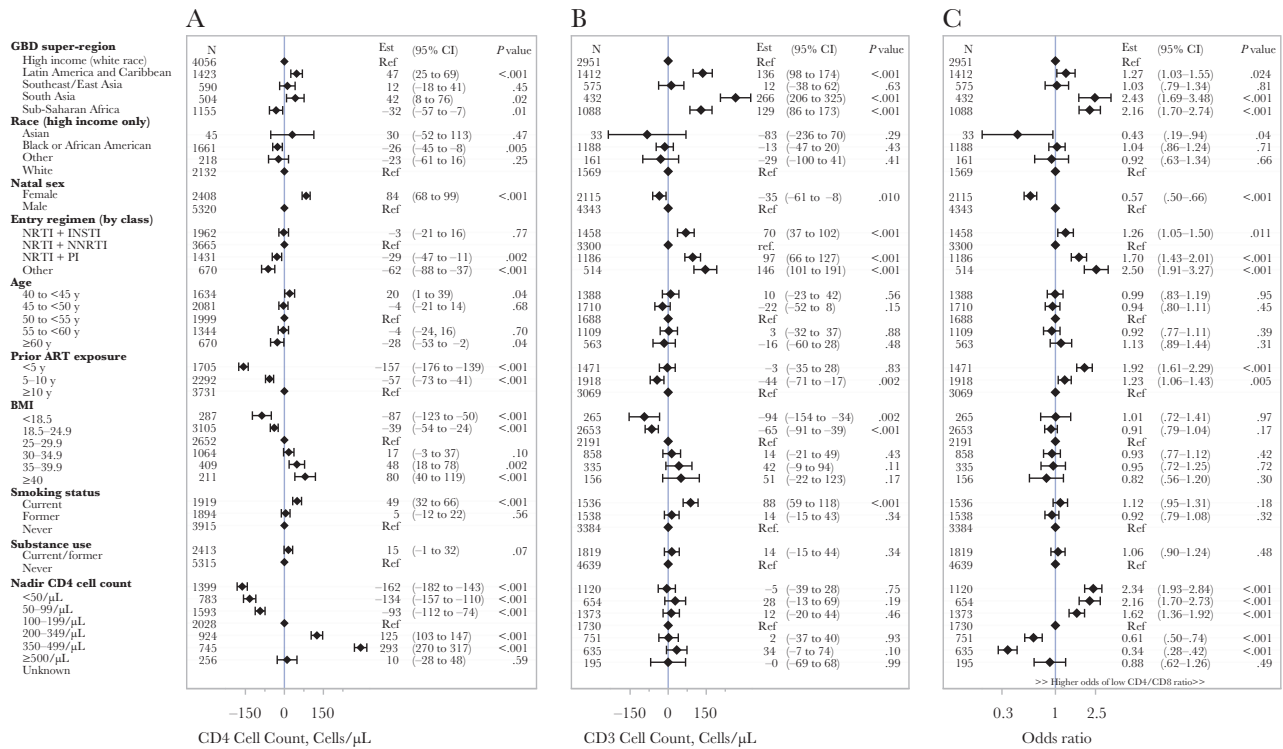


Figure 3. Adjusted regression analyses on CD4 T-cell count (A), CD8 T-cell count (B), and low (<1) CD4/CD8 ratio (C). Abbreviations: ART, antiretroviral therapy; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CI, confidence interval; Est = Estimate, and Ref = Reference; GBD, Global Burden of Disease; INSTI, integrase strand transfer inhibitor; NRTI, nucleoside/nucleotide reverse-transcriptase inhibitor; NNRTI, nonnucleoside reverse-transcriptase inhibitor; PI, protease inhibitor; Ref, reference.

indicating that women have higher CD4 cell counts than men, which is what we observed in the current study [22–24]. Nadir CD4 cell counts and CD4/CD8 ratios have been demonstrated to be important predictors of clinical outcomes in PWH [25, 26]. In particular, CVD outcomes are associated with lower nadir CD4 cell counts [27, 28].

Finally, higher CD8 cell counts were observed in sub-Saharan Africa, South Asia and Latin America and Caribbean GBD regions than in high-income and Southeast/East Asia regions. The explanation for these differences is not clear. It is possible that unmeasured inflammatory stimuli in some regions may amplify CD8 cell counts [29]. Petoumenos et al [30] reported similar CD8 cell counts between a cohort in Southeast Asia and a high-income country cohort in Australia. This is similar to what we observed. We were not able to find publications that compared CD8 cell counts between other GBD regions in the era of potent ART. Further investigation is required to understand these differences by GBD regions.

Recently, since 2019, weight gain and higher BMIs have been reported in PWH, particularly with the initiation of INSTI-based ART [31–33]. Interestingly, we noted greater proportions of participants receiving INSTI-based entry regimens with increasingly higher entry BMIs, which were most striking among participants starting their entry regimen within a year

of REPRIEVE enrollment (Supplementary Figure 7). In the Women’s Interagency Study of HIV, women switching to INSTIs gained an average 2.1 kg with an increase of 0.8 in BMI, compared with women who remained on non-INSTI ART regimens [33]. DTG use was associated with more weight gain over 18 months in the Vanderbilt cohort (6- vs 2.6-kg increase with NNRTIs; $P < .05$) [31].

Of note, not all groups have documented increased weight gain with INSTI use [34, 35]. The observations within the REPRIEVE cohort are consistent with most of published reports of higher BMI with the use of INSTIs but must be interpreted with caution. ART in the REPRIEVE trial is not randomized, and these descriptive, cross-sectional analyses make no adjustments to control for confounding by indication, whereby heavier people may have been assigned to INSTI-based ART. Further prospective studies are needed, and REPRIEVE may be leveraged in the future to assess potential confounding factors associated with INSTI use and BMI. In addition, the relationships between INSTI use, weight gain, and major adverse cardiovascular events can be evaluated in REPRIEVE to determine whether there are cardiovascular consequences of weight gain in this population.

Another interesting observation was the association between BMI and immunologic profiles. Lower CD4 and CD8 cell counts

were associated with lower BMI. For CD4 cell counts, there was an overall positive association across the full BMI distribution. Although the associations were most consistently seen in high-income and sub-Saharan African GBD super-regions, they were robust, remaining apparent in multivariable analyses controlling for GBD region, race, natal sex, ART entry regimen, prior ART exposure, and nadir CD4 cell counts, and in subgroup analyses by region, natal sex, and prior ART exposure.

Several other groups have evaluated the relationship between BMI and CD4 T-cell recovery. In the ALLRT trial, investigators reported a blunted CD4 cell recovery in those with lower BMI [36]. In contrast, the NA-ACCORD investigators found a more complicated relationship with attenuation of CD4 cell recovery in more obese populations [37]. A significant literature exists relating increasing weight to improved immune function [38]. Teleologically, greater weight provided a greater survival advantage to fight infectious diseases, such as tuberculosis [39, 40].

Moreover, existing data suggest an important relationship between adipose tissue and immune function. Some data suggest that leptin signaling can explain the link between adiposity and immune function [41–44]. For example, leptin deficiency is associated with a reduction in CD4 T cells and overall T-cell production, with consequential increase in childhood infections [43, 44]. Mice deficient in leptin have a reduction in circulating T cells, and leptin replacement has been shown to increase T-cell response, reversing starvation-induced immunosuppression [42]. The cohort enrolled in REPRIEVE have been taking ART for a median of almost 10 years, and the vast majority have HIV-1 RNA levels below the assay quantification limits or at very low quantifiable levels. This cohort likely reflects PWH who have experienced substantial CD4 cell recovery with the use of ART. Thus, the positive association between CD4 and CD8 cell counts and BMI may reflect the level of immunologic recovery in response to ART. The REPRIEVE trial is an ideal setting to improve our understanding of the cardiometabolic consequences of weight gain, BMI, and the interplay with the immune system.

The current analysis has a number of strengths and weaknesses. Although REPRIEVE carefully assessed ART use and other key immune and participant characteristics in a global population across GBD regions, in the current era of ART, it is a cross-sectional evaluation of individuals >40 years old who have enrolled in a randomized clinical trial, and the results may not be applicable to broader populations with HIV. The study population has a well-preserved CD4 cell count (median, 620/ μ L) and other immunologic parameters that are similar to those in other large cohorts. Nonetheless, we did recruit a relatively healthy population interested in pursuing CVD prevention. Some of the results in this study may reflect the known evolution in changes of the immune system over time in response to ART and differences in the severity of illness between study participants before enrollment and may not be related to the

use of specific antiretroviral regimens. The absence of longitudinal clinical information before enrollment makes it difficult to know why specific prior ART regimens or agents were chosen or changed. However, the patterns track with the availability of different antiretrovirals and evolving practice guidelines [45]. We do not have information on within-individual changes in specific parameters, such as BMI, CD4 cell count, and CD4/CD8 ratio, that might influence choice of antiretrovirals; firm conclusions are thus challenging to make.

In summary, we have demonstrated differences in the use of ART regimens and specific antiretrovirals over time and region among a global cohort of REPRIEVE trial participants. A number of associations between demographic and health related factors were observed with CD4 cell counts and CD4/CD8 ratio. The most important implications of this analysis are that the study population recruited is reflective of PWH with suppressed viral replication and preserved CD4 cell counts, representing the ideal group to study CVD prevention. Furthermore, knowing the ART history and entry immune profile sets the stage for future analyses that can correlate with prospective clinical outcomes with the REPRIEVE trial. These observations should also help inform future prospective analyses of the relationship between ART, the immune system, other specific health characteristics and outcomes within other global studies of PWH.

Supplementary Data

Supplementary materials are available at *The Journal of Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Acknowledgments. The study investigators thank the study participants, site staff, and study-associated personnel for their ongoing participation and contributions to the trial. They also thank the AIDS Clinical Trial Group (ACTG) for clinical site support; ACTG Clinical Trials Specialists for regulatory support; the data management center, Frontier Science Foundation, for data support; and the Center for Biostatistics in AIDS Research for statistical support.

REPRIEVE Investigators – Author List: Adrian Curran, MD, PhD, Adrienne Baranauskas, RN, BSN, Aimee Wilkin, MD, MPH, Alexandra J. Abrams-Downey, MD, Allison Ross Eckard, MD, Alysse G. Wurcel, MD MS, Ana González-Cordón, MD, PhD, Armando Paez, MD, Beverly E. Sha, MD, Breno Santos, MD, Carina Beppu Yoshida, RN, Charlotte-Paige Rolle, MD, MPH, Charurut Somboonwit, MD, Connie Funk, RN, MPH, Cristina Gómez-Ayerbe, MD, PhD, Cynthia Frank, PhD, RN, Daniel E. Nixon, DO, PhD, Daniel J. Skiest, MD, David Choi, MPH, David M. Mushatt, MD, MPH&TM,

David Rial-Crestelo, Deborah K. Perez, RN, CCRP, Deirdre J. Burke, MPH, Desirée V. G. dos Santos, MD, Dushyantha T. Jayaweera, MD, Edward M. Gardner, MD, Edwin DeJesus, MD, FACP, FIDSA, Elizabeth Connick, M.D., Emerline G. Lam, BS, Emily J. Hecker, RN, MSN, Esper G. Kallas, MD, PhD, Esteban Martinez, MD, PhD, Evan Waters, RN, BSN, BSH, Frank Rhame, MD, Fred R. Sattler, MD, Gary P. Wang, MD, PhD, Helen May Enrile Seedhom, RN BSN, Isabel C. F. Tavares, MD, MSc, Jack T. Stapleton, M.D., Jaelyn Bennet, MBBCH (Wits), James B. Brock, MD, MSCI, James Scott, BSN, Janet Forcht, RN, Javier R. Lama, MD, MPH, Javier Valencia, MD, Jennifer K. Brumfield, RN, CCRC, MHS, Jennifer K. Brumfield, RN, CCRC, MHS, Joaquin Portilla, MD, Jonathan Kumar, BS, Jordi Navarro, MD, Jorge A. Pinto, MD, DSc, Jose G. Castro, MD, Jose I. Bernardino, MD, Jose L. Casado, José Valdez Madruga, MD, Josu Baraiaetxaburu, Juan Berenguer, MD, PhD, Judith A. Aberg, MD, Judith S. Currier, MD, MSc, Karen T. Tashima, MD, Ken Ho, MD, MPH, Laura V. L. Costa, Leire Perez Latorre, MD, PhD, Lerato Mohapi, MBBCh, López-González L., MD, Lori E. Fantry, MD, MPH, Lourdes Domínguez-Domínguez, Luz Martín-Carbonero, Lynne M. Cornelissen, MBChB, DipHIVMan, Mamta K. Jain, MD, MPH, Mar Masiá, Marcus V. G. Lacerda, PhD, Maria Saumoy, PhD, Marije Van Schalkwyk, MD, GH&TM, Marina Villalobos-Hernández, MD, Mark Mall, RN, Maureen E. Kubat, RN, BSN, Melissa Carreres, Michael Frank, MD, Michael J. Kozal, MD, Mireia De la Peña, Nadim Salomon, MD, Nagalingeswaran Kumarasamy, MBBS,FRCP,PhD, Natapol Kosashunhanan, MD, Ntebo D. Mogashoa, MBChB, PDM, Nwora Lance Okeke, MD, MPH, Pamela G. Mukwekwerere, MBChB, Patcharaphan Sugandhavesa, MD, Pilar Vizcarra, Princy N. Kumar, MD, FIDSA, MACP, Renee Weinman, MPPM, Richard M. Novak, MD, Rina Chaudhary, PhD, EDS, Rodney Dawson, MD, Roger Bedimo, MD, Romina Chinchay, MSc, MBA, Sandy Pillay, MD, Sara H. Bares, MD, Sharlaa Badal-Faesens, MBBCH, Sharon L. Walmsley, CM, MD, Sigrid Perez-Frontera, MD, AAHIVS, Sondra Middleton, MHS, PA-C, Stockton Mayer, DO, Suzanne L. Adams, RN, BSN, Umesh G. Laloo, MBChB, FCP, MD, Vicente Estrada, Vicky Watson, RN, Victor Chiang.

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Financial support. This work was supported by the NHLBI (grants U01 HL123336 and U01 HL123339) and the National Institute of Allergy and Infectious Diseases (grants UM1 AI068636, UM1 AI106701, and UMI AI069501).

Supplement sponsorship. This supplement is sponsored by Massachusetts General Hospital, through NIH funding including U01HL123336.

Potential conflicts of interest. C. J. F. reports grants from Gilead Sciences, ViiV Healthcare, Janssen, Merck, Amgen, and Cytodyn, as well as personal fees from Clinical Care Options and PointofCare, outside the submitted work. H. J. R. reports grants from NIH/NHLBI and Kowa Pharmaceuticals America, during the conduct of the study. J. L. C. reports grants from NIH/NHLBI and Kowa Pharmaceuticals America, during the conduct of the study. E. T. O. reports grants from NIH during the conduct of the study; grant support through his institution from ViiV Healthcare, Gilead Sciences, Janssen, and Bavarian Nordic, outside the submitted work; and personal fees from Gilead Sciences, Theratechnologies, ViiV Healthcare, and Merck, outside the submitted work. M. V. Z. reports grant support through her institution from Gilead Sciences, during the conduct of the study. J. A. A. reports grants from Massachusetts General Hospital during the conduct of the study; and grant support from Frontier Technologies and Gilead Sciences, grant support and personal fees from Janssen, Merck, GlaxoSmithKline-ViiV Healthcare, and personal fees from Medicare and Theratechnologies, outside the submitted work. K. V. F. reports an educational grant from Gilead Sciences, outside the submitted work. E. M. reports grants from Gilead Sciences Janssen, ViiV Healthcare, and MSD, outside the submitted work. J. L. reports grants from NIH and personal fees from ViiV Healthcare and Gilead Sciences, outside the submitted work. K. M. is an employee of Gilead Sciences. C. A. S. is an employee of Kowa Pharmaceuticals America. J. S. C. reports personal fees from Merck, outside the submitted work. U. H. reports grant support through his institution from Kowa Pharmaceuticals America, for the conduct of the study, and grants from MedImmune/AstraZeneca, HeartFlow, and Duke University (Abbott), and other support from Duke University (NIH) and Recor Medical, outside the submitted work. P. S. D. reports grant support from Kowa Pharmaceuticals America and Gilead Sciences, for the conduct of the study. S. K. G. reports grant support through his institution from Kowa Pharmaceuticals America and Gilead Sciences, for the conduct of the study, and from Theratechnologies, Navidea, and ViiV Healthcare, outside the submitted work. All other authors report no potential conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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