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SUPPLEMENT ARTICLE

Leveraging a Landmark Trial of Primary Cardiovascular Disease Prevention in Human Immunodeficiency Virus: Introduction From the REPRIEVE Coprincipal Investigators

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The Randomized Trial to Prevent Vascular Events in HIV (REPRIEVE) is the largest study of cardiovascular disease in human immunodeficiency virus. Enrolling 7770 participants from 2015 to 2019 with sites across 5 continents, REPRIEVE will assess the effects of a statin as a cardiovascular disease prevention strategy in people with HIV (PWH) receiving antiretroviral therapy (ART). Although the primary purpose of REPRIEVE, and its substudy assessing coronary plaque, is to assess cardiovascular outcomes, the trial is a rich source of data on population characteristics and critical comorbidities in PWH, particularly across Global Burden of Disease (GBD) regions, reflective of the ethnic, racial, and gender diversity in this global epidemic. The purpose of this Supplement is to leverage the rich phenotyping in REPRIEVE, to provide data on detailed patterns of baseline ART and immune function by GBD region, reproductive aging among cisgender women, and data on the participation and clinical characteristics of transgender participants. We also leveraged REPRIEVE to assess critical comorbidities, including renal dysfunction, muscle function and frailty, and myocardial steatosis. REPRIEVE is a remarkable collaboration between funders, trial networks, clinical research sites, clinical and data coordinating centers, and willing participants who devoted their time to make the trial possible.

Keywords. cardiovascular; comorbidity; global disease burden; HIV; prevention.

The Randomized Trial to Prevent Vascular Events in HIV (REPRIEVE) trial (ClinicalTrials.gov Identifier NCT02344290) is, to our knowledge, the largest study of cardiovascular disease (CVD) in human immunodeficiency virus (HIV). The trial enrolled participants globally from 2015 to 2019 with participation from sites in North and South America, sub-Saharan Africa, Europe, and Asia. The primary aim of REPRIEVE is to assess the effects of a statin (pitavastatin calcium) to reduce major adverse cardiovascular events (MACE) in people with HIV (PWH), receiving antiretroviral therapy (ART), at low to moderate traditional CVD risk as determined by the American College of Cardiology/American Heart Association (ACC/AHA) Atherosclerotic Cardiovascular Disease (ASCVD) risk score [1] and low-density lipoprotein (LDL) cholesterol levels, without prior history of CVD. The design and aims of REPRIEVE, as well as its major substudy, assessing effects of pitavastatin on coronary plaque through dedicated coronary computed tomography angiography, have recently been described [2, 3]. These aims are critical in the current era of HIV, in which ART is effective, PWH are living longer, and non-acquired immune deficiency syndrome (AIDS) comorbidities are increasingly prevalent. REPRIEVE is designed to address CVD prevention in PWH, with specific goals to determine whether early use of statins provide an effective preventive strategy for CVD, and the manner in which immune function, inflammation, and other factors contribute to CVD and affect that prevention strategy. Although REPRIEVE will assess a key CVD prevention strategy for MACE among PWH, the trial will also provide a wealth of prospectively attained and adjudicated information on critical CVD phenotyping beyond MACE, including characterization of myocardial infarction type, unique coronary plaque characteristics, race and sex-specific effects, utility of traditional risk scoring algorithms, and baseline electrocardiograph patterns. In addition, REPRIEVE is collecting critical information on statin effects on non-CVD events, including AIDS events and other comorbidities in PWH.

As discussed in the primary design article [2], REPRIEVE is primarily funded by the National Heart Lung and Blood Institute (NHLBI) of the National Institutes of Health (NIH), with site support and trial oversight (including site monitoring and pharmacy support) from the National Institutes of Allergy

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and Infectious Diseases (NIAID) and the AIDS Clinical Trials Group (ACTG). Pharmaceutical support for the trial has been received from Kowa Pharmaceuticals America, Inc. and Gilead Sciences, Inc. By design and due to regulatory considerations, European participants were recruited into an identical protocol REPRIEVE-EU, with monitoring by the European Network for the Treatment of HIV, Hepatitis and Global Infectious Diseases (NEAT ID), and regulatory oversight by the Clinical Coordinating Center staff and the Massachusetts General Hospital, in compliance with General Data Protection (GDPR) guidelines. The protocol and operational plans are approved by the Partners Human Research Committee. Regulatory and institutional review board approvals were obtained as previously described both for the central coordination of the trial and for enrollment of participants at each site [2].

REPRIEVE is now fully enrolled with 7770 participants, including European enrollment, achieving the enrollment goals of the trial. Participants are being followed to achieve the primary aims of the study. Enrollment occurred across more than 100 clinical sites, including sites from the ACTG, Canadian HIV Trials Network (CTN), and other non-ACTG sites, in 12 countries, located in North America, South America, the Caribbean, Africa, Asia, and most recently in Europe through NEAT ID. The baseline characteristics of the full REPRIEVE trial cohort are shown in Tables 1 and 2. These tables highlight critical strengths of REPRIEVE, including the diversity of its population across nationalities, Global Burden of Disease (GBD) regions, race, ethnicity, and natal sex, with more than 60% of participants nonwhite and over 30% female. The global diversity achieved in REPRIEVE makes the cohort uniquely representative of the current epidemic.

REPRIEVE is well poised to address the efficacy of a primary CVD prevention strategy on a global scale, matching the increasing global burden of HIV CVD [4]. More important, REPRIEVE has enrolled a population for whom CVD prevention is a key consideration, based on prior studies identifying subclinical disease across a range of traditional risk factors [5–9], but for whom no data exist assessing preventative strategies on MACE. The REPRIEVE population is reflective of PWH seeking guidance on this question, with a median age of 50, longstanding HIV, receiving ART for almost a decade, and demonstrating relatively well preserved immune function (Tables 1 and 2). Low-density lipoprotein cholesterol (LDL-C) levels may not be significantly elevated among this group, as shown by the median and lower and upper quartiles of 108 (87, 128) mg/dL. However, the LDL and other characteristics of the recruited population may, in part, reflect the entry criteria of the study, selecting a primary prevention population using a specific CVD risk algorithm. Median body mass index (BMI) is relatively normal, but increased weight is a concern in some participants, as seen by the BMI distribution of the trial, with 22% in the obese category (BMI $\geq$30 kg/m^2). A relatively large proportion of participants continue to smoke cigarettes, although the range of data is broad, showing regional differences. In short, REPRIEVE is representative of the diverse population of ART-treated PWH across the globe today, for whom a primary CVD prevention strategy is relevant.

As can be further seen in Tables 1 and 2, there are differences in the REPRIEVE population across recruitment zones, with respect not only to specific CVD risk parameters, but also to body composition, renal function, ART exposure, and many other HIV-related factors, including HIV duration, CD4 cell count, viral load, nadir CD4 cell count, and others. This diversity by GBD region provides a rich opportunity to understand how these differences, as well as race and sex considerations, impact CVD and HIV outcomes and are more fully explored in the articles included in this Supplement. Future articles will incorporate this richness into longitudinal analyses. A description of the methodology of the collection of data common to the articles is included in an online Supplemental Methods Appendix. Methodologies for data collection procedures uniquely relevant to specific articles within the Supplement will be described in these individual articles.

REPRIEVE is also an important global trial to assess non-CVD comorbidities in the current era of HIV and ART. With comprehensive data collection and a diverse population, including participants in high- and low-income global areas affected by HIV, utilizing differing ART regimens, REPRIEVE provides a wealth of information on emerging critical non-CVD comorbidities in PWH. For example, among REPRIEVE trial participants, cancer was previously diagnosed in 4% of the trial population, with chronic viral hepatitis B virus in 3% and chronic viral hepatitis C virus in 2% (Table 2). A recent article authored by Dr. Anthony Fauci (Director of NIAID) and others highlighted the importance of understanding such comorbidities, and their relevance for a longer-living HIV population on effective ART [10]. Until a cure for HIV is achieved, comorbidities, including cardiac and noncardiac, must remain a major focus of HIV care. In this regard, the REPRIEVE trial has been leveraged, with additional funding to enable ascertainment of further knowledge. In particular, NIH grants from NHLBI, NIAID, National Institute on Aging, and National Institute of Diabetes and Digestive and Kidney Diseases have been received to understand sex-specific mechanisms of CVD risk and risk reduction, kidney function, physical function and frailty, and myocardial structure and function, leveraging REPRIEVE to expand our integrated understanding of the "whole person" impact of HIV.

Although future manuscripts will describe in depth the cardiovascular status of REPRIEVE participants, including a more complete description of the baseline ASCVD risk score and its correlates, the current set of articles in this Supplement describes the broader outlines of the enrolled REPRIEVE population, with a goal to characterize key comorbidities in this population while

Table 1. Demographic and Cardiovascular Characteristics[a]

			High Income			Latin America and Caribbean				Southeast/ East Asia	South Asia	Sub-Saharan Africa			
Characteristic	Descriptor	Total (N = 7770)	Canada (N = 131)	Spain (N = 213)	USA (N = 3752)[b]	Brazil (N = 1099)	Haiti (N = 140)	Peru (N = 148)	Puerto Rico (N = 36)	Thailand (N = 590)	India (N = 504)	Botswana (N = 281)	South Africa (N = 570)	Uganda (N = 181)	Zimbabwe (N = 125)
Demographics and Behavioral															
Age (years)	Median (Q1, Q3)	50 (45, 55)	53 (49, 57)	54 (51, 57)	51 (46, 55)	49 (45, 54)	54 (49, 58)	48 (43, 53)	51 (48, 55)	47 (44, 52)	47 (44, 52)	51 (45, 56)	47 (43, 52)	52 (47, 55)	51 (47, 56)
	40–49	3730 (48%)	37 (28%)	41 (19%)	1646 (44%)	561 (51%)	39 (28%)	82 (55%)	12 (33%)	371 (63%)	335 (66%)	122 (43%)	364 (64%)	73 (40%)	47 (38%)
	50–59	3362 (43%)	82 (63%)	150 (70%)	1765 (47%)	432 (39%)	71 (51%)	59 (40%)	21 (58%)	194 (33%)	140 (28%)	125 (44%)	174 (31%)	84 (46%)	65 (52%)
	60+	678 (9%)	12 (9%)	22 (10%)	341 (9%)	106 (10%)	30 (21%)	7 (5%)	3 (8%)	25 (4%)	29 (6%)	34 (12%)	32 (6%)	24 (13%)	13 (10%)
Natal sex	Male	5352 (69%)	118 (90%)	194 (91%)	2906 (77%)	777 (71%)	81 (58%)	136 (92%)	26 (72%)	257 (44%)	375 (74%)	104 (37%)	195 (34%)	88 (49%)	95 (76%)
	Female	2418 (31%)	13 (10%)	19 (9%)	846 (23%)	322 (29%)	59 (42%)	12 (8%)	10 (28%)	333 (56%)	129 (26%)	177 (63%)	375 (66%)	93 (51%)	30 (24%)
Gender identity[c]	Cisgender	7363 (95%)													
	Transgender Spectrum	129 (2%)													
	Not reported	278 (4%)													
Race[d]	Black or African American	3378 (43%)	15 (11%)	2 (1%)	1657 (44%)	400 (36%)	140 (100%)	2 (1%)	8 (22%)	0 (0%)	0 (0%)	280 (100%)	568 (100%)	181 (100%)	125 (100%)
	White	2701 (35%)	99 (76%)	207 (97%)	1849 (49%)	514 (47%)	0 (0%)	9 (6%)	19 (53%)	2 (<.5%)	0 (0%)	0 (0%)	2 (<.5%)	0 (0%)	0 (0%)
	Asian	1139 (15%)	8 (6%)	0 (0%)	37 (1%)	2 (<.5%)	0 (0%)	0 (0%)	0 (0%)	588 (100%)	504 (100%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
	Other	552 (7%)	9 (7%)	4 (2%)	209 (6%)	183 (17%)	0 (0%)	137 (93%)	9 (25%)	0 (0%)	0 (0%)	1 (<.5%)	0 (0%)	0 (0%)	0 (0%)
Ethnicity[e]	Hispanic or Latino	698 (18%)	6 (5%)	-	656 (17%)	-	-	-	36 (100%)	-	-	-	-	-	-
	Not Hispanic or Latino	3187 (81%)	125 (95%)	-	3062 (82%)	-	-	-	0 (0%)	-	-	-	-	-	-
	Unknown	34 (1%)	0 (0%)	-	34 (1%)	-	-	-	0 (0%)	-	-	-	-	-	-
Smoking status	Current	1933 (25%)	36 (27%)	122 (58%)	1131 (30%)	203 (18%)	5 (4%)	78 (53%)	5 (14%)	69 (12%)	69 (14%)	22 (8%)	137 (24%)	5 (3%)	51 (41%)
	Former	1906 (25%)	50 (38%)	59 (28%)	1109 (30%)	310 (28%)	15 (11%)	32 (22%)	12 (33%)	122 (21%)	21 (4%)	51 (18%)	72 (13%)	29 (16%)	24 (19%)
	Never	3923 (51%)	45 (34%)	31 (15%)	1505 (40%)	586 (53%)	120 (86%)	38 (26%)	19 (53%)	399 (68%)	414 (82%)	208 (74%)	361 (63%)	147 (81%)	50 (40%)
Substance use[f]	Current	152 (2%)	14 (11%)	5 (2%)	105 (3%)	23 (2%)	0 (0%)	1 (1%)	0 (0%)	4 (1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
	Former	2277 (29%)	55 (42%)	117 (55%)	1886 (50%)	150 (14%)	0 (0%)	19 (13%)	7 (19%)	39 (7%)	0 (0%)	0 (0%)	4 (1%)	0 (0%)	0 (0%)
	Never	5333 (69%)	62 (47%)	91 (43%)	1753 (47%)	926 (84%)	140 (100%)	128 (86%)	29 (81%)	547 (93%)	504 (100%)	281 (100%)	566 (99%)	181 (100%)	125 (100%)
Cardiovascular and Metabolic															
History of hypertension		1785 (23%)	18 (14%)	26 (12%)	1027 (27%)	243 (22%)	31 (22%)	16 (11%)	8 (22%)	111 (19%)	45 (9%)	72 (26%)	114 (20%)	54 (30%)	20 (16%)
History of diabetes		66 (1%)	0 (0%)	2 (1%)	48 (1%)	7 (1%)	0 (0%)	2 (1%)	0 (0%)	2 (<.5%)	4 (1%)	0 (0%)	0 (0%)	0 (0%)	1 (1%)
BMI (kg/m^2)	Median (Q1, Q3)	25.8 (22.8,29.4)	25.6 (23.1, 28.6)	25.4 (23.3, 27.8)	26.9 (24.0, 30.8)	25.8 (23.3, 28.7)	24.7 (22.0, 28.0)	26.2 (24.3, 28.8)	27.1 (24.7, 30.5)	22.7 (20.5, 25.0)	22.9 (20.2, 25.9)	23.7 (20.6, 27.5)	26.8 (22.3, 31.5)	24.6 (21.6, 28.3)	21.3 (19.1, 24.9)
	<18.5	288 (4%)	2 (2%)	5 (2%)	49 (1%)	16 (1%)	6 (4%)	0 (0%)	0 (0%)	49 (8%)	63 (13%)	28 (10%)	41 (7%)	7 (4%)	22 (18%)
	18.5–24.9	3115 (40%)	51 (39%)	87 (41%)	1214 (32%)	454 (41%)	68 (49%)	49 (33%)	10 (28%)	393 (67%)	285 (57%)	144 (51%)	195 (34%)	92 (51%)	73 (58%)
	25–29.9	2664 (34%)	52 (40%)	91 (43%)	1393 (37%)	434 (39%)	46 (33%)	76 (51%)	16 (44%)	138 (23%)	123 (24%)	64 (23%)	152 (27%)	54 (30%)	25 (20%)

Table 1. Continued

Characteristic	Descriptor	Total (N = 7770)	High Income			Latin America and Caribbean				Southeast/ East Asia	South Asia	Sub-Saharan Africa			
			Canada (N = 131)	Spain (N = 213)	USA (N = 3752)[b]	Brazil (N = 1099)	Haiti (N = 140)	Peru (N = 148)	Puerto Rico (N = 36)	Thailand (N = 590)	India (N = 504)	Botswana (N = 281)	South Africa (N = 570)	Uganda (N = 181)	Zimbabwe (N = 125)
	≥30	1696 (22%)	25 (19%)	28 (13%)	1092 (29%)	195 (18%)	20 (14%)	23 (16%)	10 (28%)	10 (2%)	33 (7%)	45 (16%)	182 (32%)	28 (15%)	5 (4%)
Triglycerides (mg/dL)	Median (Q1, Q3)	114 (80, 169)	119 (85, 174)	121 (88, 177)	111 (80, 163)	138 (95, 200)	97 (68, 125)	198 (139, 270)	120 (88, 167)	122 (87, 179)	137 (96, 205)	82 (64, 121)	89 (63, 124)	109 (81, 159)	87 (69, 125)
LDL-C (mg/dL)	Median (Q1, Q3)	108 (87, 128)	114 (92, 133)	119 (104, 138)	106 (86, 125)	116 (95, 136)	104 (82, 127)	111 (88, 132)	111 (90, 127)	122 (103, 141)	107 (87, 126)	99 (81, 120)	96 (76, 116)	102 (81, 127)	89 (68, 107)
HDL-C (mg/dL)	Median (Q1, Q3)	48 (39, 59)	46 (38, 54)	46 (40, 55)	49 (40, 60)	43 (36, 53)	58 (46, 71)	41 (33, 47)	50 (42, 67)	48 (40, 57)	41 (35, 51)	56 (47, 68)	54 (44, 65)	55 (43, 66)	55 (43, 69)

Abbreviations: BMI, body mass index; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol.

[a]Frequency (%) for categorical measures, median with lower and upper quartiles (Q1, Q3) for continuous measures. All statistics are calculated out of participants with data collected. Missing data include the following: smoking status (n = 8); substance use (n = 8); BMI (n = 7); medical history (n = 6).

[b]US enrollment excludes participants in Puerto Rico based on Global Burden of Disease Super Region classification.

[c]Collection of gender identity was implemented after start of study; for participants already enrolled at that time, it may not reflect the gender identify at study entry. See Smeaton et al. [11].

[d]"Other" race includes participants self-identifying as follows: native or indigenous to the enrollment region; more than 1 race (with no single race noted as predominant); or of unknown race.

[e]Ethnicity presented per National Institutes of Health definition for participants in United States (including Puerto Rico) and Canada only.

[f]Substance use includes use of cocaine, methamphetamine, and intravenous drugs.

Table 2. HIV Disease Characteristics and Other Comorbid Conditions[a]

Characteristic	Descriptor	Total (N = 7770)	High Income			Latin America and Caribbean				Southeast/ East Asia	South Asia	Sub-Saharan Africa			
			Canada (N = 131)	Spain (N = 213)	USA (N = 3752)[b]	Brazil (N = 1099)	Haiti (N = 140)	Peru (N = 148)	Puerto Rico (N = 36)	Thailand (N = 590)	India (N = 504)	Botswana (N = 281)	South Africa (N = 570)	Uganda (N = 181)	Zimbabwe (N = 125)
HIV-Related Health Status															
Time since HIV diagnosis (years)	Median (Q1, Q3)	13 (8, 19)	16 (10, 23)	19 (11, 26)	15 (9, 22)	10 (6, 16)	6 (4, 11)	9 (5, 12)	15 (7, 21)	17 (12, 20)	10 (7, 13)	13 (11, 14)	8 (5, 12)	12 (8, 16)	9 (6, 11)
Mode of HIV acquisition[c]	Heterosexual contact	3955 (51%)	17 (13%)	33 (15%)	1179 (31%)	589 (54%)	139 (99%)	22 (15%)	12 (33%)	476 (81%)	480 (95%)	226 (80%)	486 (85%)	179 (99%)	117 (94%)
	Homosexual Contact	2754 (35%)	77 (59%)	106 (50%)	1937 (52%)	393 (36%)	1 (1%)	123 (83%)	20 (56%)	84 (14%)	5 (1%)	3 (1%)	4 (1%)	1 (1%)	0 (0%)
	Injection Drug Use	199 (3%)	15 (11%)	51 (24%)	116 (3%)	4 (<.5%)	0 (0%)	0 (0%)	4 (11%)	9 (2%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
	Multiple modes	284 (4%)	5 (4%)	5 (2%)	208 (6%)	47 (4%)	0 (0%)	0 (0%)	0 (0%)	13 (2%)	6 (1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
	Other	99 (1%)	2 (2%)	1 (<.5%)	56 (1%)	15 (1%)	0 (0%)	0 (0%)	0 (0%)	5 (1%)	7 (1%)	8 (3%)	4 (1%)	0 (0%)	1 (1%)
	Unknown	475 (6%)	15 (11%)	17 (8%)	252 (7%)	51 (5%)	0 (0%)	3 (2%)	0 (0%)	3 (1%)	6 (1%)	44 (16%)	76 (13%)	1 (1%)	7 (6%)
Nadir CD4 count (cells/mm^3)	<50	1406 (18%)	25 (19%)	22 (10%)	814 (22%)	170 (15%)	7 (5%)	24 (16%)	4 (11%)	127 (22%)	83 (16%)	36 (13%)	50 (9%)	34 (19%)	10 (8%)

Table 2. Continued

Characteristic	Descriptor	Total (N = 7770)	High Income			Latin America and Caribbean				Southeast/ East Asia	South Asia	Sub-Saharan Africa			
			Canada (N = 131)	Spain (N = 213)	USA (N = 3752)[b]	Brazil (N = 1099)	Haiti (N = 140)	Peru (N = 148)	Puerto Rico (N = 36)	Thailand (N = 590)	India (N = 504)	Botswana (N = 281)	South Africa (N = 570)	Uganda (N = 181)	Zimbabwe (N = 125)
	50–199	2386 (31%)	38 (29%)	57 (27%)	980 (26%)	333 (30%)	27 (19%)	38 (26%)	7 (19%)	232 (39%)	230 (46%)	184 (65%)	157 (28%)	64 (35%)	39 (31%)
	200–349	2039 (26%)	39 (30%)	65 (31%)	907 (24%)	317 (29%)	34 (24%)	56 (38%)	6 (17%)	190 (32%)	141 (28%)	54 (19%)	150 (26%)	43 (24%)	37 (30%)
	≥350	1677 (22%)	29 (22%)	51 (24%)	871 (23%)	268 (24%)	70 (50%)	30 (20%)	8 (22%)	41 (7%)	50 (10%)	5 (2%)	192 (34%)	35 (19%)	27 (22%)
	Unknown	262 (3%)	0 (0%)	18 (8%)	180 (5%)	11 (1%)	2 (1%)	0 (0%)	11 (31%)	0 (0%)	0 (0%)	2 (1%)	21 (4%)	5 (3%)	12 (10%)
History of AIDS-Defining Event		1849 (24%)	21 (16%)	18 (9%)	716 (19%)	361 (33%)	1 (1%)	11 (7%)	3 (8%)	153 (26%)	250 (50%)	48 (17%)	169 (30%)	89 (49%)	9 (7%)
CD4 count (cells/ mm^3)[d]	Median (Q1, Q3)	621 (448, 827)	667 (460, 880)	702 (481, 925)	613 (443, 829)	674 (488, 885)	580 (437, 729)	653 (480, 865)	693 (469, 969)	625 (476, 784)	591 (378, 758)	591 (452, 756)	633 (449, 831)	531 (369, 764)	542 (398, 806)
HIV-1 RNA below LLQ	<20	2819 (47%)	19 (15%)	64 (30%)	2518 (70%)	0 (0%)	0 (0%)	4 (17%)	15 (65%)	59 (12%)	3 (4%)	0 (0%)	136 (50%)	0 (0%)	1 (6%)
	<40	2243 (37%)	101 (79%)	94 (45%)	537 (15%)	911 (94%)	60 (87%)	15 (63%)	4 (17%)	415 (85%)	50 (66%)	0 (0%)	48 (18%)	0 (0%)	8 (44%)
	<400	188 (3%)	0 (0%)	38 (18%)	18 (<0.5%)	1 (<.5%)	0 (0%)	0 (0%)	0 (0%)	1 (<.5%)	9 (12%)	93 (98%)	27 (10%)	0 (0%)	1 (6%)
	≥LLQ	748 (12%)	8 (6%)	15 (7%)	544 (15%)	60 (6%)	9 (13%)	5 (21%)	4 (17%)	16 (3%)	14 (18%)	2 (2%)	63 (23%)	0 (0%)	8 (44%)
HIV-1 RNA (log_{10} cp/mL)[e]	Median (Q1, Q3)	1.8 (1.5, 2.3)	1.8 (1.7, 2.0)	1.6 (1.5, 2.0)	1.7 (1.5, 2.2)	2.1 (1.8, 2.7)	3.0 (2.4, 3.7)	1.7 (1.5, 2.4)	1.5 (1.5, 1.7)	1.7 (1.5, 1.8)	3.8 (2.1, 4.8)	2.9 (2.9, 3.0)	2.0 (1.6, 2.4)	-	2.6 (2.3, 3.0)
Total ART use (years)	Median (Q1, Q3)	10 (5, 15)	11 (7, 17)	16 (9, 22)	11 (6, 17)	7 (4, 13)	4 (3, 7)	6 (4, 10)	11 (6, 17)	13 (9, 16)	7 (5, 11)	12 (9, 13)	5 (3, 8)	10 (5, 14)	8 (6, 10)
ART regimen class	NRTI + INSTI	1978 (25%)	72 (55%)	97 (46%)	1698 (45%)	52 (5%)	11 (8%)	2 (1%)	17 (47%)	3 (1%)	2 (<.5%)	15 (5%)	3 (1%)	6 (3%)	0 (0%)
	NRTI + NNRTI	3676 (47%)	26 (20%)	60 (28%)	912 (24%)	590 (54%)	102 (73%)	118 (80%)	7 (19%)	465 (79%)	410 (81%)	237 (84%)	502 (88%)	126 (70%)	121 (97%)
	NRTI + PI	1439 (19%)	11 (8%)	26 (12%)	637 (17%)	383 (35%)	26 (19%)	26 (18%)	5 (14%)	106 (18%)	83 (16%)	28 (10%)	61 (11%)	43 (24%)	4 (3%)
	NRTI-sparing	199 (3%)	8 (6%)	21 (10%)	131 (3%)	15 (1%)	0 (0%)	0 (0%)	2 (6%)	9 (2%)	9 (2%)	1 (<.5%)	2 (<.5%)	1 (1%)	0 (0%)
	Other NRTI-containing	476 (6%)	14 (11%)	8 (4%)	373 (10%)	59 (5%)	1 (1%)	2 (1%)	5 (14%)	7 (1%)	0 (0%)	0 (0%)	2 (<.5%)	5 (3%)	0 (0%)
Other Comorbidities															
History of cancer		287 (4%)	5 (4%)	9 (4%)	201 (5%)	45 (4%)	0 (0%)	1 (1%)	1 (3%)	10 (2%)	0 (0%)	2 (1%)	3 (1%)	10 (6%)	0 (0%)
History of non-AIDS cancer		152 (2%)	3 (2%)	5 (2%)	121 (3%)	14 (1%)	0 (0%)	1 (1%)	0 (0%)	7 (1%)	0 (0%)	0 (0%)	0 (0%)	1 (1%)	0 (0%)
History of kidney disease		29 (<.5%)	0 (0%)	0 (0%)	23 (1%)	3 (<.5%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (<.5%)	0 (0%)	1 (<.5%)	0 (0%)	1 (1%)
Chronic active HBV		210 (3%)	4 (3%)	5 (2%)	122 (3%)	17 (2%)	0 (0%)	5 (3%)	1 (3%)	39 (7%)	1 (<.5%)	0 (0%)	16 (3%)	0 (0%)	0 (0%)
Chronic active HCV		156 (2%)	2 (2%)	2 (1%)	128 (3%)	6 (1%)	0 (0%)	0 (0%)	1 (3%)	16 (3%)	0 (0%)	0 (0%)	1 (<.5%)	0 (0%)	0 (0%)

Abbreviations: AIDS, acquired immunodeficiency syndrome; ART, antiretroviral therapy; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; INSTI, integrase strand transfer inhibitor; LLQ, lower limit of quantitation; NNRTI, nonnucleoside reverse-transcriptase inhibitor; NRTI, nucleoside reverse-transcriptase inhibitor; PI, protease inhibitor; RNA, ribonucleic acid.

[a]Frequency (%) for categorical measures, median with lower and upper quartiles (Q1, Q3) for continuous measures. All statistics are calculated out of participants with data collected. Missing data include the following: time since HIV diagnosis (n = 4); HIV-1 RNA below LLQ (n = 1772); total ART use (n = 2); ART regimen class (n = 2); medical history (n = 6).

[b]US enrollment excludes participants in Puerto Rico based on Global Burden of Disease Super Region classification.

[c]Participant self-report of most likely mode of HIV acquisition; "Other" includes transfusion, occupational exposure, and hemophilia-associated injections.

[d]CD4 count obtained at screening.

[e]Among participants with quantifiable HIV-1 RNA.

preserving blinding and maximizing participant retention while follow up is ongoing. This Supplement includes 6 articles, along with this introduction, all covering relevant topics to REPRIEVE and the general global population of PWH. These manuscripts focus on ART and immune function, reproductive aging among cisgender women with HIV, the emerging population of PWH identifying across the transgender spectrum, kidney function, physical function and frailty, as well as assessment of myocardial steatosis. Data collected and presented in this Supplement significantly increase our understanding of the global population with HIV. For example, these studies demonstrate emerging time trends in ART use that vary radically across the globe, specific factors that are associated with preserved immune function, and relationships with ART. These studies, through assessment of antimullerian hormone and detailed menstrual history, characterize reproductive aging in women, identifying critical correlates, with implications for cardiometabolic health. Physical function is reduced, and frailty increased in PWH, with potentially important implications for quality of life and disability. Kidney function tracks with specific risk factors among PWH, whereas use of specific calculators may result in levels of glomerular filtration rates that differ across critical thresholds. Intramyocardial lipid content is increased in a high proportion, with potential implications for heart failure. Finally, this Supplement provides new information on the transgender population with HIV, for whom little is known with respect to comorbidities and cardiovascular risk.

CONCLUSIONS

REPRIEVE has been a major effort and remains an important focus for NIH. REPRIEVE represents a remarkable example of cooperation and collaboration across the following organizations: NIH; key industry funders; AIDS trial networks including ACTG, the CTN, and NEAT ID; academic centers of the principal investigators and trial leadership, including the Center for Biostatistics in AIDS Research (CBAR) at the Harvard T. H. Chan School of Public Health, providing critical data analyses, as well as Social and Scientific Systems for trial management; PPD for site monitoring; and Frontier Science Foundation for data management. Most importantly, REPRIEVE has been successful due to the willing participation of trial participants and the hard work of clinical research sites to recruit and retain participants over a long study. The trial leadership is extremely grateful for these contributions. A major goal of REPRIEVE in this regard is to provide knowledge back to the field including clinicians and PWH, which it has begun to do with this Supplement and the first description of the baseline population of recruited participants. REPRIEVE will continue to provide additional information in subsequent manuscripts as it advances towards achieving its primary goals.

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

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