Risk of obesity, diabetes, hypertension, and major adverse cardiovascular events after a switch to an integrase inhibitor: a target trial emulation in REPRIEVE

Emma M Kileel, Carlos D Malvestutto, Markella V Zanni, Emma Davies-Smith, Carl J Fichtenbaum, Jordan E Lake, Janet Lo, Judith A Aberg, Esteban Martinez, Kunjal Patel, Gerald S Bloomfield, Sarah M Chu, Aya Awwad, Marissa R Diggs, Alex B Lu, Sara H Bares, Daniel Berrner, Marek Smieja, Nwora Lance Okeke, Princy Kumar, Esau João, Judith S Currier, Michael T Lu, Matthew P Fox, Alana T Brennan, Pamela S Douglas, Steven K Grinspoon, Heather J Ribaudo

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Department of Epidemiology, Boston University School of Public Health, Boston, MA, USA (E M Kileel PhD, Prof M P Fox DSc, A T Brennan PhD); **Department of Global Health, Boston University School of Public Health, Boston, MA, USA** (E M Kileel, Prof M P Fox, A T Brennan); **Division of Infectious Diseases, Ohio State University Medical Center, Columbus, OH, USA** (C D Malvestutto MD); **Metabolism Unit, Massachusetts General Hospital and Harvard Medical School, Boston, MA, USA** (Prof M V Zanni MD, J Lo MD, S M Chu MSN, A Awwad MD, M R Diggs BA, A B Lu BAS, Prof S K Grinspoon MD); **Center for Biostatistics in AIDS Research, Harvard T H Chan School of Public Health, Boston, MA, USA** (E Davies-Smith PhD, K Patel PhD, H J Ribaudo PhD); **Division of Infectious Diseases, Department of Medicine, University of Cincinnati, Cincinnati, OH, USA** (Prof C J Fichtenbaum MD); **Department of Medicine, McGovern Medical School, Houston, TX, USA** (Prof J E Lake MD); **Division of Infectious Diseases, Department of Medicine, Icahn School of Medicine at Mount Sinai, New York, NY, USA** (Prof J A Aberg MD); **Infectious Diseases Service, Hospital Clinic and University of Barcelona, Barcelona, Spain** (E Martinez MD); **CIBER de Enfermedades Infecciosas, Institute de Salud Carlos III,**

Summary

Background Integrase strand-transfer inhibitors (INSTIs) are linked to weight gain, but data on their cardiometabolic effects, particularly major adverse cardiovascular events (MACE), are scarce. We aimed to estimate the risk of obesity, diabetes, hypertension, and MACE after switching to an INSTI in people with HIV at low-to-moderate cardiovascular risk.

Methods In this retrospective cohort study, we used data from the global Randomized Trial to Prevent Vascular Events in HIV (REPRIEVE) to emulate a series of trials comparing switching to an INSTI versus remaining on a non-INSTI regimen on risk of incident obesity, diabetes, hypertension, and MACE. The REPRIEVE trial collected data across 12 countries from participants aged 40–75 years, on a stable antiretroviral therapy regimen for at least 6 months, with a CD4 count of >100 cells per µL, and with low-to-moderate risk for atherosclerotic cardiovascular disease. From this cohort, we included participants without a previous diagnosis of the outcomes or previous INSTI use and used data for a follow-up period of 5 years, until the outcome event, loss to follow-up, death, or study end. Data from emulated trials were pooled and hazard ratios (HRs) were estimated with weighted Cox proportional hazard models, accounting for competing events.

Findings 5114 participants met eligibility criteria for at least one emulated trial, representing 99 357 person-trials (median age 49 years [45–54]; 62 826 [63·2%] of 99 357 were male; 36 531 [36·8%] were female). 2981 (58·3%) of 5114 participants were captured as an INSTI switcher in at least one trial. Most switchers (2412 [80·9%] of 2981) initiated a dolutegravir-based regimen and most (47 263 [67·1%] of 70 458) non-switchers were on an efavirenz-based regimen. The HR of obesity (HR 1·41, 95% CI 1·22–1·59), diabetes (1·50, 1·24–1·81), and hypertension (1·45, 1·26–1·67) was higher in switchers than non-switchers. We did not observe an effect on MACE (1·17, 0·87–1·57).

Interpretation The increase in cardiometabolic risk profile suggests long-term observation of people with HIV switching to INSTIs will be crucial to ensure appropriate management of comorbidities and to assess for future development of MACE.

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Introduction

Integrase strand-transfer inhibitors (INSTIs), a class of antiretroviral therapy (ART) that includes the drugs dolutegravir, raltegravir, elvitegravir, bictegravir, and cabotegravir, have been widely recognised for their superior safety profiles and enhanced resistance barriers and are now the recommended ART regimens globally.[1] Although these drugs have shown improved tolerability and adherence compared with other ARTs,[2] there has been growing concern over their association with weight gain. Evidence suggests that INSTIs, compared with protease inhibitors or non-nucleoside reverse transcriptase inhibitors, are associated with excess weight gain, even in those who are virally suppressed at the time of initiation.[3] The effect appears to be heightened in specific groups, including women.[3]

INSTI-associated weight gain is particularly concerning given the well established connection between weight and cardiometabolic conditions.[4] Irrespective of treatment strategy, conditions such as diabetes, hypertension, and cardiovascular disease are occurring at higher rates and younger ages in people with HIV than in people without HIV.[5] Whether INSTI use and its associated weight gain exacerbates cardiometabolic disease risk remains unclear. Although studies evaluating the cardiometabolic consequences of INSTI use have started to emerge, results have been conflicting and follow-up periods, in general, have been limited to

Research in context

Evidence before this study

We searched PubMed for literature published between Jan 1, 2015, and April 1, 2025, with the terms "integrase inhibitors" AND ("weight" OR "weight gain" OR "obesity" OR "diabetes" OR "hypertension" OR "major adverse cardiovascular events" OR "cardiovascular disease"). A large body of evidence shows disproportionate weight gain in people with HIV initiating integrase strand-transfer inhibitor (INSTI)-containing antiretroviral therapy (ART) regimens compared with protease inhibitor-containing or non-nucleoside reverse transcriptase inhibitor-containing regimens. Studies evaluating the cardiometabolic consequences of INSTI use are less common and have been done primarily in high-income regions with follow-up periods typically of 12–24 months. Only four studies have evaluated the cardiovascular effect of INSTI use. A study from the RESPOND cohort found an elevated risk of cardiovascular disease events in those exposed to INSTIs versus those with no INSTI exposure. However, these results were contradicted by findings from the Swiss HIV Cohort Study and the HIV-CAUSAL Collaboration, which found no effect of INSTI use on cardiovascular disease events. These studies were limited to high-income regions, specifically Europe and North America.

Added value of this study

Our analysis with data from the global REPRIEVE trial contributes important findings to the existing body of data evaluating the cardiometabolic consequences of INSTI use. Currently, many studies have been limited to new ART initiators and do not extend beyond 2 years of follow-up. Our study evaluates new-onset obesity, diabetes, hypertension, and clinically adjudicated major adverse cardiovascular events (MACE) over 5 years of follow-up in a global population of ART-experienced people with HIV at low-to-moderate cardiovascular disease risk.

Implications of all the available evidence

The increasing cardiometabolic risk profile developing in INSTI switchers compared with non-switchers suggests such patients, particularly women, will need long-term monitoring of comorbidities and close follow-up for the potential development of MACE.

12 months and 24 months.[6–8] Moreover, most studies have been restricted to specific geographical regions, with the majority done in high-income settings such as Europe and North America.

The Randomized Trial to Prevent Vascular Events in HIV (REPRIEVE) is an ideal cohort to further the understanding of the metabolic and cardiovascular effect of INSTI use. REPRIEVE was the first large-scale primary prevention trial of cardiovascular disease in people with HIV, designed to test whether daily pitavastatin reduced the risk of major adverse cardiovascular events (MACE) in people with HIV at low-to-moderate cardiovascular disease risk.[9] We aimed to do a secondary analysis of REPRIEVE data to evaluate the effect of switching to an INSTI-containing regimen on cardiometabolic outcomes. Using this global cohort of ART-experienced people with HIV, we emulated a series of target trials to estimate the effect of switching to an INSTI-based treatment regimen versus remaining on a regimen based on protease inhibitors or non-nucleoside reverse transcriptase inhibitors on the risk of incident obesity, diabetes, hypertension, and MACE during 5 years of follow-up.

Methods

Study design and participants

For this retrospective, cohort study, we used the target trial emulation framework. The target trial framework involves first specifying components of the protocol for a hypothetical trial that would have been done (the target trial) to answer the research question of interest and then emulating this protocol with observational data.[10] The protocol of our target trial would be as follows: people with HIV aged 40–75 years who have been on a stable non-INSTI-containing ART regimen for at least 6 months, with no previous INSTI exposure and no history of the event of interest, would be eligible for the trial. Eligible participants would be randomly assigned to one of two treatment strategies: switch to an INSTI-containing ART regimen or remain on a non-INSTI-containing ART regimen. The outcomes of interest would be incident obesity, diabetes, hypertension, and clinically adjudicated MACE. Participants would be followed up from treatment assignment until the event of interest, death, loss to follow-up, or end of the trial at a maximum of 5 years. The causal contrast of interest would be the intention-to-treat effect. These components are further described in the appendix (pp 2–3).

We emulated the target trial with longitudinal data collected in REPRIEVE. Although REPRIEVE (NCT02344290) is a multicentre, phase 3, double-blind, randomised trial, for the purposes of this analysis we treated its routinely collected measurements as observational data to approximate the protocol of the hypothetical trial. Individuals were eligible for REPRIEVE if they were aged 40–75 years, on a stable ART regimen for at least 6 months, had a CD4 count of >100 cells per μL, and were considered low-to-moderate risk for atherosclerotic cardiovascular disease.[9] Between March 26, 2015, and July 31, 2019, REPRIEVE enrolled 7769 participants in 12 countries (the USA, Botswana, Brazil, Canada, Haiti, India, Peru, South Africa, Spain, Thailand, Uganda, and Zimbabwe) from hospitals, community clinics, and clinical research sites. The trial was stopped for efficacy in March, 2023, after it was found that participants in the

Madrid, Spain (E Martinez); **Department of Epidemiology, Harvard T H Chan School of Public Health, Boston, MA, USA** (K Patel); **Department of Medicine, Duke Global Health Institute and Duke Clinical Research Institute, Duke University, Durham, NC, USA** (G S Bloomfield MD); **Division of Infectious Diseases, University of Nebraska Medical Center, Omaha, NE, USA** (S H Bares MD); **Division of HIV, Infectious Diseases & Global Medicine, University of California San Francisco at Zuckerberg San Francisco General Hospital, San Francisco, CA, USA** (D Berrner MD); **Department of Pathology and Molecular Medicine, McMaster University, Hamilton, ON, Canada** (M Smieja MD); **Department of Population Health Sciences and Department of Medicine, Duke University School of Medicine, Durham, NC, USA** (N L Okeke MD); **Division of Infectious Diseases and Travel Medicine, Georgetown University School of Medicine, Washington, DC, USA** (P Kumar MD); **Infectious Diseases Department, Hospital Federal dos Servidores do Estado, Rio de Janeiro, Brazil** (E João MD); **Department of Medicine, David Geffen School of Medicine, University of California Los Angeles, Los Angeles, CA, USA** (Prof J S Currier MD); **Cardiovascular Imaging Research Center, Massachusetts General Hospital and Harvard Medical School, Boston, MA, USA** (M T Lu MD); **Duke University Research Institute, Duke University School of Medicine, Durham, NC, USA** (Prof P S Douglas MD)

Correspondence to:
Prof Steven K Grinspoon, Metabolism Unit, Massachusetts General Hospital and Harvard Medical School, Boston, MA 02114, USA
sgrinspoon@mgh.harvard.edu

See Online for appendix

pitavastatin group had a 35% reduction in the hazard of MACE compared with participants in the placebo group.[11,12] Study closeout visits were completed by August, 2023, allowing for a minimum of 4 years and a maximum of 8 years of follow-up, depending on participants' enrolment date (median follow-up of 5·6 years).

REPRIEVE received approval from the Massachusetts General Brigham Human Research Committee (approval number 2013P001898), and each clinical research site obtained authorisation from relevant regulatory bodies. No further approval was needed for this analysis. Written informed consent was collected from all participants.

Procedures

Data elements were assessed in REPRIEVE participants according to previously described procedures.[9,11] Specifically, sex at birth was self-reported (options were male or female) and data on race were collected as per Advancing Clinical Therapeutics Globally guidance. We identified participants eligible for our trial emulation starting on day 0 of follow-up in REPRIEVE. Eligible participants were then assigned to the treatment strategy that was compatible with their data in the subsequent 60-day baseline period, meaning that if a participant switched to an INSTI-based regimen between days 0 and 59 of REPRIEVE, they were considered a switcher and if a participant did not switch to an INSTI-based regimen during the baseline period, they were considered a non-switcher. Time to the outcome of interest was assessed from the end of the baseline period to a maximum follow-up of 5 years. We repeated this process every 60 days until day 2160 of REPRIEVE, emulating a total of 37 sequential trials, each with the potential for at least 2 years of follow-up. For a visual representation of this approach and a description of how a participant could move through trials, see the appendix (pp 4–5).

The protocol components of the observational emulations were the same as the target trial components with three exceptions. First, since we did not have participants' full ART histories in REPRIEVE, we could not conclusively rule out any previous INSTI exposure. However, participants who enrolled in REPRIEVE on an INSTI-based regimen were ineligible for all target trial emulations and those who switched to an INSTI during REPRIEVE follow-up were ineligible for all subsequent trials after INSTI switch. Second, participants enrolled in low-income and middle-income regions, including Latin America, southeast Asia, and sub-Saharan Africa, were not considered for trial eligibility until 2018 due to INSTI unavailability in these regions. Third, as switching to an INSTI was at the discretion of the participants and their clinicians in REPRIEVE, randomisation in the observational emulation was assumed conditional on a set of measured baseline covariates.

The causal contrast of interest of the emulated trial was the observational analogue of the intention-to-treat effect of a single timepoint intervention (switch now *vs* do not switch now with the potential to switch later), defined as the marginal causal effect of assignment at that timepoint, regardless of adherence or subsequent changes in regimen. This approach aligns with the clinical reality that people with HIV have the potential to change ART regimens at any visit with their clinician.

Outcomes

Target trials were emulated for four distinct outcome measures, including incident obesity, diabetes, hypertension, and clinically adjudicated MACE. Incident obesity was defined as BMI ≥27·7 kg/m² for Asian participants and BMI ≥30·0 kg/m² otherwise. Incident diabetes was defined as fasting blood glucose ≥7 mmol/L, use of an antidiabetic medication, or documented diagnosis of diabetes. Incident hypertension was defined as systolic blood pressure ≥140 mm Hg and/or diastolic blood pressure ≥90 mm Hg, or use of antihypertensive treatment for elevated blood pressure, or documented hypertension diagnosis. MACE was defined as a composite outcome of cardiovascular death, myocardial infarction, hospitalisation for unstable angina, stroke, transient ischaemic attack, peripheral arterial ischaemia, revascularisation (coronary, carotid, or peripheral arterial), or death from an undetermined cause. All four outcomes were assessed in the intention-to-treat cohort.

Statistical analysis

We used inverse probability of treatment weights (IPTWs) to achieve balance of measured confounders between switchers and non-switchers at the start of each sequential trial. We used logistic regression models to predict the probability of treatment assignment (ie, switch=1) based on a set of confounding characteristics identified a priori (appendix p 6), including sex at birth; age; race; REPRIEVE enrolment region and year; alcohol, cigarette, and substance use; diet quality; physical activity levels; total ART duration at REPRIEVE entry; nadir CD4 cell count; estimated glomerular filtration rate at REPRIEVE entry; statin randomisation group; atherosclerotic cardiovascular disease (ASCVD) risk score at REPRIEVE entry; and BMI at the start of each trial. Sequential trial number was included as a covariate in both the numerator and denominator of the IPTW models. To improve precision and reduce variability of the estimates, weights were stabilised by multiplying the IPTWs by the marginal probability of the treatment received. We assessed model specification by calculating standardised differences of covariates after weighting and means and standard deviations of stabilised IPTWs for each trial.

To estimate the effect of switch versus no switch on the outcomes of interest, we used IPTW cause-specific Cox proportional regression models with data pooled across all sequential trials. Death was considered a competing event. Estimated hazard ratios (HRs) provide an average HR over the follow-up period, reflecting a summary of

the relative hazard over 5 years. To account for the repeated use of participants over sequential trials, we used non-parametric bootstrapping with 500 replicates to generate percentile-based 95% CIs. Both the IPTW models and hazard models were estimated within each bootstrap sample, allowing the bootstrap CIs to account for the uncertainty in both the estimation of the IPTW model and the hazard model.[13] All analyses were done in the overall eligible population and in individuals born male and female separately. Analyses were done with SAS (version 9.4) on a Linux operating environment.

We did the following sensitivity analyses: (1) adjusting for tenofovir alafenamide use at sequential trial baseline due to its association with weight gain;[14] (2) adjusting for tenofovir disoproxil fumarate use at sequential trial baseline due to potential weight suppressive effects;[14] (3) adding an eligibility criterion requiring participants to be taking tenofovir disoproxil fumarate at sequential trial baseline to further understand the degree to which weight suppressive effects of tenofovir disoproxil fumarate contributed to our findings; (4) adding an eligibility criterion requiring participants to be taking efavirenz at trial baseline to evaluate the effect of efavirenz, which has similarly been shown to have weight suppressive properties;[15] (5) adding a criterion requiring switchers to switch to a dolutegravir-based regimen to try and isolate the effects of specific INSTI regimens; (6) adjusting for waist circumference measured at REPRIEVE entry as a proxy for lipodystrophy and body composition changes; (7) for the outcome of MACE, adding an eligibility criterion requiring participants to have an ASCVD risk score >2·5 to assess whether results differ in those with some degree of baseline ASCVD risk; (8) using a 30-day baseline period to determine the extent to which the size of the baseline period affected our study; (9) limiting sequential trial emulation to trials with the potential for at least 5 years of follow-up to evaluate whether differing lengths of follow-up in sequential trials affected our analysis; (10) censoring the sequential trial emulation at 3 years of follow-up to evaluate variability in the average treatment effect over varying follow-up time; and (11) using a pooled logistic regression with time as a functional form for estimation to ensure approximation to the hazard model.

We did the following exploratory, post-hoc analyses: (1) evaluating the effect of weight gain on the outcomes of diabetes, hypertension, and MACE by adjusting for time-updated percentage change in BMI; (2) stratifying analyses by region (high-income countries and low-income to middle-income countries); and (3) evaluating the outcome of hard MACE, a more stringent composite outcome of myocardial infarction, stroke, and cardiovascular death.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

	INSTI switchers (n=2981 person-trials; 2981 unique individuals)	Non-switchers (n=96 376 person-trials; 5059 unique individuals)	Total (n=99 357 person-trials; 5114 unique individuals)
Age, years			
Median (IQR)	49 (45–55)	49 (45–54)	49 (45–54)
40–49	1493 (50·1%)	50 767 (52·7%)	52 260 (52·6%)
50–59	1238 (41·5%)	38 245 (39·7%)	39 483 (39·7%)
≥60	250 (8·4%)	7364 (7·6%)	7614 (7·7%)
Sex at birth			
Male	1869 (62·7%)	60 957 (63·2%)	62 826 (63·2%)
Female	1112 (37·3%)	35 419 (36·8%)	36 531 (36·8%)
Gender identity			
Cisgender	2927 (98·2%)	94 143 (97·7%)	97 070 (97·7%)
Transgender	39 (1·3%)	1480 (1·5%)	1519 (1·5%)
Not reported	15 (0·5%)	753 (0·8%)	768 (0·8%)
Race			
Black or African American	1328 (44·5%)	36 476 (37·8%)	37 804 (38·0%)
White	687 (23·0%)	25 323 (26·3%)	26 010 (26·2%)
Asian	685 (23·0%)	23 037 (23·9%)	23 722 (23·9%)
Other	281 (9·4%)	11 540 (12·0%)	11 821 (11·9%)
Ethnicity			
Not Hispanic or Latino	714 (24·0%)	22 484 (23·3%)	23 198 (23·3%)
Hispanic or Latino	158 (5·3%)	5920 (6·1%)	6078 (6·1%)
Unknown	2109 (70·7%)	67 972 (70·5%)	70 081 (70·5%)
Country or region of enrolment			
North America	955 (32·0%)	30 573 (31·7%)	31 528 (31·7%)
South America	555 (18·6%)	23 351 (24·2%)	23 906 (24·1%)
Africa	767 (25·7%)	18 113 (18·8%)	18 880 (19·0%)
Thailand	360 (12·1%)	13 687 (14·2%)	14 047 (14·1%)
India	316 (10·6%)	8917 (9·3%)	9233 (9·3%)
Spain	28 (0·9%)	1735 (1·8%)	1763 (1·8%)
Smoking status			
Current	618 (20·7%)	20 937 (21·7%)	21 555 (21·7%)
Former	631 (21·2%)	21 102 (21·9%)	21 733 (21·9%)
Never	1729 (58·0%)	54 260 (56·3%)	55 989 (56·4%)
Alcohol use			
Missing	2 (0·1%)	123 (0·1%)	125 (0·1%)
Rarely or never	2292 (76·9%)	72 275 (75·0%)	74 567 (75·0%)
Usually, often, or sometimes	687 (23·0%)	23 978 (24·9%)	24 665 (24·8%)
Substance use			
Current or former	590 (19·8%)	20 166 (20·9%)	20 756 (20·9%)
Never	2387 (80·1%)	76 120 (79·0%)	78 507 (79·0%)
Diet			
Ideal	531 (17·8%)	16 941 (17·6%)	17 472 (17·6%)
Intermediate	1577 (52·9%)	54 020 (56·1%)	55 597 (56·0%)
Poor	870 (29·2%)	25 229 (26·2%)	26 099 (26·3%)
Physical activity			
Ideal	346 (11·6%)	11 660 (12·1%)	12 006 (12·1%)
Intermediate	1392 (46·7%)	46 081 (47·8%)	47 473 (47·8%)
Poor	1238 (41·5%)	38 386 (39·8%)	39 624 (39·9%)

Data are n (%) unless otherwise specified. INSTI=integrase strand-transfer inhibitor.

Table 1: **Demographic and behavioural characteristics of included participants**

Results

For each outcome of interest, we emulated 37 sequential trials. Overall, 5114 participants were eligible for at least one emulated trial (appendix p 7). Of these, 2981 (58·3%) were captured as an INSTI switcher in exactly one trial for at least one outcome and 5059 were captured as a non-switcher in at least one trial, contributing to a total of 99 357 person-trials. Demographic, behavioural, and cardiometabolic characteristics were largely similar between switchers and non-switchers (tables 1, 2). The majority of non-switchers were on an efavirenz-based regimen and the majority also received tenofovir disoproxil fumarate (table 3). This combination was also the most common regimen before an INSTI switch.

	INSTI switchers (n=2981 person-trials; 2981 unique individuals)	Non-switchers (n=96 376 person-trials; 5059 unique individuals)	Total (n=99 357 person-trials; 5114 unique individuals)
BMI, kg/m²			
Median (IQR)	25·0 (22·1–28·7)	25·4 (22·4–29·0)	25·4 (22·3–28·9)
<25·0	1481 (49·7%)	45 114 (46·8%)	46 595 (46·9%)
25·0–29·9	955 (32·0%)	32 203 (33·4%)	33 158 (33·4%)
≥30·0	544 (18·2%)	19 053 (19·8%)	19 597 (19·7%)
Fasting glucose, mg/dL			
Median (IQR)	90 (84–97)	91 (84–98)	91 (84–98)
Systolic blood pressure, mm Hg			
Median (IQR)	122 (112–132)	121 (111–132)	121 (111–132)
Diastolic blood pressure, mm Hg			
Median (IQR)	80 (71–85)	79 (70–84)	79 (70–84)
eGFR by CKD-EPI, mL/min per 1·73 mm²			
Median (IQR)	102·3 (88·6–114·1)	101·4 (88·0–112·1)	101·4 (88·0–112·1)
≥90	2026 (68·0%)	64 916 (67·4%)	66 942 (67·4%)
60 to <90	912 (30·6%)	29 917 (31·0%)	30 829 (31·0%)
<60	43 (1·4%)	1543 (1·6%)	1586 (1·6%)
ASCVD risk score, %			
Median (IQR)	3·9 (1·8–6·6)	3·7 (1·6–6·5)	3·7 (1·6–6·5)
0 to <2·5	947 (31·8%)	33 029 (34·3%)	33 976 (34·2%)
2·5 to <7·5	1504 (50·5%)	46 230 (48·0%)	47 734 (48·0%)
7·5–10	354 (11·9%)	11 493 (11·9%)	11 847 (11·9%)
>10	176 (5·9%)	5624 (5·8%)	5800 (5·8%)
Nadir CD4 count, cells per µL			
<200	1522 (51·1%)	46 616 (48·4%)	48 138 (48·4%)
200–349	833 (27·9%)	26 608 (27·6%)	27 441 (27·6%)
≥350	558 (18·7%)	20 745 (21·5%)	21 303 (21·4%)
Unknown	68 (2·3%)	2407 (2·5%)	2475 (2·5%)
Total ART use, years			
<5	646 (21·7%)	23 408 (24·3%)	24 054 (24·2%)
5–10	933 (31·3%)	30 917 (32·1%)	31 850 (32·1%)
≥10	1402 (47·0%)	42 027 (43·6%)	43 429 (43·7%)
Unknown	0	24 (<0·1%)	24 (<0·1%)
CD4 count, cells per µL			
≥500	2027 (68·0%)	66 236 (68·7%)	68 263 (68·7%)
<500	954 (32·0%)	30 140 (31·3%)	31 094 (31·3%)
HIV-1 RNA, copies per mL			
<LLQ	1725 (57·9%)	61 170 (63·5%)	62 895 (63·3%)
LLQ to <400	167 (5·6%)	5375 (5·6%)	5542 (5·6%)
≥400	35 (1·2%)	1456 (1·5%)	1491 (1·5%)
Unknown	1054 (35·4%)	28 375 (29·4%)	29 429 (29·6%)

Data are n (%) unless otherwise specified. ART=antiretroviral therapy. ASCVD=atherosclerotic cardiovascular disease. CKD-EPI=Chronic Kidney Disease Epidemiology Collaboration. eGFR=estimated glomerular filtration rate. INSTI=integrase strand-transfer inhibitor. LLQ=lower limit of quantitation.

Table 2: **Cardiometabolic and HIV-related health characteristics of included participants**

	INSTI switchers (n=2981 person-trials; 2981 unique individuals)		Non-switchers (n=96 376 person-trials; 5059 unique individuals)	Total (n=99 357 person-trials; 5114 unique individuals)*
	Pre-switch	At switch		
ART regimen class				
NRTI and INSTI	..	2765 (92·8%)	..	2765 (2·8%)
NRTI and NNRTI	2089 (70·1%)	0	69 335 (71·9%)	69 335 (69·8%)
NRTI and PI	814 (27·3%)	0	25 070 (26·0%)	25 070 (25·2%)
NRTI-sparing	23 (0·8%)	107 (3·6%)	555 (0·6%)	662 (0·7%)
Other NRTI-containing	55 (1·8%)	109 (3·7%)	1416 (1·5%)	1525 (1·5%)
Choice of INSTI				
Dolutegravir	..	2412 (80·9%)	..	2412 (81·0%)
Bictegravir	..	369 (12·4%)	..	369 (12·4%)
Elvitegravir	..	172 (5·8%)	..	172 (5·8%)
Cabotegravir	..	14 (0·5%)	..	14 (0·5%)
Raltegravir	..	12 (0·4%)	..	12 (0·4%)
Choice of NRTI†				
Tenofovir disoproxil fumarate plus emtricitabine or lamivudine	2096/2958 (70·9%)	1718/2873 (59·8%)	64 714/95 821 (67·5%)	66 432/98 695 (67·3%)
Tenofovir alafenamide plus emtricitabine or lamivudine	214/2958 (7·2%)	733/2873 (25·5%)	13 855/95 821 (14·5%)	14 588/98 695 (14·8%)
Zidovudine plus emtricitabine or lamivudine	401/2958 (13·6%)	41/2873 (1·4%)	9514/95 821 (9·9%)	9555/98 695 (9·7%)
Abacavir plus emtricitabine or lamivudine	177/2958 (6·0%)	202/2873 (7·0%)	6027/95 821 (6·3%)	6229/98 695 (6·3%)
Other NRTI	70/2958 (2·4%)	180/2873 (6·3%)	1711/95 821 (1·8%)	1891/98 695 (1·9%)
Choice of NNRTI†				
Efavirenz	1532/2127 (72·0%)	1/92 (1·1%)	47 263/70 458 (67·1%)	47 281/70 549 (67·0%)
Rilpivirine	253/2127 (11·9%)	61/92 (66·3%)	15 820/70 458 (22·5%)	15 881/70 549 (22·5%)
Nevirapine	323/2127 (15·2%)	4/92 (4·3%)	6770/70 458 (9·6%)	6774/70 549 (9·6%)
Etravirine	18/2127 (0·8%)	5/92 (5·4%)	465/70 458 (0·7%)	470/70 549 (0·7%)
Doravirine	1/2127 (<0·1%)	2/92 (2·2%)	139/70 458 (0·2%)	141/70 549 (0·2%)
Choice of PI†				
Atazanavir	489/863 (56·7%)	14/123 (11·4%)	12 245/26 551 (46·1%)	12 255/26 671 (45·9%)
Darunavir	228/863 (26·4%)	103/123 (83·7%)	10 243/26 551 (38·6%)	10 346/26 671 (38·8%)
Lopinavir	137/863 (15·9%)	5/123 (4·1%)	3825/26 551 (14·4%)	3830/26 671 (14·4%)
Other PI	9/863 (1·0%)	1/123 (0·8%)	238/26 551 (0·9%)	239/26 671 (0·9%)

ART=antiretroviral therapy. NRTI=nucleoside reverse transcriptase inhibitor. INSTI=integrase strand-transfer inhibitor. NNRTI=non-nucleoside reverse transcriptase inhibitor. PI=protease inhibitor. *Total column represents summation between non-switchers and switchers at the time of switch. †Percentages are calculated within each ART regimen class.

***Table 3*: Details of ART regimens for included participants**

Most switchers initiated a dolutegravir-based regimen and the proportion on tenofovir alafenamide increased from 7·2% (214/2958) pre-switch to 25·5% (733/2873) at the time of the switch. For summaries of baseline confounding characteristics in those eligible for each outcome analysis, see the appendix (pp 8–11).

During sequential trial follow-up, 113 (3·8%) of 2981 switchers discontinued their INSTI and 2926 (57·8%) of 5059 non-switchers started an INSTI (these individuals were captured as switchers in later sequential trials). Over a median follow-up time of 2·8 years (IQR 1·6–4·1), 214 (9·3%) of 2289 participants who switched to an INSTI developed obesity, 130 (4·5%) of 2920 developed diabetes, 187 (10·2%) of 1830 developed hypertension, and 50 (1·7%) of 2967 had a MACE. In non-switchers, 5909 (8·2%) of 72 473 developed obesity, 3190 (3·4%) of 94 306 developed diabetes, 4995 (8·1%) of 61 701 developed hypertension, and 1498 (1·6%) of 95 802 had a MACE over a median follow-up time of 3·3 years (IQR 1·9–4·4). 2240 (2·3%) of all 99 357 participants had a non-MACE-related death.

Weighted standardised differences were 0·1 or less for all confounders (appendix pp 8–11), and mean stabilised IPTWs were near 1·0 in each trial (appendix pp 12–13), indicating adequate balance, correct model specification, and no extreme inflation of sample sizes. In pooled Cox proportional hazard models, participants who switched to an INSTI had a higher HR of obesity (HR 1·41, 95% CI

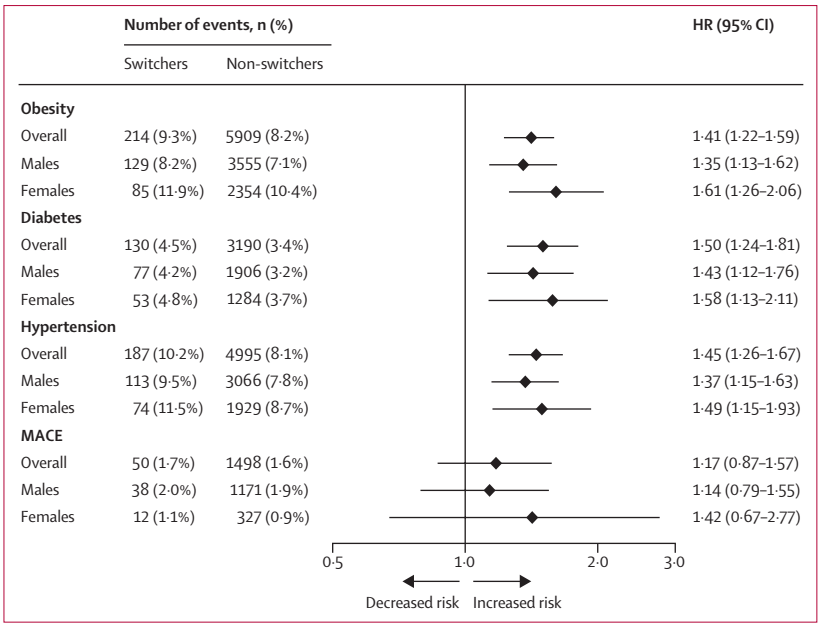

Figure: **HRs for obesity, diabetes, hypertension, and MACE over 5 years of follow-up**
The x-axis is shown on the logarithmic scale. HR estimates use inverse probability of treatment weights to adjust for sex at birth; age; race; REPRIEVE enrolment region and year; alcohol, cigarette, and substance use; diet quality; physical activity levels; total antiretroviral therapy duration; nadir CD4 cell count; estimated glomerular filtration rate at REPRIEVE entry; statin randomisation status; atherosclerotic cardiovascular disease risk score; and BMI at the start of each sequential trial. Number of events in non-switchers represent the total events contributed by repeated trials. The denominator differs across outcomes due to outcome-specific eligibility criteria in the target trial. 5909 obesity events among non-switchers corresponds to 541 unique events; 3190 diabetes events among non-switchers corresponds to 264 unique events; 4995 hypertension events among non-switchers corresponds to 444 unique events; 1498 MACE among non-switchers corresponds to 120 unique events. HR=hazard ratio. MACE=major adverse cardiovascular events.

1·22–1·59), diabetes (1·50, 1·24–1·81), and hypertension (1·45, 1·26–1·67) than participants who remained on a non-INSTI-based regimen (figure). We did not observe a difference in the HR ratio of MACE between switchers and non-switchers (HR 1·17, 95% CI 0·87–1·57).

In analyses stratified by sex at birth, point estimates for all outcomes were higher in females, although 95% CIs were overlapping (figure). Notably, the observed risk of MACE was higher in females who switched to an INSTI-containing regimen than females who did not switch; however, this finding was imprecise (figure).

Results were largely consistent with overlapping 95% CIs across all sensitivity and post-hoc analyses (table 4). Findings were consistent after adjustment for tenofovir alafenamide or tenofovir disoproxil fumarate use and when restricted to those taking tenofovir disoproxil fumarate. Results were similar when restricted to those on an efavirenz regimen at sequential trial baseline. In analyses restricted to participants with some degree of baseline cardiovascular risk (ASCVD ≥2·5), we observed a greater effect of switching on MACE, although this finding was estimated with a wide 95% CI (table 4). Results were similar with a 30-day baseline period (rather than 60-day period) and when restricted to sequential trials with at least 5 years of follow-up. The estimated effect of switching to an INSTI on the HR of obesity and diabetes was slightly larger when emulated trials were censored at 3 years (rather than 5 years), suggesting that the risk might be higher in the first few years after a switch.

In post-hoc analyses adjusting for time-updated percentage change in BMI, we found the HRs for diabetes, hypertension, and MACE were similar to primary estimates, although less precise (table 4). We saw little evidence of regional variation in risk. Additionally, the HR for hard MACE was similar to that of primary MACE (table 4).

Discussion

In a global cohort of ART-experienced people with HIV at low-to-moderate cardiovascular disease risk, we found an increased risk of cardiometabolic complications after a switch to an INSTI over 5 years of follow-up. Although we did not observe an increased risk of MACE, the heightened risk of obesity, diabetes, and hypertension—all of which are known to be important contributors to cardiovascular disease risk—raise concern that INSTIs could contribute to an increased risk of MACE in the long term.

Consistent with previous studies,[3,16] we observed a higher risk of obesity in people who switched to an INSTI versus non-switchers. Although mechanisms remain unclear, evidence suggests ART regimens before the switch could shape weight trajectories after the switch.[17] In particular, greater weight gain has been seen in those switching from efavirenz-based regimens than protease inhibitor-based regimens.[15] Given that the majority of participants in our study who switched to an INSTI were previously on efavirenz, this effect might partly account for some of the weight gain observed in this study. However, sensitivity analyses suggest cessation of weight suppressive efavirenz was not driving our overall results. Choice of NRTI has also been shown to influence weight trajectories, with some data suggesting a weight suppressive effect of tenofovir disoproxil fumarate.[15] However, our findings of an elevated risk of obesity after switching to an INSTI were unchanged when restricted to those who continued or initiated tenofovir disoproxil fumarate.

Although the role of the pre-switch regimen and NRTI medication warrant further investigation, neither pathway explains why females tend to have greater weight gain post-switch than males,[3] as was observed in our study. These findings could be due to differences in oestrogen concentrations and hormonal milieu, which could affect adipocytes, leading to a greater propensity for fat accumulation in women than men.[18,19] Findings from the Women's Interagency HIV Study cohort found that menopausal phase at the time of a switch to an INSTI-based regimen differentially affected post-switch weight, with females in perimenopause or menopause having faster increases in waist circumference and BMI.[20] Participants in our study were generally in their late 40s to early 50s, an age range that, for many women,

	Obesity	Diabetes	Hypertension	MACE
Primary analysis estimates	1·41 (1·22–1·59)	1·50 (1·24–1·81)	1·45 (1·26–1·67)	1·17 (0·87–1·57)
Sensitivity analysis				
Adjusted for tenofovir alafenamide use	1·36 (1·15–1·56)	1·55 (1·27–1·86)	1·40 (1·19–1·65)	1·08 (0·78–1·49)
Adjusted for tenofovir disoproxil fumarate use	1·44 (1·24–1·64)	1·44 (1·19–1·74)	1·38 (1·19–1·60)	1·05 (0·77–1·40)
Restricted to participants taking tenofovir disoproxil fumarate at sequential trial baseline*	1·59 (1·07–2·24)	1·61 (1·02–2·54)	1·76 (1·57–2·53)	..
Restricted to participants taking efavirenz at trial baseline or before INSTI switch	1·42 (1·18–1·69)	1·40 (1·05–1·85)	1·41 (1·11–1·72)	1·22 (0·67–2·09)
Restricted to switchers to dolutegravir	1·41 (1·16–1·67)	1·36 (1·05–1·68)	1·40 (1·12–1·71)	1·29 (0·87–1·80)
Adjusted for waist circumference	1·28 (1·09–1·44)	1·45 (1·02–1·66)	1·42 (1·02–1·60)	1·19 (0·92–1·51)
Restricted to participants with an ASCVD risk score ≥2·5	..	..	..	1·26 (0·89–1·72)
With a 30-day baseline period	1·43 (1·27–1·64)	1·51 (1·25–1·80)	1·47 (1·29–1·68)	1·15 (0·85–1·55)
Limited to sequential trials with a full 5 years of follow-up (trials 1–19)	1·27 (1·02–1·54)	1·60 (1·19–2·08)	1·39 (1·17–1·63)	1·27 (0·91–1·70)
Administrative censoring at 3 years	1·61 (1·19–2·35)	1·82 (1·35–2·36)	1·42 (1·20–1·66)	1·17 (0·86–1·56)
Pooled logistic regression†	1·44	1·46	1·43	1·09
Post-hoc analyses				
Adjusted for percent change in BMI	..	1·62 (0·47–1·93)	1·47 (0·43–1·71)	0·97 (0·28–1·32)
Restricted to high-income countries‡	1·41 (1·16–1·73)	1·54 (1·07–2·10)	1·25 (0·87–1·63)	0·98 (0·61–1·45)
Restricted to low-income to middle-income countries‡	1·33 (1·11–1·58)	1·49 (1·17–1·87)	1·44 (1·17–1·74)	1·30 (0·85–1·94)
With hard MACE definition	..	..	..	1·20 (0·76–1·86)

Data are hazard ratios (95% CIs). All analyses represent the effect of switching to an INSTI-based treatment regimen versus remaining on a non-INSTI-based regimen on outcomes of interest. INSTI=integrase strand-transfer inhibitor. ASCVD=atherosclerotic cardiovascular disease. MACE=major adverse cardiovascular events. *Sensitivity analysis restricted to participants taking tenofovir disoproxil fumarate at sequential trial baseline was not done for the outcome of MACE given the scarce number of events and resulting lack of precision. †CIs for the pooled logistic regression sensitivity analysis were not calculated due to the computational intensity of the estimation procedure. ‡High-income countries were the USA, Canada, and Spain. Low-income to middle-income countries were Brazil, Haiti, Peru, Thailand, India, Botswana, South Africa, Uganda, and Zimbabwe.

Table 4: **Results of sensitivity and post-hoc analyses**

overlaps with the perimenopausal transition. Different results might have been observed in studies done in younger or older populations of women with HIV.

Data evaluating the cardiometabolic effect of INSTI use remain sparse and conflicting. Although several reports have found no effect of INSTI use on the risk of diabetes,[21,22] our findings of an increased risk of diabetes in switchers are consistent with results from the RESPOND cohort that found an increased risk of diabetes in INSTI users compared with non-users (HR 1·48 [95% CI 1·29–1·71]) over a median follow-up time of 5 years.[7] Moreover, in line with previously published observational studies,[23,24] we observed a relative increase in hypertension risk after a switch to an INSTI. Although it is hypothesised that weight gain could partly mediate this risk, our exploratory post-hoc analysis showed that the association persisted after accounting for changes in BMI. One important aspect to consider is the type of fat gained after a switch to an INSTI. Greater accumulation of visceral fat, as opposed to subcutaneous fat, has been implicated in the promotion of hypertension and other cardiovascular risk factors.[25,26] Future studies should look at the composition of fat in individuals initiating INSTIs to determine relative amounts of visceral and subcutaneous fat and the contributions to long-term cardiometabolic disease risk.

Understanding the mechanism through which INSTIs might disrupt cardiometabolic pathways is crucial, particularly as it relates to long-term prevention of MACE. Our findings on MACE contrast with that of the RESPOND study, which found an increase in cardiovascular disease risk in the first 24 months after INSTI initiation.[8] However, our results align with findings from the Swiss HIV Cohort Study and the HIV-CAUSAL Collaboration/Antiretroviral Therapy Cohort Collaboration, both of which similarly used an explicit target trial emulation approach to minimise bias.[27,28] In these studies, as well as our own, an increased risk of MACE or cardiovascular disease was not observed. However, our study raises concerns by finding significant increases in the risk of obesity, diabetes, and hypertension, all of which are crucial risk factors for MACE. Importantly, our findings apply to the highly relevant population of people with HIV with low-to-moderate cardiovascular risk, in whom it gives a clear indication of expected risk. Estimates could differ and there might be a larger effect on MACE in those with a greater degree of baseline cardiometabolic risk.

A few limitations must be considered when interpreting the results of this study. First, despite the use of a sophisticated modelling approach, involving the emulation of sequential target trials and IPTW to

estimate the causal effect of switching to an INSTI regimen, we cannot rule out the possibility of unmeasured confounding. Second, a smaller baseline period would result in better alignment of treatment assignment and time-zero. We favoured a 60-day period to ensure a sufficient number of switchers in each trial and avoid violating positivity assumptions, particularly when stratifying by sex at birth. We ran models with a 30-day baseline period and found similar results, suggesting little effect of this bias in our study. Third, our estimated intention-to-treat effect is assumed to be smaller than the corresponding direct effect of switching to an INSTI in the hypothetical scenario of full compliance to assigned INSTI switch strategy. Our intention-to-treat estimate assumes that non-adherence to assigned treatment observed in our study reflects the real-world scenario. Fourth, the number of MACE in our study was relatively small, limiting our statistical power to detect differences between groups. Nevertheless, a major strength is that MACE was the primary adjudicated endpoint for REPRIEVE, providing high internal validity and setting our analysis apart from studies that rely on non-adjudicated outcomes identified through coded electronic health record or claims data. Fifth, most of our cohort switched to a dolutegravir-containing regimen, limiting our ability to investigate differential effects by individual INSTI agents. Finally, estimation of HRs as the population summary of interest has limitations.[29] HRs cannot be interpreted as unconditional causal effects for the entire randomised population at each timepoint, and their magnitude could vary during follow-up if the treatment effect is not constant over time. However, HRs remain a valid and informative measure of effect when properly interpreted as a comparison of average hazard functions over a given time period. Recent work has shown that concerns about collider bias vanish under this interpretation and simulation studies have shown that substantial time-varying bias due to depletion of the risk set only arises under extreme heterogeneity in baseline risk[30,31]—a scenario unlikely in our study given the strict eligibility criteria of the REPRIEVE trial, which ensured that all participants had similar levels of baseline risk.

In conclusion, in an ART-experienced, virologically controlled, global cohort of people with HIV at low-to-moderate risk of cardiovascular disease, switching to an INSTI-containing regimen resulted in an increased risk of new-onset obesity, diabetes, and hypertension. Although the absolute risk of these outcomes was small, given the elevated risk profile, long-term observation of people with HIV switching to INSTIs will be crucial to ensure appropriate management of developing comorbidities and to assess for future development of MACE.

Contributors

EMK, SKG, HJR, JL, ED-S, MPF, ATB, and KP contributed to the conception and design of the work, data analysis, and interpretation. SKG, HJR, JL, CDM, MVZ, CJF, JEL, JAA, EM, GSB, SMC, AA, MRD, ABL, SHB, DB, MS, NLO, PK, EJ, JSC, MTL, and PSD contributed to data acquisition and interpretation. EMK, HJR, and ED-S directly accessed and verified the data. All authors critically reviewed the work for intellectual content and gave final approval for submission. All authors had full access to all the data in the study and agree to be accountable for all aspects of the work.

Declaration of interests

CDM reports institutional research support by Lilly and personal fees from ViiV Healthcare and Gilead Sciences for participation in advisory board meetings outside the submitted work. MVZ reports grant support through her institution from US National Institutes of Health (NIH), National Institute of Allergy and Infectious Diseases (NIAID), and Gilead Sciences, relevant to the conduct of the study; support for attending the Conference on Retroviruses and Opportunistic Infections and the International Workshop for HIV and Women from conference organising committees as an abstract reviewer and/or speaker; participation in a data safety monitoring board for NIH-funded studies; and grants from NIH, NIAID, and US National Heart, Lung, and Blood Institute (NHLBI). CJF reports grant support through his institution from Gilead Sciences, ViiV Healthcare, GSK, and Merck, all outside the submitted work. JEL reports consultancy to ViiV Healthcare and CytoDyn, outside the submitted work. JL reports consulting fees from ViiV Healthcare and investigator-initiated research grant support from ViiV Healthcare related to this work. JAA reports grants from Massachusetts General Hospital during the study; institutional research support for clinical trials from Gilead Sciences, GlaxoSmithKline, Janssen, Macrogenics, Merck, Pfizer, Regeneron, and ViiV Healthcare; personal fees for advisory boards from GlaxoSmithKline and ViiV Healthcare, Invivyd, Merck and Regeneron; and participation on a data safety monitoring board for Kintor Pharmaceuticals, all outside the submitted work. EM has received honoraria for lectures or advisory boards from Gilead, Janssen, MSD, and ViiV and his institution has received research grants from MSD and ViiV, all outside the submitted work. SHB reports serving as a scientific advisor to Gilead Sciences including payment for expert testimony and research grants to their institution from Gilead Sciences, ViiV Healthcare, and Janssen unrelated to the submitted work. MS reports research funding from Merck Canada. NLO reports grants from NIH and NHLBI during the conduct of the study and consulting fees from Gilead Sciences, unrelated to the submitted work. PK serves as a consultant and receives research funding from ViiV Healthcare, Merck, Theratechnologies, and Gilead and owns stock in Pfizer, Gilead, Merck, GSK, and Moderna. JSC reports consulting fees from Merck. MTL reports grant support through his institution from NIH and NHLBI and Kowa Pharmaceuticals America for the conduct of the study; grant support to his institutions from the American Heart Association, AstraZeneca, Ionis, Johnson & Johnson, MedImmune, the National Academy of Medicine, the NIH and NHLBI, and the Risk Management Foundation of the Harvard Medical Institutions, outside of the current work. SKG reports grants from NIH, Kowa Pharmaceuticals America, Gilead Sciences, and ViiV Healthcare during the conduct of the study; personal consulting fees from TheraTechnologies and ViiV Healthcare; and service on the Scientific Advisory Board of Marathon Asset Management and Exavir Therapeutics, all outside the submitted work. HJR reports grants from NIH and NHLBI, Kowa Pharmaceuticals America, Gilead Sciences, and ViiV Healthcare during the conduct of the study and grants from NIH, NIAID, and NHLBI, US National Institute of Diabetes and Digestive and Kidney Diseases, and US National Institute on Aging, outside the submitted work. All other authors report no competing interests.

Data sharing

Data from the REPRIEVE trial are available upon reasonable request to mghreprievetrial@mgb.org. Shared data might include individual participant data that underlie the results reported in this Article, after de-identification (text, tables, figures, and appendices). To gain access, data requestors will need to sign a data access agreement. Study protocols for the REPRIEVE study are available at https://clinicaltrials.gov/study/NCT02344290. Analysis code is available at https://github.com/ekileel93/seqtrials.

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