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Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: Kileel EM, Malvestutto CD, Zanni MV, et al. Risk of obesity, diabetes, hypertension, and major adverse cardiovascular events after a switch to an integrase inhibitor: a target trial emulation in REPRIEVE. *Lancet HIV* 2026; published online March 27. https://doi.org/10.1016/S2352-3018(25)00354-6.

APPENDIX

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Appendix I. Target Trial Emulation Protocols

Supplemental Table 1. Protocol components of the hypothetical target trial and observational emulation for the outcome of obesity.

Component	Target Trial	Observational Emulation
Eligibility criteria	Treatment experienced (≥ 6 months of stable ART use) non-pregnant adults, aged 40-75 years, with no previous INSTI exposure and no known history of obesity.	Treatment experienced (≥ 6 months of stable ART use) non-pregnant adults, aged 40-75 years, not on an INSTI-based regimen at trial entry and no known diagnosis of obesity at trial entry.
Treatment strategies	Switch to an INSTI-based treatment regimen vs remain on a PI- or NNRTI-based treatment regimen	Same criteria
Treatment assignment mechanism	Randomization	Inverse probability of treatment weighting to emulate randomization
Start of follow-up	At randomization	Once eligibility criteria are met (i.e., at the end of the baseline period)
End of follow-up	Event occurrence, death, loss to follow-up, or administrative censoring at 5 years	Same criteria
Outcome	Incident obesity defined as: BMI ≥ 27.7 kg/m^2 for participants of Asian race, BMI ≥ 30 kg/m^2 otherwise	Same criteria
Causal contrast	Intent-to-treat effect	Observational analogue of the intent-to-treat effect

Supplemental Table 2. Protocol components of the hypothetical target trial and observational emulation for the outcome of diabetes

Component	Target Trial	Observational Emulation
Eligibility criteria	Treatment experienced (≥ 6 months of stable ART use) non-pregnant adults, aged 40-75 years, with no previous INSTI exposure and no known history of diabetes.	Treatment experienced (≥ 6 months of stable ART use) non-pregnant adults, aged 40-75 years, not on an INSTI-based regimen at trial entry and no known diagnosis of diabetes at trial entry.
Treatment strategies	Switch to an INSTI-based treatment regimen vs remain on a PI- or NNRTI-based treatment regimen	Same criteria
Treatment assignment mechanism	Randomization	Inverse probability of treatment weighting to emulate randomization
Start of follow-up	At randomization	Once eligibility criteria are met (i.e., at the end of the baseline period)
End of follow-up	Event occurrence, death, loss to follow-up, or administrative censoring at 5 years	Same criteria
Outcome	Incident diabetes defined as: fasting blood glucose ≥ 7 mmol/L, or use of an antidiabetic medication, or documented diagnosis of diabetes	Same criteria
Causal contrast	Intent-to-treat effect	Observational analogue of the intent-to-treat effect

Supplemental Table 3. Protocol components of the hypothetical target trial and observational emulation for the outcome of hypertension

Component	Target Trial	Observational Emulation
Eligibility criteria	Treatment experienced (≥ 6 months of stable ART use) non-pregnant adults, aged 40-75 years, with no previous INSTI exposure and no known history of hypertension	Treatment experienced (≥ 6 months of stable ART use) non-pregnant adults, aged 40-75 years, not on an INSTI-based regimen at trial entry and no known diagnosis of hypertension at trial entry
Treatment strategies	Switch to an INSTI-based treatment regimen vs remain on a PI- or NNRTI-based treatment regimen	Same criteria
Treatment assignment mechanism	Randomization	Inverse probability of treatment weighting to emulate randomization
Start of follow-up	At randomization	Once eligibility criteria are met (i.e., at the end of the baseline period)
End of follow-up	Event occurrence, death, loss to follow-up, or administrative censoring at 5 years	Same criteria
Outcome	Incident hypertension defined as: systolic blood pressure ≥ 140 mmHG and/or diastolic blood pressure ≥ 90 mmHG, or use of antihypertensive treatment for elevated blood pressure, or documented hypertension diagnosis	Same criteria
Causal contrast	Intent-to-treat effect	Observational analogue of the intent-to-treat effect

Supplemental Table 4. Protocol components of the hypothetical target trial and observational emulation for the outcome of major adverse cardiovascular events (MACE)

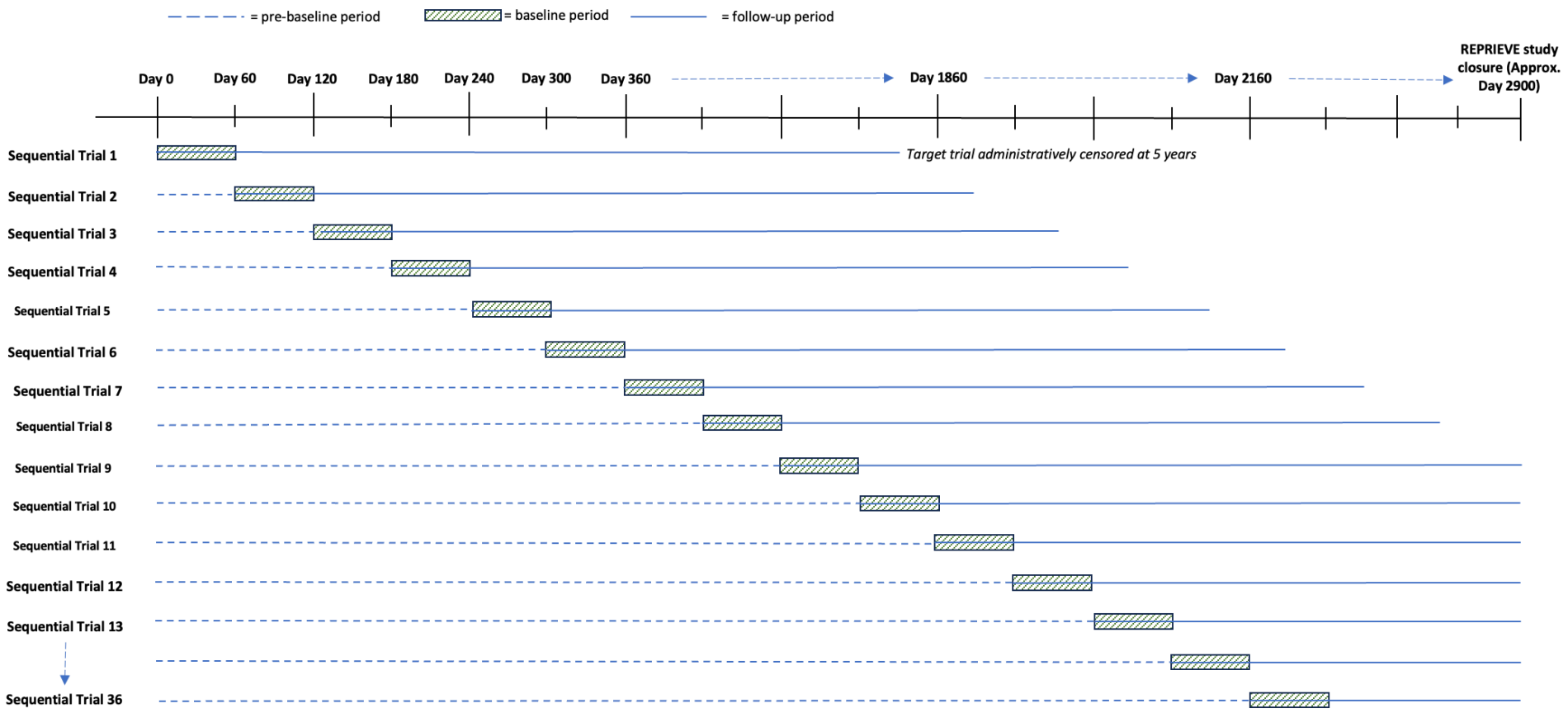
Component	Target Trial	Observational Emulation
Eligibility criteria	Treatment experienced (≥ 6 months of stable ART use) non-pregnant adults, aged 40-75 years, with no previous INSTI exposure and no known history of MACE	Treatment experienced (≥ 6 months of stable ART use) non-pregnant adults, aged 40-75 years, with no previous INSTI exposure and no history of MACE and has not experienced a MACE event at the start of the trial
Treatment strategies	Switch to an INSTI-based treatment regimen vs remain on a PI- or NNRTI-based treatment regimen	Same criteria
Treatment assignment mechanism	Randomization	Inverse probability of treatment weighting to emulate randomization
Start of follow-up	At randomization	Once eligibility criteria are met (i.e., at the end of the baseline period)
End of follow-up	Event occurrence, death, loss to follow-up, or administrative censoring at 5 years	Same criteria
Outcome	Major Adverse Cardiovascular Event: composite outcome of cardiovascular death, myocardial infarction, hospitalization for unstable angina, stroke, transient ischemic attack (TIA), peripheral arterial ischemia, revascularization (coronary, carotid or peripheral arterial), or death from an undetermined cause	Same criteria
Causal contrast	Intent-to-treat effect	Observational analogue of the intent-to-treat effect

Appendix II. Text and visual description of sequential target trial emulation and directed acyclic graph

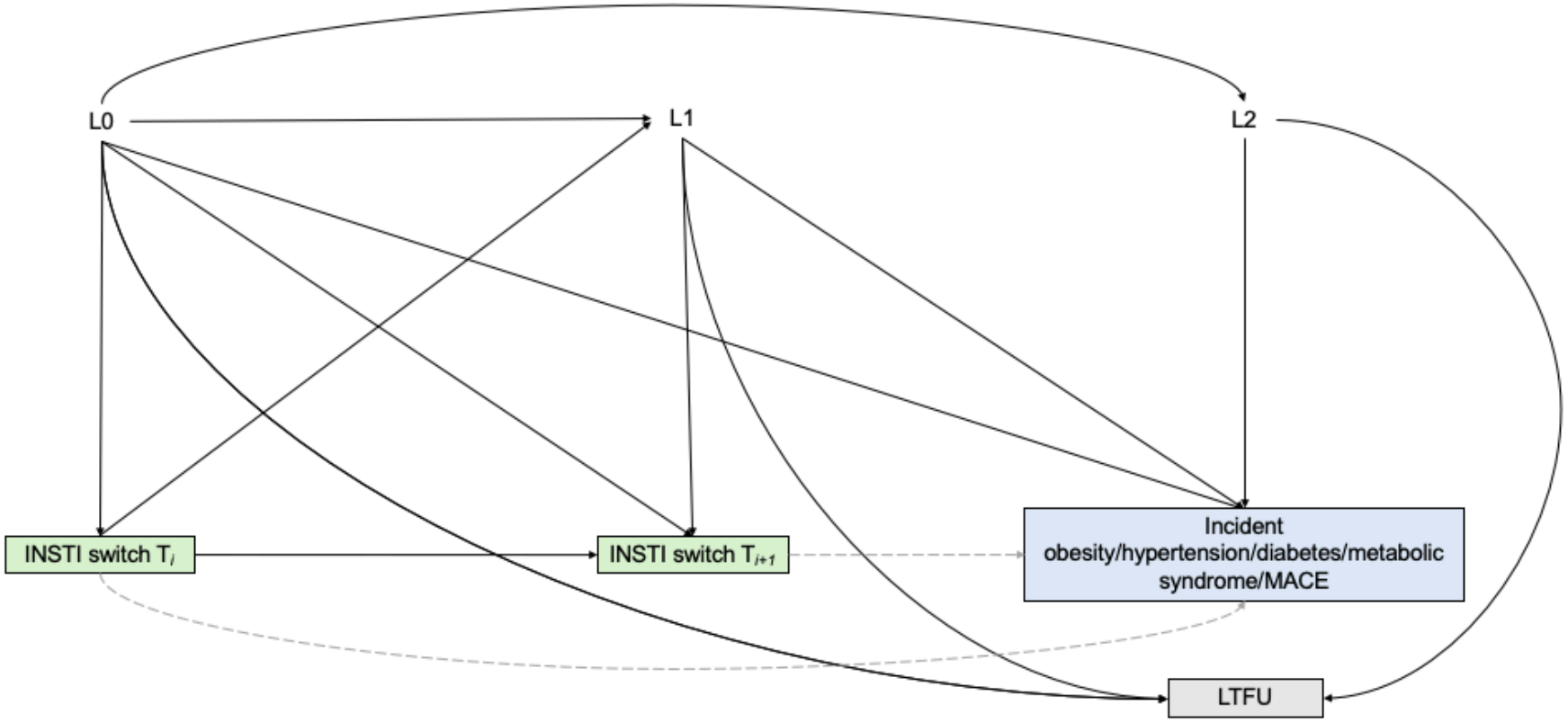
As described in the main manuscript, we emulated a new target trial every 60-days in REPRIEVE. For each trial, we identified eligible individuals during the 60-day baseline period and assigned them to the treatment strategy that was compatible with their data during the baseline period. Meaning that, for a participant who met eligibility criteria trial N=1, if they switched to an INSTI-based regimen between days 0-59 they were considered a "switcher" in that trial and would be ineligible for subsequent trials. Alternatively, if a participant did not switch to an INSTI-based regimen during the baseline period, they were considered a non-switcher in that trial and would be eligible for subsequent trials. Additionally, participants experiencing events or dying during the baseline period would not meet target trial eligibility. This process was repeated every 60 days until day 2160, approximately 6 years into REPRIEVE, to ensure participants in each trial were eligible for a least two years of follow-up. In total, we emulated a sequence of 37 target trials with varying time zero (see Supplemental Figure 1).

Of the 37 target trials, 18 (50%) had a full 5-years of follow-up. The remaining trials had decreasing amounts of follow-up time until a minimum of 2-year of follow-up was reached. Follow-up time as structured in intervals, with interval size depending on the outcome. The outcomes of diabetes, hypertension, and MACE were pre-specified clinical outcomes in REPRIEVE, meaning that if a diagnosis occurred in clinical care the diagnosis and the corresponding date would be captured in study documents. As a result, these outcomes could occur at any time during follow-up in REPRIEVE. For these outcomes we used 60-day follow-up intervals, meaning that we assessed outcome occurrence every 60-days. Alternatively, the outcome of obesity was determined according to clinical biomarkers measured annually in REPRIEVE. As a result, this diagnosis could only be observed at annual timepoints in the study. Therefore, for the outcome of obesity, follow-up time was structured in 365.25-day intervals. For all outcomes follow-up time began after the baseline interval.

Descriptive example of how individuals could move through the sequential trials: Person A enrolls in REPRIEVE on an efavirenz-based regimen (for e.g.). At the start of Sequential Trial 1 (e.g., day 0 in REPRIEVE) they are still on their efavirenz-based regimen. However, on day 29 of follow-up in REPRIEVE, Person A switches to an INSTI-based treatment regimen. Person A is classified as a "switched" in Sequential Trial 1. At the start of Sequential Trial 2 (e.g. day 60 in REPRIEVE) Person A has already switched to an INSTI-based regimen and therefore does not meet the trial eligibility criteria. As such, Person A is not included in Sequential Trial 2 nor any of the subsequent emulated trials and is only ever included in Sequential Trial 1. Alternatively, Person B enrolls in REPRIEVE on a PI-based regimen (for e.g.) and does not switch to an INSTI-based treatment regimen until day 730 of REPRIEVE follow-up. Person B will be classified as a non-switcher in sequential trials 1-11 as they are on a non-INSTI based regimen at the start of each trial and do not switch during the 60-day baseline period. However, Person B switches during the baseline period of sequential trial 12 and is therefore classified as a "switcher" in that trial and would then be ineligible for all subsequent trials. If Person C enrolled in REPRIEVE on a non-INSTI based regimen and remained on a non-INSTI-based regimen throughout the duration of follow-up in REPRIEVE, but developed the event of interest (diabetes, for e.g.) on their 2000th day of follow-up in REPRIEVE, this individual would be eligible for all sequential trials that start before day 2000 (trials 1-33) but ineligible for trial 34 and subsequent trials when evaluating the outcome of diabetes as they now have a known history of the event. Because this individual never switched to an INSTI-, they would be classified as a non-switcher in all sequential trials for which they are eligible.



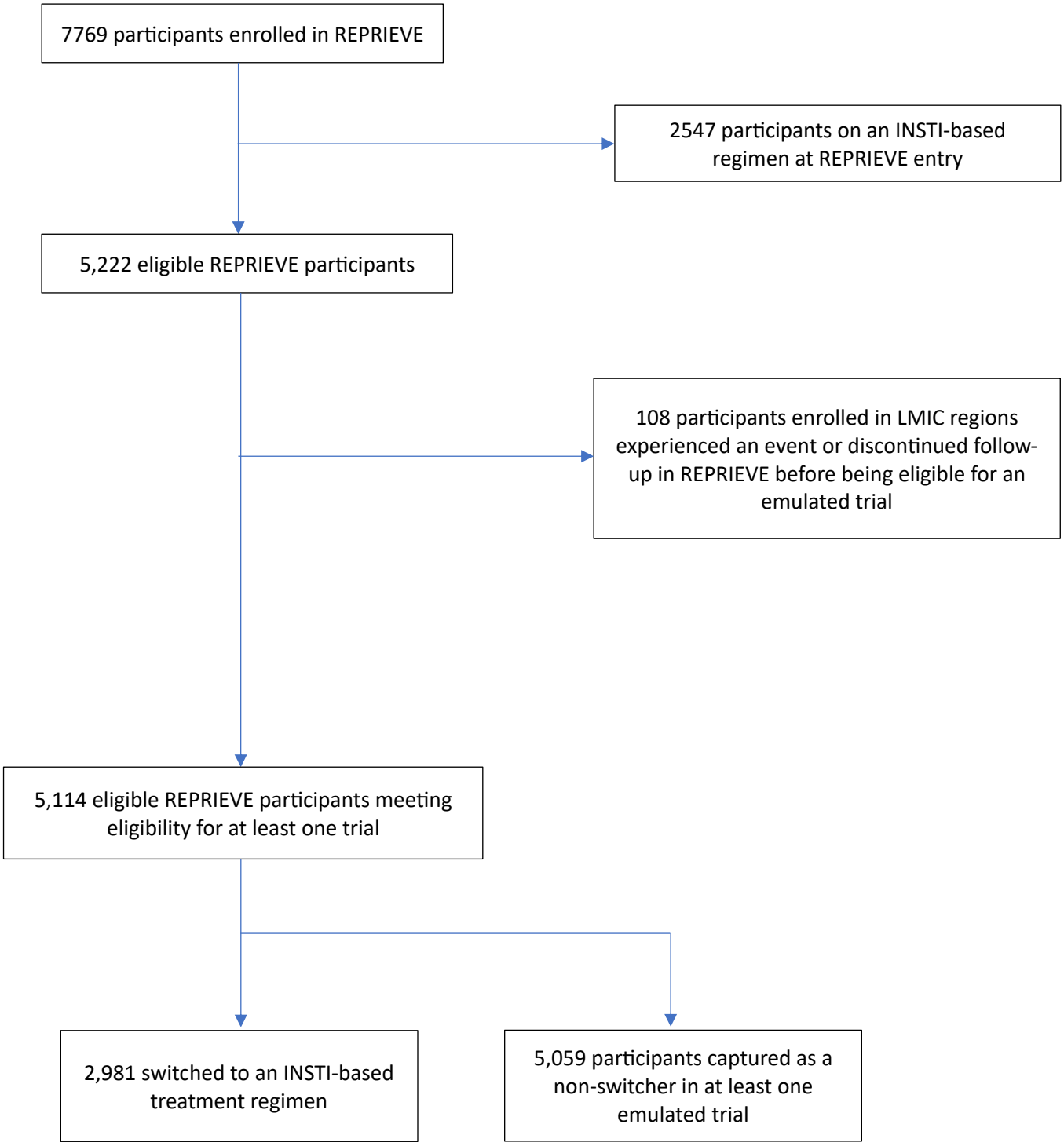
Supplemental Figure 1. Target trial emulation sequence



L0: natal sex, age, smoking status, alcohol use, substance use, kidney function, time on ART, nadir CD4, REPRIEVE enrollment region and year
L1: body mass index (BMI)
L2: diet quality, physical activity levels, statin use

Supplemental Figure 2. Longitudinal confounding patterns of the association between switching to an integrase inhibitor (INSTI)-based regimen and incident outcomes of interest.

Appendix III. Consort diagram



Appendix IV. Baseline tables of confounding characteristics by INSTI switch status in each set of target trials

Supplemental Table 5. Unweighted distribution of confounding characteristics and standardized mean differences after weighting among participants included in the emulation of a target trial of the effect of switching to an INSTI vs not switching nested within the REPRIEVE trial, among those eligible for the analysis on obesity.

		INSTI switchers (N=2289 person-trials; 2289 unique individuals)	Non switchers (N=72,473 person-trials; 4022 unique individuals)	Total (N=74,762 person-trials; 4062 unique individuals)	Standardized Difference After Weighting
Age (years)	Median (Q1, Q3)	50 (45, 55)	49 (45, 54)	49 (45, 54)	0.007
	<50	1,118 (48.8%)	36,382 (50.2%)	37,500 (50.2%)	
	50+	1,171 (51.2%)	36,091 (49.8%)	37,262 (49.8%)	
Natal sex	Male	1,574 (68.8%)	49,874 (68.8%)	51,448 (68.8%)	0.001
	Female	715 (31.2%)	22,599 (31.2%)	23,314 (31.2%)	
Race	Black or African American	962 (42.0%)	24,643 (34.0%)	25,605 (34.2%)	0.083
	White	532 (23.2%)	19,548 (27.0%)	20,080 (26.9%)	
	Asian	580 (25.3%)	19,529 (26.9%)	20,109 (26.9%)	
	Other	215 (9.4%)	8,753 (12.1%)	8,968 (12.0%)	
Enrollment region	HIC	632 (27.6%)	21,099 (29.1%)	21,731 (29.1%)	0.023
	LMIC	1,657 (72.4%)	51,374 (70.9%)	53,031 (70.9%)	
Smoking status	Never	1,277 (55.8%)	39,627 (54.7%)	40,904 (54.7%)	0.006
	Current/Former	1,012 (44.2%)	32,846 (45.3%)	33,858 (45.3%)	
Alcohol use	Rarely/Never	1,733 (75.7%)	53,916 (74.4%)	55,649 (74.4%)	0.000
	Usually/Often/Sometimes	556 (24.3%)	18,557 (25.6%)	19,113 (25.6%)	
Substance use	Never	1,848 (80.7%)	57,254 (79.0%)	59,102 (79.1%)	0.012
	Current/Former	441 (19.3%)	15,219 (21.0%)	15,660 (20.9%)	
Diet score	Ideal/Intermediate	1,652 (72.2%)	54,064 (74.6%)	55,716 (74.5%)	0.006
	Poor	637 (27.8%)	18,409 (25.4%)	19,046 (25.5%)	
Physical activity score	Ideal/Intermediate	1,378 (60.2%)	44,210 (61.0%)	45,588 (61.0%)	0.006
	Poor	911 (39.8%)	28,263 (39.0%)	29,174 (39.0%)	
eGFR by CKD-EPI (<90 vs 90+)	90+	1,587 (69.3%)	49,487 (68.3%)	51,074 (68.3%)	0.012
	<90	702 (30.7%)	22,986 (31.7%)	23,688 (31.7%)	
Total duration ART use (<10 vs 10+)	10+	1,571 (68.6%)	49,546 (68.4%)	51,117 (68.4%)	0.001
	<10	718 (31.4%)	22,927 (31.6%)	23,645 (31.6%)	
Nadir CD4 (cells/mm3)	200+	1,098 (48.0%)	37,120 (51.2%)	38,218 (51.1%)	0.008
	<200	1,191 (52.0%)	35,353 (48.8%)	36,544 (48.9%)	
Treatment Group	Placebo	1,132 (49.5%)	36,144 (49.9%)	37,276 (49.9%)	0.002
	Pitavastatin	1,157 (50.5%)	36,329 (50.1%)	37,486 (50.1%)	
ASCVD risk score (%)	Median (Q1, Q3)	4.1 (1.9, 6.7)	3.8 (1.7, 6.6)	3.8 (1.7, 6.6)	0.017
	<5	1,343 (58.7%)	43,440 (59.9%)	44,783 (59.9%)	
	5+	946 (41.3%)	29,033 (40.1%)	29,979 (40.1%)	
BMI (kg/m²)	Median (Q1, Q3)	23.7 (21.2, 26.2)	23.9 (21.5, 26.3)	23.9 (21.5, 26.3)	0.013
	<25	1,472 (64.3%)	44,899 (62.0%)	46,371 (62.0%)	
	25-29.9	816 (35.7%)	27,568 (38.0%)	28,384 (38.0%)	

Abbreviations: INSTI=integrase strand transfer inhibitor; HIC=high income country; LMIC=low- to middle-income country; eGFR=estimated glomerular filtration rate; ART=antiretroviral therapy; ASCVD=atherosclerotic cardiovascular disease; BMI=body mass index.

[*] *Data are summarized at the first visit at which trial emulation eligibility criteria were met.*

[†] *Switch status is defined according to whether a participant ever met that criteria for any target trial.*

Supplemental Table 6. Unweighted distribution of confounding characteristics and standardized mean differences after weighting among participants included in the emulation of a target trial of the effect of switching to an INSTI vs not switching nested within the REPRIEVE trial, among those eligible for the analysis on diabetes.

		INSTI switchers (N=2920 person-trials; 2920 unique individuals)	Non switchers (N=94,306 person-trials; 5028 unique individuals)	Total (N=97,226 person-trials; 5028 unique individuals)	Standardized Difference After Weighting
Age (years)	Median (Q1, Q3)	49 (45, 55)	49 (44, 54)	49 (44, 54)	0.014
	<50	1,464 (50.1%)	49,739 (52.7%)	51,203 (52.7%)	
	50+	1,456 (49.9%)	44,567 (47.3%)	46,023 (47.3%)	
Natal sex	Male	1,823 (62.4%)	59,614 (63.2%)	61,437 (63.2%)	0.031
	Female	1,097 (37.6%)	34,692 (36.8%)	35,789 (36.8%)	
Race	Black or African American	1,312 (44.9%)	35,867 (38.0%)	37,179 (38.2%)	0.014
	White	674 (23.1%)	24,906 (26.4%)	25,580 (26.3%)	
	Asian	663 (22.7%)	22,356 (23.7%)	23,019 (23.7%)	
	Other	271 (9.3%)	11,177 (11.9%)	11,448 (11.8%)	
Enrollment region	HIC	886 (30.3%)	29,735 (31.5%)	30,621 (31.5%)	0.132
	LMIC	2,034 (69.7%)	64,571 (68.5%)	66,605 (68.5%)	
Smoking status	Never	1,698 (58.2%)	53,271 (56.5%)	54,969 (56.5%)	0.026
	Current/Former	1,222 (41.8%)	41,035 (43.5%)	42,257 (43.5%)	
Alcohol use	Rarely/Never	2,249 (77.0%)	70,846 (75.1%)	73,095 (75.2%)	0.000
	Usually/Often/Sometimes	671 (23.0%)	23,460 (24.9%)	24,131 (24.8%)	
Substance use	Never	2,340 (80.1%)	74,456 (79.0%)	76,796 (79.0%)	0.060
	Current/Former	580 (19.9%)	19,850 (21.0%)	20,430 (21.0%)	
Diet score	Ideal/Intermediate	2,062 (70.6%)	69,391 (73.6%)	71,453 (73.5%)	
	Poor	858 (29.4%)	24,915 (26.4%)	25,773 (26.5%)	0.001
Physical activity score	Ideal/Intermediate	1,701 (58.3%)	56,533 (59.9%)	58,234 (59.9%)	0.014
	Poor	1,219 (41.7%)	37,773 (40.1%)	38,992 (40.1%)	
eGFR by CKD-EPI (<90 vs 90+)	90+	1,980 (67.8%)	63,590 (67.4%)	65,570 (67.4%)	0.069
	<90	940 (32.2%)	30,716 (32.6%)	31,656 (32.6%)	
Total duration ART use (<10 vs 10+)	10+	2,001 (68.5%)	64,082 (68.0%)	66,083 (68.0%)	0.005
	<10	919 (31.5%)	30,224 (32.0%)	31,143 (32.0%)	
Nadir CD4 (cells/mm3)	200+	1,434 (49.1%)	48,852 (51.8%)	50,286 (51.7%)	0.016
	<200	1,486 (50.9%)	45,454 (48.2%)	46,940 (48.3%)	
Treatment Group	Placebo	1,458 (49.9%)	47,197 (50.0%)	48,655 (50.0%)	0.002
	Pitavastatin	1,462 (50.1%)	47,109 (50.0%)	48,571 (50.0%)	
ASCVD risk score (%)	Median (Q1, Q3)	3.9 (1.7, 6.5)	3.7 (1.6, 6.4)	3.7 (1.6, 6.4)	0.025
	<5	1,752 (60.0%)	57,937 (61.4%)	59,689 (61.4%)	
	5+	1,168 (40.0%)	36,369 (38.6%)	37,537 (38.6%)	
BMI (kg/m²)	Median (Q1, Q3)	25.0 (22.0, 28.6)	25.3 (22.3, 28.9)	25.3 (22.3, 28.9)	0.102
	<25	1,465 (50.2%)	44,647 (47.3%)	46,112 (47.4%)	
	25-29.9	929 (31.8%)	31,350 (33.2%)	32,279 (33.2%)	

Abbreviations: INSTI=integrase strand transfer inhibitor; HIC=high income country; LMIC=low- to middle-income country; eGFR=estimated glomerular filtration rate; ART=antiretroviral therapy; ASCVD=atherosclerotic cardiovascular disease; BMI=body mass index.

[*] *Data are summarized at the first visit at which trial emulation eligibility criteria were met.*

[†] *Switch status is defined according to whether a participant ever met that criteria for any target trial.*

Supplemental Table 7. Unweighted distribution of confounding characteristics and standardized mean differences after weighting among participants included in the emulation of a target trial of the effect of switching to an INSTI vs not switching nested within the REPRIEVE trial, among those eligible for the analysis on hypertension.

		INSTI switchers (N=1830 person-trials; 1830 unique individuals)	Non switchers (N=61,701 person-trials; 3315 unique individuals)	Total (N=63,531 person-trials; 3348 unique individuals)	Standardized Difference After Weighting
Age (years)	Median (Q1, Q3)	49 (44, 54)	48 (44, 53)	48 (44, 53)	0.025
	<50	999 (54.6%)	35,153 (57.0%)	36,152 (56.9%)	
	50+	831 (45.4%)	26,548 (43.0%)	27,379 (43.1%)	
Natal sex	Male	1,185 (64.8%)	39,455 (63.9%)	40,640 (64.0%)	0.038
	Female	645 (35.2%)	22,246 (36.1%)	22,891 (36.0%)	
Race	Black or African American	746 (40.8%)	21,118 (34.2%)	21,864 (34.4%)	0.008
	White	450 (24.6%)	16,875 (27.3%)	17,325 (27.3%)	
	Asian	457 (25.0%)	16,318 (26.4%)	16,775 (26.4%)	
	Other	177 (9.7%)	7,390 (12.0%)	7,567 (11.9%)	
Enrollment region	HIC	557 (30.4%)	18,632 (30.2%)	19,189 (30.2%)	0.137
	LMIC	1,273 (69.6%)	43,069 (69.8%)	44,342 (69.8%)	
Smoking status	Never	1,035 (56.6%)	34,835 (56.5%)	35,870 (56.5%)	0.024
	Current/Former	795 (43.4%)	26,866 (43.5%)	27,661 (43.5%)	
Alcohol use	Rarely/Never	1,427 (78.0%)	46,853 (75.9%)	48,280 (76.0%)	0.005
	Usually/Often/Sometimes	403 (22.0%)	14,848 (24.1%)	15,251 (24.0%)	
Substance use	Never	1,456 (79.6%)	48,545 (78.7%)	50,001 (78.7%)	0.058
	Current/Former	374 (20.4%)	13,156 (21.3%)	13,530 (21.3%)	
Diet score	Ideal/Intermediate	1,306 (71.4%)	45,576 (73.9%)	46,882 (73.8%)	0.006
	Poor	524 (28.6%)	16,125 (26.1%)	16,649 (26.2%)	
Physical activity score	Ideal/Intermediate	1,078 (58.9%)	37,150 (60.2%)	38,228 (60.2%)	0.013
	Poor	752 (41.1%)	24,551 (39.8%)	25,303 (39.8%)	
eGFR by CKD-EPI (<90 vs 90+)	90+	1,292 (70.6%)	43,242 (70.1%)	44,534 (70.1%)	0.063
	<90	538 (29.4%)	18,459 (29.9%)	18,997 (29.9%)	
Total duration ART use (<10 vs 10+)	10+	1,238 (67.7%)	41,254 (66.9%)	42,492 (66.9%)	0.002
	<10	592 (32.3%)	20,447 (33.1%)	21,039 (33.1%)	
Nadir CD4 (cells/mm3)	200+	932 (50.9%)	33,014 (53.5%)	33,946 (53.4%)	0.024
	<200	898 (49.1%)	28,687 (46.5%)	29,585 (46.6%)	
Treatment Group	Placebo	894 (48.9%)	30,422 (49.3%)	31,316 (49.3%)	0.002
	Pitavastatin	936 (51.1%)	31,279 (50.7%)	32,215 (50.7%)	
ASCVD risk score (%)	Median (Q1, Q3)	3.3 (1.3, 5.7)	3.0 (1.2, 5.5)	3.0 (1.2, 5.5)	0.026
	<5	1,248 (68.2%)	43,297 (70.2%)	44,545 (70.1%)	
	5+	582 (31.8%)	18,404 (29.8%)	18,986 (29.9%)	
BMI (kg/m²)	Median (Q1, Q3)	24.3 (21.5, 27.6)	24.7 (21.9, 28.1)	24.7 (21.8, 28.1)	0.058
	<25	1,030 (56.3%)	32,270 (52.3%)	33,300 (52.4%)	
	25-29.9	549 (30.0%)	19,803 (32.1%)	20,352 (32.0%)	

Abbreviations: INSTI=integrase strand transfer inhibitor; HIC=high income country; LMIC=low- to middle-income country; eGFR=estimated glomerular filtration rate; ART=antiretroviral therapy; ASCVD=atherosclerotic cardiovascular disease; BMI=body mass index.

[*] *Data are summarized at the first visit at which trial emulation eligibility criteria were met.*

[†] *Switch status is defined according to whether a participant ever met that criteria for any target trial.*

Supplemental Table 8. Unweighted distribution of confounding characteristics and standardized mean differences after weighting among participants included in the emulation of a target trial of the effect of switching to an INSTI vs not switching nested within the REPRIEVE trial, among those eligible for the analysis on major adverse cardiovascular events (MACE).

		INSTI switchers (N=2967 person-trials; 2967 unique individuals)	Non switchers (N=95,802 person-trials; 5056 unique individuals)	Total (N=98,769 person-trials; 5111 unique individuals)	Standardized Difference After Weighting
Age (years)	Median (Q1, Q3)	49 (45, 55)	49 (45, 54)	49 (45, 54)	0.013
	<50	1,490 (50.2%)	50,483 (52.7%)	51,973 (52.6%)	
	50+	1,477 (49.8%)	45,319 (47.3%)	46,796 (47.4%)	
Natal sex	Male	1,860 (62.7%)	60,544 (63.2%)	62,404 (63.2%)	0.028
	Female	1,107 (37.3%)	35,258 (36.8%)	36,365 (36.8%)	
Race	Black or African American	1,323 (44.6%)	36,253 (37.8%)	37,576 (38.0%)	0.013
	White	684 (23.1%)	25,207 (26.3%)	25,891 (26.2%)	
	Asian	682 (23.0%)	22,919 (23.9%)	23,601 (23.9%)	
	Other	278 (9.4%)	11,423 (11.9%)	11,701 (11.8%)	
Enrollment region	HIC	892 (30.1%)	30,036 (31.4%)	30,928 (31.3%)	0.131
	LMIC	2,075 (69.9%)	65,766 (68.6%)	67,841 (68.7%)	
Smoking status	Never	1,728 (58.2%)	54,081 (56.5%)	55,809 (56.5%)	0.027
	Current/Former	1,239 (41.8%)	41,721 (43.5%)	42,960 (43.5%)	
Alcohol use	Rarely/Never	2,285 (77.0%)	72,019 (75.2%)	74,304 (75.2%)	0.001
	Usually/Often/Sometimes	682 (23.0%)	23,783 (24.8%)	24,465 (24.8%)	
Substance use	Never	2,382 (80.3%)	75,844 (79.2%)	78,226 (79.2%)	0.062
	Current/Former	585 (19.7%)	19,958 (20.8%)	20,543 (20.8%)	
Diet score	Ideal/Intermediate	2,099 (70.7%)	70,500 (73.6%)	72,599 (73.5%)	0.000
	Poor	868 (29.3%)	25,302 (26.4%)	26,170 (26.5%)	
Physical activity score	Ideal/Intermediate	1,730 (58.3%)	57,394 (59.9%)	59,124 (59.9%)	0.015
	Poor	1,237 (41.7%)	38,408 (40.1%)	39,645 (40.1%)	
eGFR by CKD-EPI (<90 vs 90+)	90+	2,019 (68.0%)	64,669 (67.5%)	66,688 (67.5%)	0.067
	<90	948 (32.0%)	31,133 (32.5%)	32,081 (32.5%)	
Total duration ART use (<10 vs 10+)	10+	2,040 (68.8%)	65,072 (67.9%)	67,112 (67.9%)	0.003
	<10	927 (31.2%)	30,730 (32.1%)	31,657 (32.1%)	
Nadir CD4 (cells/mm3)	200+	1,452 (48.9%)	49,572 (51.7%)	51,024 (51.7%)	0.014
	<200	1,515 (51.1%)	46,230 (48.3%)	47,745 (48.3%)	
Treatment Group	Placebo	1,481 (49.9%)	47,704 (49.8%)	49,185 (49.8%)	0.005
	Pitavastatin	1,486 (50.1%)	48,098 (50.2%)	49,584 (50.2%)	
ASCVD risk score (%)	Median (Q1, Q3)	3.9 (1.8, 6.6)	3.7 (1.6, 6.5)	3.7 (1.6, 6.5)	0.024
	<5	1,774 (59.8%)	58,727 (61.3%)	60,501 (61.3%)	
	5+	1,193 (40.2%)	37,075 (38.7%)	38,268 (38.7%)	
BMI (kg/m²)	Median (Q1, Q3)	25.0 (22.1, 28.7)	25.4 (22.4, 28.9)	25.4 (22.3, 28.9)	0.062
	<25	1,476 (49.8%)	44,894 (46.9%)	46,370 (47.0%)	
	25-29.9	948 (32.0%)	31,974 (33.4%)	32,922 (33.3%)	

Abbreviations: INSTI=integrase strand transfer inhibitor; HIC=high income country; LMIC=low- to middle-income country; eGFR=estimated glomerular filtration rate; ART=antiretroviral therapy; ASCVD=atherosclerotic cardiovascular disease; BMI=body mass index.

[*]Data are summarized at the first visit at which trial emulation eligibility criteria were met.

[†]Switch status is defined according to whether a participant ever met that criteria for any target trial.

Appendix V: Summary of individuals contributing to each sequential trial and mean of inverse probability of treatment weights by sequential trial

Supplemental Table 9. Summary of individuals contributing to each sequential trial, overall and by switch strategy, as well as mean inverse probability treatment weights (IPTW) estimated for each trial.

	Obesity				Diabetes				Hypertension				MACE			
Seq Trial Number	Number eligible	Non-switchers	Switchers	Mean IPTW (SD)	Number eligible	Non-switchers	Switchers	Mean IPTW (SD)	Number eligible	Non-switchers	Switchers	Mean IPTW (SD)	Number eligible	Non-switchers	Switchers	Mean IPTW (SD)
1*	2549	2509	40	1.00 (0.12)	3168	3114	54	1.00 (0.10)	1945	1912	33	1.00 (0.16)	3187	3132	55	1.00 (0.10)
2*	2751	2708	43	1.00 (0.12)	3404	3339	65	1.00 (0.09)	2127	2092	35	1.00 (0.14)	3426	3361	65	1.00 (0.09)
3*	2937	2867	70	1.00 (0.09)	3614	3521	93	1.00 (0.09)	2285	2234	51	1.00 (0.07)	3637	3544	93	1.00 (0.09)
4*	3098	3032	66	1.00 (0.10)	3825	3740	85	1.00 (0.11)	2442	2382	60	1.00 (0.12)	3846	3761	85	1.00 (0.11)
5*	3086	2997	89	1.00 (0.10)	3811	3708	103	1.00 (0.10)	2432	2372	60	1.00 (0.08)	3838	3734	104	1.00 (0.10)
6*	1965	1914	51	1.00 (0.24)	2463	2395	68	1.00 (0.19)	1587	1544	43	1.00 (0.16)	2484	2416	68	1.00 (0.19)
7*	3102	3024	78	1.00 (0.07)	3973	3871	102	1.00 (0.07)	2572	2502	70	1.00 (0.09)	4006	3904	102	1.00 (0.07)
8	3132	3066	66	1.00 (0.08)	4013	3926	87	1.00 (0.07)	2594	2535	59	1.00 (0.06)	4048	3958	90	1.00 (0.06)
9	3108	3017	91	1.00 (0.07)	3966	3844	122	1.00 (0.07)	2574	2498	76	1.00 (0.08)	4004	3880	124	1.00 (0.07)
10	3042	2936	106	1.00 (0.10)	3865	3751	114	1.00 (0.16)	2514	2446	68	1.00 (0.12)	3906	3792	114	1.00 (0.15)
11	2947	2865	82	1.00 (0.07)	3757	3652	105	1.00 (0.05)	2442	2382	60	1.00 (0.08)	3799	3692	107	1.00 (0.05)
12	2630	2564	66	1.00 (0.12)	3372	3283	89	1.00 (0.08)	2192	2145	47	1.00 (0.16)	3409	3321	88	1.00 (0.07)
13	2741	2644	97	1.00 (0.20)	3551	3435	116	1.00 (0.21)	2317	2251	66	1.00 (0.14)	3596	3478	118	1.00 (0.20)
14	2662	2577	85	1.00 (0.11)	3462	3359	103	1.00 (0.10)	2273	2211	62	1.00 (0.12)	3508	3401	107	1.00 (0.09)
15	2603	2512	91	1.00 (0.29)	3379	3261	118	1.00 (0.20)	2226	2149	77	1.00 (0.27)	3427	3307	120	1.00 (0.19)
16	2500	2417	83	1.00 (0.16)	3246	3146	100	1.00 (0.13)	2139	2078	61	1.00 (0.09)	3294	3194	100	1.00 (0.13)
17	2410	2323	87	1.00 (0.12)	3136	3039	97	1.00 (0.12)	2062	2002	60	1.00 (0.08)	3184	3086	98	1.00 (0.13)
18	2097	2040	57	1.00 (0.12)	2775	2703	72	1.00 (0.08)	1821	1777	44	1.00 (0.18)	2823	2749	74	1.00 (0.07)
19	2157	2072	85	1.00 (0.09)	2889	2771	118	1.00 (0.07)	1895	1824	71	1.00 (0.14)	2940	2822	118	1.00 (0.07)
20	2093	2017	76	1.00 (0.11)	2801	2693	108	1.00 (0.12)	1846	1781	65	1.00 (0.18)	2854	2754	109	1.00 (0.12)
21	2003	1935	68	1.00 (0.22)	2668	2574	94	1.00 (0.11)	1758	1701	57	1.00 (0.14)	2724	2629	95	1.00 (0.12)
22	1921	1849	72	1.00 (0.17)	2552	2453	99	1.00 (0.15)	1688	1627	61	1.00 (0.12)	2612	2512	93	1.00 (0.16)
23	1835	1766	69	1.00 (0.08)	2433	2346	87	1.00 (0.10)	1612	1546	66	1.00 (0.11)	2495	2402	93	1.00 (0.09)

24	1596	1547	49	1.00 (0.23)	2134	2072	62	1.00 (0.14)	1416	1372	44	1.00 (0.21)	2198	2132	66	1.00 (0.15)
25	1615	1567	48	1.00 (0.11)	2182	2113	69	1.00 (0.10)	1441	1392	49	1.00 (0.13)	2239	2168	71	1.00 (0.10)
26	1565	1508	57	1.00 (0.16)	2113	2045	68	1.00 (0.18)	1391	1348	43	1.00 (0.23)	2172	2101	71	1.00 (0.17)
27	1478	1432	46	1.00 (0.17)	1999	1939	60	1.00 (0.11)	1324	1290	34	1.00 (0.11)	2053	1993	60	1.00 (0.13)
28	1401	1347	54	1.00 (0.23)	1892	1828	64	1.00 (0.16)	1262	1224	38	1.00 (0.22)	1947	1883	64	1.00 (0.16)
29	1310	1281	29	1.00 (0.18)	1772	1740	32	1.00 (0.15)	1194	1171	23	1.00 (0.44)	1826	1792	34	1.00 (0.18)
30	1142	1106	36	1.00 (0.09)	1560	1507	53	1.00 (0.11)	1058	1027	31	1.00 (0.15)	1612	1557	55	1.00 (0.11)
31	1104	1064	40	1.00 (0.13)	1533	1482	51	1.00 (0.13)	1044	1012	32	1.00 (0.22)	1581	1529	52	1.00 (0.12)
32	1020	975	45	1.00 (0.26)	1431	1372	59	1.00 (0.22)	983	949	34	1.00 (0.34)	1476	1416	60	1.00 (0.20)
33	876	836	40	1.00 (0.90)	1239	1189	50	1.00 (0.51)	863	827	36	1.00 (0.34)	1279	1228	51	1.00 (0.51)
34	735	689	46	1.00 (0.21)	1043	989	54	1.00 (0.23)	712	677	35	1.00 (0.21)	1073	1019	54	1.00 (0.22)
35	624	601	23	1.00 (0.14)	885	858	27	1.00 (0.17)	597	577	20	1.00 (0.31)	910	881	29	1.00 (0.21)
36	494	464	30	1.00 (0.31)	708	669	39	1.00 (0.22)	485	456	29	0.99 (0.21)	725	686	39	1.00 (0.37)
37	433	405	28	1.00 (0.49)	612	579	33	1.00 (0.25)	418	388	30	0.99 (0.25)	631	597	34	0.99 (0.21)

**Participants enrolled in low- and middle-income regions including Latin America, South East Asia, and Sub-Saharan Africa weren't considered for eligibility until study year 2018, explaining the variability in the number of eligible participants in the early set of target trials.*

Appendix VI. Age breakdown by sex

Supplemental Table 10. Age breakdown by natal sex and INSTI switch status among participants included in the emulation of a target trial of the effect of switching to an INSTI vs not switching nested within the REPRIEVE trial.

		Males		Females	
		Non switchers (N=60,958 person-trials; 3236 unique individuals)	**Switchers (N=1869 person-trials; 1869 unique individuals)**	**Non switchers (N=35,418 person-trials; 1823 unique individuals)**	**Switchers (N=1112 person-trials; 1112 unique individuals)**
Age (years)	Median (Q1, Q3)	50 (45, 54)	50 (45, 55)	48 (44, 53)	49 (44, 54)
	40-49	29,510 (48.4%)	893 (47.8%)	21,256 (60.0%)	600 (54.0%)
	50-59	26,713 (43.8%)	833 (44.6%)	11,533 (32.6%)	405 (36.4%)
	60+	4,735 (7.8%)	143 (7.7%)	2,629 (7.4%)	107 (9.6%)

Appendix VII. The TARGET Checklist

Item no.		Checklist item	Location reported	
Abstract				
1	a	Identify that the study attempts to emulate a target trial using observational data. State the study objectives and briefly summarize the specified target trial.	Page 3	
	b	Report the data sources used for emulation.	Page 3	
	c	Summarize key assumptions, statistical methods, findings and conclusions.	Page 3	
Introduction				
2	Background	Describe the scientific background of the study and the gap in knowledge.	Page 5	
3	Causal question	Summarize the causal question.	Page 5	
4	Rationale	Describe the rationale for emulating a target trial with the available data. Cite randomized trials informing the design of the target trial if applicable.	Page 6	
Methods				
5	Data sources	Cite the data sources contributing to the analyses and for each one describe the following: original purpose, type, the geographic locations, setting and time-period. If relevant, describe how the data were linked or pooled.		
6	**Target trial specification**	**7** **Target trial emulation**	**Location item 6 (specification) reported**	**Location item 7 (emulation) reported**
	Specify the components of the target trial protocol that would answer the causal question.	Describe how the components of the target trial protocol were emulated with the observational data, including how all variables were measured or ascertained.	Page 6 and Appendix Pages 2-4	Page 6 and Appendix Pages 2-4
	Eligibility criteria	**Eligibility criteria**		

a	Describe the eligibility criteria.	a	Describe how the eligibility criteria were operationalized with the data.	Page 6 and Appendix Pages 2-4	
Treatment strategies		**Treatment strategies**		Page 6 and Appendix Pages 2-4	Page 6 and Appendix Pages 2-4
b	Describe the treatment strategies that would be compared.	b	Describe how the treatment strategies were operationalized with the data.		
Assignment procedures		**Assignment procedures**		Page 6 and Appendix Pages 2-4	Page 6-7 and Appendix Pages 2-4
c	Report that eligible individuals would be randomly assigned to treatment strategies and may be aware of their treatment allocation.	c	Describe how assignment to treatment strategies was operationalized with the data.		
Follow-up		**Follow-up**		Page 6 and Appendix Pages 2-4	Page 6 and Appendix Pages 2-4
d	Clarify that follow-up would start at time of assignment to the treatment strategies. Specify when follow-up would end.	d	Clarify that follow-up starts at the time individuals were assigned to the treatment strategies. Describe how the end of follow-up was operationalized with the data.		
Outcomes		**Outcomes**		Page 6 and Appendix Pages 2-4	Page 6 and Appendix Pages 2-4
e	Describe the outcomes.	e	Describe how the outcomes were operationalized with the data.		
Causal contrasts		**Causal contrasts**		Page 6 and Appendix Pages 2-4	Page 6 and Appendix Pages 2-4
f	Describe the causal contrasts of interest, including effect measures.	f	Describe how the causal contrasts were operationalized with the data, including effect measures.		
Identifying assumptions		**Identifying assumptions**		Page 6	Page 6, Page 10
g	Describe assumptions that would be made to identify each causal estimand. Describe the variables, if any, related to these assumptions.	g.i	For each causal estimand, describe assumptions made to identify it, including assumptions		

				regarding baseline confounding due to lack of randomization.		
			g.ii	Describe how the variables related to these assumptions were operationalized with the data		
	Data analysis plan		**Data analysis plan**			
	h	For each causal estimand, describe the data analysis procedures and any associated statistical modelling assumptions, including approaches for handling missing data.	h.i	For each causal estimand, describe the data analysis procedures and any associated statistical modelling assumptions, including approaches for handling missing data.	Page 6-7	Page 6-7
			h.ii	For each causal estimand, describe any additional analyses conducted to assess the sensitivity of the results to the choice of operationalizations, assumptions and analysis.		
Results						
8	Participant selection	Report numbers of individuals assessed for eligibility, eligible, and assigned to each treatment strategy. A flow diagram is strongly recommended.			Page 8 and Appendix Page 8	
9	Baseline data	Describe the distribution of characteristics of individuals at baseline, by treatment strategy.			Table 1 - 3	
10	Follow-up	Summarize length of follow-up and describe reasons for end of follow-up for each treatment strategy and causal contrast.			Page 8	
11	Missing data	Describe the frequency of missing data in all variables, by treatment strategy when applicable.				
12	Outcomes	Describe the frequency or distribution of each outcome, by treatment strategy.			Page 8	
13	Effect estimates	Report the effect estimates for each causal contrast with corresponding measures of precision, including both absolute and relative measures of effect, when applicable.			Page 8	
14	Additional analyses	Report results of all analyses to assess the sensitivity of the estimates to choices in operationalizations, assumptions and analysis.			Page 9, Table 4	
Discussion						

15	Interpretation	Provide an interpretation of the key findings.	Page 9-10
16	Limitations	Discuss the limitations of the study considering differences between the target trial and its emulation and the plausibility of assumptions, including assumptions regarding baseline confounding due to lack of randomization.	Page 9-10
Other information			
17	Ethics	Provide the institutional research board or ethics committee that approved the study and approval numbers, if relevant.	Page 6
18	Registration	State whether, when and where the study protocol was registered.	NCT of REPRIEVE reported on page 5
19	Sharing of study materials	Provide information on whether data, analytic code and/or other materials are accessible, and where and how they can be accessed.	Page 11
20	Funding sources	Provide the sources of funding and detail the role of the funders in the design, conduct and reporting of the study.	Page 8
21	Conflicts of interest	State any conflicts of interest and financial disclosures for all authors.	Page 12-13