Risk of obesity, cardiometabolic disease and MACE after switching to an integrase inhibitor in REPRIEVE

838

Emma M Kileel[1], Carlos D Malvestutto[2], Markella V Zanni[3], Carl J Fichtenbaum[4], Judith A Aberg[5], Esteban Martinez[6,7], Aya Awwad[3], Sara H Bares[8], Daniel Berrner[9], Marek Smieja[10], Matthew P Fox[1,11], Alana T Brennan[1,11], Pamela S Douglas[12], Heather J Ribaudo[13], Steven K Grinspoon[3] for the Randomized Trial to Prevent Vascular Events in HIV (REPRIEVE)

[1]Boston University School of Public Health, Boston, MA, USA; [2]Ohio State University Medical Center, Columbus, OH, USA; [3]Massachusetts General Hospital and Harvard Medical School, Boston, MA, USA; [4]University of Cincinnati College of Medicine, Cincinnati, OH, USA; [5]Icahn School of Medicine at Mount Sinai, New York City, NY, USA; [6]Hospital Clinic and University of Barcelona, Barcelona, Spain; [7]Institute de Salud Carlos III, Madrid, Spain; [8]University of Nebraska Medical Center, Omaha, NE, USA; [9]University of California San Francisco at Zuckerberg San Francisco General Hospital, San Francisco, CA, USA; [10]McMaster University, Hamilton, ON, Canada; [11]Health Economics and Epidemiology Research Office at the University of Witwatersrand, Johannesburg, South Africa; [12]Duke University Research Institute, Durham, NC, USA; [13]Harvard School of Public Health, Boston, MA, USA.

BACKGROUND

- Integrase strand transfer inhibitor (INSTI)—based antiretroviral therapy (ART) regimens have been associated with disproportionate weight gain compared to protease inhibitor (PI)- or non-nucleoside reverse transcriptase inhibitor (NNRTI)-based regimens.
- Few studies have explored weight and cardiometabolic consequences of INSTIs beyond 2 years of use and fewer have examined effects on major adverse cardiovascular events (MACE).
- Using target trial emulation, we sought to understand the effect of switching to an INSTI-based treatment regimen on new-onset obesity, diabetes, hypertension, metabolic syndrome, and MACE, over 5 years of follow-up in a global cohort of treatment-experienced people with HIV (PWH),

METHODS

- REPRIEVE (NCT02344290) was a multicenter phase 3 double-blind, placebo controlled ASCVD prevention trial of PWH between ages 40 and 76 on stable ART.
- We emulated a series of target trials beginning every 90 days in REPRIEVE where participants were “randomized” to either switch their ART strategy to an INSTI-based regimen or remain on a non-INSTI-based regimen.
- Participants not on an INSTI regimen and event free at the start of each trial were eligible and followed until the event of interest, loss to follow-up, death (competing event), or censoring at 5 years.
- Inverse probability of treatment weights were estimated at the start of each trial to adjust for key confounders including natal sex, age, race, enrollment region, ASCVD risk score, statin use, ART duration, and BMI.
- Hazard ratios (HRs) were estimated using weighted Cox-proportional cause-specific hazard models with data pooled across all trials (N=24) and 95% confidence intervals (CIs) obtained via non-parametric bootstrapping (500 samples).

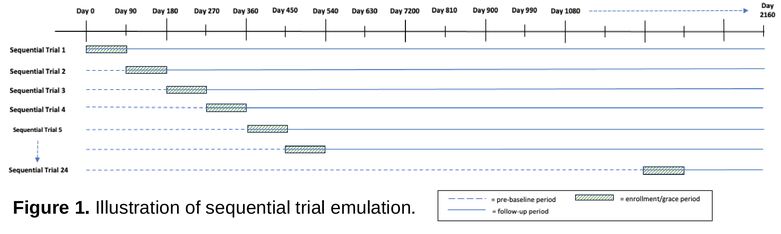


Figure 1. Illustration of sequential trial emulation.

In a global cohort of treatment experienced PWH, we found an increased risk of obesity, diabetes, and hypertension, but not MACE, over an average of 3.4 years of follow-up after a switch to an INSTI.

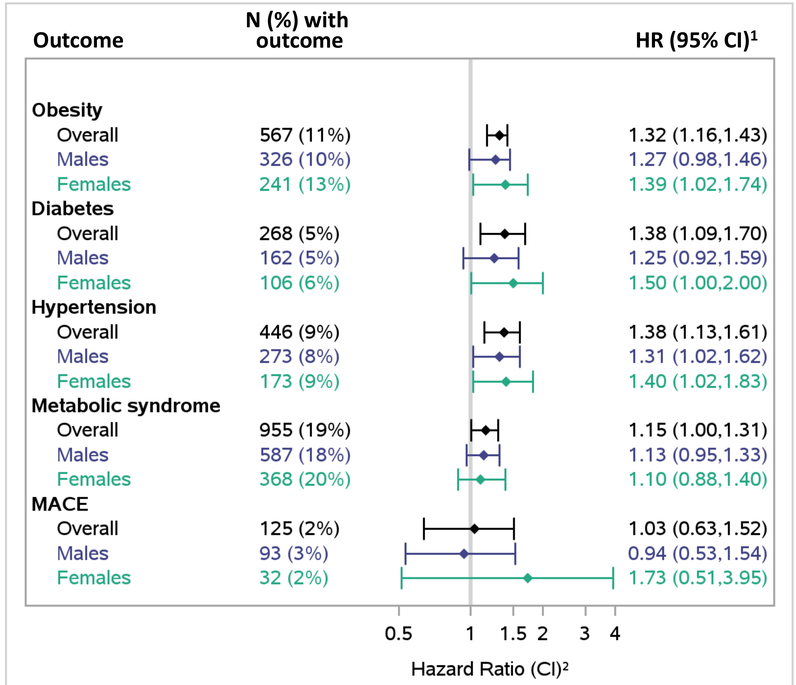
RESULTS

- 5162 participants were eligible for at least one trial. Of these, 1846 (36%) were female and 2708 (52%) switched to an INSTI, predominantly dolutegravir (82%).
- Overall, 11% developed obesity, 5% developed diabetes, 9% developed hypertension, 19% developed metabolic syndrome, and 2% experienced a MACE event.
- With data pooled across 24 trials we estimated an increased hazard of developing obesity (HR: 1.32, 95% CI: 1.07-1.47), diabetes (HR: 1.38, 95% CI: 1.10-1.69), hypertension (HR: 1.38, 95% CI: 1.13-1.61), and metabolic syndrome (HR: 1.15, 95% CI: 1.00-1.31), but not MACE (HR: 1.03, 95% CI: 0.63-1.52) among participants who switched to an INSTI (vs non-switchers).
- Estimated hazards for most outcomes were elevated in analyses restricted to participants born female, particularly MACE.
- Results were generally similar when accounting for choice of NRTI and time-updated percent change in BMI.

Table. Characteristics of key confounding variables by switch status.

		Switchers (N=2708)[1]	Never Switchers (N=2454)[1]
Age (years)	Median (Q1, Q3)	50 (45, 55)	49 (45, 54)
Natal sex	Male	1,688 (62%)	1,628 (66%)
	Female	1,020 (38%)	826 (34%)
Race	Black	1,237 (46%)	925 (38%)
	White	634 (23%)	728 (30%)
	Asian	576 (21%)	510 (21%)
	Other	261 (10%)	291 (12%)
Enrollment region	High income country[2]	805 (30%)	940 (38%)
	Low-middle income country[2]	1903 (70%)	1514 (62%)
Smoking status	Current/Former	1,139 (42%)	1,148 (47%)
	Never	1,568 (58%)	1,303 (53%)
Diet quality	Ideal/intermediate	1,898 (70%)	1,824 (75%)
	Poor	807 (30%)	619 (25%)
Physical activity levels	Ideal/intermediate	1,574 (58%)	1500 (61%)
	Poor	1,129 (42%)	942 (39%)
ASCVD risk score	Median (Q1, Q3)	4 (2, 7)	4 (2, 7)
BMI (kg/m^2)	Median (Q1, Q3)	25.0 (22.0, 28.4)	25.4 (22.4, 29.0)

[1]Data are summarized at the first visit at which trial emulation eligibility criteria were met. Switch status is defined according to whether a participant was ever classified as a switcher for any target trial; otherwise, they were a never switcher.
[2]High income countries included United States, Canada, and Spain; low-middle income countries included Botswana, Brazil, Haiti, India, Peru, South Africa, Thailand, Uganda, Zimbabwe.



[1]Hazard ratio (HR) estimates use inverse probability of treatment weights to adjust for natal sex, age, race, REPRIEVE enrollment region and year, alcohol, cigarette, and substance use, diet quality, physical activity levels, total ART duration, nadir CD4 cell count, eGFR at REPRIEVE entry, statin randomization status, ASCVD risk score, and BMI at the start of each sequential trial.
[2]For visual purposes, data on the x-axis are shown on the log scale.

Figure 2. Estimated hazard of obesity, diabetes, hypertension, metabolic syndrome, and MACE, among participants who switch to an INSTI-based regimen compared to non-switchers.

CONCLUSIONS

- In an ART-experienced, virally controlled global cohort of PWH, switching to an INSTI containing regimen resulted in an increased risk of new onset obesity, diabetes and hypertension.
- While the absolute risk of these outcomes was small, long-term observation of PWH initiating INSTIs will be critical to assess for future development of cardiometabolic complications and MACE, particularly among females.

AUTHOR CONTACT INFORMATION

Emma M Kileel, MPH
ekileel@bu.edu

REPRIEVE is supported through NIH grants U01HL123336 and U01HL123339, the ACTG, Kowa Pharmaceuticals, Gilead Sciences, and VIIV Healthcare.
We gratefully thank the study participants, site staff, and study-associated personnel for their participation and efforts in REPRIEVE.