Metabolic syndrome and cardiovascular risk on INSTIs

Published Online
March 27, 2026
https://doi.org/10.1016/
S2352-3018(25)00371-6

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Treatment regimens containing integrase strand-transfer inhibitors (INSTIs) are taken lifelong by most people with HIV. The potency, tolerability, and high resistance barrier of INSTIs make them the treatment of choice. Widespread long-term use requires vigilance for rare or delayed adverse effects. Within real-world evidence frameworks, inferring causality requires considerably more than a statistically significant association. Apparent effects might merely reflect who receives which treatment. In the RESPOND cohort[1] for example, people with HIV on antiretroviral therapy (ART) with a moderate D:A:D 5-year cardiovascular risk score had higher odds of being switched to an INSTI (odds ratio 1·26, 95% CI 1·20–1·33; p<0·001), rising to an odds ratio of 1·51 (95% CI 1·40–1·63; p<0·001) with high or very high risk, compared with those at low risk. Such non-trivial differences that precede INSTI exposure illustrate why stringent adjustment for confounding, together with biological plausibility and consistency across datasets, are essential before inferring causality.

In *The Lancet HIV*, two analyses offer intriguing insights into the possible metabolic consequences of switching to an INSTI. The NA-ACCORD cohort analysis by Y Joseph Hwang and colleagues reflects real-world complexity, capturing multimorbidity and diverse treatment histories.[2] The REPRIEVE study analysis by Emma M Kileel and colleagues provides the structure of a randomised trial through a secondary analysis, with lower baseline comorbidity, exclusion of individuals with previous cardiovascular disease, and prospective cardiometabolic assessments.[3]

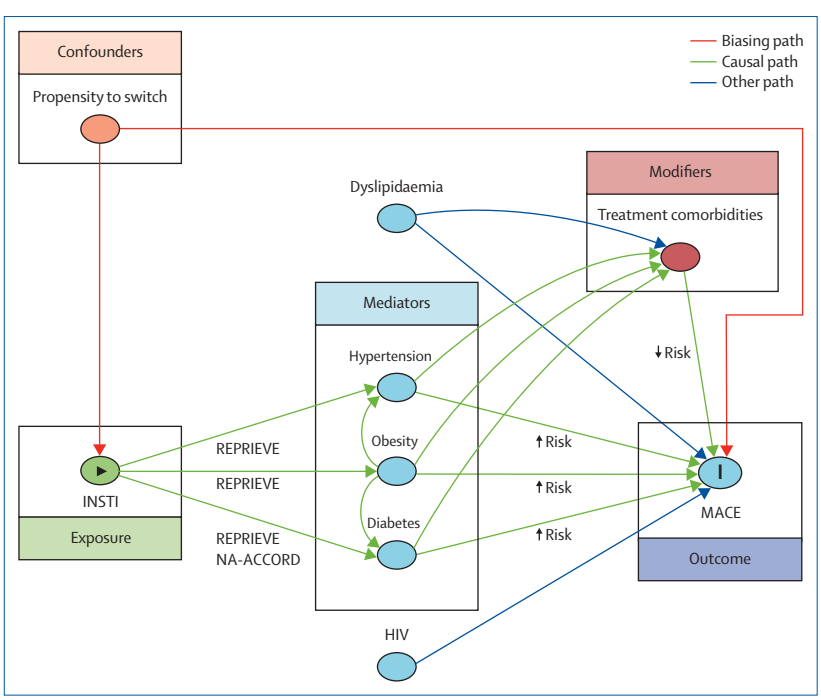

Figure: **Directed acyclic graph for metabolic complications and MACE from cohorts with INSTI exposure**
Some potential confounding pathways are omitted for clarity. INSTI= integrase strand-transfer inhibitor. MACE=major cardiovascular adverse events.

Despite these differences, the findings are strikingly consistent. After adjusting for baseline imbalances with counterfactual methods, both studies report an increased risk of diabetes after switching to an INSTI. In REPRIEVE, switches were also associated with higher risks of hypertension and obesity than not switching. Consistency across populations, datasets, and designs strengthens the case for a causal relationship.[4] Reversibility would add further support for causal inference, but evidence of weight loss after stopping an INSTI is scarce and metabolic improvements remain uncertain. Mechanistic evidence adds credibility. Preclinical work[5] suggests that dolutegravir and bictegravir can directly induce insulin resistance, adipogenesis, and fibrosis in human and simian adipose tissue. These in vitro observations are not definitive proof but provide biologically plausible pathways that align with emerging clinical data.

These results raise a key question: do the early metabolic disturbances observed with INSTI exposure ultimately lead to higher rates of major adverse cardiovascular events (MACE)? In this context, RESPOND[1] reported increased cardiovascular events in the first 2 years of INSTI exposure. We found this early timing difficult to reconcile with a pathway mediated by incidental diabetes, hypertension, or obesity, which would affect outcomes over longer timeframes. In contrast, HIV-CAUSAL[6] analyses did not find excess cardiovascular risk, consistent with the current REPRIEVE analysis. Some of the observed discrepancies might reflect partial indication bias or differences in study populations. Women, particularly post-menopausal women, have a higher risk of diabetes and MACE, and Black and South Asian individuals are at greater risk of both diabetes and MACE than White people. REPRIEVE participants with low-to-moderate cardiovascular risk

were followed up for 5 years, during which relatively few MACE occurred. Although hazard ratios were statistically significant, the absolute risk differences for obesity, hypertension, and diabetes were also low. About half of participants received statins, which likely further prevented cardiovascular risk.[7] As a result, it is possible that an effect of INSTI exposure on MACE, if any, takes longer to become apparent. Of note, as observed in REPRIEVE,[7] people with HIV receiving pitavastatin had a higher rate of diabetes than the placebo group (incidence rate ratio 1·35, 95% CI 1·09–1·66), in line with other trials using statins.[8] In a secondary analysis, high BMI, prediabetes, and metabolic syndrome components were strongly associated with new-onset diabetes (all p<0·005).[9]

To contextualise these findings, we include a directed acyclic graph summarising the causal structure underpinning metabolic and cardiovascular outcomes associated with INSTI exposure (figure). The figure highlights three points. First, it shows probable direct links between INSTI exposure and hypertension or diabetes, as observed in the studies: not all metabolic toxicity can be attributed to weight gain alone. Second, it emphasises that timely intervention (ie, the treatment of metabolic comorbidities, such as diabetes, hypertension, and obesity) interacts favourably with the natural trajectory of metabolic syndrome towards MACE. Third, it is a reminder that unboosted INSTIs are generally lipid-neutral, unlike protease inhibitors or efavirenz.[10] This profile helps balance overall cardiovascular risk and supports a personalised, precision-medicine approach to ART selection. A further reminder is that HIV itself elevates cardiovascular risk through viral replication, chronic inflammation, and immune activation, independent of ART.

Taken together, these findings begin to elucidate what we perceive as the INSTI metabolic syndrome but cardiac reprieve paradox. Just as test and treat transformed HIV care through early therapy and prevention benefits, screening early and proactively managing modifiable cardiovascular risk factors could avert long-term harm.

JJP has received speaking, advising fees, and research grants to their institution from Gilead Sciences, Merck, and ViiV Healthcare. FB has received speaking, advising fees, and research grants to their institution from Servier, AstraZeneca, Sanofi, NovoNordisk, Novartis, Gilead Sciences, Merck, and ViiV Healthcare. We would like to thank Esteban Martinez who reviewed an earlier version of this Comment.

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1 Neesgaard B, Greenberg L, Miró JM, et al. Associations between integrase strand-transfer inhibitors and cardiovascular disease in people living with HIV: a multicentre prospective study from the RESPOND cohort consortium. *Lancet HIV* 2022; **9:** e474–85.
2 Hwang YJ, Lesko CR, Brown TT, et al. Incident diabetes after switching to integrase strand transfer inhibitors in people with HIV in the USA and Canada: a cohort study. *Lancet HIV* 2026; published online March 27. https://doi.org/10.1016/S2352-3018(25)00335-2.
3 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.
4 Rupasinghe D, Bansi-Matharu L, Law M, et al. Integrase strand transfer inhibitor-related changes in body mass index and risk of diabetes: a prospective study from the RESPOND cohort consortium. *Clin Infect Dis* 2025; **80:** 404–16.
5 Ngono Ayissi K, Gorwood J, Le Pelletier L, et al. Inhibition of adipose tissue beiging by HIV integrase inhibitors, dolutegravir and bictegravir, is associated with adipocyte hypertrophy, hypoxia, elevated fibrosis, and insulin resistance in simian adipose tissue and human adipocytes. *Cells* 2022; **11:** 1841.
6 Rein SM, Lodi S, Logan RW, et al. Integrase strand-transfer inhibitor use and cardiovascular events in adults with HIV: an emulation of target trials in the HIV-CAUSAL Collaboration and the Antiretroviral Therapy Cohort Collaboration. *Lancet HIV* 2023; **10:** e723–32.
7 Grinspoon SK, Fitch KV, Zanni MV, et al. Pitavastatin to prevent cardiovascular disease in HIV infection. *N Engl J Med* 2023; **389:** 687–99.
8 Reith C, Preiss D, Blackwell L, et al. Effects of statin therapy on diagnoses of new-onset diabetes and worsening glycaemia in large-scale randomised blinded statin trials: an individual participant data meta-analysis. *Lancet Diabetes Endocrinol* 2024; **12:** 306–19.
9 Fitch KV, Zanni MV, Manne-Goehler J, et al. Diabetes risk factors in people with HIV receiving pitavastatin versus placebo for cardiovascular disease prevention: a randomized trial. *Ann Intern Med* 2024; **177:** 1449–61.
10 Parienti J-J, Massari V, Rey D, Poubeau P, Verdon R. Efavirenz to nevirapine switch in HIV-1-infected patients with dyslipidemia: a randomized, controlled study. *Clin Infect Dis* 2007; **45:** 263–66.

Long-acting PrEP and equitable HIV prevention in Brazil

Published **Online**
February 23, 2026
https://doi.org/10.1016/S2352-3018(26)00029-9

On Jan 12, 2026, the Brazilian Health Regulatory Agency (Anvisa) approved a new indication for lenacapavir as a long-acting injectable agent for HIV pre-exposure prophylaxis (PrEP) in adults and adolescents older than 12 years with a bodyweight of at least 35 kg.[1] This decision is a major regulatory milestone for HIV prevention in Brazil, formally introducing a twice-yearly injectable PrEP option within a universal public