Incident diabetes after switching to integrase strand transfer inhibitors in people with HIV in the USA and Canada: a cohort study

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Summary

Background Integrase strand transfer inhibitor (INSTI) initiation has been associated with diabetes in antiretroviral therapy (ART)-naive people with HIV. We aimed to examine the effect of switching to INSTIs on incident diabetes in ART-experienced people with HIV.

Methods In this target trial emulation, we retrospectively used individual-level data from 27 longitudinal cohorts of people with HIV in the USA and Canada. We included participants aged at least 18 years without diabetes who had used non-nucleoside reverse transcriptase inhibitors (NNRTIs) or protease inhibitors for at least 180 days (in 2016–22) but had never used an INSTI. We used data from any clinical encounters in which participants continued an NNRTI or protease inhibitor versus switched to an INSTI, with a follow-up period of up to 5 years. The effect of switching to INSTIs on incident diabetes was estimated with weighted Cox regression with robust variance. We further assessed whether the effect varied by time since the switch and was explained by weight gain in the first year.

Findings 13 071 participants were followed up from 2702 encounters in which they switched to an INSTI from an NNRTI, 54 766 encounters in which they continued an NNRTI, 1714 encounters in which they switched to an INSTI from a protease inhibitor, and 26 599 encounters in which they continued a protease inhibitor. Switching from protease inhibitors to INSTIs conferred an adjusted hazard ratio (HR) of 1·38 (95% CI 1·06–1·80) for incident diabetes, whereas switching from NNRTIs to INSTIs conferred an adjusted HR of 1·10 (0·87–1·39). The diabetes risk was higher during the first 2 years after switching from protease inhibitors to INSTIs (HR 1·67, 95% CI 1·21–2·30), but not thereafter (1·08, 0·75–1·57; $p_{interaction}$=0·064). The effect of switching from protease inhibitors to INSTIs on diabetes did not appear to be explained by weight gain. In the sensitivity analysis in which weight gain did not exceed 5% in the first year after, the switch from NNRTIs to INSTIs had a HR of 1·03 (95% CI 0·79–1·36) and the switch from protease inhibitors to INSTIs had a HR of 1·37 (1·02–1·84).

Interpretation The increased diabetes risk after switching from protease inhibitors to INSTIs highlights a metabolic implication of regimen change and could warrant close monitoring early after switch, regardless of weight gain.

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Introduction

Diabetes affects more than 10% of people with HIV and incidence is rising as this population ages.[1] Antiretroviral therapy (ART) contributes to metabolic complications, with various agents associated with weight gain, lipohypertrophy, and insulin resistance.[2] Since 2015, integrase strand transfer inhibitor (INSTI)-based regimens have been recommended as first-line therapy for most people with HIV due to their virological efficacy.[3] Although multiple real-world studies have reported an increased diabetes risk in ART-naive people with HIV initiating INSTI-based regimens compared with other ART regimens,[4–6] this association has not been consistent across all studies.[7] Furthermore, INSTI-based regimens have been associated with greater weight gain than non-nucleoside reverse transcriptase inhibitor (NNRTI)-based regimens and, to a lesser extent, protease inhibitor-based regimens in both randomised and observational studies,[8–10] and weight gain on ART is a major risk factor for type 2 diabetes.[11]

Evidence on the diabetes risk associated with prevalent INSTI use in ART-experienced people with HIV has been mixed. Some observational studies have identified INSTI use as a risk factor in this population, whereas others have not observed such an association.[12–14] With a target trial emulation approach, we previously reported an 11% increased risk of diabetes—although not statistically significant—after switching from an NNRTI-based or

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*Collaborating cohorts and their representatives are listed in the appendix (p 7)

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See Online for appendix

Research in context

Evidence before this study

We searched PubMed for observational and randomised studies evaluating the risk of incident diabetes associated with integrase strand transfer inhibitors (INSTIs) in people with HIV. Search terms were "integrase strand transfer inhibitor", "INSTI", "bictegravir", "dolutegravir", "elvitegravir", "raltegravir", and "diabetes", covering the period from Jan 1, 2007, to June 30, 2024. We identified observational studies of heterogeneous scale that evaluated diabetes risk associated with the initiation or prevalent use of INSTIs in people with HIV. Four studies investigated the diabetes risk associated with initiating INSTIs: one study found a higher diabetes risk than with initiating non-nucleoside reverse transcriptase inhibitors (NNRTIs) and two studies found higher risk of diabetes than with starting non-INSTI-based regimens; however, this trend was not observed across all studies; for example, another study reported similar diabetes incidence rates between dolutegravir-based and darunavir-based regimens. In people with HIV with prevalent use of antiretroviral therapy (ART), two studies found an association between INSTI use and higher diabetes risk, whereas another study did not observe such a relationship.

Added value of this study

Although previous studies have examined the relationship between INSTI initiation or prevalent INSTI use and diabetes risk, they provide little information for ART-experienced people with HIV who are considering a switch to INSTI-based therapy. This study adds value by directly addressing this gap. Using a large multisite cohort of people with HIV receiving NNRTI-based or protease inhibitor-based regimens, we estimated the effect of switching to an INSTI on subsequent diabetes risk. Additionally, we evaluated whether diabetes risk varies according to time since switching and whether early weight gain explains the observed association. These analyses offer greater clarity on the timing and potential mechanisms of risk. Together, this study refines understanding of the potential metabolic implications of switching to INSTI-based regimens and informs clinical decision making around such regimen changes.

Implications of all the available evidence

Together with previous studies that raised concern regarding the increased risk of diabetes associated with INSTI initiation in ART-naive people with HIV, our findings indicate that ART-experienced individuals who switch from a protease inhibitor to an INSTI also have an increased risk. A growing body of evidence implicates INSTIs with diabetes risk across both ART initiation and switching contexts, underscoring the need to consider metabolic risk when selecting ART regimens.

protease inhibitor-based regimen to an INSTI-based regimen in a single HIV clinic cohort.[15] Here, we apply similar methods to a larger and more generalisable multisite cohort of ART-experienced people with HIV with the aim to assess the effect of switching from an NNRTI-based or protease inhibitor-based regimen to an INSTI-based regimen on incident diabetes risk.

Methods

Study design

In this multisite, retrospective, longitudinal cohort study of people with HIV, we emulated a target trial with data from the USA and Canada.

Data on study participants were obtained from the North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD), a consortium of 27 clinical and interval cohorts in the USA and Canada.[16] Data from these cohorts were collected during routine patient care, such that the availability and timing of measurements are driven by clinical practice. NA-ACCORD is part of the International Epidemiologic Databases to Evaluate AIDS global network. Annual standardised data submissions (eg, demographics, prescriptions, comorbidities, and laboratory results) undergo quality assurance at the Data Management Core (University of Washington, Seattle, WA, USA) and are then processed by the Epidemiology/Biostatistics Core (Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA). The activities of the NA-ACCORD were approved by the Johns Hopkins University institutional review board (JHU IRB 23533), and each participating NA-ACCORD cohort was granted ethics approval by its respective local institutional review board to share its data with NA-ACCORD. Primary data collection by each participating NA-ACCORD cohort was done in accordance with informed consent requirements and procedures established by their local institutional review boards.

We designed a target trial that would include adults with HIV without diabetes history who had received NNRTIs or protease inhibitors without previous INSTI exposure. In our emulation study, we included people with HIV aged at least 18 years from participating cohorts with at least one HIV clinical encounter between Jan 1, 2016, and Dec 31, 2022, who had no diabetes history, were on an NNRTI or protease inhibitor for at least 180 days, had never used an INSTI, and had a weight measurement within the year before the clinical encounter. The study period (2016–22) aligns with INSTI-based regimens being recommended as first-line ART,[3] minimising confounding by indication from earlier periods when people with HIV with metabolic risk factors could have preferentially switched from older regimens with known metabolic toxicity.

Procedures

We used a nested trials approach to emulate a target trial, in which each time participants meet the inclusion criteria at an HIV clinical encounter, they would be

randomly assigned to either continue an NNRTI or protease inhibitor versus switch to an INSTI.[17] In our study, each time participants treated with an NNRTI or protease inhibitor had a clinical encounter, they were eligible to switch to an INSTI. Antiretroviral drug exposure was ascertained from prescription records. We classified each eligible clinical encounter (the index encounter and unit of observation) as a switch to INSTI if the participant had a new INSTI prescription within 14 days (either side) of the index encounter. Otherwise, an observation was classified as continuing an NNRTI or protease inhibitor. Participants could contribute multiple observations in which they continued an NNRTI or protease inhibitor, but at most one observation in which they switched to an INSTI. We excluded encounters occurring within 30 days of a previous qualifying encounter, ensuring at least a 1-month interval between observations.[15]

In both the target trial and our study, follow-up began on the date of the index encounter and continued until the first occurrence of incident diabetes (the outcome) or a censoring event. In our study, the censoring events were loss to clinical follow-up (defined as the last encounter before a gap between encounters of 1 year or more), death, 5 years after the index encounter, administrative closure or end of observation window for diabetes for the corresponding cohort site,[18] or the end of administrative follow-up on Dec 31, 2022. After the index encounter, observations were not censored at the end of study antiretroviral prescription, per the intention-to-treat principle. However, those continuing an NNRTI or protease inhibitor at the index encounter were censored upon a later switch to an INSTI.

Age, sex at birth (male or female), and race (Black, White, other, or unknown) were measured via the electronic medical record. BMI (categorised as either: underweight, <18·5 kg/m²; normal weight, 18·5–24·9 kg/m²; overweight, 25·0–29·9 kg/m²; or obese, ≥30·0 kg/m²), viral suppression (HIV viral load ≤200 copies per mL), and CD4 count of 200 cells per µL or less were ascertained based on the most recent measurement within the year leading up to the index encounter. We assessed whether the participants had a history of hypertension, hyperlipidaemia, and chronic kidney disease stage 3 or greater (definitions detailed in appendix p 2) before the index encounter.[19] We assessed the presence of prescriptions for antithrombotics, antidepressants, antipsychotics, and opioid analgesics at the index encounter. We also assessed use of tenofovir disoproxil fumarate and tenofovir alafenamide.

Outcomes

The main outcome was incident diabetes. Incident diabetes was defined as the first occurrence of either a laboratory glycated haemoglobin (HbA_{1c}) value of 6·5% or more, initiation of a diabetes-specific medication, or a new diabetes diagnosis plus initiation of a diabetes-related medication. This is a commonly used definition by the NA-ACCORD.[4,19] Diabetes-specific and diabetes-related medications are detailed in the appendix (p 1). Type 1 diabetes and gestational diabetes were excluded from the diagnosis-based definition. In secondary analyses, we evaluated whether the association between switching to an INSTI and incident diabetes varied by specific INSTI agent, time since switching, and baseline BMI. In sensitivity analyses, we evaluated the extent to which weight gain might explain the relationship between INSTI switch and diabetes and examined this association over an extended period spanning from 2007 to 2022.

Statistical analysis

In the target trial, treatment assignment—switching to an INSTI or continuing an NNRTI or protease inhibitor—would be random. In our emulated study, treatment assignment was non-random; therefore, identification of causal effects relied on the assumption of no unmeasured confounding after covariate adjustments (exchangeability assumption). To account for confounding from non-random treatment assignment, we used inverse probability of treatment weights.[20] Two separate inverse probability of treatment weights were derived: one from a logistic model predicting the probability of switching to an INSTI versus continuing an NNRTI and another from a logistic model predicting the probability of switching to an INSTI versus continuing a protease inhibitor, conditional on all covariates described previously. Additionally, we used inverse probability of censoring weights to mitigate potential bias from informative censoring. We estimated the weights separately for censoring due to loss to clinical follow-up and a subsequent switch to an INSTI after index encounters in which an NNRTI or protease inhibitor was continued. Both censoring weights were estimated with a multivariable logistic model for the probability of censoring in each 90-day block after the index encounter, conditional on the covariates at the index encounter, exposure, time since the index encounter, and time-updated covariates. The final weights were the cumulative product of the censoring and treatment weights.

Covariates were selected based on their relationship with treatment exposure or outcome, or both. Switching from tenofovir disoproxil fumarate to tenofovir alafenamide is associated with weight gain and often coincides with an INSTI switch.[21] To isolate INSTI effects, we classified tenofovir alafenamide changes as: initiation (no tenofovir alafenamide in the 180–14 days before, but prescribed 14–180 days after the index encounter); discontinuation (tenofovir alafenamide prescribed 180–14 days before, but not 14–180 days after the index encounter); continuation (tenofovir alafenamide

	Switch to INSTI *vs* continued NNRTI		Switch to INSTI *vs* continued PI	
	Switched to INSTI	Continued NNRTI	Switched to INSTI	Continued PI
Participants who contributed at least one observation	2702	7895	1714	4459
Clinical encounters	2702	54766	1714	26599
Age, years	55 (46–62)	56 (47–64)	55 (47–62)	55 (47–63)
Sex at birth				
Male	2452 (90·7%)	50551 (92·3%)	1446 (84·4%)	23218 (87·3%)
Female	250 (9·3%)	4215 (7·7%)	268 (15·6%)	3381 (12·7%)
Race				
Black	1052 (38·9%)	21305 (38·9%)	753 (43·9%)	11432 (43·0%)
White	1382 (51·1%)	27625 (50·4%)	806 (47·0%)	13170 (49·5%)
Other	198 (7·3%)	4494 (8·2%)	118 (6·9%)	1524 (5·7%)
Unknown	70 (2·6%)	1342 (2·5%)	37 (2·2%)	473 (1·8%)
Year of encounter				
2016	973 (36·0%)	17281 (31·6%)	776 (45·3%)*	9650 (36·3%)
2017–18	1105 (40·9%)	22412 (40·9%)	651 (38·0%)	10898 (41·0%)
2019–20	548 (20·3%)	10582 (19·3%)	244 (14·2%)	4379 (16·5%)
2021–22	76 (2·8%)†	4491 (8·2%)	43 (2·5%)*	1672 (6·3%)
Duration of NNRTI or PI use before clinical encounter, years	6 (3–10)	8 (4–11)	5 (3–9)	7 (4–11)
HbA_{1c}‡	5·5 (5·2–5·8)	5·5 (5·2–5·8)	5·4 (5·1–5·7)	5·4 (5·1–5·7)
BMI, kg/m²	26 (23–30)	27 (24–30)	26 (23–30)	26 (23–30)
BMI categories				
Underweight	65 (2·4%)	1198 (2·2%)	40 (2·3%)	721 (2·7%)
Typical weight	984 (36·4%)	18944 (34·6%)	609 (35·5%)	9146 (34·4%)
Overweight	1004 (37·2%)	20311 (37·1%)	641 (37·4%)	9773 (36·7%)
Obese	649 (24·0%)	14313 (26·1%)	424 (24·7%)	6959 (26·2%)
Viral suppression	2556 (94·6%)	52380 (95·6%)	1578 (92·1%)	24532 (92·2%)
CD4 count ≤200 cells per μL	44 (1·6%)	732 (1·3%)	73 (4·3%)	953 (3·6%)
Comorbidities				
Hypertension	1082 (40·0%)	23761 (43·4%)	678 (39·6%)	11440 (43·0%)
Hyperlipidaemia	1220 (45·2%)	26444 (48·3%)	758 (44·2%)	12927 (48·6%)
Chronic kidney disease	349 (12·9%)	7108 (13·0%)	347 (20·2%)	5002 (18·8%)
Other medications				
Antithrombotic	61 (2·3%)	1212 (2·2%)	46 (2·7%)	794 (3·0%)
Antidepressant	584 (21·6%)	12115 (22·1%)	421 (24·6%)	7371 (27·7%)
Antipsychotic	98 (3·6%)	1585 (2·9%)	88 (5·1%)	1834 (6·9%)
Opioid	237 (8·8%)	5019 (9·2%)	195 (11·4%)	3927 (14·8%)
Concomitant TAF use at clinical encounter				
Initiated TAF	1532 (56·7%)†	5594 (10·2%)	696 (40·6%)*	3202 (12·0%)
Continued TAF	263 (9·7%)†	16058 (29·3%)	290 (16·9%)*	7796 (29·3%)
Discontinued TAF	30 (1·1%)	188 (0·3%)	15 (0·9%)	152 (0·6%)
None	877 (32·5%)†	32926 (60·1%)	713 (41·6%)*	15449 (58·1%)
Concomitant TDF use at clinical encounter				
Initiated TDF	14 (0·5%)	103 (0·2%)	26 (1·5%)	161 (0·6%)
Continued TDF	1101 (40·7%)†	32913 (60·1%)	526 (30·7%)*	12452 (46·8%)
Discontinued TDF	1011 (37·4%)†	2857 (5·2%)	468 (27·3%)*	1877 (7·1%)
None	576 (21·3%)†	18893 (34·5%)	694 (40·5%)	12109 (45·5%)

Data are n, n (%), or median (interquartile interval). INSTI=integrase strand transfer inhibitor. NNRTI=non-nucleoside reverse transcriptase inhibitor. PI=protease inhibitor. TAF=tenofovir alafenamide. TDF=tenofovir disoproxil fumarate. *Indicates absolute standardised mean differences greater than 0·10 when comparing clinical encounters in which participants switched to an INSTI with those in which participants continued a PI. †Indicates absolute standardised mean differences greater than 0·10 when comparing clinical encounters in which participants switched to an INSTI with those in which participants continued an NNRTI. ‡The most recent HbA_{1c} measurement within the year leading up to the clinical encounter; such measurement was available for 1201 (44%) switches from an NNRTI to an INSTI, 26842 (49%) continuations with an NNRTI, 721 (42%) switches from a PI to an INSTI, and 12556 (47%) continuations of a PI.

Table 1: **Characteristics of participants at HIV clinical encounters**

prescribed in both periods); and no tenofovir alafenamide (never prescribed in both periods). Tenofovir disoproxil fumarate changes were classified similarly.[15]

We assessed between-group differences in covariates at the index encounter through pairwise standardised mean differences for switching to INSTI versus continuing NNRTI and switching to INSTI versus continuing protease inhibitor.[20] An absolute standardised mean difference of more than 0·10 was considered indicative of meaningful imbalance.

In our main analysis, we estimated hazard ratios (HRs) and 95% CIs for incident diabetes associated with switching to any INSTI versus continuing an NNRTI or protease inhibitor with weighted Cox regression with robust variance estimators to account for repeated observations on participants and uncertainty in the estimation of the weights.

We did three secondary analyses to further investigate the relationship between INSTI switch and diabetes. First, we assessed the diabetes risk associated with specific agents (ie, bictegravir, dolutegravir, elvitegravir, or raltegravir) compared with continuing an NNRTI or protease inhibitor. Through a multinomial logistic model, we derived inverse probability of treatment weights based on the predicted probability of switching to specific INSTI agents.

Second, to assess whether diabetes risk varied by time since switching to INSTIs, we included an interaction term for follow-up period (first 2 years *vs* subsequent years) and INSTI switch, informed by findings from a previous single-site study that reported a significant interaction between INSTI switch and time since switching on diabetes risk.[15]

Third, to assess whether the risk of diabetes differed by BMI before switching to INSTI, we included an interaction term for BMI (≥25 kg/m² *vs* <25 kg/m²) based on the most recent measurement within the year leading up to the index encounter. This threshold was selected to distinguish people with overweight or obesity from those with normal or underweight BMI.

To evaluate the extent to which weight gain might explain the relationship between INSTI switch and diabetes, we did a sensitivity analysis estimating the effect of switching therapy in a hypothetical intervention restricting weight gain to 5% or less within the first year.[22,23] This analysis represents the controlled direct effect of INSTI switch independent of weight gain. To operationalise this analysis, we censored follow-up at the first time a participant's weight exceeded 105% of their weight at the index encounter. We then applied another set of inverse probability of censoring weights to account for the potential selection bias introduced by this censoring.

In a second sensitivity analysis, we explored the main effect over an extended period (Jan 1, 2007, to Dec 31, 2022), during which switching decisions could have varied as NNRTI-based and protease inhibitor-based regimens were phased out and INSTI-based regimens became the recommended first-line therapy. Similar censoring criteria were applied for follow-up, except the maximum follow-up time was expanded from 5 years to 10 years.

We did all analyses with R version (4.3.1) and used the Generalised Estimating Equation Package (geepack) and Survival Package (survival).

Role of the funding source

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

Results

13 071 participants were followed up between 2016 and 2022 from 2702 encounters in which they switched to an

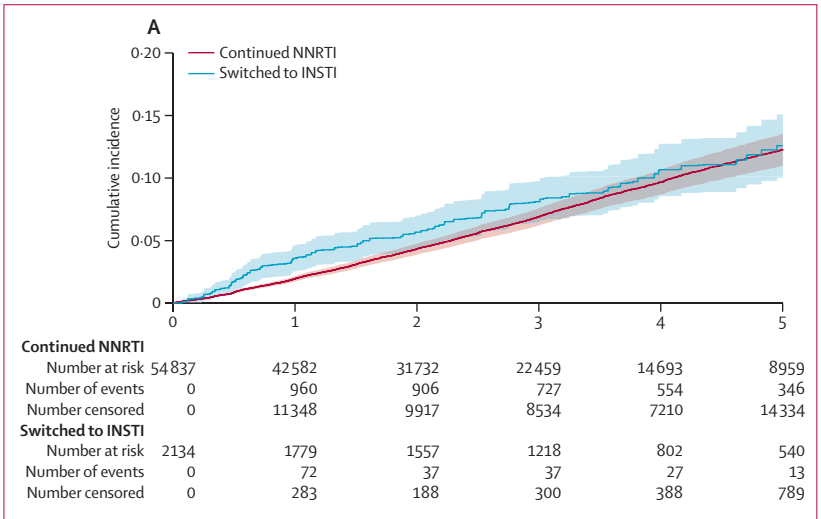
	Number of people with HIV who ever contributed observations	Number of events/number of encounters (%)	Adjusted incidence rate per 1000 person-years (95% CI)	Adjusted hazard ratio (95% CI)*
Switching from NNRTI to INSTI				
Continued NNRTI	7895	3459/54 766 (6·3%)	24·5 (23·7–25·3)	1 (ref)
Switched to INSTI	2702	250/2702 (9·3%)	27·7 (23·9–32·0)	1·10 (0·87–1·39)
Switching from PI to INSTI				
Continued PI	4459	1509/26 599 (5·7%)	22·7 (21·6–23·9)	1 (ref)
Switched to INSTI	1714	150/1714 (8·8%)	30·4 (25·7–35·7)	1·38 (1·06–1·80)
Specific INSTI				
NNRTI or PI	12 237	5041/81 365 (6·2%)	23·9 (23·2–24·5)	1 (ref)
Bictegravir	1097	87/1097 (7·9%)	29·4 (18·6–44·1)	1·17 (0·81–1·70)
Dolutegravir	1953	182/1953 (9·3%)	27·8 (23·5–32·6)	1·10 (0·87–1·40)
Elvitegravir	1322	127/1322 (9·6%)	30·1 (22·8–39·0)	1·21 (0·83–1·75)
Raltegravir	44	4/44 (9·1%)	28·7 (9·3–67·0)	1·14 (0·30–4·41)

INSTI=integrase strand transfer inhibitor. NNRTI=non-nucleoside reverse transcriptase inhibitor. PI=protease inhibitor. *Adjusted hazard ratios were derived from weighted Cox regression that accounted for demographic and HIV-related characteristics, comorbidities, co-medications, and laboratory measurements.

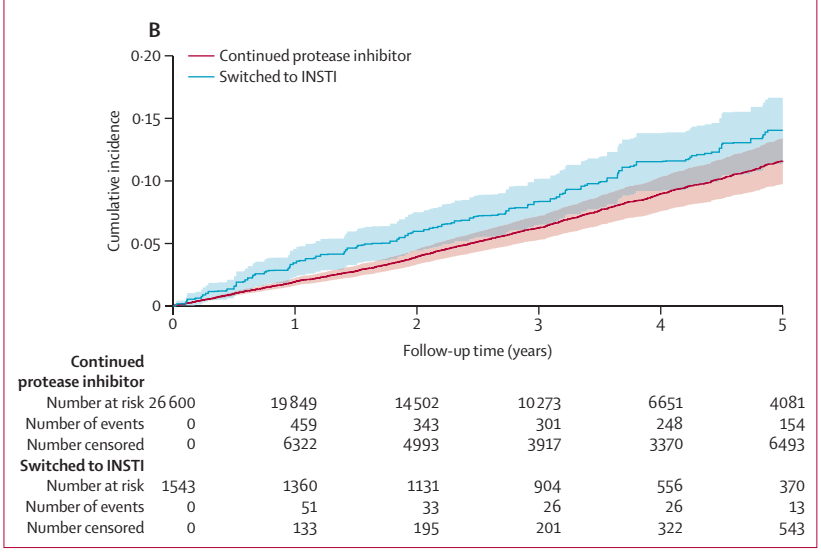
Table 2: **The risk of incident diabetes associated with switching to INSTIs**

INSTI from an NNRTI, 54766 encounters in which they continued an NNRTI, 1714 encounters in which they switched to an INSTI from a protease inhibitor, and 26599 encounters in which they continued a protease inhibitor (table 1; see appendix p 6 for study sample derivation). Efavirenz accounted for 38722 (70·7%) of 54766 participants using NNRTI at the index encounters. Participants were followed up for a median of 2·5 years (interquartile interval 1·1–4·2).

In the main analysis, switching from NNRTIs to INSTIs was associated with an adjusted HR of 1·10 (95% CI 0·87–1·39; table 2). Switching from protease inhibitors to INSTIs was associated with an adjusted HR of 1·38 (1·06–1·80). The adjusted cumulative incidence of diabetes for both comparisons is shown in the figure.



Continued NNRTI						
Number at risk	54837	42582	31732	22459	14693	8959
Number of events	0	960	906	727	554	346
Number censored	0	11348	9917	8534	7210	14334
Switched to INSTI						
Number at risk	2134	1779	1557	1218	802	540
Number of events	0	72	37	37	27	13
Number censored	0	283	188	300	388	789



Continued protease inhibitor						
Number at risk	26600	19849	14502	10273	6651	4081
Number of events	0	459	343	301	248	154
Number censored	0	6322	4993	3917	3370	6493
Switched to INSTI						
Number at risk	1543	1360	1131	904	556	370
Number of events	0	51	33	26	26	13
Number censored	0	133	195	201	322	543

Figure: **Adjusted cumulative incidence of diabetes after switching to INSTIs**
(A) Data for switching from NNRTIs to INSTIs. (B) Data for switching from protease inhibitors to INSTIs. Number at risk, number of events, and number censored represent weighted values. INSTI=integrase strand transfer inhibitor. NNRTI=non-nucleoside reverse transcriptase inhibitor.

Secondary analyses comparing switches to individual INSTI agents versus continuing NNRTIs or protease inhibitors are presented in table 2. Adjusted HRs for diabetes were broadly similar across individual INSTIs, ranging from 1·10 (95% CI 0·87–1·40) for dolutegravir to 1·21 (0·83–1·75) for elvitegravir.

The diabetes risk was concentrated in the first 2 years after switching to INSTIs. Compared with continuing NNRTIs, the HR of diabetes when switching to INSTIs was 1·30 (95% CI 0·98–1·72) during the first 2 years after the switch and 0·89 (0·62–1·26; $p_{interaction}$=0·084) thereafter. At 2 years, the cumulative risk of diabetes was 5·7% in those who switched to an INSTI versus 4·4% in those who continued an NNRTI (adjusted relative risk 1·30, 95% CI 1·01–1·69). Similarly, compared with continuing protease inhibitors, the HR of diabetes when switching to INSTIs was 1·67 (95% CI 1·21–2·30) during the first 2 years and 1·08 (0·75–1·57; $p_{interaction}$=0·064) thereafter. At 2 years, the cumulative risk was 6·0% in those who switched to an INSTI versus 4·0% in those who continued a protease inhibitor (adjusted relative risk 1·51, 95% CI 1·12–2·05).

We did not find significant effect modification by BMI at the index encounter. In participants switching from NNRTIs to INSTIs, the adjusted HR for incident diabetes was 1·02 (95% CI 0·79–1·32) for those with a BMI of at least 25 kg/m² and 1·47 (0·88–2·45) for those with a BMI of less than 25 kg/m² ($p_{interaction}$=0·17). Similarly, in participants switching from protease inhibitors to INSTIs, the adjusted HR was 1·40 (95% CI 1·04–1·88) for those with a BMI of at least 25 kg/m² and 1·30 (0·73–2·33) for those with a BMI of less than 25 kg/m² ($p_{interaction}$=0·82).

In the sensitivity analysis estimating diabetes risk in a hypothetical scenario in which weight gain did not exceed 5% during the first year, the HR of diabetes after switching from NNRTIs to INSTIs was 1·03 (95% CI 0·79–1·36) and from protease inhibitors to INSTIs was 1·37 (1·02–1·84), findings that were similar to those observed in the main analysis.

The sample characteristics for the expanded study period from Jan 1, 2007, to Dec 31, 2022, are presented in the appendix (pp 3–4). In this analysis, switching from NNRTIs to INSTIs was associated with an adjusted HR of 1·28 (95% CI 1·10–1·49), and switching from protease inhibitors to INSTIs was associated with an adjusted HR of 1·27 (1·12–1·45). Switches to individual INSTI agents, compared with continuing an NNRTI or protease inhibitor, were associated with an increased risk of diabetes, with qualitatively similar risk estimates observed across agents during the expanded study period (appendix p 5).

Discussion

In this longitudinal, large-scale cohort of people with HIV in the USA and Canada, switching from protease inhibitors to INSTIs was associated with a higher risk of

incident diabetes in ART-experienced individuals. In contrast, switching from NNRTIs to INSTIs was associated with a non-significant increase in risk. The excess diabetes risk after a switch from a protease inhibitor to an INSTI was concentrated in the first 2 years after the regimen change, but not thereafter. Importantly, the diabetes risk after switching to INSTIs did not appear to be explained by weight gain in the first year after switching.

Evidence on the association between prevalent INSTI use and diabetes risk in ART-experienced people with HIV has been mixed.[12–14] Through target trial emulation, we followed up ART-experienced people with HIV from the decision point to either continue an NNRTI or protease inhibitor or switch to an INSTI. The higher HR for diabetes we observed when switching from protease inhibitors compared with NNRTIs might reflect the greater metabolic toxicity associated with protease inhibitor use, rendering these individuals more vulnerable to additional effects of INSTI exposure, particularly in the period shortly after the switch. An alternative explanation would be the contribution of residual confounding, whereby those with higher baseline diabetes risk were preferentially switched from protease inhibitors to INSTIs. Although direct comparisons of INSTIs versus protease inhibitors for diabetes risk have been scarce in the real-world setting, the observed HR of 1·10 for diabetes after switching to INSTI versus continuing NNRTI in our study was similar to the HR of 1·17 for diabetes reported in a study of ART-naive people with HIV initiating INSTIs versus NNRTIs in NA-ACCORD.[4] Another cohort study comparing the initiation of INSTIs with non-INSTIs (NNRTIs or protease inhibitors) in ART-naive people with HIV also found approximately 30% increased risk of diabetes or hyperglycaemia, defined with diagnosis codes at 6 months of follow-up.[5]

Switching to individual INSTI agents produced qualitatively similar effects for new-onset diabetes. Although none of the individual risk estimates reached statistical significance in our main analysis, spanning 2016–22, the sensitivity analysis extending the study period to 2007–22 yielded similar but statistically significant estimates with this larger sample. The ordering of point estimates across agents differed by period, and previous studies in ART-naive people with HIV have also reported inconsistent rankings.[4,5] Overall, our findings suggest a consistent diabetes risk across INSTI agents, supporting a potential class effect that merits consideration in clinical decision making.

Importantly, accounting for weight gain during the first year after switching to INSTIs only modestly attenuated this association, consistent with previous findings in ART-naive populations showing a 5% reduction after adjusting for 1-year weight change.[4] Together, these findings imply that mechanisms beyond weight gain alone might contribute to the increased risk of diabetes observed with INSTI use. In particular, insulin resistance has been shown to develop soon after INSTI initiation, preceding measurable changes in bodyweight or fat distribution, raising the possibility of direct drug effects on glucose metabolism.[24] Inflammatory and immune activation pathways might also contribute to this effect, and a translational study showed that INSTIs can directly affect adipocyte biology, leading to oxidative stress, mitochondrial dysfunction, and insulin resistance.[25] Thus, the metabolic consequences of INSTIs are probably multifactorial, with several potential pathways contributing to the elevated diabetes risk.

Our analysis indicates that people with HIV switching to INSTIs have a significantly increased risk of diabetes within the first 2 years, suggesting a possible period of heightened vulnerability. Previous studies have also reported early metabolic changes, including increased insulin resistance, soon after INSTI initiation.[24,26] These findings underscore the need for close monitoring shortly after switching, although they warrant cautious interpretation given potential residual confounding. Notably, this temporal pattern parallels observations for cardiovascular disease risk in other cohorts. In the RESPOND cohort (in Europe and Australia), cardiovascular disease risk was higher during the first 2 years after INSTI exposure compared with no INSTI exposure.[27] Similarly, the HIV-CAUSAL Collaboration (in North America and Europe) reported an early separation of cardiovascular disease risk curves, indicating a higher risk with INSTI exposure than with non-exposure, which later converged.[28] Although our study did not evaluate cardiovascular disease risk, these parallels raise the possibility that cardiometabolic effects of INSTIs might be most pronounced early in the exposure period, a hypothesis that warrants further investigation. Diabetes risk did not differ by BMI in our study, consistent with a study from the RESPOND cohort, in which BMI adjustment only modestly attenuated diabetes risk.[14]

Our study is a real-world investigation of diabetes risk after switching to INSTIs, using large-scale longitudinal data representative of people with HIV in the USA, which supports external validity.[29] We emulated a target trial with a nested trials approach, comparing switching to INSTIs versus continuing NNRTIs or protease inhibitors, a rigorous design to mitigate biases and strengthen internal validity.[17] We used inverse probability weighting to address potential confounding from non-random treatment assignment and informative censoring. We also accounted for concurrent changes and use of tenofovir disoproxil fumarate and tenofovir alafenamide, further enhancing the robustness of our findings. Nonetheless, the effect of switching from tenofovir disoproxil fumarate to tenofovir alafenamide on diabetes risk remains an important question that warrants dedicated investigation.

Our study also has limitations. First, as an observational analysis, residual confounding is possible despite our rigorous methods. Confounding by indication could exist

if clinicians preferentially switched people with HIV with a greater metabolic risk to INSTIs. We addressed this confounding by adjusting for measured risk factors and restricting the main analysis to 2016–22, when INSTIs were recommended as first-line ART.[3] Nonetheless, the higher diabetes risk observed when switching from protease inhibitors, agents with known metabolic adverse events, than from NNRTIs could still reflect residual confounding, even after adjustment for cardiometabolic risk factors. Unmeasured factors such as diet or physical activity could have also influenced results. Additionally, the attenuation of the association after the first 2 years might be inconsistent with a typical dose–response. This attenuation could reflect a short-term induction effect, in which risk increases only initially, or residual confounding despite rigorous methods. Second, as prescription records were used to ascertain drug exposure, the actual intake of these drugs by the participants could not be guaranteed. Third, HbA_{1c} measurements might underestimate glycaemia in people with HIV, which could have led to underestimation of diabetes cases.[30] Fourth, our study setting was the USA and Canada, which might limit generalisability in other regions. Lastly, long-acting cabotegravir was not assessed.

In conclusion, switching to INSTIs from protease inhibitors was associated with a significantly increased risk of incident diabetes in ART-experienced people with HIV in diverse, longitudinal HIV cohorts in the USA and Canada. As cardiometabolic diseases increasingly drive morbidity and mortality in people with HIV, understanding the potential metabolic effect of ART is increasingly important. Our analysis is not intended to discourage switching to INSTIs, but rather to inform people with HIV and their treating clinicians of the potential metabolic risks that should be considered in making individualised treatment decisions in such common clinical scenarios. For example, our findings could help guide shared decision making when switching to INSTIs is considered and highlight the importance of diabetes screening, particularly during the first 2 years after the switch. Future studies could compare diabetes risk in people with HIV switching to INSTIs versus switching to other antiretroviral classes and could identify subpopulations who might be at higher risk after switching.

Contributors

YJH, CRL, TTB, and ATF conceived the study. YJH, CRL, and ATF did the statistical analysis. YJH and ATF have accessed and verified all the data in the study. YJH drafted the manuscript. All authors contributed to data interpretation, had access to the data, critically revised the manuscript, and were responsible for the decision to submit for publication.

Declaration of interests

TTB has served as a consultant to ViiV Healthcare, Gilead Sciences, Janssen, and EMD Serono. GCA is the past Chair of the US Food and Drug Administration's Peripheral and Central Nervous System Advisory Committee and a co-founding Principal and equity holder in Stage Analytics. GCA's arrangements have been reviewed and approved by Johns Hopkins University in accordance with its conflict-of-interest policies. KNA received grants from the US National Institutes of Health (NIH), royalties from a Coursera specialisation that she directs, and travel and lodging support for her role on the Scientific Steering Committee of the International Workshop on HIV and Hepatitis C virus Observational Databases. JDP received grants from the NIH. OF-N received grants from the NIH and AbbVie, received consulting fees from Gilead Sciences, and served a leadership role in the International Network on Health and Hepatitis in Substance Users. RDM received grants from the NIH. VCM received grants from the US Department of Veterans Affairs, US Centers for Disease Control and Prevention, NIH, Gilead Sciences, ViiV Healthcare, and Merck; served on the advisory board for the IL-1b inhibitor study, OuTSMART, CLEAR HIV, ECLIPSE, and VB201; and served as a study section chair for the NIH. JRK served as an advisor to, and received grants from, Merck and Gilead Sciences. MAH received grants from the NIH. TRS received grants from the NIH. All other authors declare no competing interests.

Data sharing

The data used in this study were obtained from the North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD). These data are subject to data use agreements and governance policies established by the NA-ACCORD. As such, individual investigators are not permitted to share the data directly. Researchers interested in accessing NA-ACCORD data can submit a formal request through NA-ACCORD (naaccord.org), subject to review and approval in accordance with established procedures.

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