Association between switching to integrase strand transfer inhibitors and incident diabetes in people with HIV

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Objective: Integrase strand transfer inhibitors (INSTI) are associated with weight gain in people with HIV (PWH), but their impact on diabetes is unclear. We evaluated the association between switching from nonnucleoside reverse-transcriptase inhibitors (NNRTI) or protease inhibitors (PI) to INSTI and incident diabetes.

Design: Longitudinal cohort study.

Methods: We included PWH aged ≥18 years from the Johns Hopkins HIV Clinical Cohort (2007–2023) without history of diabetes who had used NNRTI or PI for ≥180 days. We followed participants up to 10 years from HIV primary care visits where they switched to INSTI or continued NNRTI or PI. We estimated the hazard of incident diabetes associated with switching to INSTI using weighted Cox regression with robust variance estimator.

Results: We included 2075 PWH who attended 22 116 visits where they continued NNRTI or PI and 631 visits where they switched to INSTI. Switching to INSTI was associated with a weighted hazard ratio (wHR) of 1.11 [95% confidence interval (CI), 0.77–1.59] for incident diabetes. The association if no weight gain occurred during the first two years was not qualitatively different (wHR 1.22; 95% CI, 0.82–1.80). In a posthoc analysis, switching to INSTI conferred a significant wHR of 1.79 (95% CI, 1.13–2.84) for diabetes within the first two years but not after.

Conclusions: Switching from NNRTI or PI to INSTI did not significantly increase overall diabetes incidence in PWH, although there may be elevated risk in the first two years. These findings can inform considerations when switching to INSTI-based regimens.

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Introduction

Diabetes mellitus affects 10% of people with HIV (PWH) in the Unites States [1]. Its rising prevalence is of concern among aging PWH who are affected by unique metabolic risk factors and are at increased risk of cardiovascular diseases [2–4]. Antiretroviral drugs are an important iatrogenic contributor to metabolic comorbidities in

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PWH. These drugs have been implicated in insulin resistance and lipodystrophy, and represent a major contributor to diabetes burden in PWH [4,5].

Among antiretroviral therapies (ARTs), integrase strand transfer inhibitor (INSTI)-based regimens have been recommended as first-line treatments for most PWH given their efficacy in achieving sustained viral suppression and rare treatment failure [6,7]. However, recent studies have raised concerns regarding the risks of weight gain and hyperglycemia associated with initiating INSTIs as first-line treatment or switching to INSTIs from other classes of antiretroviral drugs [8–12]. ART-naïve PWH who initiate INSTIs may have a higher hazard of new-onset diabetes than those who initiate other classes of antiretroviral drugs [12,13]. However, the majority of PWH in HIV clinical care are ART-experienced, and little is known about diabetes risk associated with switching to an INSTI to guide their ART management decisions.

We quantified the risk of incident diabetes associated with switching from a nonnucleoside reverse transcriptase inhibitor (NNRTI)- or protease inhibitor (PI)-based regimen to an INSTI-based regimen in a cohort of PWH in HIV clinical care.

Methods

Study sample and setting

We studied PWH enrolled in the Johns Hopkins HIV Clinical Cohort (JHHCC). The JHHCC includes PWH aged ≥18 years who receive continuity care in the Johns Hopkins John G. Bartlett Specialty Practice, a comprehensive HIV clinic serving patients in Baltimore, Maryland, United States and its surrounding region, and who consent to share their data. Details about the JHHCC have been previously described [14]. Briefly, information on demographic characteristics, medication prescriptions, diagnoses, laboratory measurements, and clinical encounters were abstracted from electronic health records data. The study was approved by an institutional review board of the Johns Hopkins University. We followed the STROBE guidelines for reporting this study (Table S1, Supplemental Digital Content, http://links.lww.com/QAD/D252) [15].

For this analysis, we included PWH who attended ≥1 HIV primary care visit between January 1, 2007 and September 30, 2023 who (1) had no history of diabetes prior to the visit, (2) were prescribed an NNRTI or PI for ≥180 days leading up to the clinic visit, and (3) had no history of an INSTI prescription prior to the visit.

Study design, exposure, and follow-up

We used a nested clinical trials approach to emulate a clinical trial [16,17]. Thus, each time participants meeting inclusion criteria attended an HIV primary care visit, they were followed forward from that visit (the index clinic visit). Participants could contribute ≥1 observation. We excluded clinic visits where another qualifying clinic visit had taken place in the preceding 30 days.

In the target trial, each time an eligible participant attended a qualifying clinic visit, they would be randomized to either continue NNRTI- or PI-based ART or to switch to INSTI-based ART. In our observational study, we classified each eligible clinic visits as exposed to switch to INSTI-based ART if the participant had a new prescription for an INSTI within the 14 days before or after the clinic visit. Otherwise, visits were classified as exposed to continue NNRTI- or PI-based ART.

We followed participants from the date of each eligible HIV primary care visit (i.e., index clinic visit date) until the first occurrence of (1) onset of incident diabetes, (2) loss to clinical follow-up, defined as a gap between HIV primary care visits ≥1 year, (3) death, (4) 10 years from the index clinic visit date, or (5) the end of administrative follow-up on September 30, 2023. Additionally, observations from index clinic visits where participants continued on an NNRTI or PI, were censored, if a switch to an INSTI later occurred, on the date of the new INSTI prescription.

Outcome definition

Our primary outcome was incident diabetes, which we defined as the first occurrence of: (1) laboratory hemoglobin A1c value ≥6.5%, (2) initiation of a diabetes-specific medication, or (3) new diabetes diagnosis and initiation of a diabetes-related medication [12]. Diabetes-specific and diabetes-related medications are detailed in Table S2, Supplemental Digital Content, http://links.lww.com/QAD/D252. We used the *International Classification of Diseases, Ninth Revision* (ICD-9) and *Tenth Revision* (ICD-10) codes to identify diabetes diagnoses (Table S3, Supplemental Digital Content, http://links.lww.com/QAD/D252).

Covariates

We adjusted for baseline demographic characteristics: age (as a restricted quadratic spline with knots at the 20th, 40th, 60th, and 80th percentiles [18]), sex at birth (male or female), and race and ethnicity (White, Black, Hispanic, or Other). We also adjusted for baseline body mass index (BMI), categorized as underweight (<18.5 kg/m^2), normal weight (18.5–24.9 kg/m^2), overweight (25–29.9 kg/m^2), or obese (≥30 kg/m^2) derived from the most recently measured weight in the year leading up to the index clinic visit date. HIV viral load ≤200 copies/ml was considered virally suppressed, and the status of viral suppression was accounted for in our analysis. We also adjusted for the presence or absence of diagnoses of coronary artery disease, cerebrovascular disease, chronic liver disease, chronic kidney disease, dyslipidemia, and hypertension based on the ICD-9 or

ICD-10 codes in the two years prior to the index clinic visit date (Table S3, Supplemental Digital Content, http://links.lww.com/QAD/D252).

We further adjusted for whether patients had documented prescriptions for the following categories of medications at the index clinic visit: anticoagulants, antidepressants, antihypertensives, antiplatelets, antipsychotics, lipid-lowering drugs, and opioid analgesics. As the nucleoside reverse transcriptase inhibitors (NRTIs) tenofovir alafenamide fumarate (TAF) and tenofovir disoproxil fumarate (TDF) may be associated with weight change [19], we adjusted for changes in prescriptions for both TAF and TDF. We classified changes to TAF as either: (1) initiation of TAF (no prescription in the 180 to 14 days prior to the index clinic visit date, but with an active prescription between 14 and 180 days after); (2) discontinuation of TAF (a prescription in the 180 to 14 days prior to the index clinic visit date, but no active prescription in the 14 to 180 days after); (3) continuation of TAF (an active prescription for TAF both in the 180 to 14 days prior to and in the 14 to 180 days after the index clinic visit date); and (4) no TAF (no prescription for TAF before or after the index clinic visit date). We made an analogous classification of changes to TDF.

Statistical approach

We used inverse probability of treatment weighting (IPTW) to adjust for the demographic characteristics, BMI, HIV viral suppression status, comorbidities, and concomitant prescriptions described in the 'Covariates' section [20]. We estimated weights from a multivariable pooled logistic model for the probability of switching to an INSTI versus continuing on an NNRTI or PI, conditional on the covariates. Moreover, we used inverse probability of censoring weighting (IPCW) to mitigate potential bias from informative censoring [21]. We estimated weights separately for censoring due to loss to clinical follow-up and, for censoring due to a subsequent switch to INSTI-based ART following index visits classified as remaining on NNRTI- or PI-based ART. IPCW were estimated using a multivariable pooled logistic model for the probability of censoring in each 90-day block after the index clinic visit, conditional on the baseline covariates defined above, exposure, and time-updated BMI, comorbidities and co-prescriptions. The final weights were the cumulative product of the censoring weights times the baseline treatment weights.

We reported hazard ratios (HRs) and 95% confidence intervals (CIs) for incident diabetes associated with switching to any INSTI versus continuing an NNRTI or PI from weighted Cox proportional hazards regression with robust variance estimators to account for repeated observations on participants and uncertainty in the estimation of the weights. We performed all analyses using R version 4.3.1. Generalized Estimating Equation Package ('geepack') and Survival Package ('survival') were used [22,23].

Secondary analyses

We performed four prespecified secondary analyses and one posthoc secondary analysis. First, we quantified the incident diabetes risk after switching to each individual INSTI – bictegravir, dolutegravir, elvitegravir, or raltegravir – compared to continuing on an NNRTI or PI. In our secondary analysis of individual INSTI agents, the propensity score for the probability of switching to a specific INSTI drug, versus continuing an NNRTI or PI, was estimated using multinomial pooled logistic regression.

Second, we evaluated the risk of incident diabetes in subgroups identified by the use of NNRTI or PI at the time of an eligible HIV primary care visit. Among visits attended by NNRTI users, we assessed the diabetes risk associated with switching to an INSTI against continuing an NNRTI. Among visits attended by PI users, we evaluated the diabetes risk associated with switching to an INSTI against continuing a PI.

Third, we applied a more stringent definition of the outcome in which the laboratory-based criterion for diabetes diagnosis required a second, confirmatory laboratory hemoglobin A1c value $\geq$6.5% within a year of the first hemoglobin A1c value $\geq$6.5% during the follow-up period.

Fourth, we attempted to investigate the mediating role of weight gain in any possible effect of INSTI-based ART on diabetes by estimating the effect of switching to an INSTI under a hypothetical intervention to prevent weight gain $>$5% in the (i) first year and (ii) first two years after eligible HIV primary care visits [24]. To estimate this effect of INSTI-based ART on risk of diabetes controlling for weight gain, we included only index clinic visits where a weight measurement was recorded within the year prior to the visit (a baseline weight), and censored observations if participants' measured weight exceeded 5% more than their baseline weight during the two specified follow-up periods. We adjusted for any selection bias this censoring might have introduced with another set of IPCW.

Finally, we performed a posthoc analysis of the effect of switching to any INSTI on risk of incident diabetes stratified by time since switching: $\leq$2 years and $>$2 years after the index clinic visit date.

The IPTW and IPCW approaches described in Statistical Approach to adjust for baseline and time updated covariates were also applied in each of the secondary analyses.

Results

Study sample

The study sample included 2075 unique participants who were followed from 22 747 HIV clinic visits. Participants

contributed a median [interquartile interval (IQI) of 8 (3–16] clinic visits to the analysis. A third of participants ($n = 631$, 30%) switched to an INSTI-based regimen during the study period. The most common INSTI was dolutegravir (40%), followed by raltegravir (31%), elvitegravir (21%), and bictegravir (9%). Baseline characteristics at HIV primary care visits where PWH switched to an INSTI and where PWH continued an NNRTI or PI are presented in Table 1. The median (IQI) BMI was 26.6 (23.6–30.9) kg/m^2 at clinic visits where a switch to an INSTI was made and 26.4 (23.1–30.5) kg/m^2 at clinic visits where an NNRTI or PI was continued. Concomitant initiation of TAF was more frequent at clinic visits where a switch to an INSTI was made (21.6%) compared to clinic visits where an NNRTI or PI was continued (1.7%). Conversely, continuation of TDF was more common at clinic visits where an NNRTI or PI was continued (63.6%) compared to clinic visits where a switch to an INSTI was made (44.1%).

Incident diabetes

Participants were observed for a median (IQI) of 3.3 (1.4–6.0) years from the index clinic visit. In the study sample, the weighted incidence rate of diabetes was 21.3 (95% CI, 20.4–22.3) per 1000 person-years with continuing an NNRTI or PI and 24.9 (95% CI,

Table 1. Baseline characteristics at HIV primary care visits where PWH switched to an INSTI and where PWH continued an NNRTI or PI.

	Clinic visits where PWH s witched to an INSTI (no. of visits = 631)	Clinic visits where PWH continued an NNRTI or PI (no. of visits = 22 116)
No. of participants who ever contributed observations	631	2016
Age in years, median (IQI)	52 (44–58)	50 (43–56)
Male sex at birth	424 (67.2%)	14 585 (65.9%)
Race and ethnicity		
White	130 (20.6%)	4163 (18.8%)
Black	471 (74.6%)	17 135 (77.5%)
Hispanic	21 (3.3%)	538 (2.4%)
Other	9 (1.4%)	280 (1.3%)
Year of the clinic visit		
2007–2010	132 (20.9%)	9976 (45.1%)
2011–2014	121 (19.2%)	8001 (36.2%)
2015–2018	327 (51.8%)	3206 (14.5%)
2019–2023	51 (8.1%)	933 (4.2%)
BMI in kg/m^2, median (IQI)[a,b]	26.6 (23.4–30.9)	26.4 (23.1–30.5)
BMI categories[a,b]		
Underweight	27 (4.3%)	706 (3.2%)
Normal weight	198 (31.4%)	7703 (34.8%)
Overweight	225 (35.7%)	7254 (32.8%)
Obese	171 (27.1%)	5872 (26.6%)
Viral suppression[c]	514 (81.5%)	19 385 (87.7%)
Comorbidities		
Coronary artery disease	44 (7.0%)	849 (3.8%)
Chronic kidney disease	87 (13.8%)	2079 (9.4%)
Chronic liver disease	162 (25.7%)	4415 (20.0%)
Cerebrovascular disease	19 (3.0%)	421 (1.9%)
Dyslipidemia	205 (32.5%)	4240 (19.2%)
Hypertension	275 (43.6%)	7052 (31.9%)
Concomitant prescriptions		
Anticoagulant	16 (2.5%)	508 (2.3%)
Antidepressant	192 (30.4%)	6087 (27.5%)
Antihypertensive	236 (37.4%)	8192 (37.0%)
Antiplatelet	19 (3.0%)	277 (1.3%)
Antipsychotic	73 (11.6%)	2387 (10.8%)
Lipid-lowering drug	170 (26.9%)	4781 (21.6%)
Opioid analgesic	129 (20.4%)	4841 (21.9%)
Concomitant TAF/TDF use at the clinic visit		
Initiated on TAF	136 (21.6%)	377 (1.7%)
Continued TAF	61 (9.7%)	1156 (5.2%)
Discontinued TAF	2 (0.3%)	14 (0.1%)
Initiated on TDF	16 (2.5%)	275 (1.2%)
Continued TDF	278 (44.1%)	14 064 (63.6%)
Discontinued TDF	93 (14.7%)	660 (3.0%)

ART, antiretroviral therapy; BMI, body mass index; INSTI, integrase strand transfer inhibitors; IQI, interquartile interval; PWH, people with HIV; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.

[a]621 (98.4%) clinic visits where a switch was made to an INSTI and 21 535 (97.4%) where an NNRTI or PI was continued had a baseline weight measurement.

[b]BMI was calculated by multiplying 703 by the quotient of the weight (in pounds) divided by height (in inches) squared.

[c]HIV viral load ≤200 copies/mL was considered virally suppressed.

Table 2. Risk of incident diabetes associated with switching to an INSTI compared to continuing an NNRTI or PI.

	No. of participants who ever contributed observations	No. of events/no. of observations from clinic visits (%)	Weighted incidence rate, per 1000 person-years (95% CI)	Weighted hazard ratio (95% CI) [a]
Continued NNRTI/PI	2016	1859/22 116 (8.4)	21.3 (20.4– 22.3)	Reference
Switched to any INSTI	631	94/631 (14.9)	24.9 (19.6–31.2)	1.11 (0.77–1.59)
Specific INSTI switched to:				
Bictegravir	55	7/55 (12.7)	80.9 (2.0–450.5)	1.97 (0.72–5.40)
Dolutegravir	252	43/252 (17.1)	24.7 (16.1–36.1)	1.10 (0.66–1.81)
Elvitegravir	130	18/130 (13.8)	20.1 (10.7–34.3)	0.93 (0.23–3.82)
Raltegravir	194	26/194 (13.4)	35.3 (24.1–49.8)	1.64 (0.76–3.55)

CI, confidence intervals; INSTI, integrase strand transfer inhibitor; NNRTI, nonnucleoside reverse transcriptase inhibitor; PI, protease inhibitor. [a]The following covariates were weighted in the Cox proportional hazards regression: age; sex at birth; race and ethnicity; year of clinic visit; body mass index categories; comorbid coronary artery disease, chronic kidney disease, chronic liver disease, cerebrovascular disease, dyslipidemia, and hypertension; concomitant prescriptions for anticoagulant, antidepressant, antihypertensive, antiplatelet, antipsychotic, lipid-lowering drug, opioid analgesic, tenofovir alafenamide, and tenofovir disoproxil fumarate.

19.6–31.2) per 1000 person-years following switch to an INSTI. The weighted incidence rates of diabetes following switch to specific INSTI agents are provided in Table 2. The weighted cumulative incidence of diabetes associated with switching to an INSTI versus continuing an NNRTI or PI is illustrated in Fig. 1. In the weighted survival analysis, the HR for switching to any INSTI, as compared to continuing an NNRTI or PI, was 1.11 (95% CI, 0.77–1.59).

Secondary analyses

None of the weighed HRs for switching to specific INSTI agents were statistically significantly different from one or from each another, ranging from 0.93 (95% CI, 0.23–3.82) for elvitegravir to 1.97 (95% CI, 0.72–5.40) for bictegravir (Table 2).

In the subgroup analysis, weighted HR for incident diabetes associated with switching to an INSTI was 1.16 (95% CI, 0.60–2.22) compared to continuing an NNRTI and 1.07 (95% CI, 0.69–1.69) compared to continuing a PI.

When we used a stricter definition of diabetes that required a confirmatory hemoglobin A1c value ≥6.5%, the diabetes risk associated with switching to an INSTI was similar to our primary analysis (weighted HR, 1.11; 95% CI, 0.76–1.64).

We estimated the HR for diabetes associated with switching to an INSTI-based regimen if weight gain were prevented in the first year of follow-up (an effect of INSTI-based regimen on diabetes not through weight gain) was not substantially different from the total effect (weighted HR, 1.15; 95% CI, 0.78–1.70). The estimated HR for diabetes associated with such a regimen change if weight gain were prevented in the first two years of follow-up was also similar (weighted HR, 1.22; 95% CI, 0.82–1.80).

In a posthoc secondary analysis stratifying by follow-up time since index visit, the risk of incident diabetes within the first two years after switching to an INSTI was significantly higher than after continuing an NNRTI or PI (weighted HR, 1.79; 95% CI, 1.13–2.84). There was no difference after 2 years from the index clinic visit

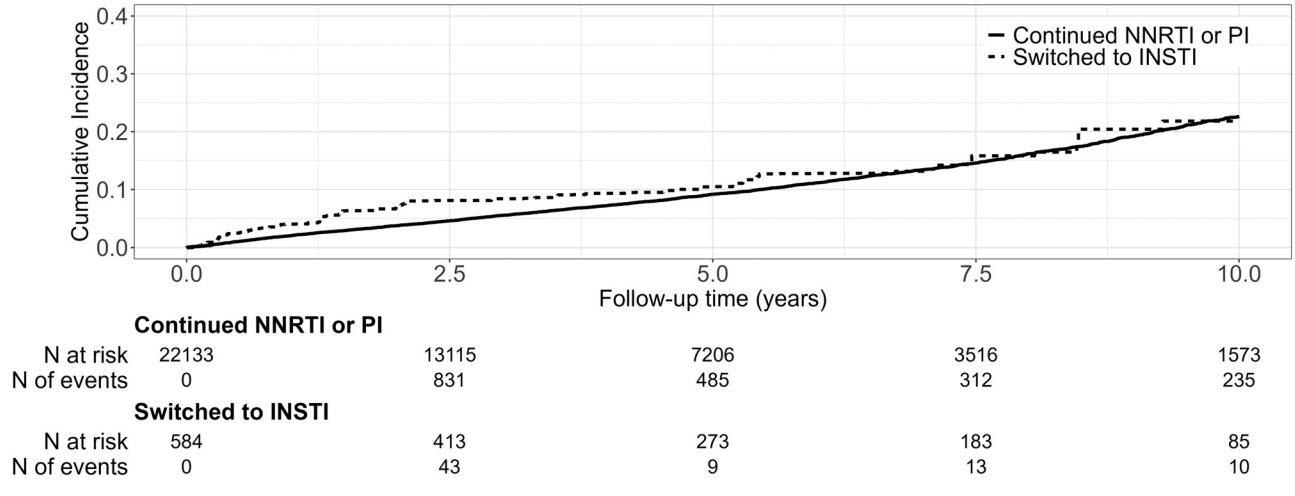

Fig. 1. Weighted cumulative incidence of diabetes after switching to an INSTI compared to continuing an NNRTI or PI. N at risk and N of events represent weighted values.

(weighted HR, 0.78; 95% CI, 0.50–1.23; P for interaction between follow-up time and switch to INSTI < 0.01).

Discussion

In this longitudinal cohort of PWH in HIV clinical care, there was no significant effect of switching from an NNRTI- or PI-based therapy to an INSTI-based regimen on the hazard of subsequent incident diabetes averaged over 10 years. Neither did we observe a significant effect of switching to specific INSTI agents – bictegravir, dolutegravir, elvitegravir, and raltegravir – although our estimates for individual INSTI agents carried large uncertainty due to low sample size. A similar, numerically increased risk of new-onset diabetes was found with switching to INSTI-based therapies from both NNRTI- and PI-based regimens. These findings persisted when we estimated the association between switching to INSTI-based ART and incident diabetes if no weight gain occurred during the two years after switching. In a posthoc secondary analysis that controlled for baseline and time-updated BMI as in the main analysis, switching to INSTI-based ART was significantly associated with incident diabetes within the first two years following the switch, but not after two years.

Switching antiretroviral regimens is common among PWH, and beyond achieving virologic suppression, reasons for such therapeutic changes include tolerability, adherence, and long-term health consequences. In an era where PWH in the United States have life expectancy approaching that of the general population, ART-related risks beyond virologic efficacy have increasingly become influential factors in treatment decisions [3,25]. Switching to INSTI-based regimens has been associated with weight gain, with greater risks among women and Black patients [9,11]. However, there have been limited real-world studies of the risk of new-onset diabetes associated with such a switch in ART.

Diabetes is an increasingly prevalent comorbidity in PWH that may further increase the risk of cardiovascular and renal complications [2]. The hazard ratio for incident diabetes observed in our study (1.11) was similar in magnitude to the 17% numerically increased risk observed in a study of initiation of INSTI versus NNRTI among ART-naïve PWH from the North American AIDS Cohort (NA-ACCORD), which used the same definition of diabetes [12]. A study of commercially and Medicaid-insured PWH found a larger 31% elevation in the risk of new-onset diabetes or hyperglycemia (per ICD codes) among ART-naïve PWH who started an INSTI- versus non-INSTI based regimen [13]. Our findings suggest the diabetes risk associated with switching to an INSTI may be more pronounced in the earlier years following the switch, although this was based on a posthoc analysis.

Our study has several strengths. Rigorous real-world studies provide evidence on therapeutic comparisons in pragmatic settings that reflect routine clinical practice. Our assessment of incident diabetes associated with switching from an NNRTI or PI to an INSTI was performed among PWH who attend a multidisciplinary HIV clinic, allowing the results to be generalizable to outpatient care settings in the United States. We applied a nested clinical trials design to emulate randomized trials to categorize eligible PWH to the two comparison groups at HIV primary care clinic visits [16], using weighting to account for potential informative censoring and confounding [21].

We also note several limitations to our study. It was observational, and thus could be subject to residual confounding by indication with respect to switching to INSTI-based ART compared to remaining on NNRTI- or PI-based regimens that is not reflected by recorded comorbidities alone. Exposure to medications was ascertained using prescription records, and thus actual medication intake by patients could not be guaranteed. Our study cohort comprised PWH receiving care at a single urban comprehensive HIV clinic in the United States, which may limit the generalizability of the findings. For example, our findings may have limited external validity to care settings outside the United States where the patterns of ART use and comorbidities may differ from our study setting. However, our cohort also includes PWH from groups that have been poorly represented in prior studies: Black patients and women. Our number of observations for specific INSTI agents were small, limiting our ability to estimate agent-specific treatment effects. Larger pharmacoepidemiologic studies involving more geographic regions would be needed to further evaluate the risk of new-onset diabetes in PWH who are changing their ART to an INSTI-based regimen from an NNRTI- or PI-based regimen, and whether this risk depends on time since switch to INSTI-based therapy.

In conclusion, we did not observe a significant effect of switching from an NNRTI- or PI-therapy to an INSTI-based regimen on the risk of incident diabetes in a cohort of PWH in HIV clinical care. Our findings have the potential to inform risk-benefit considerations by PWH and their care providers in common clinical scenarios where switching to INSTI-based ART is considered.

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F. obtained funding for the study cohort. Y.J.H., C.R.L., and A.T.F. performed statistical analysis. Y.J.H. drafted the manuscript. All authors reviewed the manuscript, contributed to the interpretation of data, and provided critical revision of the manuscript.

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Conflicts of interest

Dr Alexander is past Chair of FDA's Peripheral and Central Nervous System Advisory Committee and a co-founding Principal and equity holder in Stage Analytics. These arrangements have been reviewed and approved by Johns Hopkins University in accordance with its conflict-of-interest policies. Dr Brown has served as a consultant to ViiV Healthcare, Gilead Sciences, Janssen, and EMD Serono. Dr Falade-Nwulia has received grants from AbbVie paid to Johns Hopkins Hospital and has served as a consultant for AbbVie. Other authors have no potential conflicts of interest to report.

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