Changes in weight and glycemia after initiation of integrase strand transfer inhibitors among people with HIV and diabetes

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Objective: Evaluate the impact of initiating integrase strand transfer inhibitor (INSTI) – vs. nonnucleoside reverse transcriptase inhibitor (NNRTI) – or protease inhibitor-based regimens on weight and glycemia among people with HIV (PWH) and type 2 diabetes.

Design: Cohort study.

Methods: From multisite HIV cohorts in the United States and Canada (2007–2022), we identified PWH with diabetes who newly initiated INSTI-based, NNRTI-based, or protease inhibitor-based therapy. We used inverse probability of treatment-weighted (IPTW) generalized linear models to compare changes in weight and hemoglobin A1c (HbA1c) at approximately 12 months after antiretroviral therapy (ART) initiation. We assessed time to at least 5% weight gain and to glucose-lowering therapy augmentation or HbA1c increase at least 0.5 percentage points with IPTW Cox regression.

Results: Among 1279 PWH with diabetes, 548 initiated an INSTI-based regimen, 511 an NNRTI-based regimen, and 220 a protease inhibitor-based regimen. Compared with NNRTI users, INSTI users had greater adjusted mean weight gain [2.1 kg; 95% confidence interval (CI), 1.1–3.1], while the difference in HbA1c change was modest (0.2%; 95% CI, 0.0–0.5); both changes were similar between INSTI and protease inhibitor users. INSTI users had higher risk of at least 5% weight gain [adjusted hazard ratio (aHR), 1.35;

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95% CI, 1.15–1.59] and glucose-lowering therapy augmentation or HbA1c increase at least 0.5% (aHR, 1.19; 95% CI, 1.02–1.41) compared with NNRTI users although similar risk vs. protease inhibitor users.

Conclusion: Among PWH with diabetes, initiating INSTIs conferred modestly greater weight gain and worse glycemic outcomes vs. NNRTIs, but outcomes comparable to PIs, which is recognized for adverse metabolic effects. These findings inform the metabolic implications of INSTIs and support clinical monitoring after ART initiation.

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Introduction

Type 2 diabetes is a common comorbidity among people with HIV (PWH), affecting more than one in ten individuals [1,2]. Antiretroviral therapy (ART) is an iatrogenic contributor to adverse metabolic outcomes in this population, with several antiretroviral agents implicated in weight gain, lipohypertrophy, and insulin resistance [3]. Since 2015, integrase strand transfer inhibitor (INSTI)-based regimens have become the preferred first-line treatment for most PWH due to their superior virologic efficacy [4]. However, both randomized and observational studies have shown that INSTI-based regimens confer greater weight gain compared to nonnucleoside reverse transcriptase inhibitor (NNRTI)-based and, to a lesser extent, protease inhibitor-based regimens [5–7]. In ART-naive PWH without diabetes, observational studies have associated INSTI-based regimens with a higher risk of new-onset diabetes compared to other regimens [8,9]. Moreover, prevalent INSTI use has also been implicated with increased diabetes risk among ART-experienced PWH [10].

Despite growing evidence on metabolic risks associated with INSTI use, limited data exist on their effects among PWH with preexisting diabetes, particularly with respect to changes in weight and glycemia. This is important because among adults with diabetes, weight gain is associated with worsened glycemic control, while poor glycemic control increases cardiorenal risk [11]. We used multisite HIV cohorts to quantify changes in weight and glycemia among ART-naive PWH with diabetes who were newly treated with INSTI-based regimens, compared to those newly treated with NNRTI-based or protease inhibitor-based regimens, across the United States and Canada.

Methods

Study setting

We used data from the North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD) – a collaboration of over 20 longitudinal HIV cohorts across the United States and Canada [12]. The NA-ACCORD is a participating region of the International Epidemiologic Database to Evaluate AIDS (IeDEA) global network. Demographics, drug prescriptions, diagnoses, and laboratory measurements are submitted via standardized annual submission to the Data Management Core (University of Washington) where quality assurance is conducted. Data are then transferred to the Epidemiology/Biostatistics Core at the Johns Hopkins Bloomberg School of Public Health, where additional quality assurance is conducted and analytic-ready datasets are prepared. The activities of NA-ACCORD are reviewed and approved by Institutional review boards at each participating site and at the Johns Hopkins Bloomberg School of Public Health.

Study design and sample

We used a new-user, active-comparator design to estimate the comparative effects of INSTI-based vs. either NNRTI-based or protease inhibitor-based regimens [13–15]. We included PWH aged at least 18 years who were enrolled in one of the participating cohorts and newly prescribed an oral INSTI-based, NNRTI-based, or protease inhibitor-based regimen between 1 January 2007 and 31 December 2022. Eligible participants had a history of diabetes prior to the ART initiation, defined using standard NA-ACCORD criteria: a hemoglobin A1c (HbA1c) at least 6.5%, use of a diabetes-specific medication, or a diabetes diagnosis plus use of a diabetes-related medication [8,16,17]. Each criterion previously demonstrated sensitivity ranging from 73 to 78% and specificity of 100% for identifying type 2 diabetes cases in PWH [18]. Diabetes-specific and diabetes-related medications are detailed in Supplementary Table 1, http://links.lww.com/QAD/D834. Type 1 diabetes and gestational diabetes were excluded from the diagnosis-based definition.

To ensure inclusion of individuals who were newly treated with ART, we restricted the study sample to PWH who had no prior antiretroviral drug prescription and had a measured HIV viral load at least 400 copies/ml

within the 12 months prior to ART initiation. Where more than one viral load measurements were available within the 12-month window, the latest value prior to ART initiation was used to determine study inclusion. Finally, we restricted the study sample to individuals with at least one weight and HbA1c measurements in the 12 months prior to, and between 6 and 18 months following, the date of ART initiation.

Outcomes and follow-up

The primary outcomes were changes in weight and HbA1c defined as the difference between baseline (before starting ART) and follow-up (after starting ART) measurements. Weight was obtained during routine clinical encounters, and HbA1c values were obtained from laboratory measurements. Baseline weight and HbA1c were defined as the most recent values recorded within the 12 months leading up to the date of ART initiation. Follow-up values were defined as those recorded between 6 and 18 months after ART initiation; when multiple values were available, the measurement closest to the 12-month mark was selected. This follow-up window was chosen to capture short-term metabolic changes associated with ART initiation and to align with clinical guidelines recommending HbA1c testing up to quarterly in adults with diabetes [19].

As secondary outcomes, we also evaluated time to $\geq$5% weight gain from baseline [20], time to glucose-lowering therapy augmentation, and time to an absolute increase in HbA1c of $\geq$0.5 percentage points from baseline. Moreover, we assessed time to glucose-lowering therapy augmentation or to an absolute increase in HbA1c of $\geq$0.5 percentage points from baseline as a composite outcome. Glucose-lowering therapy augmentation was defined as an increase of at least one glucose-lowering drug class compared with the regimen in use at ART initiation, including initiation of the first glucose-lowering agent among those not on therapy at baseline. Both diabetes-specific and diabetes-related medications were considered. Information on medication dosing was not available; therefore, dose escalation could not be assessed. The threshold of a 0.5 percentage point increase in HbA1c was chosen to represent a clinically meaningful change, consistent with the magnitude of glycemic improvement commonly required for regulatory approval of glucose-lowering agents [21]. We followed each participant from the date of ART initiation until the first occurrence of respective outcome, loss to clinical follow-up, defined as the last clinical encounter before a gap between encounters at least 1 year, death, 5 years after ART initiation, administrative closure or end of observation window for diabetes for the corresponding cohort site [22], or the end of administrative follow-up on 31 December 2022.

All outcomes were assessed based on the intention-to-treat principle, whereby each participant was analyzed according to their initially assigned treatment group at ART initiation, regardless of subsequent treatment changes during follow-up [23].

Covariates

The approach to covariate adjustment is described in detail in the 'Statistical Analysis' section. We accounted for participant age at ART initiation, sex at birth, race (Black, White, other, or unknown), Hispanic ethnicity, and calendar year of ART initiation. BMI – categorized as underweight ($<$18.5 kg/m^2), normal weight (18.5–24.9 kg/m^2), overweight (25.0–29.9 kg/m^2), or obese ($\geq$30 kg/m^2) – as well as baseline HbA1c, HIV viral load, and CD4$^+$ cell count were ascertained based on the most recent measurement within the year prior to ART initiation. We accounted for the time interval (in years) between meeting the study definition of diabetes and ART initiation. History of hypertension, hyperlipidemia, and chronic kidney disease stage 3 or higher (definitions detailed in Supplementary Table 2, http://links.lww.com/QAD/D834) prior to ART initiation was ascertained [16]. We assessed co-medications at the time of ART initiation. To account for concomitant glucose-lowering therapy, we assessed the presence of prescriptions for metformin, sulfonylureas, insulin, glucagon-like peptide-1 receptor agonists, dipeptidyl peptidase-4 inhibitors, sodium-glucose cotransporter-2 inhibitors, and other glucose-lowering agents. Additionally, we adjusted for co-medications associated with adverse metabolic outcomes – specifically antidepressants, antipsychotics, and opioid analgesics [24–26]. Given the differential effects of tenofovir formulations on weight, we accounted for concomitant use of tenofovir disoproxil fumarate (TDF) and tenofovir alafenamide (TAF) [27].

Statistical analysis

We addressed confounding from nonrandom treatment assignment using inverse probability of treatment weights (IPTW) [28]. We derived these weights from a multivariable multinomial model that predicted the probability (i.e. propensity score) for starting an NNRTI or protease inhibitor vs. INSTI, conditional on baseline demographic and HIV-related characteristics, comorbidities, and co-medications (all covariates detailed in the 'Covariates' section). We assessed between-group differences in the baseline characteristic before and after IPTW using pairwise standardized mean differences, which were illustrated using a Love plot [29].

For the primary outcomes change in weight and change in HbA1c, we used IPTW generalized linear models to estimate the adjusted mean differences and 95% confidence intervals (CI) associated with starting an NNRTI or protease inhibitor vs. INSTI.

We performed time-to-event analyses for the four secondary outcomes. In addition to IPTW, we applied inverse probability of censoring weights (IPCW) to mitigate bias from informative censoring, estimating weights for censoring due to loss to clinical follow-up.

The censoring weight was estimated using a multivariable logistic model for the probability of censoring in each 90-day block after ART initiation, conditional on the previously defined covariates defined at ART initiation, exposure, time since the index encounter, and time-updated BMI, comorbidities, and co-medications. The final weights were the product of censoring and treatment weights. We used weighted Cox proportional hazards model to estimate the hazard ratios and 95% CI associated with initiating an NNRTI or protease inhibitor vs. INSTI.

Additional analysis

We conducted two subgroup analyses for the primary outcomes – changes in weight and HbA1c. Because diabetes severity may influence metabolic outcomes, we first stratified participants by glycemic control at ART initiation: well controlled diabetes, defined as HbA1c 8% or less, and poorly controlled diabetes, defined as HbA1c greater than 8%. The second analysis stratified participants by calendar year of ART initiation: 2007–2015 and 2016–2022. We chose the calendar year cutoff point to coincide with the adoption of INSTI-based regimens as the first-line ART [4].

We performed all analyses using R version 4.5.0.

Results

Participant characteristics

The study sample comprised 1279 ART-naive PWH with type 2 diabetes, of whom 548 initiated an INSTI-based regimen, 511 an NNRTI-based regimen, and 220 a protease inhibitor-based regimen between January 2007 and December 2022. The median (IQI) duration of the ART regimen was 25 (10–50) months for the INSTI group, 30 (7–61) months for the NNRTI group, and 17 (5–47) months for the protease inhibitor group. Baseline characteristics of participants at ART initiation are presented in Table 1. Between-group standardized mean differences for baseline characteristics were illustrated in a Love plot (Supplementary Figure 1, http://links.lww.com/QAD/D834).

Primary outcomes: changes in weight and hemoglobin A1c

Median (IQI) time between baseline and follow-up weight measurement was 12 (12−13) months (Table 2). The mean (standard deviation [SD]) increase in weight was 3.9 (8.2) kg in the INSTI group, 1.4 (7.6) kg in the NNRTI group, and 3.4 (8.5) kg in the protease inhibitor group. The adjusted mean difference in change in weight for the INSTI group was 2.1 kg (95% CI, 1.1–3.1) compared to the NNRTI group and 0.7 kg (95% CI, –0.5 to 1.9) compared to the protease inhibitor group.

Median (IQI) time between baseline and follow-up HbA1c measurement was 14 (12–16) months (Table 2). The mean (SD) change in HbA1c was −0.2 (2.2) percentage points among INSTI users, −0.5 (1.9) percentage points among NNRTI users, and −0.3 (2.2) percentage points among protease inhibitor users. The adjusted mean difference in change in HbA1c for the INSTI group was 0.2 percentage points (95% CI, 0.0–0.5) compared to the NNRTI group and 0.1 percentage points (95% CI, −0.2 to 0.4) compared to the protease inhibitor group.

Secondary weight and glycemic outcomes

Secondary outcomes are presented in Table 3. The INSTI group had a higher risk of at least 5% weight gain compared to the NNRTI group (adjusted HR, 1.35; 95% CI, 1.15–1.59), but not compared to the protease inhibitor group (adjusted hazard ratio, 1.01; 95% CI, 0.81–1.25). Adjusted cumulative incidence of weight gain is illustrated in Fig. 1a. When assessed as a composite glycemic outcome, the risk of glucose-lowering therapy augmentation or increase in HbA1c at least 0.5 percentage point was higher in the INSTI group compared to the NNRTI group (adjusted hazard ratio, 1.19; 95% CI, 1.02–1.41) but not compared to the protease inhibitor group (adjusted hazard ratio, 0.97; 95% CI, 0.80–1.19). Adjusted cumulative incidence of the composite glycemic outcome is illustrated in Fig. 1b.

Subgroup analysis by baseline glycemic control

The changes in weight among PWH with diabetes who were treated with INSTI-based regimens vs. NNRTI-based and vs. protease inhibitor-based regimens were similar across the subgroups with well controlled and poorly controlled diabetes (interaction $P = 0.87$ for INSTI vs. NNRTI and interaction $P = 0.32$ for INSTI vs. protease inhibitor; Supplementary Figure 2, http://links.lww.com/QAD/D834). The changes in HbA1c in the INSTI group vs. NNRTI group and vs. protease inhibitor group were also similar across the subgroups stratified by baseline glycemic control (interaction $P = 0.89$ for INSTI vs. NNRTI and interaction $P = 0.48$ for INSTI vs. protease inhibitor; Supplementary Figure 3, http://links.lww.com/QAD/D834).

Subgroup analysis by year of antiretroviral therapy initiation

The changes in weight in the INSTI group vs. NNRTI group and vs. protease inhibitor group were not statistically different across participants who started ART in 2007–2015 and those who initiated ART in 2016–2022 (interaction $P = 0.47$ for INSTI vs. NNRTI and interaction $P = 0.15$ for INSTI vs. protease inhibitor; Supplementary Figure 2, http://links.lww.com/QAD/D834). The changes in HbA1c in the INSTI group vs. NNRTI group and vs. protease inhibitor group also were not statistically different across the subgroups stratified by

Table 1. Baseline characteristics of PWH with diabetes who initiated an integrase strand transfer inhibitor-based, nonnucleoside reverse transcriptase inhibitor-based, or protease inhibitor-based regimen between 2007 and 2022.

	INSTI group (*N* = 548)	NNRTI group (*N* = 511)	PI group (*N* = 220)
Age in years [median (IQI)]	55 (47–62)	55 (47–62)	55 (47.75–61)
Male sex at birth	461 (84%)	447 (87%)	188 (85%)
Race			
Black	305 (56%)	272 (53%)	126 (57%)
White	200 (36%)	180 (35%)	63 (29%)
Other	26 (5%)	46 (9%)	19 (9%)
Unknown	17 (3%)	13 (3%)	12 (5%)
Hispanic ethnicity	53 (10%)	55 (11%)	20 (9%)
Year of ART initiation			
2007–2010	23 (4%)	246 (48%)	111 (50%)
2011–2014	144 (26%)	228 (45%)	92 (42%)
2015–2018	258 (47%)	34 (7%)	16 (7%)
2019–2022	123 (22%)	3 (0.6%)	1 (0.5%)
Time between onset of diabetes and ART initiation in years [median (IQI)]	3 (0.3–8)	3 (0.8–7)	2 (0.2–7)
Hemoglobin A1c in % [median (IQI)]	7.2 (6.5–9.2)	7.0 (6.4–8.6)	7.4 (6.5–9.3)
Weight in kg [median (IQI)]	91 (78–106)	89 (77–104)	87 (74–101)
BMI in kg/m^2 [median (IQI)]	30 (26–34)	29 (25–33)	28 (24–32)
BMI categories			
Underweight	8 (1%)	5 (1%)	1 (0.5%)
Normal weight	97 (18%)	118 (23%)	60 (27%)
Overweight	185 (34%)	166 (32%)	78 (35%)
Obese	258 (47%)	222 (43%)	81 (37%)
HIV viral load in copies/ml [median (IQI)]	61 240 (17 535–176 250)	36 800 (10 514–130 601)	54 583 (15 607–164 000)
$CD4^+$ cell count <200 cells/μl	133 (24%)	138 (27%)	76 (35%)
Comorbidities			
Hypertension	353 (64%)	357 (70%)	131 (60%)
Hyperlipidemia	342 (62%)	307 (60%)	108 (49%)
Chronic kidney disease	108 (20%)	82 (16%)	51 (23%)
Co-medications			
Metformin	219 (40%)	200 (39%)	70 (32%)
Sulfonylurea	96 (18%)	137 (27%)	56 (25%)
Insulin	151 (28%)	127 (25%)	50 (23%)
GLP1RA	10 (2%)	0 (0%)	0 (0%)
DPP4i	14 (3%)	4 (0.8%)	2 (1%)
SGLT2i	7 (1%)	0 (0%)	0 (0%)
Other glucose- lowering agents	11 (2%)	13 (3%)	3 (1%)
Antithrombotic	20 (4%)	15 (3%)	2 (1%)
Antidepressant	114 (21%)	99 (19%)	53 (24%)
Antipsychotic	20 (4%)	22 (4%)	15 (7%)
Opioid	67 (12%)	85 (17%)	28 (13%)
Tenofovir disoproxil fumarate	167 (30%)	452 (88%)	146 (66%)
Tenofovir alafenamide	198 (36%)	18 (4%)	3 (1%)

N (%) are reported unless otherwise noted. DPP4i, dipeptidyl peptidase-4 inhibitor; GLP1RA, glucagon-like peptide-1 receptor agonist; INSTI, integrase strand transfer inhibitor; IQI, interquartile interval; NNRTI, nonnucleoside reverse transcriptase inhibitor; PI, protease inhibitor; PWH, people with HIV; SGLT2i, sodium-glucose cotransporter-2 inhibitor.

the calendar year of ART initiation (interaction $P = 0.31$ for INSTI vs. NNRTI and interaction $P = 0.97$ for INSTI vs. protease inhibitor; Supplementary Figure 3, http://links.lww.com/QAD/D834).

Discussion

In multisite longitudinal cohorts of PWH across the United States and Canada, we evaluated the changes in weight and glycemia after initiating INSTI-based regimens compared to NNRTI-based or protease inhibitor-based regimens among ART-naive PWH with type 2 diabetes. At approximately 1 year after ART initiation, those treated with INSTIs gained an average of 2.1 kg more than those initiating NNRTIs. When weight gain of at least 5% was assessed as a time-to-event outcome, INSTI users had a 35% higher risk relative to NNRTI users. In contrast, the INSTI and protease inhibitor groups had similar weight outcomes on both continuous and dichotomous scales. On average, HbA1c levels decreased across all regimen groups, primarily among those with poor glycemic control at baseline (HbA1c >8%), compared with modest increase among those with baseline HbA1c 8% or less. The mean reductions were similar among individuals initiating INSTI-based, NNRTI-based, and protease inhibitor-based regimens. However, in time-to-event analyses, INSTI users had a 19% higher risk of either glucose-lowering therapy

Table 2. Changes in weight and hemoglobin A1c among people with HIV with diabetes who initiated an integrase strand transfer inhibitor-based, nonnucleoside reverse transcriptase inhibitor-based, or protease inhibitor-based regimen between 2007 and 2022.

Outcome[a]	Comparison group	Unadjusted mean change (SD)	Adjusted mean difference (95% CI)[b]	*P* value
Change in weight (kg)	INSTI (*N* = 548)	3.9 (8.2)	Reference	–
	NNRTI (*N* = 511)	1.4 (7.6)	−2.1 (−3.1 to −1.1)	<0.01
	PI (*N* = 220)	3.4 (8.5)	−0.7 (−1.9 to 0.5)	0.25
Change in hemoglobin A1c, percentage point	INSTI (*N* = 548)	−0.2 (2.2)	Reference	–
	NNRTI (*N* = 511)	−0.5 (1.9)	−0.2 (−0.5 to 0.0)	0.09
	PI (*N* = 220)	−0.3 (2.2)	−0.1 (−0.4 to 0.2)	0.60

CI, confidence intervals; INSTI, integrase strand transfer inhibitor; NNRTI, nonnucleoside reverse transcriptase inhibitor; PI, protease inhibitor; PWH, people with HIV; SD, standard deviation.
[a]Median (interquartile interval [IQI]) time between baseline and follow-up weight measurement was 12 (12–13) months. Median (IQI) time between baseline and follow-up hemoglobin A1c measurement was 14 (12–16) months.
[b]Adjusted mean differences were derived using inverse probability of treatment-weighted generalized linear models that accounted for all characteristics in Table 1, including demographics, HIV-related characteristics, comorbidities, and co-medications.

augmentation or at least 0.5 percentage point increase in HbA1c compared with NNRTI users, whereas the risk was comparable between INSTI and protease inhibitor users.

Our comparative assessment of metabolic outcomes among the three different ART regimen classes focused exclusively on the growing population of PWH with diabetes [2]. We observed weight gain across all three ART groups. While a 'return-to-health' phenomenon may have contributed to these increases, the adverse metabolic effects of ART may account for a greater proportion of weight gain in this cohort, given that most participants were already overweight or obese at the time of ART initiation. The comparative effect of initiating INSTI-based regimens vs. other regimens on weight among PWH with diabetes appeared similar to that observed in the broader populations with HIV without diabetes: greater weight gain was seen in ART-naive PWH treated with INSTI-based regimens compared to those treated with NNRTI-based regimens, but not compared to those treated with protease inhibitor-based regimens [5–7]. We also found that the comparative pattern of weight change following initiation of INSTIs compared to NNRTIs or protease inhibitors remained consistent between subgroups with well controlled and poorly controlled diabetes prior to starting ART. While no significant statistical interaction was found between the ART class and year of initiation, interpretation should be made with caution due the smaller number of NNRTI and protease inhibitor initiators between 2016 and 2022.

Unique to our study, we examined glycemic changes following ART initiation among PWH who had preexisting diabetes. Overall, participants treated with INSTIs experienced modestly worse glycemic outcomes than those treated with NNRTIs. Although the mean change in HbA1c did not differ significantly between the

Table 3. Secondary weight and glycemic outcomes among people with HIV with diabetes who initiated an integrase strand transfer inhibitor-based, nonnucleoside reverse transcriptase inhibitor-based, or protease inhibitor-based regimen between 2007 and 2022.

Outcome	Comparison group	Events (%)	Adjusted incidence rate, per 100 person-years (95% CI)	Adjusted hazard ratio (95% CI)[a]
≥5% weight gain	INSTI (*N* = 548)	340 (62)	39.3 (35.0–44.0)	Reference
	NNRTI (*N* = 511)	291 (57)	26.2 (23.1–29.6)	0.74 (0.63–0.87)
	PI (*N* = 220)	146 (66)	37.8 (32.1–44.2)	0.99 (0.80–1.23)
Augmentation of glucose-lowering therapy	INSTI (*N* = 548)	199 (36)	15.0 (12.9–17.4)	Reference
	NNRTI (*N* = 511)	170 (33)	11.5 (9.7–13.4)	0.82 (0.66–1.02)
	PI (*N* = 220)	91 (41)	15.9 (13.0–19.4)	1.12 (0.86–1.46)
≥0.5 percentage point increase in hemoglobin A1c	INSTI (*N* = 548)	314 (57)	31.2 (27.7–35.0)	Reference
	NNRTI (*N* = 511)	283 (55)	23.6 (20.8–26.7)	0.82 (0.69–0.97)
	PI (*N* = 220)	130 (59)	25.9 (21.8–30.5)	0.88 (0.71–1.09)
Glucose-lowering therapy augmentation or increase in hemoglobin A1c	INSTI (*N* = 548)	362 (66)	43.4 (38.9–48.4)	Reference
	NNRTI (*N* = 511)	320 (63)	32.9 (29.2–36.9)	0.84 (0.71–0.98)
	PI (*N* = 220)	157 (71)	42.4 (36.3–49.2)	1.03 (0.84–1.25)

CI, confidence intervals; INSTI, integrase strand transfer inhibitor; NNRTI, nonnucleoside reverse transcriptase inhibitor; PI, protease inhibitor; PWH, people with HIV.
[a]Adjusted hazard ratios were derived using inverse probability of treatment-weighted Cox proportional hazards models that accounted for all characteristics in Table 1, including demographics, HIV-related characteristics, comorbidities, and co-medications.

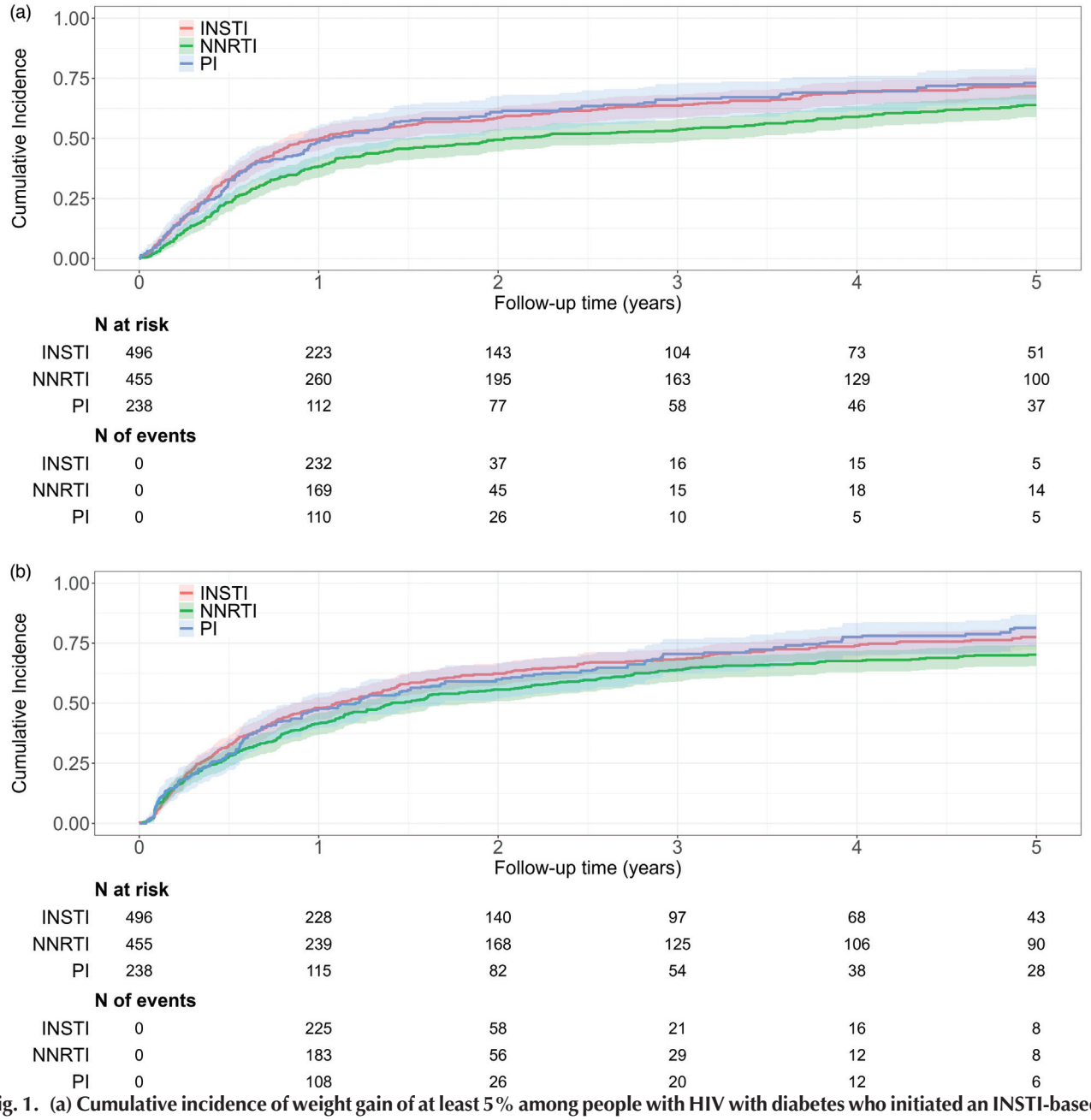

Fig. 1. (a) Cumulative incidence of weight gain of at least 5% among people with HIV with diabetes who initiated an INSTI-based, NNRTI-based, or PI-based regimen between 2007 and 2022. (b) Cumulative incidence of glucose-lowering therapy augmentation or at least 0.5% increase in hemoglobin A1c among PWH with diabetes who initiated an INSTI-based, NNRTI-based, or PI-based regimen between 2007 and 2022. *N* at risk and *N* of events represent weighted values. INSTI, integrase strand transfer inhibitor; NNRTI, nonnucleoside reverse transcriptase inhibitor; PI, protease inhibitor; PWH, people with HIV.

two groups, INSTI users had a higher risk of the composite outcome of glucose-lowering therapy intensification or an increase in HbA1c of at least 0.5% compared with NNRTI users. In contrast, the risk of glycemic outcomes was similar between the INSTI and protease inhibitor groups. Stratified analyses by baseline glycemic control revealed that participants with poorly controlled diabetes experienced declines in HbA1c across all treatment groups, while those with well controlled diabetes showed modest increases. The observed improvements in glycemic control among PWH with poorly controlled diabetes may reflect integration of cardiometabolic management within HIV care [30]. Notably, comparative changes in HbA1c between treatment groups did not differ significantly across subgroups defined by baseline glycemic control or year of ART initiation. However, the smaller number of NNRTI and protease inhibitor initiators between 2016 and 2022 warrants cautious interpretation of the estimates due to the possibility of type II error.

Our study was a real-world investigation of changes in weight and glycemia among ART-naive PWH with preexisting diabetes who were newly treated with ART in the NA-ACCORD. According to CDC surveillance data, the NA-ACCORD cohorts reflect the demographic and clinical characteristics of PWH in the United States, supporting the generalizability of our findings to this population [31]. To strengthen the internal validity of our study, we employed a new-user, active-comparator design to mitigate confounding by indication and immortal time bias that can arise when comparing patients at different stages of treatment [13,14]. Additionally, we used IPTW to address potential confounding from nonrandom treatment assignment inherent to observational studies [28].

There are also limitations to our study. First, despite our rigorous pharmacoepidemiologic approaches, residual confounding cannot be completely ruled out due to the observational design. For example, confounding by indication remains possible if participants perceived to have worse metabolic risks were preferentially started on one study regimen over another. Moreover, INSTI users tended to initiate treatment later in the study period than NNRTI or protease inhibitor users, which could introduce bias from evolving clinical practices in diabetes management. While we adjusted for calendar time of ART initiation (i.e. time of study entry), individual cardiometabolic profiles, and concomitant use of glucose-lowering agents, these adjustments may not have fully eliminated such bias. Second, while our study included participants from North America, results may not generalize to populations in other geographic settings, particularly those with differing dietary patterns, physical activity levels, or food security. Third, although misclassification of diabetes type is possible, it is unlikely to meaningfully affect our findings, as type 1 diabetes accounts for only approximately 4% of all diabetes cases among PWH [32]. Fourth, information on medication dose was not available; therefore, glucose-lowering drug dose augmentation could not be assessed as an outcome. Fifth, we assessed that the sample size was insufficient to reliably investigate individual INSTI agents. Sixth, we did not evaluate other antiretroviral regimens beyond the three types of oral regimens based on INSTIs, NNRTIs, and protease inhibitors. No long-acting injectable formulations were studied. Lastly, we did not examine the specific biological mechanisms underlying the adverse metabolic effects of INSTIs; dedicated mechanistic studies are warranted.

In conclusion, our findings provide new insights into the comparative metabolic effects of initiating INSTI-based compared to NNRTI-based or protease inhibitor-based therapy among PWH with diabetes. Individuals treated with INSTI-based regimens experienced modestly greater weight gain and worse glycemic outcomes compared to those treated with NNRTI-based regimens, while changes in both weight and glycemia were similar between those treated with INSTI-based and protease inhibitor-based regimens. Our findings are intended not to discourage INSTI use, but to inform the growing population with HIV and diabetes and their clinicians of potential metabolic implications to guide shared decisions on monitoring and intervention. Future studies estimating the impact of switching to INSTI-based regimens from older therapies among ART-experienced PWH with diabetes would provide important additional insights to inform clinical decision-making in routine care settings.

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Conflicts of interest

T.T.B. has served as a consultant to ViiV Healthcare, Gilead Sciences, Janssen, and EMD Serono. G.C.A 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. O.F.-N. received grants from AbbVie to the institution and received advisory fees from Gilead Sciences. V.C.M. has received investigator-initiated research grants (to the institution) and research support from Eli Lilly, Bayer, Gilead Sciences, Merck, Pfizer, and ViiV Healthcare. S.G.K contributed to the development of HIV educational materials for VINDICO CME. Other authors have no potential conflicts of interest to report.

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