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Integrase Strand Transfer Inhibitor–Related Changes in Body Mass Index and Risk of Diabetes: A Prospective Study From the RESPOND Cohort Consortium

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Background. With integrase strand transfer inhibitor (INSTI) use associated with increased body mass index (BMI) and BMI increases associated with higher diabetes mellitus (DM) risk, we explored the relationships between INSTI/non-INSTI regimens, BMI changes, and DM risk.

Methods. RESPOND participants were included if they had CD4, human immunodeficiency virus (HIV) RNA, and ≥2 BMI measurements during follow-up. Those with prior DM were excluded. DM was defined as a random blood glucose ≥11.1 mmol/L, hemoglobin A1c ≥6.5%/48 mmol/mol, use of antidiabetic medication, or site-reported clinical diagnosis. Poisson regression was used to assess the association between natural log (ln) of time-updated BMI and current INSTI/non-INSTI and their interactions on DM risk.

Results. Among 20 865 people with HIV included, most were male (74%) and White (73%). Baseline median age was 45 years (interquartile range [IQR], 37–52), with a median BMI of 24 kg/m^2 (IQR, 22–26). There were 785 DM diagnoses with a crude rate of 0.73 (95% confidence interval [CI], .68–.78)/100 person-years of follow-up. ln(BMI) was strongly associated with DM (adjusted incidence rate ratio [aIRR], 16.54 per log increase; 95% CI, 11.33–24.13; $P < .001$). Current INSTI use was associated with increased DM risk (IRR, 1.58; 95% CI, 1.37–1.82; $P < .001$) in univariate analyses and only partially attenuated when adjusted for variables including ln(BMI) (aIRR, 1.48; 95% CI, 1.29–1.71; $P < .001$). There were no interactions between ln(BMI), INSTI, and non-INSTI use and DM ($P = .130$).

Conclusions. In RESPOND, compared with non-INSTIs, current use of INSTIs was associated with an increased DM risk, which partially attenuated when adjusted for BMI changes and other variables.

Keywords. people living with HIV; INSTI use; BMI; weight gain; diabetes.

Integrase strand transfer inhibitors (INSTIs) are now recommended by the World Health Organization as the preferred first- and second-line antiretroviral therapy (ART) for treating human immunodeficiency virus (HIV) [1]. Currently, 5 approved INSTIs are available for people with HIV: raltegravir (RAL), cobicistat-boosted elvitegravir (EVG/c), dolutegravir (DTG), bictegravir (BIC), and cabotegravir (CAB) for those virologically suppressed. With high efficacy for viral suppression, easy use, better tolerability, higher resistance barrier in DTG and BIC, and relatively low cost, most countries have now adopted DTG-containing regimens as the preferred first-line therapy [1].

Despite a good short-term safety profile and high tolerability [2], INSTIs have been linked to weight gain and treatment-emergent obesity, increasing the risk of weight-related comorbidities such as incident diabetes mellitus (DM) [3, 4]. This weight gain has been observed with DTG, RAL, and

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BIC [5–7]. Women and people of Black race have been shown to experience weight gain [6, 8]. Additionally, switching from tenofovir disoproxil fumarate (TDF) to tenofovir alafenamide (TAF) has been linked to higher weight gain compared with continuous use of TDF [9, 10].

Higher body mass index (BMI) is known to increase the risk of DM [11, 12]. Cohort studies, including previous Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) analyses and clinical trials, have shown that people with HIV have an increased DM risk with higher current BMI [7, 13, 14]. It remains uncertain how BMI gains in individuals receiving INSTIs impact the risk of clinical events traditionally associated with increased BMI. This strong relationship between time-updated BMI and DM risk provides an opportunity to determine whether the BMI increases seen with INSTI use translate into increased DM risk. Our aim in this study was to compare INSTI- and non-INSTI–based regimens in terms of the association between BMI and risk of incident DM (see Supplementary Figure 1 on directed acyclic graph).

METHODS

This study was conducted within the RESPOND consortium, a prospective, multicohort collaboration that includes data from 19 well-established observational cohorts and more than 30 000 people with HIV in Europe and Australia. RESPOND has been described in detail previously [2, 7, 15]. The collected data include demographics, ART, blood pressure (BP), comorbidities (such as cardiovascular disease, cancer, fractures, DM), and laboratory parameters. These data are transferred annually to a central coordinating center. All cohorts and the coordinating center perform quality-control checks to ensure data completeness and accuracy.

Study Population and Analysis Period

Participants aged ≥18 years on dual or triple combination ART therapy who had height, weight, and more than 1 BMI measurement during follow-up were included in the study. Baseline for the study was latest of cohort entry, 1 January 2012, start of combination ART, or first BMI measurement. Participants were followed from baseline until the first event of DM, final follow-up visit, or cohort administering censor date of 31 December 2019, whichever occurred first. Participants also required CD4 cell counts and HIV viral load measurements within 1 year prior to baseline or 3 months after. Those with DM prior to baseline were excluded. A flowchart of participant inclusion is shown in Figure 1.

Statistical Analyses

DM was defined previously [2,7, 16] according to laboratory values (blood glucose levels >11.1 mmol/L or hemoglobin A1c (HbA1C) >6.5%/48 mmol/L), use of antidiabetic medication, or site-reported clinical diagnosis. Participant characteristics were summarized at baseline for the study population and those with and without DM. The characteristics at the start of each drug class are summarized in Supplementary Table 1. Factors associated with DM were assessed using Poisson regression with random effects on person (using time variable as exposure with individual random effect on random intercepts) adjusting for time-fixed and time-updated covariates.

Time-fixed covariates included sex, mode of HIV acquisition, race, region, prior AIDS, ART-naive status, and viral hepatitis B (HBV) and hepatitis C (HCV) co-infection. Participants were HCV-positive if they had a positive antibody test, positive HCV-RNA, HCV genotype tests, or received HCV therapy. HBV infection was defined as a positive HBV surface antigen and/or a prior positive HBV-DNA. Values closest to the baseline date, but within 1 year prior and up to 7 days after, were considered baseline.

Time-updated covariates were CD4 cell counts, HIV viral load, BMI (lagged by 12 months to reduce bias from reverse causation), age, INSTI use, ART use, smoking status, total cholesterol, and BP. The relationship between BMI and DM was modeled as the natural log (ln) of time-updated BMI, reflecting the exponential increasing risk of DM with higher BMI seen in previous data [13]. A similar approach was used for age. Current use of RAL, EVG/c, DTG, BIC, or CAB in their ART regimen was categorized as current INSTI use. ART use was categorized as current use of TDF, TAF, and non-TDF/TAF. Smoking was categorized as current, past, never, and unknown. Total cholesterol levels were categorized as <200 and ≥200 mg/dL, and high BP was defined by systolic BP ≥140 mmHg and/or diastolic BP ≥90 mmHg or use of antihypertensives.

The consistency of the relationship between ln(BMI) and DM in INSTI/non-INSTI regimens was assessed by testing for an interaction between time-updated ln(BMI) and INSTI/non-INSTI use. Interactions between ln(BMI) and sex and ln(age) were also assessed.

Sensitivity Analyses

Several sensitivity analyses were conducted to assess robustness of results. First, the relationship between BMI and DM was tested with time-updated BMI categorized as <21, 21–23, 23–26, 27–30, and >30 kg/m^2 and with a categorical 7% increase [17–19] in BMI for comparison. Drug class was categorized as containing INSTIs, protease inhibitor (PIs), or non-nucleoside reverse transcriptase inhibitors (NNRTIs) using a hierarchical method without considering the nucleoside reverse transcriptase inhibitors (NRTIs) backbone, as defined previously [7]. Interactions between these ways of modeling BMI and INSTI/non-INSTI use were also assessed.

Second, we assessed the associations between ln(BMI) and DM for individual INSTIs (if each had close to 100 or

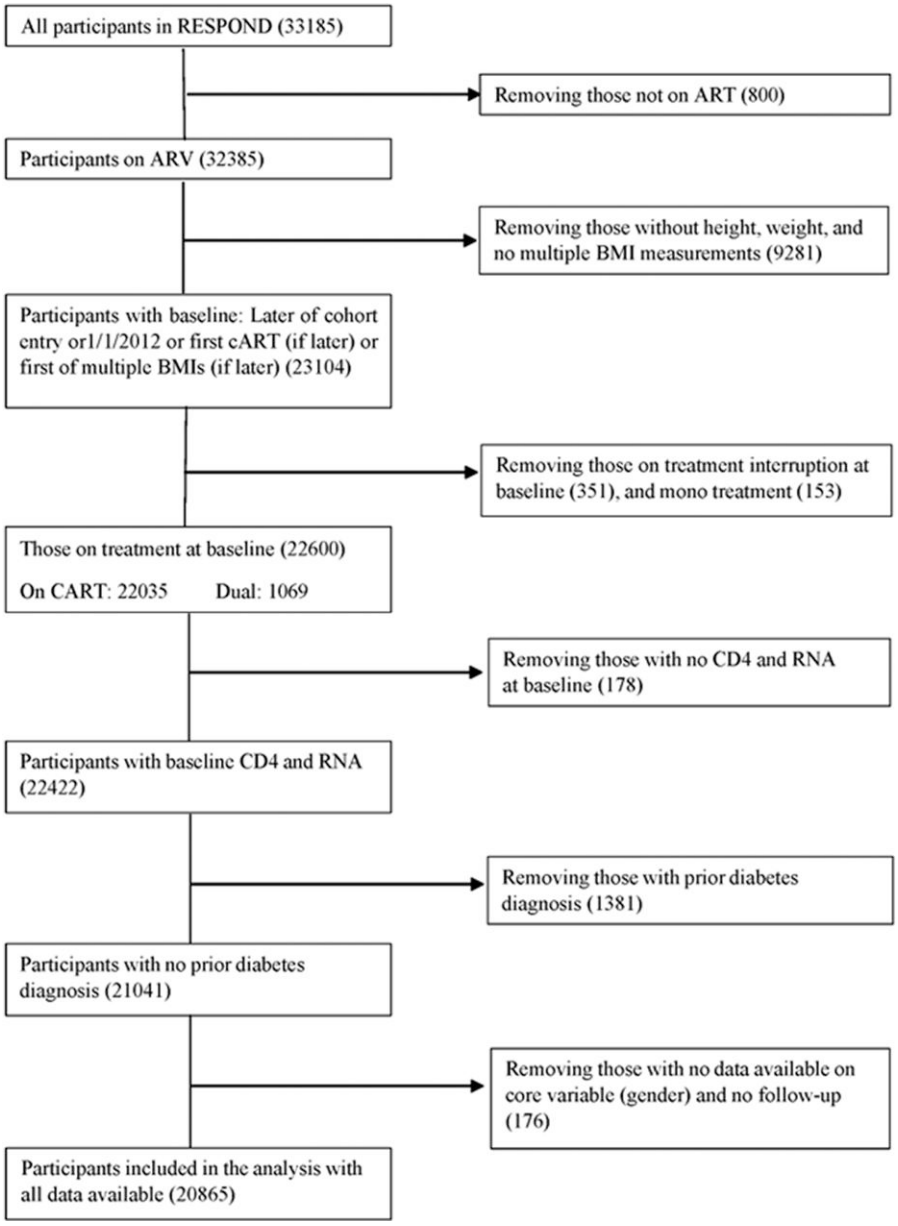

Figure 1. Study population. Abbreviations: ART, antiretroviral therapy; ARV, antiretroviral; BMI, body mass index; cART, combination antiretroviral therapy.

more DM events accumulated), cumulative INSTI exposure, current use of TDF or TAF, and use of TDF or TAF on the INSTI effect. The INSTI effect on DM was also explored between those who were treatment-naive and those who were treatment-experienced.

Third, to assess for possible channeling bias, the DM risk score, which predicts the short-term risk of DM, was calculated at the start of each drug class using the D:A:D risk score equation and included in the model [17].

Fourth, to observe early DM events after starting an INSTI compared with PI and NNRTI, a Kaplan–Meier plot from the start of drug class to DM event was plotted.

Finally, additional sensitivity analyses were performed using confirmed fasting glucose >7.0 mmol/L and confirmed random blood glucose >11.1 mmol/L as part of the DM definition. For all analyses, covariates in the univariate analysis with $P < .10$ were fitted into the multivariate model. A backward-stepwise selection process was used, and covariates with $P < .05$ were considered statistically significant and retained in the multivariate model. A sensitivity analysis that included all variables was also performed for comparison. SAS Enterprise Guide (SAS Institute Inc, Cary, NC) and Stata software version 16.1 (StataCorp, College Station, TX) were used to perform all data management and statistical analyses.

RESULTS

Participant Characteristics

In total, 20 865 people with HIV were included, with the majority being male (74%), White (73%), and from Western Europe (46%). Primary risk of HIV acquisition was via men who have sex with men (45%). At baseline, the median age was 45 years (interquartile range [IQR], 37–52), with a median CD4 cell count of 551 cells/μL (IQR, 380–750) and median BMI of 23.8 kg/m^2 (IQR, 21.5–26.3). Twenty-three percent had an HIV viral load ≥200 copies/mL, and 2% were coinfected with hepatitis B or C virus. At baseline, 25% of participants were on an INSTI-containing regimen, 58% on TDF and 6% on TAF. Participants with onset DM were older (median age, 50 years; IQR, 44–57) and had a higher median BMI (26.5 kg/m^2; IQR, 23.2–30.0) compared with the overall study population (Table 1).

Factors Associated With Incident DM

During 107 641 person-years of follow-up (PYFU), there were 785 incident diagnoses of DM, determined by random blood glucose >11.1 mmol/L (n = 254), HbA1c >6.5%/48 mmol/mol (n = 239), and/or use of antidiabetic medication or site-reported clinical diagnosis (n = 292), giving a crude rate of 0.73 (95% confidence interval [CI], .68–.78)/100 PYFU. ln(BMI) was strongly associated with DM (adjusted incident rate ratio [aIRR], 16.54 per log increase; 95% CI, 11.33–24.13; $P < .001$). Current INSTI use was associated with increased DM risk (IRR, 1.58; 95% CI, 1.37–1.82; $P < .001$) in the univariate analysis, which only partially attenuated when adjusted for other variables including ln(BMI) (aIRR, 1.48; 95% CI, 1.29–1.71; $P < .001$; Table 2). The adjusted absolute risk difference between INSTI and non-INSTI was 0.29/1000 PYFU (95% CI, .28–.29). Among those with BMI = 25 kg/m^2, the predicted DM risk for BMI by current INSTI use showed the absolute risk difference between INSTI and non-INSTI use to be 0.21/1000 PYFU. This was low compared with a 0.41/1000 PYFU difference among those with BMI = 30 kg/m^2 (Figure 2*A*). We found no evidence that the association between ln(BMI) and DM differed according to INSTI/non-INSTI users (interaction, $P = .130$). Similarly, this association did not differ when assessed by ln(age) (interaction, $P = .811$) and sex (interaction, $P = .325$). Current TAF and TDF use was not associated with DM and had similar DM risk (aIRR, 1.01; 95% CI, .82–1.25; $P = .912$). Females had a lower DM risk (aIRR, 0.69; 95% CI, .57–.85; $P < .001$) compared with males. Additionally, ln(age), injection drug use, mode of HIV acquisition, Black and other race, lower CD4 cell counts, and high BP were associated with increased DM risk (Table 2).

Sensitivity Analyses

The overall median frequencies of BMI, glucose, and HbA1c monitoring per participant per year were 2.10 (IQR, 1.50–3.40), 6.7 (IQR, 3.6–12.5), and 4.9 (IQR, 1.5–11.1), respectively. Their overall testing rates were 16.6 (95% CI, 16.5–16.7)/100 PY, 18.7 (95% CI, 18.6–18.7)/100 PY, and 13.4 (95% CI, 13.3–13.5)/PY, respectively. The various sensitivity analyses are summarized in Table 3. First, assessment of individual INSTIs with sufficient power found that DTG use (aIRR, 1.54; 95% CI, 1.31–1.82; $P < .001$) and RAL use (aIRR, 1.72; 95% CI, 1.35–2.19; $P < .001$) were associated with DM compared with PI/NNRTI regimens. Cumulative INSTI exposure of 1–3 years (1–2 years: aIRR, 1.50; 95% CI, 1.16–1.94; $P = .002$ and 2–3 years: aIRR, 1.47; 95% CI, 1.16–1.87; $P = .001$) had an increased DM risk compared with no exposure.

Furthermore, while not significant, consistent association with DM was observed when INSTIs were used with TDF (aIRR, 1.26; 95% CI, .97–1.65; $P = .080$), TAF (aIRR, 1.22; 95% CI, .95–1.56; $P = .120$), or non-TDF/TAF antiretrovirals (ARVs; aIRR, 1.34; 95% CI, 1.08–1.66; $P = .007$). Similarly, TDF and TAF with ARVs other than INSTIs also had similar risk for DM (other + TDF: aIRR, 0.78; 95% CI, .64–.96; $P = .020$ and other + TAF: aIRR, 0.86; 95% CI, .62–1.20; $P = .381$).

There was no significant INSTI association among those who were treatment-naive (aIRR, 0.92; 95% CI, .58–1.46; $P = .725$) compared with non-INSTI users who were treatment-naive, although the number of events in those who were treatment-naive was small and CIs were wide (Table 3).

Second, the baseline 1-year DM risk/100 PYFU for INSTIs (mean, 0.43; standard deviation [SD], 1.23) and other drug classes (PIs: mean, 0.48; SD, 1.25 and NNRTIs: mean, 0.47; SD, 1.22) was similar. While a higher DM risk score among INSTI users would suggest INSTI channeling bias, similar results among drug classes showed little evidence of it. Furthermore, the Kaplan–Meier plot of time to DM events from the start of each drug class demonstrated higher probability of DM among INSTI users compared with PI or NNRTI users and did not show high DM risk shortly after starting an INSTI (Figure 2*B*).

All additional sensitivity analyses found supporting or similar results to the main findings (Table 3, Supplementary Tables 2–6).

DISCUSSION

During a median follow-up of 4.8 years, we found 785 incident DM diagnoses with a crude rate of 0.73 (95% CI, .68–.78)/100 PYFU. As expected, ln(BMI) was strongly associated with DM, and the association between current INSTI use and DM risk was only partially attenuated when adjusted for ln(BMI) and other variables. The absolute risk difference between INSTIs and non-INSTIs was 0.29 (95% CI, .28–.29)/1000 PYFU. There were no interactions observed between ln(BMI), INSTI and non-INSTI use, and DM risk, suggesting that INSTI-associated weight changes have the same implications

Table 1. Participant Characteristics at Baseline*

	Total Patients n (%)	No Incident DM n (%)	Incident DM n (%)
Total	20 865 (100)	20 080 (96)	785 (4)
Sex			
Male	15 529 (74)	14 912 (74)	617 (79)
Female	5336 (26)	5168 (26)	168 (21)
Age, y			
Median (IQR)	45 (37–52)	45 (36–52)	50 (44–57)
<40	6786 (33)	6668 (33)	118 (15)
≥40	14 079 (67)	13 412 (67)	667 (85)
HIV acquisition risk			
Heterosexual contact	7158 (34)	6851 (34)	307 (39)
Men who have sex with men	9358 (45)	9052 (45)	306 (39)
Injection drug users	3108 (15)	2990 (15)	118 (15)
Other	507 (2)	484 (2)	23 (3)
Unknown or missing	734 (4)	703 (4)	31 (4)
Race			
White	15 161 (73)	14 615 (73)	546 (70)
Black	1510 (7)	1417 (7)	93 (12)
Other	699 (3)	672 (3)	27 (3)
Unknown	3495 (17)	3376 (17)	119 (15)
Hepatitis C			
Negative	3206 (15)	3119 (16)	87 (11)
Positive	364 (2)	358 (2)	6 (1)
Unknown	17 295 (83)	16 603 (83)	692 (88)
Hepatitis B			
Negative	6618 (32)	6369 (32)	249 (32)
Positive	313 (2)	295 (1)	18 (2)
Unknown	13 934 (67)	13 416 (67)	518 (66)
CD4 cell count, cells/μL			
Median (IQR)	551 (380–750)	550 (380–749)	562 (380–783)
≤200	1726 (8)	1641 (8)	85 (11)
201–350	2787 (13)	2702 (13)	85 (11)
≥350	16 352 (78)	15 737 (78)	615 (78)
HIV viral load, copies/mL			
Median (IQR)	39 (19–104)	39 (19–110)	27 (19–49)
<200	160 967 (77)	15 447 (77)	649 (83)
≥200	4769 (23)	4633 (23)	136 (17)
Prior AIDS			
No	19 332 (93)	18 607 (93)	725 (92)
Yes	1533 (7)	1473 (7)	60 (7)
Body mass index, kg/m^2			
Median (IQR)	23.8 (21.5–26.3)	23.7 (21.4–26.3)	26.5 (23.2–30.0)
<21	4166 (20)	4086 (20)	80 (10)
21–23	4413 (21)	4315 (21)	98 (12)
23–26	6403 (31)	6222 (31)	181 (23)
27–30	4060 (19)	3838 (19)	222 (28)
>30	1823 (9)	1619 (8)	204 (26)
ART-naive			
No	17 681 (85)	16 968 (85)	713 (91)
Yes	3184 (15)	3112 (15)	72 (9)
ART treatment			
TDF	12 157 (58)	11 695 (58)	462 (59)
TAF	1175 (6)	1148 (6)	27 (3)
No TDF/No TAF	7533 (36)	7237 (36)	296 (38)
INSTI use[a]			
No	15 590 (75)	14 967 (75)	623 (79)
Yes	5275 (25)	5113 (25)	162 (21)

Table 1. Continued

	Total Patients n (%)	No Incident DM n (%)	Incident DM n (%)
Smoking			
Current	5976 (29)	5741 (29)	235 (30)
Past	1608 (8)	1542 (8)	66 (8)
Never	2582 (12)	2493 (12)	89 (11)
Unknown	10 699 (51)	10 304 (51)	395 (50)
Glucose, mmol/L			
Median (IQR)	5.1 (4.7–5.6)	5.10 (4.7–5.6)	5.9 (5.1–6.7)
≤7.0	16 700 (80)	16 153 (80)	547 (70)
>7.0	577 (3)	435 (2)	122 (16)
Not tested	3608 (17)	3492 (17)	116 (15)
High blood pressure[b]			
No	12 146 (58)	11 551 (60)	594 (42)
Yes	2587 (12)	2370 (12)	217 (15)
Not tested	6088 (29)	5488 (28)	599 (42)
HDL–cholesterol, mg/dL			
Median (IQR)	46 (39–62)	46 (39–62)	43 (35–54)
<60	12 254 (58)	11 628 (58)	526 (67)
≥60	2080 (29)	3954 (20)	126 (16)
Not tested	4631 (22)	4498 (22)	133 (17)
Triglyceride, mg/dL			
Median (IQR)	124 (89–177)	124 (80–177)	159 (115–239)
<200	17 267 (83)	16 613 (83)	654 (83)
≥200	295 (1)	265 (1)	30 (4)
Not tested	3303 (16)	3202 (16)	101 (13)
Total cholesterol, mg/dL			
Median (IQR)	178 (150–213)	178 (150–213)	193 (159–236)
<200	11 868 (57)	11 206 (58)	661 (47)
≥200	5147 (25)	4638 (24)	509 (36)
Not tested	3806 (18)	3565 (18)	240 (17)
Region[c]			
Western Europe	9643 (46)	9231 (46)	412 (52)
Southern Europe and Argentina	2017 (10)	1971 (10)	46 (6)
Northern Europe and Australia	8959 (43)	8632 (43)	327 (42)
Eastern and East Central Europe	246 (1)	246 (1)	0 (0)

*Baseline is later of cohort entry, 1 January 2012, first combination ART (if later), or first of multiple body mass index measurements (if later).

Abbreviations: ART, antiretroviral therapy; DM, diabetes mellitus; HDL, high-density lipoprotein; HIV, human immunodeficiency virus; IQR, interquartile range; INSTI, integrase strand transfer inhibitor;TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.

[a]INSTI use at baseline consisted of raltegravir (932, 18%), elvitegravir (1214, 23%), dolutegravir (3040, 58%), bictegravir (89, 2%), cabotegravir (1, 0%).

[b]High blood pressure (BP) defined as systolic BP measurements ≥140 mmHg and/or diastolic BP ≥90 mmHg or use of antihypertensives.

[c]Regions: Western Europe (Austria, Belgium, France, Germany, Luxembourg, and Switzerland), Southern Europe and Argentina (Greece, Israel, Italy, Portugal, Spain and Argentina), Northern Europe and Australia (Denmark, Finland, Iceland, Ireland, the Netherlands, Norway, Sweden, the United Kingdom, and Australia), Eastern and East Central Europe (Belarus, Estonia, Georgia, Latvia, Lithuania, Russia, and Ukraine).

for DM as weight changes for other reasons. In adjusted analyses, current TAF use had similar lack of DM risk compared with current TDF use. Other factors associated with DM were male sex, ln(age), injection drug use, Black and other race, lower CD4 cells counts, and high BP.

The incidence rate of DM among people with HIV varies across region, country income level, and follow-up. High rates of DM (1.0–4.7/100 PYFU) have been reported in US cohort studies, which included mostly African-Americans [18, 19] and Asia [20] compared to Europe [14, 21]. The rate in our study was comparable to the unadjusted DM rate found in several HIV cohorts (European cohort: 0.81/100 PYFU; 95% CI, .77–.86 and Canadian cohort: 0.74/100 PYFU; 95% CI, .62–.88) [11, 16]. The follow-up time of our study was similar to the follow-up times for these studies, which ranged from 6 to 9 years. Our rate was also comparable to DM rates found in non-HIV populations in Canada [11] and Spain [12] with similar follow-up periods but in earlier years, suggesting possible improvement in DM treatment and adherence [11]. Furthermore, a previous D:A:D study reported a lower DM rate of 0.57/100 PYFU [14]. The wide range of DM rates is possibly attributable to differences in DM diagnosis definition, for example, use of fasting blood glucose, confirmatory test, increase in DM cases over time, and wider use of INSTIs and

Table 2. Factors Associated With Incident Diabetes Mellitus

					Univariate			Multivariate		
	Total Participants n (%)	Follow-up (years)	No. of Diabetes Mellitus Events	Crude Rate/100 Person-Years	Incident Rate Ratio	95% CI	P Value	Adjusted Indicient Rate Ratio	95% CI	P Value
Total	20 865 (100)	107 640.53	785	0.73						
Sex										
Male	15 529 (74)	79 276.67	617	0.78	1			1		
Female	5336 (26)	28 363.86	168	0.59	0.76	(0.64–0.90)	**.002**	0.69	(0.57–0.85)	**<.001**
Age (lnAge)[a]										
Per unit increase	~	~	~	~	8.42	(6.12–11.61)	**<.001**	7.28	(5.19–10.22)	**<.001**
HIV acquisition risk							**.028**			**.004**
Heterosexual contact	7158 (34)	38 219.52	307	0.80	1			1		
Men who have sex with men	9358 (45)	48 080.80	306	0.64	0.79	(0.68–0.93)	.004	0.86	(0.71–1.04)	.117
Injection drug users	3108 (15)	15 204.66	118	0.78	0.97	(0.78–1.19)	.751	1.26	(1.00–1.58)	.049
Other	507 (2)	2645.09	23	0.87	1.08	(0.71–1.65)	.714	1.34	(0.87–2.05)	.181
Unknown or missing	734 (4)	3490.46	31	0.89	1.11	(0.76–1.60)	.594	1.01	(0.69–1.46)	.969
Race							**<.001**			**<.001**
White	15 161 (73)	79 196.05	546	0.69	1			1		
Black	1510 (7)	8153.40	93	1.14	1.65	(1.33–2.06)	<.001	1.78	(1.40–2.28)	<.001
Other	699 (3)	3551.78	27	0.76	1.1	(0.75–1.62)	.62	1.81	(1.22–2.68)	.003
Unknown	3495 (17)	16 739.29	119	0.71	1.03	(0.85–1.26)	.762	1.09	(0.89–1.34)	.389
Hepatitis C										
Negative	3206 (15)	14 476.27	87	0.60	1					
Positive	364 (2)	1632.19	6	0.37	0.61	(0.27–1.40)	.244			
Unknown	17 295 (83)	91 532.07	692	0.76						
Hepatitis B										
Negative	6618 (32)	32 368.38	249	0.77	1					
Positive	313 (2)	1547.98	18	1.16	1.51	(0.94–2.44)	**.091**			
Unknown	13 934 (67)	73 724.18	518	0.70						
CD4 cell counts, cells/μL[b]							**<.001**			**<.001**
≤200	~	3541.44	52	1.47	2.08	(1.57–2.76)	<.001	2.24	(1.69–2.98)	<.001
201–350	~	9868.63	69	0.70	0.99	(0.77–1.27)	.951	0.96	(0.75–1.23)	.762
≥350	~	94 230.46	664	0.70	1			1		
HIV viral load, copies/mL[b]										
<200	~	101 484.98	738	0.73	1					
≥200	~	6155.55	47	0.76	1.05	(0.78–1.41)	.746			
Prior AIDS										
No	19 332 (93)	99 263.38	725	0.73	1					
Yes	1533 (7)	8377.14	60	0.72	0.98	(0.75–1.28)	.884			
BMI (lnBMI)[a]	~	~	~	~	20.04	(13.98–28.73)	**<.001**	16.54	(11.33–24.13)	**<.001**
ART naive										
No	17 681 (85)	92 879.16	713	0.77	1					
Yes	3184 (15)	14 761.37	72	0.49	1.12	(0.97–1.30)	.115			
ART treatment[b]							**.003**			.278
TDF	~	47 399.17	298	0.63	1			1		
TAF	~	18 901.94	151	0.80	1.27	(1.04–1.55)	.016	1.01	(0.82–1.25)	.912
No TDF/No TAF	~	41 339.42	336	0.81	1.29	(1.11–1.51)	.001	1.13	(0.96–1.33)	.143
INSTI use[b]										
No	~	68 656.31	414	0.60	1			1		
Yes	~	38 984.22	371	0.95	1.58	(1.37–1.82)	**<.001**	1.48	(1.29–1.71)	**<.001**

Table 2. Continued

	Total Participants n (%)	Follow-up (years)	No. of Diabetes Mellitus Events	Crude Rate/100 Person-Years	Univariate			Multivariate		
					Incident Rate Ratio	95% CI	P Value	Adjusted Indicient Rate Ratio	95% CI	P Value
Smoking[b]							.387			
Never	~	16 497.00	117	0.71	1					
Current	~	36 197.27	258	0.71	1.00	(0.81–1.25)	.964			
Past	~	11 126.93	96	0.86	1.22	(0.93–1.59)	.155			
Unknown	~	43 819.32	314	0.72	1.01	(0.82–1.25)	.924			
High blood pressure[b,c]										
No	~	64 147.41	335	0.52	1			1		
Yes	~	29 158.71	311	1.07	2.04	(1.75–2.38)	**<.001**	1.43	(1.22–1.67)	**<.001**
Unknown	~	14 334.41	139	0.97						
Total cholesterol, mmol/L[b]										
<200	~	60 562.55	429	0.71	1					
≥200	~	35 282.05	248	0.7	0.99	(0.85–1.16)	.923			
Not tested	~	11 795.94	108	0.92						
Region[d]							**.008**			
Western Europe	9643 (46)	50 469.47	412	0.82	1					
Southern Europe and Argentina	2017 (10)	8817.81	46	0.52	0.64	(0.47–0.87)	.004			
Northern Europe and Australia	8959 (43)	48 002.5	327	0.68	0.83	(0.72–0.96)	.015			
Eastern and East Central Europe	246 (1)	350.75	0	0						

Not tested values were included in the analysis as a separate category but were excluded from test for heterogeneity.

Bold values indicate significant covariates in univariate and multivariate analysis.

Abbreviations: ART, antiretroviral therapy; BMI, body mass index; HIV, human immunodeficiency virus; INSTI, integrase strand transfer inhibitor;TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.

[a]Uses natural log. Total participant number varies due to multiple measures; therefore, this is not provided.

[b]Time-updated variables. Total participant number varies due to multiple measures; therefore, this is not provided.

[c]High blood pressure (BP) defined as systolic BP measurements ≥140 mmHg and/or diastolic BP ≥90 mmHg or use of antihypertensives.

[d]Regions: Western Europe (Austria, Belgium, France, Germany, Luxembourg, and Switzerland), Southern Europe and Argentina (Greece, Israel, Italy, Portugal, Spain, and Argentina), Northern Europe and Australia (Denmark, Finland, Iceland, Ireland, the Netherlands, Norway, Sweden, the United Kingdom, and Australia), Eastern and East Central Europe (Belarus, Estonia, Georgia, Latvia, Lithuania, Russia, and Ukraine).

other antivirals associated with DM. Additionally, DM testing patterns at clinical sites, ethnicity, co-infections, age distribution, and behavioral factors such as alcohol consumption and smoking could impact DM incidence in cohorts [22, 23].

We found similar non-HIV–related predictors of onset DM, namely, male sex, Black/other race, older age, high BP, and increasing BMI as found in the general population [11, 12]. We also found lower CD4 cell counts [11], injection drug use [11, 14], and INSTI use [18, 21, 24, 25] associated with DM risk. Unlike other studies, we did not find an association between viral hepatitis co-infection and DM [3, 26], possibly due to the relatively low proportion of participants tested for viral hepatitis.

As expected, we found that increasing BMI was strongly associated with DM [5,7]. Factors that contribute to high BMI or excess weight gain include genetics, uncontrolled diet, physical inactivity, and behavioral risks, such as alcohol consumption, in both people with and without HIV. Studies on ART have shown that weight gain occurs 1–2 years after initiation of certain drug classes [3, 4]. Therefore, implementing approaches such as weight loss and vigilant monitoring and management of weight/BMI, especially for those on certain ART drug classes for more than a year, could prevent or delay the onset of DM.

We found that those on INSTI regimens were more likely to develop DM compared with those on non-INSTI regimens [18, 25]. The crude incidence rate of DM by INSTI use was partially attenuated when adjusted for ln(BMI) and other confounders, indicating it as a strong predictor of DM. This effect was limited to DTG and RAL, though we lacked sufficient power to draw conclusions for other INSTIs. A North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD) study identified RAL as a strong predictor of DM but found no association between DM and overall INSTI drug class when adjusted for weight gain after 1 year on INSTIs [18]. Similarly, the Dat'AIDS French cohort study found no association between INSTI use and DM after adjusting for BMI [21].

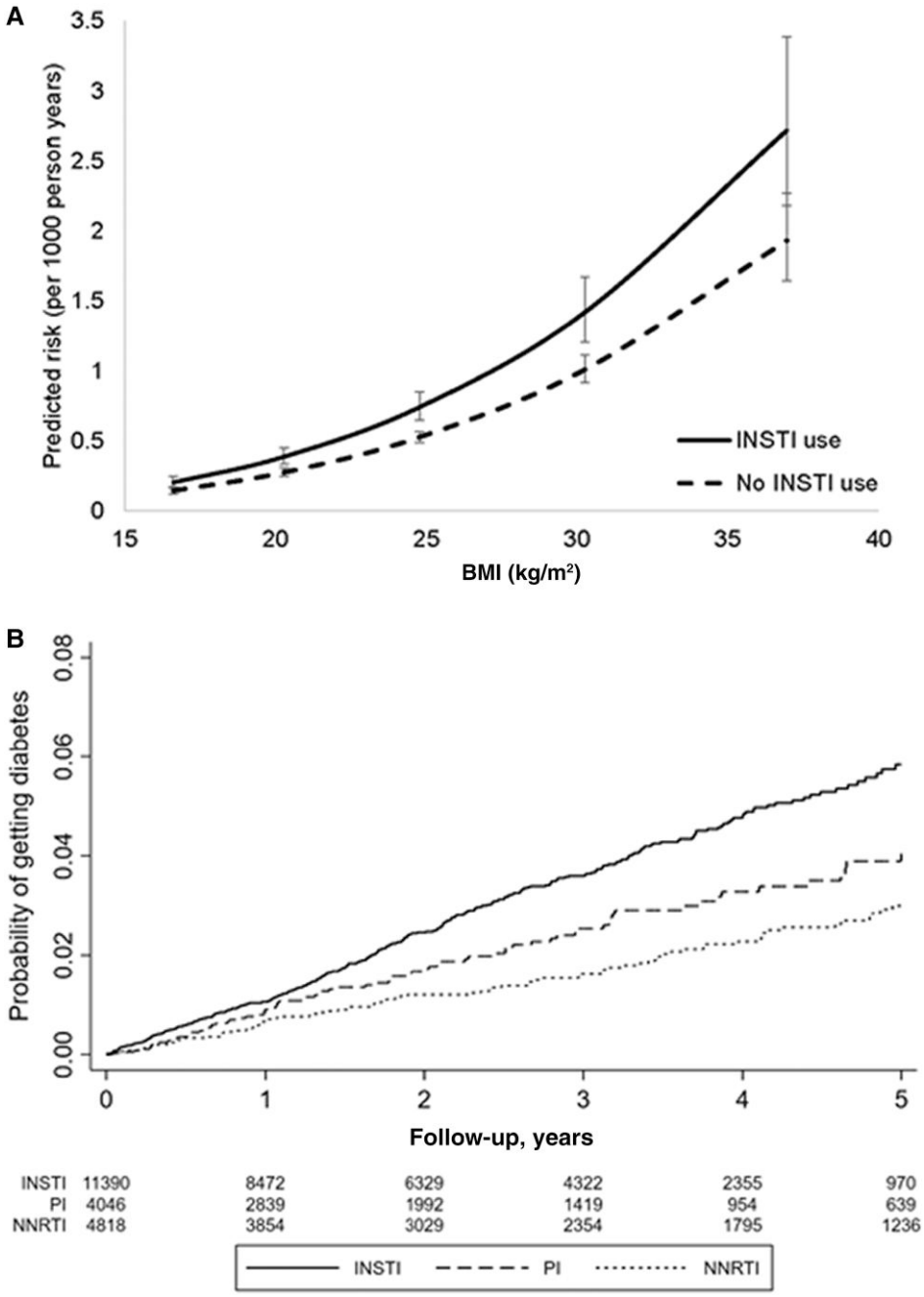

Figure 2. *A,* Predicted risk of diabetes mellitus (DM) by current INSTI use and BMI. The predicted risk per 1000 person-years of DM for BMI among INSTI and non-INSTI users when adjusted for sex, natural log of age, human immunodeficiency virus risk group, ethnicity, CD4 cell counts, blood pressure, current tenofovir disoproxil fumarate/tenofovir alafenamide use. Among INSTI users, 12% were on raltegravir, 60% on dolutegravir, and 28% on other INSTIs (cobicistat-boosted elvitegravir, bictegravir, and cabotegravir). *B,* Kaplan–Meier plot demonstrating the time to DM event from the start of drug class. Abbreviations: BMI, body mass index; INSTI, integrase strand transfer inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; PI, protease inhibitor.

However, our findings align with studies that suggest INSTIs affect insulin sensitivity independent of weight gain [27].

Previous analyses suggested that increased BMI while on INSTIs is partially due to concurrent TAF use [9, 28]. These studies found similar DM risk while on INSTIs with TDF, TAF, or other NRTIs and to have an increased DM risk compared with other regimens that did not include INSTIs, TAF, or TDF [9]. We further investigated TDF and TAF use with and without INSTIs. Our adjusted analyses consistently showed no difference in DM risk between TDF andTAF, indicating no impact of TAF or TDF on DM after adjusting for change in BMI.

Table 3. Sensitivity Analyses on Factors Associated With Diabetes Mellitus With Different Fittings of Body Mass Index and Antiretroviral Therapy

		DM Events/ Person-Years of Follow-up	Crude Rate/100 Person-Years	Unadjusted Incident Rate Ratio (CI)	Adjusted Incidnet Rate Ratio (CI)	P Value
Time-updated continuous BMI	**BMI, kg/m^2**					<.001
	<21	79/21 344	0.37	1	1	
	21–23	108/22 930	0.47	1.27 (0.95–1.70)	1.24 (0.93–1.66)	.150
	23–26	195/32 995	0.59	1.6 (1.23–2.07)	1.45 (1.11–1.89)	.006
	27–30	211/21 156	1	2.69 (2.08–3.49)	2.35 (1.80–3.05)	<.001
	>30	192/9216	2.08	5.63 (4.33–7.31)	5.03 (3.84–6.58)	<.001
	Current ART treatment					.277
	TDF	298/47 399	0.63	1	1	
	TAF	151/18 902	0.8	1.27 (1.04–1.55)	1.00 (0.81–1.23)	.999
	No TDF/No TAF	336/41 339	0.81	1.29 (1.11–1.51)	1.13 (0.96–1.32)	.156
	Current INSTI use					
	No	414/68 656	0.6	1	1	
	Yes	371/38 984	0.95	1.58 (1.37–1.82)	1.48 (1.28–1.70)	<.001
BMI increases defined as a 7% increase in current BMI compared with last BMI of previous regimen	**7% BMI increase**					
	No (n = 18 108)	697/101 901	0.68	1	1	
	Yes (n = 2757)	88/5740	1.53	2.24 (1.80–2.80)	1.86 (1.48–2.35)	<.001
	Current ART treatment					.822
	TDF	298/47 399	0.63	1	1	
	TAF	151/18 902	0.8	1.27 (1.04–1.55)	1.01 (0.82–1.25)	.905
	No TDF/No TAF	336/41 339	0.81	1.29 (1.11–1.51)	1.05(0.89–1.24)	.550
	Current INSTI use					
	No	414/68 656	0.6	1	1	
	Yes	371/38 984	0.95	1.58 (1.37–1.82)	1.37 (1.17–1.60)	<.001
Individual INSTIs	**BMI (lnBMI)[b]**	~	~	20.04 (13.98–28.73)	16.71 (11.46–24.36)	<.001
	Current ART treatment					.487
	TDF	298/47 399	0.63	1	1	
	TAF	151/18 902	0.8	1.27 (1.04–1.55)	1.10 (0.88–1.36)	.396
	No TDF/No TAF				1.10 (0.93–1.30)	.265
	Current INSTI use					<.001
	DTG use	226/22 790	0.99	1.64 (1.40–1.93)	1.54 (1.31–1.82)	<.001
	RAL use	79/6690	1.18	1.96 (1.54–2.49)	1.72 (1.35–2.19)	<.001
	Other INSTIs	66/9504	0.69	1.15 (0.89–1.49)	1.14 (0.88–1.48)	.315
	PI/NNRTIs	414/68 656	0.6	1	1	
Cumulative use of INSTIs	**BMI (lnBMI)[b]**	~	~	20.04 (13.98–28.73)	16.41 (11.24–23.96)	<.001
	Current ART treatment					.089
	TDF use	298/47 399	0.63	1	1	
	TAF use	151/18 902	0.8	1.27 (1.04–1.55)	0.98 (0.80–1.21)	.854
	No TDF/No TAF	336/41 339	0.81	1.29 (1.11–1.51)	1.17 (0.99–1.37)	.060
	Cumulative INSTI use					.001
	Never on INSTI	421/60 777	0.69	1	1	
	0–1 y	44/5169	0.85	1.23 (0.90–1.68)	1.19 (0.87–1.62)	.283
	1–2 y	68/6308	1.08	1.56 (1.20–2.01)	1.50 (1.16–1.94)	.002
	2–3 y	82/8031	1.02	1.47 (1.16–1.87)	1.47 (1.16–1.87)	.001
	>3 y	169/19 168	0.88	1.27 (1.06–1.52)	1.19 (0.99–1.42)	.059
Current use of INSTI, TAF, and TDF combinations	**BMI (lnBMI)[b]**	~	~	20.04 (13.98–28.73)	17.00 (11.63–24.84)	<.001
	Current ART treatment					<.001
	INSTI + TAF	104/11 438	0.91	1.29 (1.01–1.65)	1.22 (0.95–1.56)	.120
	INSTI + TDF	86/9227	0.93	1.32 (1.02–1.72)	1.26 (0.97–1.65)	.080
	INSTI + (no TDF or TAF)	181/18 319	0.99	1.4 (1.14–1.73)	1.34 (1.08–1.66)	.007
	Other + TDF	204/38 199	0.53	0.76 (0.62–0.93)	0.78 (0.64–0.96)	.020
	Other + TAF	46/7171	0.64	0.91 (0.66–1.26)	0.86 (0.62–1.20)	.381
	Other	164/23 286	0.7	1	1	

Table 3. Continued

		DM Events/ Person-Years of Follow-up	Crude Rate/100 Person-Years	Unadjusted Incident Rate Ratio (CI)	Adjusted Incidnet Rate Ratio (CI)	P Value
Using TE/TN with INSTI use	**BMI (lnBMI)[b]**	~	~	20.04 (13.98–28.73)	17.00 (11.63–24.84)	<.001
	TE/TN INSTI use					<.001
	TE non-INSTI	377/60 823	0.62	1.31 (0.94–1.84)	0.88 (0.63–1.24)	.464
	Naive non-INSTI	37/7833	0.47	1	1	
	Experienced INSTI	336/32 056	1.05	2.22 (1.58–3.12)	1.38 (0.98–1.95)	.067
	Naive INSTI	35/6928	0.51	1.07 (0.67–1.70)	0.92 (0.58–1.46)	.725
	Current ART treatment					.329
	TDF	298/47 399	0.63	1	1	
	TAF	151/18 902	0.8	1.27 (1.04–1.55)	1.02 (0.83–1.26)	.817
	No TDF/No TAF	336/41 339	0.81	1.29 (1.11–1.51)	1.12 (0.96–1.32)	.158
1-year DM risk per 100 PYS DM risk score[a]	**BMI (lnBMI)[b]**	~	~	20.04 (13.98–28.73)	16.35 (10.55–25.33)	<.001
	Current INSTI use					
	No	414/68 656	0.6	1	1	
	Yes	371/38 984	0.95	1.58 (1.37–1.82)	1.58 (1.36–1.83)	<.001
	DM risk score per 100 PYS			1.42 (1.30,1.55)	1.21(1.11–1.33)	<.001
	Current ART treatment					.051
	TDF	298/47 399	0.63	1	1	
	TAF	151/18 902	0.8	1.27 (1.04– 1.55)	1.06 (0.86–1.30)	.601
	No TDF/No TAF	336/41 339	0.81	1.29 (1.11–1.51)	1.22 (1.03–1.44)	.018

ART, antiretroviral therapy; BMI, body mass index ; CI, confidence interval; DM, diabetes mellitus; DTG, dolutegravir; INSTI, integrase strand transfer inhibitor; NNRTI, non-nucleoside reverse transcriptase; PI, protease inhibitor; PYS, person years; RAL, raltegravir; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate; TE, treatment-experienced; TN, treatment-naive.

Bold values indicate significant covariates in univariate and multivariate analysis.

[a]DM risk equation referenced from Petoumenos et al [17].

[b]Uses natural log. Total participant number varies due to multiple measures; therefore, DM events/PYFU and Crude rate/100PYS is not provided.

Despite concerns about channeling bias, where those at highest risk of DM are actively switched to INSTIs instead of older ARVs, our analysis did not support this. First, the 1-year DM risk score was similar across drug class at baseline, suggesting that those selected for INSTIs had similar predicted DM risk. Second, cumulative exposure to INSTIs did not show high DM risk in the first year after INSTI initiation, which might be expected with channeling bias. Third, the Kaplan–Meier plot did not show a large DM risk shortly after starting INSTIs. Although a US study identified earlier onset of DM shortly after starting an INSTI (median time of 6 months) [25], this was not apparent in our analyses. Last, there was no INSTI signal among those who were treatment-naive compared with those who were ART-experienced and non-INSTI users, albeit with limited power [29].

These analyses have several limitations. First, height and weight measurements were relatively infrequently collected, which excluded some cohorts as per the standard RESPOND approach [7, 15]. BMI assessments were observational in nature and sometimes widely spaced, potentially leading to inadequate adjustment for increasing BMI. Second, our approach assumes that any raised DM risk due to BMI increases while on INSTIs will be captured by fitting time-updated BMI. This assumption is supported by prior D:A:D analyses. Third, other possible factors that influenceing BMI, such as co-medication of corticosteroids and, psychiatric drugs, which are known to increase appetite and affect, exercise, and diet, were not collected in RESPOND. Fourth, the DM definition is not based on fasting status and may lead to under-diagnosis of diabetes in RESPOND. However, any such under-diagnosis would affect drug classes in a similar way.

CONCLUSIONS

In RESPOND, current use of INSTIs was associated with an increased DM risk compared with PIs and NNRTIs, which partially reduced when adjusted for BMI changes and other variables. We observed no interaction between ln(BMI) and DM in INSTI and non-INSTI users. This suggests that BMI increases while on INSTIs are associated with an increase in the risk of DM by a similar amount as BMI increases for other reasons and would support interpreting INSTI-related BMI increases in terms of DM risk in a way that is similar to other BMI increases. In our data, we found little evidence of a difference in DM risk between current TAF and TDF users.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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Notes

Author contributions. All authors had full access to the data from the study and had final responsibility for the decision to submit for publication. Several authors contributed to data collection. D. R. and K. P. accessed and verified the data. D. R., M. L., and K. P. conceived the idea and developed the project proposal and a statistical analysis plan. All authors reviewed the proposal and contributed to the revised proposal and analysis plan. D. R., with the supervision of M. L., performed the statistical analysis and wrote the analysis report, which was reviewed and commented on by all authors. D. R. developed the first draft of the manuscript and revised the subsequent drafts. D. R., M. L., and K. P. reviewed all versions of the manuscript and interpreted the data. L. B. M., R. Z., A. R., P. E. T., L. G., B. N., N. J., S. d. W., F. W., A. d. M., E. F., A. C., M. S., V. B., E. F., J. B., C. M., A. S., A. A., A. G., V. V., C. C., L. Y., S. H., and L. R. contributed to the interpretation of data and reviewed and provided input for the final draft of the manuscript.

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Data sharing. Data are not publicly available. The RESPOND Scientific Steering Committee (SSC) encourages the submission of concepts for research projects. Online research concepts should be submitted to the RESPOND secretariat (respond.rigshospitalet@regionh.dk). For guidelines on how to submit research concepts, see the RESPOND governance and procedures. The secretariat will direct the proposal to the relevant scientific interest group, where the proposal will initially be discussed for scientific relevance before being submitted to the SSC for review. Once submitted to the SSC, the research concept's scientific relevance, relevance to RESPOND's ongoing scientific agenda, design, statistical power, feasibility, and overlap with already approved projects will be assessed. Upon completion of the review, feedback will be provided to the proposer or proposers. In some circumstances, a revision of the concept might be requested. If the concept is approved for implementation, a writing group will be established that consists of the proposers (up to 3 people who were centrally involved in developing the concept), representatives from RESPOND cohorts, and representatives from the Statistical Department and Coordinating Center. All individuals involved in the process of reviewing these research concepts are bound by confidentiality. All data within RESPOND from individual cohorts are de-identified. The present RESPOND data structure and a list of all collected variables and their definitions can be found online. For any inquiries regarding data sharing, please contact the RESPOND secretariat (respond.rigshospitalet@regionh.dk).

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