Incident type 2 diabetes mellitus after initiation of common HIV antiretroviral drugs

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Objectives: To describe the prevalence and incidence of prediabetes and type 2 diabetes mellitus (T2DM) among people living with HIV (PLHIV) and evaluate the association between antiretroviral therapy (ART) initiation with dolutegravir (DTG), elvitegravir/cobicistat (EVG/c), raltegravir (RAL), or boosted darunavir (bDRV) and incident T2DM.

Design: Longitudinal study based on electronic health records of 29 674 PLHIV from the Observational Pharmaco-Epidemiology Research and Analysis (OPERA) cohort.

Methods: Calculate prevalence of prediabetes and T2DM at regimen initiation. Among PLHIV without prevalent disease, estimate prediabetes and T2DM incidence (Poisson regression) and association between regimen and incident T2DM (multivariate Cox proportional hazards regression). Analyses stratified by ART experience.

Results: Among ART-naive and ART-experienced/suppressed PLHIV, the estimated prevalence of prediabetes was 8 and 11%; that of T2DM was 4 and 10%, respectively. The T2DM incidence rate was 9 per 1000 person-years [95% confidence interval (CI): 8–11] among ART-naive and 13 per 1000 person-years (95% CI: 12–15) among ART-experienced/suppressed PLHIV, with no statistically significant differences between regimens. Compared with DTG, no statistically significant association between T2DM risk and regimen was observed among ART-naive on EVG/c [adjusted hazard ratios: 0.70 (95% CI: 0.47–1.05)] or bDRV [0.53 (0.26–1.04)] and ART-experienced/suppressed on EVG/c [0.96 (0.70–1.33)], RAL [1.17 (0.70–1.96)] or bDRV [0.90 (0.57–1.42)].

Conclusion: No increased risk of T2DM was observed with EVG/c, RAL or bDRV compared with DTG in ART-naive and experienced PLHIV. However, despite a large cohort, there was a small number of events and differential risk cannot be excluded.

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Introduction

Long-term use of antiretroviral therapy (ART) has increased life expectancy [1] and affected patterns of morbidity over time for people living with HIV (PLHIV), with an increased burden of comorbidities [2]. The prevalence of prediabetes appears comparable among PLHIV (30% in a survey of predominantly African-American PLHIV on ART) [3] and the overall US population [34% among US adults in the National Health

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and Nutrition Examination Survey (NHANES)] [4]. The prevalence of type 2 diabetes mellitus (T2DM) among PLHIV has been estimated to be between 3 and 15% in the United States, Europe and Australia [5–14]. When directly compared, PLHIV on ART may have a higher prevalence of T2DM than HIV-negative individuals. In a study of over one million individuals in tertiary care hospitals in the United States, the prevalence was higher among PLHIV (12%) than HIV-negative people (7%) [7]. In 2009–2010, data from the Medical Monitoring Project and NHANES, the prevalence was also higher among PLHIV (10%) than HIV-negative people (8%) [8]. However, in the Veterans Aging Cohort Study (VACS) of mostly men, the prevalence of T2DM was lower among PLHIV (12%) than HIV-negative individuals (23%) [9].

PLHIV may be at a greater risk of developing T2DM than HIV-negative individuals. In a systematic review of 44 studies of PLHIV receiving ART, the pooled T2DM incidence rate was 19 per 1000 person-years in the Americas (range: 8–47 per 1000 person-years) and 8 per 1000 person-years in seven European countries (range: 3–29 per 1000 person-years) [15]. These estimates are higher than the incidence rates among all US adults (7 per 1000 person-years), according to 2013–2015 data from the National Health Interview Survey (NHIS) [4]. In the VACS of mostly men, the cumulative incidence of T2DM was lower among PLHIV (5%) than HIV-negative individuals (11%) for an adjusted hazard ratio (aHR) of 0.56 [95% confidence interval (CI): 0.47–0.66] [9].

A variety of ART agents have been associated with an increased risk of incident T2DM in PLHIV, including nucleoside reverse transcriptase inhibitors (NRTI) [6,10,11,16,17], nonnucleoside reverse transcriptase inhibitors (NNRTI) [10], and protease inhibitors [18]. There is evidence of weight gain with use of integrase strand transfer inhibitors (INSTI), which likely impacts risk of T2DM [19–23]. However, far less research has been done evaluating the association between current standard-of-care regimens utilizing INSTIs and clinical health outcomes, such as T2DM, which may have a bigger impact on long-term health than weight gain. In the North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD), PLHIV who initiated treatment with an INSTI were more likely to develop diabetes (aHR: 1.22, 95% CI: 0.95–1.57) than PLHIV who initiated treatment with NNRTIs; results were similar to those for protease inhibitors. Among specific INSTIs, compared with NNRTI-based ART, raltegravir (RAL) was associated with an increased risk of diabetes (aHR: 1.50, 95% CI: 1.11–2.03) whereas dolutegravir (DTG) and elvitegravir (EVG) were not (aHR: 1.14 and 0.96, respectively) [24].

Using data from a large, real-world population of PLHIV receiving care in the United States who were new users of DTG, elvitegravir with cobicistat (EVG/c), RAL, or boosted darunavir (bDRV), we sought to first describe prevalence of prediabetes and T2DM. Among the PLHIV who did not have prediabetes or T2DM prior to or at core agent initiation, we then assessed the incidence rates of prediabetes and T2DM and estimated the association between the core agents of interest and development of T2DM during follow-up in both ART-naive as well as experienced patient populations.

Methods

Study design and population

Data from the Observational Pharmaco-Epidemiology Research and Analysis (OPERA) cohort, a database of prospectively captured clinical data from the electronic health records of 94 145 PLHIV at 84 clinics across the United States (17 states and 1 US territory), were utilized. The OPERA database obtains annual institutional review board (IRB) approval from Advarra IRB, including a waiver of informed consent and authorization for the use of protected health information. The study population included PLHIV who started an ART regimen with DTG, EVG/c, RAL, or bDRV for the first time between 1 August 2013 and 31 March 2018, after inclusion in the OPERA database. Eligible PLHIV were aged 13 years and older, had never been diagnosed with type 1 or juvenile diabetes mellitus, or with gestational diabetes, and had a baseline viral load available. Each person contributed person-time from core agent initiation until a censoring event: core agent discontinuation, 12 months after the last clinical contact, death, or study end (30 September 2018).

Individuals were classified as ART-naive if they had no history of ART prior to the initiation of the core agent of interest and had a baseline HIV viral load at least 1000 copies/ml. Individuals were classified as ART-experienced/suppressed if they had a baseline HIV viral load less than 50 copies/ml, with or without evidence of a history of ART. Prior exposure to other core agents of interest was allowed if it occurred prior to inclusion in the OPERA database, or if it occurred while contributing to the OPERA database, but its use was discontinued prior to 1 August 2013. ART-experienced/viremic PLHIV (i.e. evidence of a history of ART and baseline HIV viral load $\geq$50 copies/ml, or no evidence of a history of ART, but baseline HIV viral load at least 50–$<$1000 copies/ml) were also included (Supplemental Digital Content 1–3, http://links.lww.com/QAD/B859, http://links.lww.com/QAD/B860, http://links.lww.com/QAD/B861).

Study outcomes

Prediabetes was defined as either a diagnosis of prediabetes or borderline diabetes mellitus or an abnormal lab value [HbA1c $\geq$5.7% to $<$6.5%; fasting

plasma glucose (FPG) ≥100 mg/dl to <126 mg/dl; or oral glucose tolerance test (OGTT) ≥140 mg/dl to <200 mg/dl]. T2DM was defined as either a diagnosis of T2DM/noninsulin-dependent diabetes (NIDDM), an antidiabetic prescription, or a lab indicative of T2DM (HbA1c ≥6.5%; FPG ≥126 mg/dl; or OGTT ≥200 mg/dl). Prevalent prediabetes or T2DM were indicated if a diagnosis was present before/at baseline or if the abnormal lab value was on the last lab within 12 months before or at baseline. Incident prediabetes and diabetes were evaluated only in individuals without prediabetes or T2DM at baseline; incident prediabetes required two abnormal lab values, measured at least 90 days apart.

Statistical analysis

Demographics, clinical characteristics, and all outcomes were summarized using medians with interquartile ranges (IQR) for continuous variables and frequencies and proportions for categorical variables. Statistical comparisons by core agent were performed using Pearson's chi-square or Fisher exact tests for categorical variables and Wilcoxon rank-sum test for continuous variables, as appropriate. The unadjusted prevalence of prediabetes and T2DM was calculated as the proportion of participants with prediabetes or T2DM within 12 months before or at baseline. Among PLHIV without prediabetes or T2DM at baseline, univariate Poisson regression was used to calculate the incidence rates and 95% CIs as the proportion of participants with a new diagnosis of prediabetes or T2DM during follow-up, out of the person-time at risk for the event. To evaluate the association between each core agent and incident T2DM, multivariate Cox proportional hazards regression were employed with DTG as the referent group; models were adjusted for baseline age, sex, race, hepatitis C virus (HCV) co-infection, and BMI, which were selected a priori, based on the literature. All analyses were stratified by prior ART experience (i.e. ART-naive or ART-experienced/suppressed).

Results

Of the 94 145 PLHIV in the OPERA database, 29 674 (15%) met criteria for inclusion in this study and first initiated treatment with DTG, EVG/c, RAL, or bDRV between 1 August 2013 and 31 March 2018.

Antiretroviral therapy-naive people living with HIV

Of the 8489 PLHIV classified as ART-naive (3234 DTG, 3906 EVG/c, 241 RAL, 1108 bDRV), 676 (8%) had prediabetes and 319 (4%) had T2DM before or at baseline (Table 1). Prevalence of prediabetes was lower with EVG/c (7%, $P = 0.01$) but no different with RAL (8%, $P = 0.49$) or bDRV (9%, $P = 0.83$), compared with DTG (9%). Prevalence of T2DM was also lower with EVG/c (3%, $P = 0.02$) but no different with RAL (7%, $P = 0.07$) or bDRV (4%, $P = 0.99$), compared with DTG (4%). The median duration of follow-up was significantly longer in the EVG/c group (18 months, IQR: 12–29) and significantly shorter in the RAL (11 months, IQR: 4–19) and bDRV (12 months, IQR: 7–22) groups than the DTG group (16 months, IQR: 10–27; all $P < 0.01$).

There were 7494 ART-naive PLHIV without prevalent prediabetes or T2DM (2816 DTG, 3504 EVG/c, 207 RAL, 967 bDRV). Compared with DTG, EVG/c users were less likely to be underweight; RAL users were older, and more likely to be women, obese and HCV-co-infected; and bDRV users were older, and more likely to be women, non-Hispanic black, and HCV co-infected (Table 2). The overall incidence rate for prediabetes in ART-naive PLHIV was 21 per 1000 person-years (95% CI: 19–24). There was no difference in the unadjusted incidence rate of prediabetes per 1000 person-years between DTG (incidence rate: 23, 95% CI: 19–28) and EVG/c (incidence rate: 21, 95% CI: 17–25), RAL (incidence rate: 13, 95% CI: 4–39) or bDRV (incidence rate: 20, 95% CI: 13–29).

Table 1. Prevalence of prediabetes and type 2 diabetes mellitus at baseline among antiretroviral therapy-naive ($N = 8489$) and antiretroviral therapy-experienced/suppressed ($N = 12\,322$) people living with HIV, by core agent.

Core agent	Prediabetes			Type 2 diabetes mellitus		
	n (%)	95% CI	*P* value	*n* (%)	95% CI	*P* value
ART-naive						
DTG ($N = 3234$)	284 (9)	(8–10)	–	134 (4)	(3–5)	–
EVG/c ($N = 3906$)	279 (74)	(6–8)	0.01	123 (3)	(3–4)	0.02
RAL ($N = 241$)	18 (7)	(4–12)	0.49	16 (7)	(4–11)	0.07
bDRV ($N = 1108$)	95 (9)	(7–10)	0.83	46 (4)	(3–6)	0.99
ART-experienced/suppressed						
DTG ($N = 4{,}747$)	671 (14)	(13, 15)	–	492 (10)	(10, 11)	–
EVG/c ($N = 5243$)	557 (11)	(10, 11)	<0.01	405 (8)	(7–8)	<0.01
RAL ($N = 962$)	70 (7)	(6, 9)	<0.01	162 (17)	(15–19)	<0.01
bDRV ($N = 1370$)	111 (8)	(7, 10)	<0.01	150 (11)	(9–13)	0.53

ART, antiretroviral therapy; bDRV, boosted darunavir; CI, confidence interval; DTG, dolutegravir; EVG/c, elvitegravir with cobicistat; RAL, raltegravir.

Table 2. Baseline demographic and clinical characteristics of antiretroviral therapy-naive people living with HIV ($N = 7494$) without prevalent prediabetes or type 2 diabetes mellitus at initiation of core antiretroviral therapy agent, by core agent.

Characteristic	DTG ($N = 2816$)	EVG/c ($N = 3504$)	RAL ($N = 207$)	bDRV ($N = 967$)
Age (years), median (IQR)	30 (25–40)	30 (25–40)	41 (31–50)	34 (27–44)
Female sex, *n* (%)	325 (12%)	394 (11%)	70 (34%)	160 (17%)
Race/ethnicity [*n* (%)]				
Hispanic black	33 (1%)	32 (<1%)	4 (2%)	11 (1%)
Hispanic white	690 (25%)	780 (22%)	19 (9%)	160 (17%)
Non-Hispanic black	1,200 (43%)	1618 (46%)	112 (54%)	515 (53%)
Non-Hispanic white	647 (23%)	795 (23%)	57 (28%)	213 (22%)
Other	119 (4%)	125 (4%)	5 (2%)	31 (3%)
Unknown	127 (5%)	154 (4%)	10 (5%)	37 (4%)
BMI, median (IQR)	24 (22–28)	24 (22–28)	26 (22–30)	24 (21–28)
BMI category [*n* (%)]				
Underweight	168 (6%)	148 (4%)	15 (7%)	67 (7%)
Normal weight	1327 (47%)	1751 (50%)	69 (33%)	466 (48%)
Overweight	774 (28%)	983 (28%)	58 (28%)	247 (26%)
Obese	454 (16%)	501 (14%)	51 (25%)	145 (15%)
Missing	93 (3%)	121 (4%)	14 (7%)	42 (4%)
Hepatitis C, *n* (%)	115 (4%)	136 (4%)	20 (10%)	59 (6%)
Any endocrine disorders,[a] *n* (%)	179 (6%)	208 (6%)	19 (9%)	51 (5%)
HIV viral load (copies/ml), median (IQR)	50 510 (16 710–140 395)	45 744 (13,285–131 000)	38 100 (13 370–132 000)	63 260 (17 910–203 874)
HIV viral load (copies/ml) [*n* (%)]				
At least 1000 to <10 000	481 (17%)	716 (20%)	43 (21%)	178 (18%)
At least 10 000 to < 100 000	1396 (50%)	1698 (49%)	102 (49%)	401 (42%)
>= 100 000	939 (33%)	1090 (31%)	62 (30%)	388 (40%)
Calendar year of study inclusion, median (IQR)	2016 (2015–2017)	2016 (2014–2017)	2015 (2014–2017)	2015 (2014–2017)

ART, antiretroviral therapy; bDRV, boosted darunavir; CI, confidence interval; DTG, dolutegravir; EVG/c, elvitegravir with cobicistat; IQR, interquartile range; RAL, raltegravir.
[a]Hyperlipidemia, hyperthyroidism, hypothyroidism, or thyroiditis, excluding type 2 diabetes mellitus.

The overall T2DM incidence rate was 9 per 1000 person-years (95% CI: 8–11). Similarly, there was no difference in the unadjusted incidence rate of T2DM per 1000 person-years between DTG (incidence rate: 11, 95% CI: 9–15), EVG/c (incidence rate: 7, 95% CI: 6–10), RAL (incidence rate: 13, 95% CI: 4–40), or bDRV (incidence rate: 8, 95% CI: 4–14) (Fig. 1a). After adjustments for baseline age, sex, race/ethnicity, HCV co-infection and BMI, no statistically significant association was found between core agent and incident T2DM for EVG/c (aHR: 0.70, 95% CI: 0.47–1.05) or bDRV (aHR: 0.53, 95% CI: 0.26–1.04) when compared with DTG (Fig. 1b). RAL was excluded from modeling because of the small number of incident T2DM events in this group.

Individuals with incident T2DM had higher baseline BMIs (median: 29, IQR: 26–33), compared with PLHIV who remained free of T2DM during follow-up (median: 24, IQR: 22–28). Greater increases in BMI over follow-up were observed in those who developed T2DM than those who did not (Supplemental Digital Content 4, http://links.lww.com/QAD/B862).

Antiretroviral therapy-experienced/suppressed people living with HIV

Of the 12 322 PLHIV classified as ART-experienced/suppressed, 1409 (11%) had prediabetes and 1209 (10%) had T2DM before or at baseline (Table 1). The prevalence of prediabetes was lower with EVG/c (11%), RAL (7%) and bDRV (8%), compared with DTG (14%; all $P < 0.01$). However, while the prevalence of T2DM was also lower with EVG/c (8%, $P < 0.01$), it was higher with RAL (17%, $P < 0.01$) and no different with bDRV (11%, $P = 0.53$), compared with DTG (10%). The median duration of follow-up in the DTG group was 18 months (IQR: 11–29). The EVG/c (17 months, IQR: 11–27) and RAL (14 months, IQR: 8–27) groups had significantly shorter follow-up ($P < 0.01$). Median follow-up in the bDRV group was 17 months (IQR: 10–29; $P = 0.09$). There were 9704 ART-experienced/suppressed participants without prevalent prediabetes or T2DM (3584 DTG, 4281 EVG/c, 730 RAL, 1109 bDRV). Compared with DTG users, EVG/c users were younger, and less likely to be female or HCV co-infected; RAL users were older, and more likely to be female, non-Hispanic white and HCV co-infected; and bDRV users were more likely to be female, overweight or obese, and less likely to be HCV co-infected (Table 3). The overall incidence rate for prediabetes in ART-experienced/suppressed PLHIV was 31 per 1000 person-years (95% CI: 28–34). There was no difference in the unadjusted incidence rate of prediabetes per 1000 person-years between DTG (incidence rate: 39, 95% CI: 35–45) and RAL (incidence rate: 33, 95% CI: 24–45) or bDRV (incidence rate: 28, 95% CI: 21–36), but it was lower with EVG/c (incidence rate: 25, 95% CI: 21–29) than DTG.

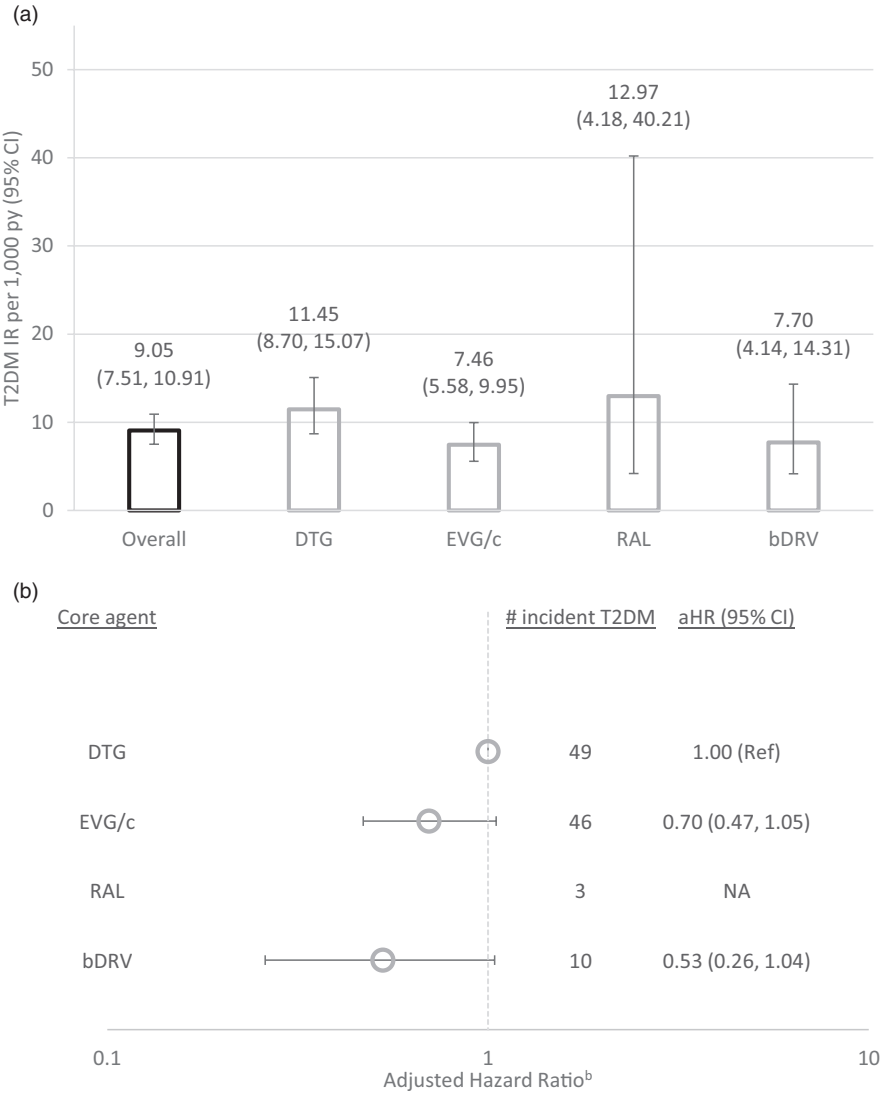

Fig. 1. (a) Incidence rates of type 2 diabetes mellitus per 1000 person-years (95% confidence interval) by core agent; (b) adjusted hazard ratios for the association between core agent and type 2 diabetes mellitus among antiretroviral therapy-naive people living with HIV[a]. aHR, adjusted hazard ratio; bDRV, boosted darunavir; CI, confidence interval; DTG, dolutegravir; EVG/c, elvitegravir with cobicistat; IR, incidence rate; RAL, raltegravir; T2DM, type 2 diabetes mellitus. [a]RAL excluded from model due to the small number of incident T2DM events. [b]Obtained from Cox proportional hazards models adjusted for baseline age, sex, race/ethnicity, HCV co-infection and BMI.

The overall T2DM incidence rate was 13 per 1000 person-years (95% CI: 12–15). However, there was no difference in the unadjusted incidence rate of T2DM per 1000 person-years between any core agents: DTG (incidence rate: 14, 95% CI: 12–18), EVG/c (incidence rate: 11, 95% CI: 9–14), RAL (incidence rate: 18, 95% CI: 12–28), or bDRV (incidence rate: 16, 95% CI: 11–23) (Fig. 2a). After adjustments for baseline age, sex, race/ethnicity, HCV co-infection and BMI, no statistically significant association was found between core agent and incident T2DM for EVG/c (aHR: 0.96, 95% CI: 0.70–1.33), RAL (aHR: 1.17, 95% CI: 0.70–1.96) or bDRV (aHR: 0.90, 95% CI: 0.57–1.42), compared with DTG (Fig. 2b).

PLHIV with incident T2DM had higher baseline BMIs (median: 29, IQR: 26–33), compared with those without incident T2DM (median: 26, IQR: 23–29), although no differences in BMI changes over time were observed (Supplemental Digital Content 4, http://links.lww.com/QAD/B862).

Discussion

Overall, the unadjusted prevalence of prediabetes (8%) and T2DM (4%) among 8489 ART-naive PLHIV was

Table 3. Baseline demographic and clinical characteristics of antiretroviral therapy-experienced/suppressed people living with HIV ($N = 9704$) without prevalent prediabetes or type 2 diabetes mellitus at initiation of core antiretroviral therapy agent, by core agent.

Characteristic	DTG ($N = 3584$)	EVG/c ($N = 4281$)	RAL ($N = 730$)	bDRV ($N = 1109$)
Age (years), median (IQR)	44 (34–53)	40 (31–50)	49 (40–55)	46 (35–53)
Female sex [*n* (%)]	516 (14%)	531 (12%)	146 (20%)	231 (21%)
Race/ethnicity [*n* (%)]				
Hispanic black	36 (1%)	35 (<1%)	3 (<1%)	14 (1%)
Hispanic white	815 (23%)	992 (23%)	109 (15%)	186 (17%)
Non-Hispanic black	1099 (31%)	1363 (32%)	200 (27%)	417 (38%)
Non-Hispanic white	1317 (37%)	1441 (34%)	346 (47%)	409 (37%)
Other	141 (4%)	155 (4%)	23 (3%)	29 (3%)
Unknown	176 (5%)	295 (7%)	49 (7%)	54 (5%)
BMI, median (IQR)	26 (23–29)	26 (23, 29)	26 (23–29)	26 (23–30)
BMI category [*n* (%)]				
Underweight	100 (3%)	115 (3%)	22 (3%)	29 (3%)
Normal weight	1348 (38%)	1647 (39%)	234 (32%)	396 (36%)
Overweight	1360 (38%)	1510 (35%)	258 (35%)	363 (33%)
Obese	646 (18%)	764 (18%)	128 (18%)	237 (21%)
Missing	130 (4%)	245 (6%)	88 (12%)	84 (8%)
Hepatitis C [*n* (%)]	398 (11%)	260 (6%)	104 (14%)	100 (9%)
Any endocrine disorders,[a] [*n* (%)]	1126 (31%)	1120 (26%)	204 (28%)	259 (23%)
Prior exposure to core agent [*n* (%)]				
DTG	8 (<1%)	1 (<1%)	0 (0%)	0 (0%)
EVG/c	10 (<1%)	44 (1%)	1 (<1%)	0 (0%)
RAL	29 (<1%)	33 (<1%)	64 (9%)	11 (1%)
bDRV	34 (<1%)	27 (<1%)	7 (1%)	37 (3%)
Calendar year of study inclusion, median (IQR)	2016 (2015–2017)	2016 (2015–2017)	2014 (2014–2016)	2015 (2014–2016)

ART, antiretroviral therapy; bDRV, boosted darunavir; CI, confidence interval; DTG, dolutegravir; EVG/c, elvitegravir with cobicistat; IQR, interquartile range; RAL, raltegravir.
[a]Hyperlipidemia, hyperthyroidism, hypothyroidism, or thyroiditis, excluding type 2 diabetes mellitus.

numerically lower than the prevalence among 12 322 ART-experienced/suppressed PLHIV (11 and 10%, respectively). In ART-naive PLHIV, these prevalences were lower in OPERA compared with the overall US population (prediabetes: 34%; T2DM: 12%) [4]. In ART-experienced/suppressed PLHIV, the unadjusted prevalence of prediabetes (11%) was lower, although that of T2DM (10%) was similar to, the overall US population. In both ART-naive and experienced suppressed PLHIV, T2DM prevalence at baseline was within the range of published estimates for PLHIV in developed countries (3–15%) [5–14]. In both groups, the unadjusted baseline prevalence of both prediabetes and T2DM was lower among users of EVG/c compared with DTG. Of note, differences in prediabetes or T2DM prevalence across core agents may reflect prescribing practices; prevalence results were not adjusted and channeling bias cannot be ruled out.

Incident T2DM was uncommon among both ART-naive (unadjusted incidence rate: 9 per 1000 person-years, 95% CI: 8–11) and ART-experienced/suppressed PLHIV (unadjusted incidence rate: 13 per 1000 person-years, 95% CI: 12–15), with no statistically significant differences among DTG, EVG/c, RAL, and bDRV. These estimates were higher than in the overall US population (6.7 per 1000 person-years) [4], and corresponded to the lower range of rates reported by studies of PLHIV using ART in the United States (8–47 per 1000 person-years) [15].

No association between T2DM risk and core agent initiation was observed in adjusted analyses in OPERA, although an increased risk of incident T2DM has been reported in the literature with several ART classes and agents, particularly when cumulative exposure is considered [6,10,11,16–18]. In the Multicenter AIDS Cohort study, the incidence of T2DM was similar among HIV-negative and HIV-positive men not on ART (14 and 17 per 1000 person-years, respectively) but significantly higher among PLHIV on ART (incidence ratio: 47 per 1000 person-years) [6]. Though the biological mechanisms through which ART may increase the risk of T2DM remain to be fully understood, many of the associations identified in the literature are with older generation agents [25]. Protease inhibitors, such as indinavir, have been associated with dyslipidemia, insulin resistance and T2DM [11,26,27]; darunavir, a newer protease inhibitor, has not been shown to affect insulin sensitivity [25]. Didanosine [27] and stavudine [6,17], NRTIs that are no longer recommended in United States guidelines, have been associated with increased risk of T2DM, possibly through lipoatrophy resulting in insulin resistance or through chronic pancreatic damage via mitochondrial toxicity. A study of PLHIV in Thailand reported a decreased risk of T2DM with cumulative exposure to tenofovir and emtricitabine [27] and inconsistent findings have been reported for lamivudine [28,29]. Considerably less research has been done on the association between INSTIs and incident T2DM. There is in-vivo evidence to suggest that an association between

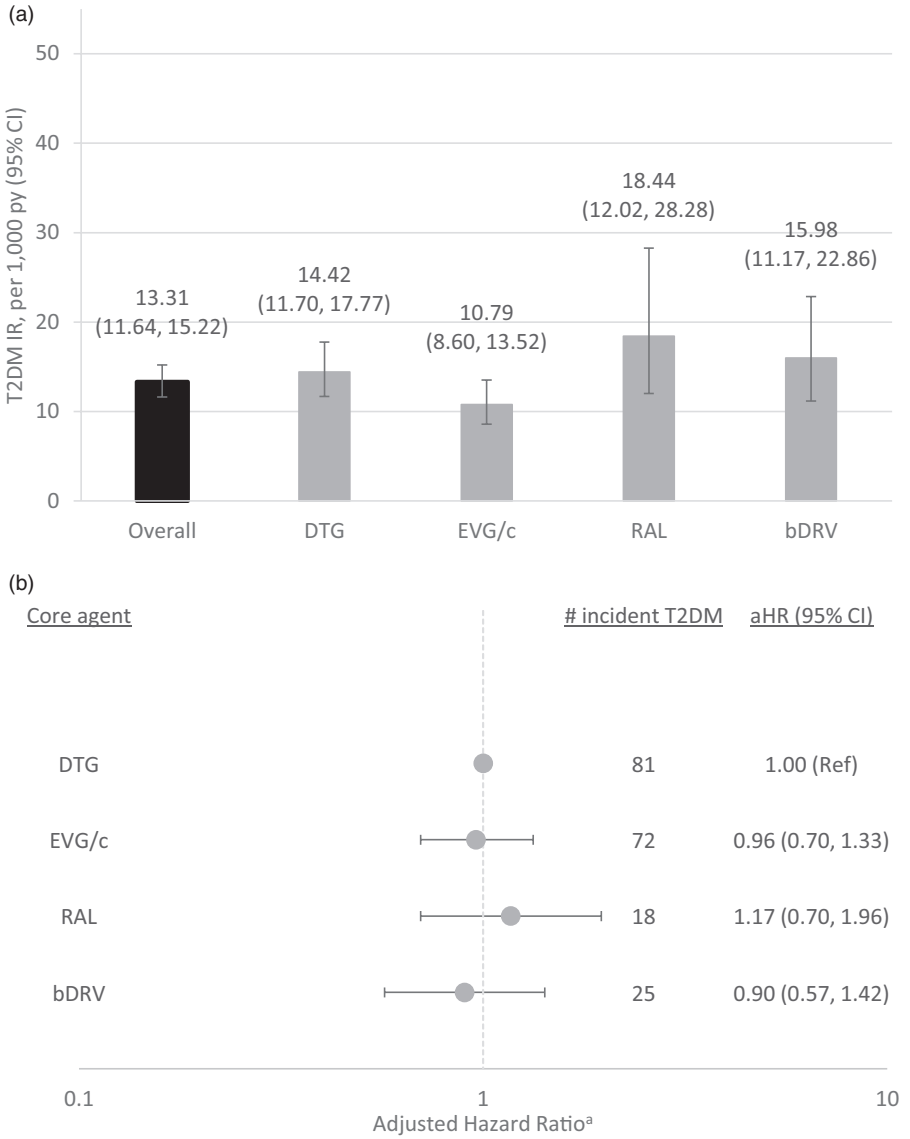

Fig. 2. (a) Incidence rates of type 2 diabetes mellitus per 1000 person-years (95% confidence interval) by core agent; (b) adjusted hazard ratios for the association between core agent and type 2 diabetes mellitus among antiretroviral therapy-experienced/suppressed people living with HIV. aHR, adjusted hazard ratio; bDRV, boosted darunavir; CI, confidence interval; DTG, dolutegravir; EVG/c, elvitegravir with cobicistat; IR, incidence rate; py, person-years; RAL, raltegravir; T2DM, type 2 diabetes mellitus. [a]Obtained from Cox proportional hazards models adjusted for baseline age, sex, race/ethnicity, HCV co-infection and BMI.

INSTIs, especially DTG, and altered metabolism affecting visceral adipogenesis, fibrosis, lipid accumulation, and insulin resistance [28,29]. However, one study has suggested that INSTIs have neutral effects on lipid levels [25], and another reported reductions in both serum leptin levels and the homeostasis model assessment of insulin resistance (HOMA-IR) when PLHIV switched from a ritonavir-boosted protease inhibitor to either RAL or DTG [30]. There was also a reported reduction in HOMA-IR among individuals who switched from a three-drug regimen containing TAF to a two-drug regimen of DTG and lamivudine in the TANGO trial, though the study could not determine if the observed reduction was because of removal of TAF versus the switch to DTG and lamivudine [31]. Yet, a pooled analysis of four clinical trials detected no difference between DTG and control arms in incident insulin resistance (HOMA-IR >2, >3, or >4) at 48 weeks [32]. Similarly, in OPERA, there was no difference between the INSTI (DTG, EVG/c, RAL) and PI (bDRV) groups with respect to T2DM incidence.

Our study, however, is not without limitations. As with all observational studies, this analysis is subject to potential

confounding bias and misclassification of the outcomes. Though our criteria allowed for both a medical diagnosis and identification of prediabetes or T2DM through lab results, misclassification is possible if lab results identified as FPG were not, in fact, fasting. This potential bias would likely result in an overestimation of prediabetes and T2DM because of higher (nonfasting) glucose levels. The potential misclassification is likely to be minimal in this analysis for several reasons: very few OGTTs were identified in the electronic health records, glucose tests performed in the morning were more likely to be fasting and were classified as such, and over half of the incident prediabetes or T2DM cases were identified through diagnoses or medications. Additionally, the number of tests and time between each test over follow-up was generally similar across all groups (Supplemental Digital Content 5, http://links.lww.com/QAD/B863). Analyses were controlled for several patient and clinical factors based on the literature, but missing data and confounders absent from electronic health records could have led to residual confounding. Analyses were not adjusted for the NRTIs used, which may have an impact on the risk of T2DM; this study, however, did not include exposure to older NRTIs such as zidovudine or stavudine [10,17]. In addition, despite including almost 25,000 PLHIV in the study, this study was limited by the small number of incident T2DM events among ART-naive PLHIV ($n = 319$; $n = 3$ on RAL); differential risk by ART agent cannot be excluded. RAL prescriptions were less common in the United States during the study period, resulting in small sample sizes (241 ART-naive and 962 ART-experienced/suppressed PLHIV using RAL) and a reduced likelihood of observing rare events.

Although there is mounting evidence of weight gain with use of INSTIs [19,20,22,23,33], the impact of weight gain, after ART initiation, on the risk of prediabetes and T2DM needs further assessment. The NA-ACCORD cohort reported a 22% increase in risk of diabetes with INSTIs, compared with NNRTIs [24]. In a mediation analysis, weight gain in the first 12 months of ART only explained a small part of the association between INSTIs and diabetes (aHR 1.16 versus 1.09); the slight attenuation in association with RAL was similar (aHR 1.50 versus 1.40), but even smaller for DTG and EVG [34]. In this OPERA study, individuals with incident T2DM were more likely to be overweight or obese at baseline, compared with participants who remained free of T2DM during follow-up. Among ART-naive PLHIV, the absolute BMI change was larger among participants with incident T2DM at 12 and 18 months than among participants without T2DM; there were no differences in absolute BMI change between ART-experienced/suppressed participants with and without incident T2DM. It is important to note, however, that the number of participants with weight measurements at specific time points was small and generally decreased over time. Nonetheless, a sensitivity analysis was performed, consisting of an inverse probability of censoring weight pooled logistic regression to address the concern that individuals may discontinue their regimen because of weight gain. There was no association between risk of T2DM and core agents when compared with DTG and results were similar to the main results presented here (Supplemental Digital Content 6, http://links.lww.com/QAD/B864).

One of the major strengths of this study is its applicability to PLHIV in the United States, The OPERA cohort is highly representative of PLHIV in care across the United States by virtue of the inclusion of 84 clinics from both small, rural clinics and large, urban health centers across 17 United States states and 1 United States territory; the 94 145 PLHIV in the OPERA cohort at the time of this study represent approximately 8% of PLHIV in the United States [35]. The use of electronic health records in this large sample of participants allowed for access to extensive patient, clinical, and laboratory information that is reflective of real-world clinical practice. To our knowledge, this is one of the first studies comparing the risk of T2DM across currently common standard of care ART core agents.

Our findings indicate that incident T2DM was uncommon among ART-naive and ART-experienced/suppressed PLHIV initiating DTG, EVG/c, RAL, or bDRV without prevalent prediabetes at baseline in this large clinical population and that there was no statistically significant increased risk of T2DM with EVG/c, RAL, or bDRV compared with DTG. Because of the small number of incident T2DM events among ART-naive PLHIV, possible differential risk cannot be excluded; monitoring HbA1c remains prudent. Additional evaluation of PLHIV in large observational studies, especially among ART-naive participants and with a thorough longitudinal evaluation of weight changes after ART initiation, is needed to fully understand the association between currently common HIV ART agents and hyperglycemic outcomes.

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J.L. and G.F. contributed to the interpretation of results. All authors have critically reviewed and approved the manuscript and have participated sufficiently in the work to take public responsibility for its content.

Conflicts of interest

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