Trends in diabetes incidence and associated risk factors among people with HIV in the current treatment era

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Objective: To examine type 2 diabetes mellitus incidence and associated risk factors among people with HIV (PWH).

Design: A retrospective clinical cohort study of PWH at a Southeastern US academic HIV clinic between 2008 and 2018.

Methods: PWH who attended at least two clinic visits were evaluated with demographic and clinical data extracted from the electronic medical record (EMR). Diabetes was defined as: hemoglobin A1C $\geq$6.5% and/or 2 glucose results >200 mg/dl (at least 30 days apart), diagnosis of diabetes in the EMR, or exposure to diabetes medication. Time to diabetes incidence was computed from the entire clinic population for each year. Multivariable Cox proportional hazard regression models with time-dependent covariates were created to evaluate the independent association between covariates and time to incident diabetes.

Results: Among 4113 PWH, we identified 252 incident cases of diabetes. Incidence increased from 1.04 incidents per 1000 person years (PY) in 2008, to 1.55 incidents per 1000 PY in 2018. Body mass index (hazard ratio [HR] 10.5 (6.2, 17.7)), liver disease (HR 1.9 (1.2, 3.1)), steroid exposure (HR 1.5 (1.1, 1.9)), and use of integrase inhibitors (HR 1.5 (1.1, 2.0)) were associated with incident diabetes. Additional associated factors included lower $CD4^+$ cell counts, duration of HIV infection, exposure to nonstatin lipid-lowering therapy, and dyslipidemia.

Conclusions: Rapidly increasing incident diabetes rates among PWH were associated with both traditional and HIV-related associated risk factors, particularly body weight, steroid exposure, and use of Integrase Inhibitors. Notably, several of the risk factors identified are modifiable and can be targeted for intervention.

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Introduction

With the significant advances in HIV treatment options, HIV infection has been transformed from a universally fatal disease to a manageable chronic illness [1]. For those with access to and engagement in HIV care and adherence to antiretroviral therapy (ART), certain non-AIDS comorbidities have become more prominent

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in the management of persons with HIV (PWH) [2]. Insulin resistance and the development of diabetes have become more commonly identified metabolic disturbances [3,4]. For many PWH, a combination of structural, socioeconomic, and health issues further contribute to an increased risk of insulin resistance and diabetes mellitus (DM) [2,3].

Due to the significant morbidity associated with having concomitant HIV infection and diabetes diagnoses, diabetes screening and prevention-focused lifestyle behavior changes recommended for the general population have emerged as important aspects of health management in PWH [5]. Previous literature supports the hypothesis that both HIV infection and ART effects likely contribute to the risk of developing type 2 diabetes. Several mechanisms have been proposed to explain the increased DM risk, including direct effects of viral proteins, persistent systemic inflammation associated with HIV, certain behavioral factors like sedentary lifestyle and poor dietary habits, and medication toxicity [6–8]. Many early ART agents, notably protease inhibitors, caused dysregulation of glucose homeostasis and increased diabetes risk [9]. Although newer agents are considered metabolically friendly, ART initiation is associated with body composition changes and significant weight gain with worsening of glucose control in at least a subset of patients [10–12].

In this analysis, we aimed to characterize the shifting incidence of diabetes in the 1917 HIV Clinic population over time and to evaluate socio-demographic factors, traditional and HIV-specific risk factors for the development of diabetes. We also report prevalence of diabetes by year. By analyzing clinic-wide population trends in the more recent ART era, we can identify key risk factors relevant to today's PWH and subsequently develop appropriate interventions to reduce the incidence of diabetes and improve the management of diabetes for those who have been diagnosed.

Methods

Data were obtained from the University of Alabama at Birmingham (UAB) 1917 HIV/AIDS Clinic Cohort Observational Database Project (UAB 1917 Clinic Cohort). This cohort forms an on-going prospective clinical study, started in 1988, that has collected detailed sociodemographic, psychosocial and clinical data from persons diagnosed with HIV. We conducted a retrospective analysis of 1917 Clinic Cohort data collected between 2008 and 2018. During this period, the 1917 Clinic used a locally maintained electronic medical record (EMR) which contained detailed provider encounter notes, laboratory values imported from the central UAB laboratory, and electronic prescriptions for all medications. The EMR and study database were quality controlled, with all provider notes reviewed to ensure appropriate data capture regarding diagnoses and medications (including start and stop dates for prescriptions). New and ongoing diagnoses were recorded in patients' active problem lists. Resolved diagnoses discontinued by the provider remained part of the patient's EMR after removal from the active problem list. The UAB Institutional Review Board (IRB) approved this study nested in the UAB 1917 Clinic Cohort.

Participants

Participants with at least two routine care HIV primary provider visits at the UAB 1917 HIV Clinic in Birmingham, Alabama between January 1, 2008 and December 31, 2018 were included in analysis of HIV incidence. For study inclusion of diabetes incidence, participants additionally were $\geq$18 years of age with a confirmed diagnosis of HIV. Exclusion criteria included no preexisting DM in the EMR at time of first HIV primary clinic visit, or an extended delay between clinic visits ($\geq$400 days or more after first visit). To report annual prevalence of HIV, the study cohort included all PWH who attended at least one routine care HIV primary provider visit between January 1, 2008 and December 31, 2018.

Study variables

Diabetes diagnosis

Diabetes was defined when at least two of the following three criteria were met: laboratory data consistent with a diagnosis as defined by the ADA SOC (hemoglobin [Hgb] A1C $\geq$ 6.5% and/or 2 glucose results >200 mg/dl (at least 30 days apart)) [13], diagnosis of diabetes in the EMR, or exposure to diabetes medication. Diabetes date of diagnosis was defined for the purposes of this study as the earliest of the following four dates (as documented in the EMR): first diabetes diagnosis, first diabetes medication initiation, first Hgb A1C $\geq$6.5% when a second A1C was also performed, second glucose >200 mg/dl, at least 30 days after first glucose >200 mg/dl. We used non-fasting blood glucose criteria >200 mg/dl versus fasting blood glucose as we could not confirm that all patients in this clinical cohort were fasting at the time of laboratory blood draw. Since some medications can be used to treat conditions other than diabetes, we further confirmed that medications were prescribed in the presence of laboratory values or diagnosis consistent with diabetes treatment, versus prescription for other conditions such as prediabetes or polycystic ovary syndrome.

Covariates

The following data elements were abstracted from the EMR: demographics and vital signs – birth sex, race, ethnicity, birth year, initial clinic visit date, HIV transmission risk factor, insurance status (public, private, uninsured), height (cm), weight (kg), systolic and diastolic blood pressure; clinical diagnoses as defined within the

Center for AIDS Research Network of Integrated Clinical Systems [14] – hypertension, cardiovascular disease, cerebrovascular disease, renal conditions, malignancies; prescribed medications: antiretroviral, antihypertensives, statins, testosterone and other hormone replacement therapy, mental health therapies; laboratory test results: $CD4^+$ T-cell count, HIV viral load, HBV and HCV testing, glucose, Hgb A1C, albumin, hemoglobin, triglycerides, LDL-C, HDL-C, total cholesterol, basic chemistries and urine studies. Body mass index (BMI) was computed as weight (kg)/height (m^2). The following categories were used to classify patients by BMI: underweight $<18.5\,kg/m^2$, normal weight $18.5–24.9\,kg/m^2$, overweight $25–29.9\,kg/m^2$, obese $\geq 30\,kg/m^2$, and class III obesity $\geq 40\,kg/m^2$.

Statistical analysis

All data were analyzed using SAS version 9.4 (SAS Institute Inc., Cary, North Carolina, USA).

The primary objective was to determine diabetes incidence and associated risk factors. Three separate analyses were conducted: diabetes incidence by year; time to incident diabetes; and diabetes prevalence by year. Diabetes incidence was computed for the full sample and for each study year as the proportion of patients who developed diabetes in a given year out of the entire clinic population included for analysis for that year. A patient was considered to be in care for a specific calendar year (2008–20018) if they had at least one visit during that year. To affirm a DM event, the participant was required to have at least one prior documented visit (i.e. cannot be considered as "incident" at the very first HIV clinic visit). The prior arrived visit could be from an earlier year. For analyses that required preexisting cases to be excluded (incident DM and time to incident DM) cases occurring before time 0 were excluded. The same definition of diabetes utilizing diabetes diagnosis, laboratory value history, and medication history was used for determining both pre and incident DM. Participants with a diabetes diagnosis date before their first arrived visit date in this analysis were excluded. Cochran-Armitage trend test with Agresti-Coull confidence limits was used to evaluate the trend over time.

To determine time to incident diabetes and correlates of diabetes incidence, survival analyses were conducted beginning with the participant's first arrived visit and ending with a diabetes diagnosis or censor at the participant's last arrived HIV clinic visit date. Patients with a gap >400 days between "arrived" visit status at any time were censored at the start of the gap. Multivariable models were fit to assess the association of covariates with diabetes diagnosis. Cox proportional hazards regression models were used to model time to diabetes diagnosis. To account for changes in health status throughout the study period, variables that changed over time were treated as time-varying covariates. Time-varying variables were carried forward up to 365 days (e.g. income, BMI, $CD4^+$ cell count, viral load) as some parameters are measured infrequently. Medication exposure variables (ART and non-ART) were considered as time-varying but remain "on" once turned on. Due to previously observed race × sex interactions in diabetes risk, race and birth sex were combined as race/sex categories.

A separate investigation of diabetes prevalence was included to investigate this change over time. For each of the 11 calendar years (2008–2018), a patient was considered "in care" if they had at least one completed HIV clinic visit during that year. Diabetes prevalence for each calendar year was computed as the proportion of participants with a diabetes diagnosis before that year (i.e. diagnosis could occur before 2008) out of the total number of patients in care that year. Change across years was evaluated via Cochran-Armitage trend test with Agresti-Coull confidence limits.

Results

Study population

Of the 5399 PWH who attended one clinic visit or patient orientation with an HIV care provider, 3492 patients met criteria for analysis of diabetes incidence and time to diabetes incidence including diabetes-related laboratory assessment, while 4113 patients met all criteria for analysis of diabetes prevalence. Descriptive characteristics at first clinic visit were not different between the two samples, thus the full sample of 4113 participants are presented in Table 1: 871 participants were female (21%), 41 transgender persons (1%); 2554 (62%) Black race, and 1424 (35%) White. At first visit, median age was 38.2 years, median BMI $24.9\,kg/m^2$, median $CD4^+$ cell count 373 cells/μl, and median HIV viral load was 5700 cp/ml.

Diabetes incidence and prevalence

Overall, among 3492 participants 252 incident cases were identified in the cohort from a total 28 391 person years (PY) of follow-up. A significant increase in diabetes incidence from 1.04 incidents per 1000 PY, to 1.55 incidents per 1000 PY (Fig. 1a, $P < 0.0188$) was observed. Study participants who developed DM had a median age of 51.9 years old at DM event, compared to an end-of-follow-up-period age of 42.7 years among patients who never developed DM.

Correlates of diabetes incidence

In univariate models assessing factors associated with DM diagnosis (Table 1), statistically significant associations at $P < 0.05$ were observed with demographic factors including Black race (hazard ratio [HR] 1.6), female sex (HR 1.8), Black female race/sex pairing (HR 2.4), older age per 10-year increase (HR 1.6), public insurance

Table 1. Baseline characteristics of the clinic cohort and association with time until incident diabetes

Variable	Total ($n=4113$)	Diabetes ($n=252$)	No diabetes ($n=3861$)	Hazard ratio (95% CI) univariate
Demographics				
Race				
Black	2554 (62.1%)	**163 (64.7%)**	**2391 (61.9%)**	**1.64 (1.26–2.14)**
White	1424 (34.6%)	87 (34.5%)	1337 (34.6%)	ref
Other/unknown	135 (3.28%)	2 (0.79%)	133 (3.44%)	0.53 (0.13–2.15)
Birth sex				
Male	3201 (77.8%)	164 (65.1%)	3037 (78.7%)	ref
Female	871 (21.1%)	**86 (34.1%)**	**785 (20.3%)**	**1.81 (1.40–2.35)**
Transgender	41 (1.00%)	2 (0.79%)	39 (1.01%)	1.62 (0.40–6.54)
Race-sex				
White male	1225 (29.8%)	77 (30.6%)	1148 (29.7%)	–ref–
White female	198 (4.81%)	9 (3.57%)	189 (4.90%)	0.88 (0.44–1.75)
Black male	1861 (45.3%)	85 (33.7%)	1776 (46.0%)	1.26 (0.92–1.73)
Black female	655 (15.9%)	**77 (30.6%)**	**578 (15.0%)**	**2.40 (1.75–3.30)**
Age (years)*	38.2 (29.2–47.1)	**45.2 (38.5–51.7)**	**37.6 (28.7–46.6)**	**1.64 (1.45–1.85)**
<30 years	1119 (27.2%)	19 (7.54%)	1100 (28.5%)	–ref–
30–50 years	2257 (54.9%)	**152 (60.3%)**	**2105 (54.5%)**	**2.73 (1.32–5.64)**
>50 years	737 (17.9%)	**81 (32.1%)**	**656 (17.0%)**	**5.69 (2.75–11.79)**
BMI	24.9 (22.0–28.9)	**28.9 (24.5–36)**	**24.8 (21.8–28.7)**	**1.08 (1.07–1.09)**
<18.5	167 (4.85%)	**6 (3.51%)**	**161 (4.92%)**	**3.41 (1.58–7.36)**
18.5–24.99	1570 (45.6%)	41 (24.0%)	1529 (46.7%)	–ref–
25–29.99	1001 (29.1%)	**47 (27.5%)**	**954 (29.1%)**	**2.21 (1.47–3.32)**
30–39.99	595 (17.3%)	**59 (34.5%)**	**536 (16.4%)**	**4.93 (3.33–7.28)**
≥40	109 (3.17%)	**18 (10.5%)**	**91 (2.78%)**	**11.72 (7.49–18.33)**
Insurance type				
Private	1553 (46.6%)	113 (48.3%)	1440 (46.5%)	–ref–
Public	1027 (30.8%)	**106 (45.3%)**	**921 (29.7%)**	**1.56 (1.20–2.03)**
Uninsured	753 (22.6%)	15 (6.41%)	738 (23.8%)	0.68 (0.39–1.17)
Education				
<12th Grade	381 (18.2%)	12 (13.0%)	369 (18.5%)	ref
12th Grade/GED	636 (30.4%)	33 (35.9%)	603 (30.1%)	1.65 (0.85–3.20)
Some college	729 (34.8%)	27 (29.4%)	702 (35.1%)	1.29 (0.65–2.54)
College degree	346 (16.5%)	20 (21.7%)	326 (16.3%)	1.99 (0.97–4.07)
Income (monthly US dollars)*	710 (0–1250)	730 (479–1300)	710 (0–1250)	1.00 (0.99–1.01)
HIV status				
$CD4^+$ T-cell count (cells/μl):				
<200	1111 (27.5%)	75 (30.6%)	1036 (27.3%)	1.29 (0.85–1.96)
200–350	797 (19.7%)	**43 (17.6%)**	**754 (19.8%)**	**1.50 (1.07–2.11)**
>350	2138 (52.8%)	127 (51.8%)	2011 (52.9%)	–ref–
Viral load* (copies/ml)	5697 (49–68778)	258 (47–39600)	6285 (49–70193)	1.00 (1.00–1.00)
First arrived visit				
1999–2007	864 (21.0%)	98 (38.9%)	766 (19.8%)	–ref–
2008–2018	3249 (79.0%)	**154 (61.1%)**	**3095 (80.2%)**	**2.92 (2.06–4.16)**
HIV duration*	1.4 (0.1–8.5)	**5.4 (0.2–12.3)**	**1.2 (0.1–8.3)**	**1.06 (1.04–1.08)**
<5 years	2646 (64.5%)	123 (49.2%)	2523 (65.5%)	–ref–
5–10 years	580 (14.1%)	37 (14.8%)	543 (14.1%)	0.97 (0.61–1.54)
>10 years	876 (21.4%)	**90 (36.0%)**	**786 (20.4%)**	**2.09 (1.45–3.02)**
HIV risk factors				
Heterosexual	1434 (36.4%)	**117 (47.1%)**	**1317 (35.7%)**	**1.64 (1.26–2.13)**
IV Drug user	335 (8.51%)	22 (8.87%)	313 (8.48%)	1.28 (0.81–2.03)
MSM	2169 (55.1%)	109 (44.0%)	2060 (55.8%)	–ref–
Antiretroviral therapy				
Integrase inhibitor	1015 (24.7%)	**969 (25.1%)**	**46 (18.3%)**	**2.13 (1.66–2.74)**
NRTIs	2202 (53.5%)	2037 (52.8%)	165 (65.5%)	0.75 (0.51–1.10)
Protease inhibitor	995 (24.2%)	909 (23.5%)	86 (34.1%)	1.02 (0.78–1.32)
NNRTIs	1138 (27.7%)	1057 (27.4%)	81 (32.1%)	0.85 (0.65–1.11)
Other prescribed medications				
Anti-HTN	935 (23.1%)	**102 (40.5%)**	**833 (21.6%)**	**3.60 (2.68–4.83)**
Aspirin	76 (1.85%)	8 (3.17%)	68 (1.76%)	1.42 (1.00–2.01)
Glucocorticoids	322 (7.83%)	**20 (7.94%)**	**302 (7.82%)**	**1.87 (1.45–2.42)**
Hormone therapy	122 (2.97%)	11 (4.37%)	111 (2.87%)	1.19 (0.86–1.65)
Statins	277 (6.73%)	**34 (13.5%)**	**243 (6.29%)**	**2.12 (1.62–2.77)**
Non-statin lipid-lowering Drugs	84 (2.04%)	**12 (4.76%)**	**72 (1.86%)**	**1.96 (1.42–2.72)**
Comorbidities				
CKD/ESRD	369 (8.97%)	**58 (23.0%)**	**311 (8.05%)**	**2.17 (1.62–2.91)**
Cirrhosis/ESLD	118 (2.87%)	**20 (7.94%)**	**98 (2.54%)**	**1.84 (1.16–2.90)**
Dyslipidemia	1304 (31.7%)	**166 (65.9%)**	**1138 (29.5%)**	**1.87 (1.43–2.44)**
Hypertension	1813 (44.1%)	**201 (79.8%)**	**1612 (41.8%)**	**2.69 (1.97–3.67)**

Anti-HTN, antihypertensives; BMI, body mass index; CKD/ESRD, chronic kidney disease/end-stage renal disease; ESLD, end-stage liver disease; IV, intravenous; MSM, men who have sex with men; NNRTIs, nonnucleoside reverse transcriptase inhibitors; NRTIs, nucleoside reverse transcriptase inhibitors.

*Hazard ratio represents a per 10-year increase for age, per 1 U increase in BMI, per 5000-ct increase for VL, per 1-year increase in HIV duration (time with HIV diagnosis), and per $100/month increase in income.

Bolded rows indicate statistical significance $P < 0.05$.

Data presented as *n* (%) for categorical variables, or median (interquartile range) for continuous variables.

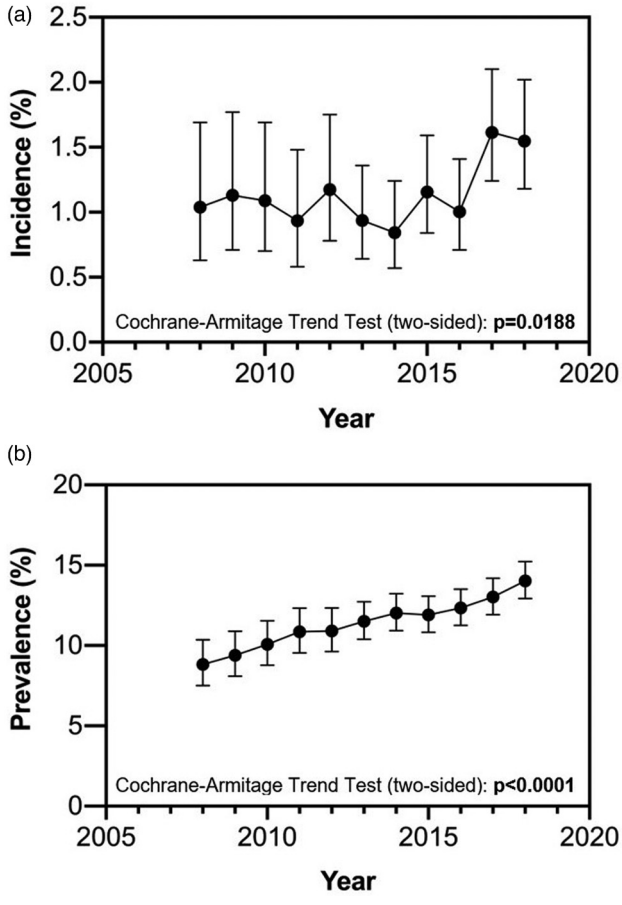

Fig. 1. (a) Incident diabetes by year (2008–2018). (b) Prevalent diabetes by year (2008–2018).

(HR 1.6), and first arrived visit between the years of 2008 and 2018 (HR 2.9). Compared to patients with normal weight, incident diabetes was greater when underweight (HR 3.4) and increased across BMI categories, particularly when participants had obesity (HR 4.9) or Class III obesity, that is BMI $>40\,kg/m^2$ (HR 11.7). Diabetes diagnosis was also observed with use of several medications at $P<0.05$, with the strongest associations for antihypertensive exposure (HR 3.6), statins (HR 2.1), nonstatin lipid-lowering drugs (2.0), and glucocorticoids (1.9). All comorbid conditions evaluated in univariate analyses – kidney disease, liver disease, dyslipidemia, and hypertension – were associated with diabetes incidence. When HIV-specific risk factors were assessed, greater diabetes diagnosis risk was observed in participants with HIV duration postdiagnosis >10 years (HR 2.1), were prescribed integrase inhibitors (HR 2.1), were heterosexual (i.e. did not report MSM, HR 1.6), had $CD4^+$ cell count of 200–350 (HR 1.5).

In multivariable analysis (Fig. 2), risk factors with the strongest associations to diabetes incidence included morbid obesity (adjusted hazard ratio [aHR] 10.5), obesity (aHR 3.9), underweight (aHR 2.8), cirrhosis/end stage liver disease (aHR 1.9), dyslipidemia (aHR 1.6), and HIV duration >10 years (aHR 1.6). Additional risk factors that remained associated with the development of DM in our clinic population were $CD4^+$ cell count between 200–350 cells/μl (aHR 1.55), integrase inhibitor exposure (aHR 1.48), glucocorticoid exposure (aHR 1.46), and nonstatin lipid-lowering drug exposure (aHR 1.54). Interestingly, Black race/female sex, exposure to statins or antihypertensive medications, and hypertension were not associated with diabetes incidence in the modern ART era in multivariable analysis.

Diabetes prevalence

We observed an increasing prevalence of diabetes from 8.8% in 2008 to 14.0% in 2018 (Fig. 1b, $P<0.001$).

Discussion

Our results show a rapid 10-year increase in incident (to 1.55%) and prevalent (14%) DM among this cohort of PWH from 2008 to 2018. It is unknown whether the rapid increase in diabetes prevalence among this clinic cohort represents a 'catch-up' period in the current treatment era, or whether diabetes prevalence among PWH will surpass that observed in the general population. Thus identification of traditional and HIV-related factors that contribute to diabetes risk among PWH is critical to develop prevention and treatment strategies tailored to this high-risk population.

Demographic risk factors have previously been linked to higher risk of developing DM [3,15]. We found that persons who self-identify as black females – as well as black race and female sex separately – correlated to a statistically significant increased hazard of developing DM compared to other race/sex groups. However, in the multivariable analysis an independent association was not found to be statistically significant. It is possible that among black females included in our analysis, clustering of other traditional risk factors (e.g. obesity) accounted for this increased risk on the univariate analysis, and a previous study from the 1917 clinic did find that the association of race/sex with a diabetes diagnosis was not observed after adjusting for BMI [8]. In fact, obesity was the single greatest risk factor associated with the development of DM in our analysis. Moreover, patients with the highest BMIs ($>40\,kg/m^2$) had the greatest risk of incident DM, with a hazard ratio exceeding 10-fold compared to the referent group (BMI 18.5–24.99 kg/m^2). At first arrived visit, our data show that 41.4% of patients had a BMI that was at least overweight (BMI $>25\,kg/m^2$) and 17.1% classified as at least obese (BMI $>30\,kg/m^2$). Our multivariable analysis confirmed a trend of increasing BMI along with increase in DM. At the last observation for each patient, the percentage of patients classified as overweight and obese had increased to 43 and 21%, respectively. This finding confirms

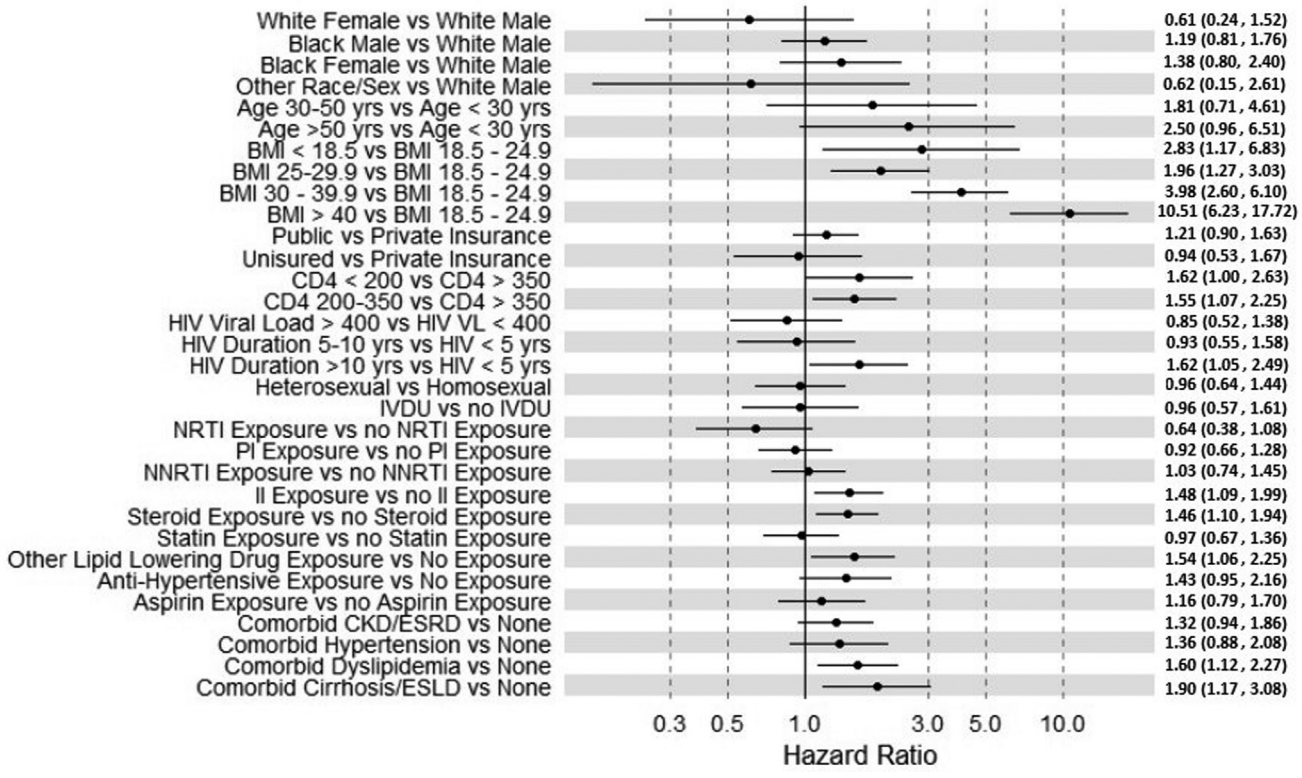

Fig. 2. Multivariable analysis of factors associated with increased risk of diabetes diagnosis among people receiving care for HIV between 2008 and 2018. BMI, body mass index; CKD/ESRD, chronic kidney disease/end-stage renal disease; ESLD, end-stage liver disease; II, integrase inhibitors; IVDU, intravenous drug user; MSM, men who have sex with men; NNRTIs, nonnucleoside reverse transcriptase inhibitors; NRTIs, nucleoside reverse transcriptase inhibitors; PI, protease inhibitor.

previous studies in which higher BMI was associated with diabetes diagnosis and impaired fasting glucose levels [6,16,17]. Given the rising diabetes rates among these PWH and added metabolic risks of HIV infection and ART, more resources should be devoted to curb excess body fat gain and related conditions in this particularly vulnerable population.

Intrinsic biochemical mechanisms of chronic HIV infection as well as ART therapy in DM pathogenesis have been well established [3,18], and are supported by our findings that having HIV for >10 years carries a statistically higher independent risk of developing DM compared to those with HIV for shorter durations. However, the only class of ART independently associated with the development of DM in our analysis were integrase inhibitors, also known as integrase strand transfer inhibitors (INSTIs). Our results are consistent with recent studies, which demonstrate an association between INSTI therapy, diabetes incidence, and weight gain, particularly dolutegravir (DTG) [19,20]. Given the well described link between obesity and DM [21], it is unsurprising then that INSTI exposure comes with a higher risk of developing DM, at least in part relating to its effects on weight gain. These other groups have reported differing effects on DM risk when comparing INSTI regimens raltegravir, dolutegravir, and elvitegravir, which were available during this study period. However, over 90% of patients prescribed INSTI in the current analysis were using raltegravir, limiting our ability to compare INSTI regimens in this study. Furthermore, some studies have shown not only an increase in weight gain on INSTIs, but also increased visceral adiposity and truncal obesity, both of which carry increased risks of insulin resistance and DM [22–24]. This phenomenon may partially account for the link between INSTI exposure and DM risk independent of the other risk factors (e.g. obesity) found in our analysis; however, INSTI remained associated with diabetes development even after controlling for BMI. Future studies are needed to identify the mechanisms underlying this association, including which INSTI agents are most implicated, and whether the length of time on these agents contributes to which patients subsequently develop diabetes.

Additional risk factors independently associated with the development of DM in our clinic population were older age, lower $CD4^+$ cell counts, longer duration of HIV infection, glucocorticoid exposure, nonstatin lipid-lowering drug exposure, comorbid cirrhosis/ESLD, and comorbid dyslipidemia. Some factors that were significant in the univariate analysis, including comorbid CKD and statin exposure, were not independently associated with DM risk in the multivariable analysis, and

earlier studies have found equivocal results in the association of these variables with diabetes risk in PWH [25,26]. This is likely explained by (1) the constellation of multimorbidity and polypharmacy in this study cohort, and (2) limitation of the study period to the most recent treatment decade in which improved HIV treatment options with less viremia-related inflammation and greater obesity prevalence outweigh other factors in diabetes risk.

Results of this study should be interpreted in context of certain limitations. In order to maximize the specificity of the DM group given its importance in this study, fairly stringent criteria were used when defining DM based on patient data from the EMR. Consequently, some patients who actually had DM may have been excluded due to failure to meet those criteria. Additionally, while some patients consistently attended scheduled appointments, others had larger gaps between visits; those with >400 days between visits were excluded from the analysis entirely. If socioeconomic factors impact DM risk, perhaps the least followed patients are also more likely to develop DM but would not be counted as cases of incident diabetes or included in the risk factor analyses. EMR data analysis is limited in the ability to connect prescribed medications, such as statins and glucocorticoids, to specific start/stop dates and diagnoses, particularly when prescribed by healthcare providers outside this EMR hospital system. This limited our ability to evaluate the association of length of exposure for some medications with diabetes risk or to determine the causal factors for association with diabetes incidence in this population. Finally, the 1917 Clinic underwent a significant expansion in patients with increased comorbidities, including diabetes, in 2016–2017 following the closure of another local HIV clinic [27], which was reflected in the diabetes incidence increase observed subsequently and limited our ability to account for factors including $CD4^+$ nadir. However, no difference in associated risk factors was observed in patients who transferred care during this period compared to the full 1917 Clinic Cohort (data not shown).

PWH have experienced a rapid and clinically meaningful increase in diabetes incidence and prevalence during the current HIV treatment area. Diabetes risk in this population is associated with a combination of HIV-specific (integrase inhibitors) and lifestyle (body fat gain) factors. Diabetes prevention and treatment for PWH must take these factors into account to be effective in reducing the negative health consequences of DM in the setting of HIV.

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Conflicts of interest

There are no conflicts of interest.

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