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HIV/AIDS

Human Immunodeficiency Virus and Risk of Type 2 Diabetes in a Large Adult Cohort in Jos, Nigeria

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Background. Human immunodeficiency virus (HIV) infection and the use of antiretroviral therapy (ART) may increase the risk of type 2 diabetes mellitus (T2DM). However, data from regions with a high burden of HIV/AIDS are limited. We determined the prevalence of T2DM at the time of presentation to a large HIV clinic in Nigeria, as well as the incidence of diabetes 12 months following ART initiation.

Methods. Data from patients enrolled for ART from 2011 to 2013 was analyzed, including 2632 patients on enrollment and 2452 reevaluated after 12 months of ART commencement. The presence of diabetes, and demographic, clinical, and biochemical data were retrieved from standardized databases. $CD4^+$, HIV RNA load, and hepatitis C virus status were noted. Bivariate and logistic regressions were used to identify risk factors for T2DM.

Results. Baseline T2DM prevalence was 2.3% (95% confidence interval, 1.8% – 2.9%); age, but not body mass index (BMI), was a risk factor for diabetes. After 12 months of ART, an additional 5.3% had developed T2DM. Newly developed diabetes was not associated with age, but was associated with BMI. There were no significant associations between prevalent or incident diabetes and $CD4^+$, viral load, or type of ART.

Conclusions. Diabetes is not uncommon in HIV-infected individuals at the time of presentation to HIV services. Patients initiating ART have a high risk of developing diabetes in the first year of ART. Excessive weight gain should be avoided, as incident diabetes was associated with a BMI $\geq$25.0 kg/m^2.

Keywords. antiretrovirals; antiretroviral therapy; diabetes; HIV/AIDS; Nigeria.

Diabetes is a major public health concern worldwide and is rapidly increasing in sub-Saharan Africa, where it is projected to affect >20 million people by 2030 [1, 2]. In Nigeria alone, diabetes affects between 0.6% and 11.0% of the population and is an increasing public health problem [3]. With its significant complication burden, diabetes presents a major burden to patients, their families, and healthcare systems.

Nigeria also has the second largest number of individuals infected with human immunodeficiency virus (HIV) in the African continent, with >3 million people living with HIV/AIDS (PLWHA) and 600 000 receiving antiretroviral therapy (ART) [4]. PLWHA nowadays have longer survival with expanding access to ART, and the prevalence of HIV/diabetes comorbidity is increasing. Despite its potential public health consequences, large studies on the relationship between HIV/AIDS and diabetes are still uncommon.

HIV [5–7], ART [8–10], and hepatitis C virus (HCV) [8, 10] have been implicated as risk factors for diabetes. HIV causes insulin resistance and dyslipidemia [11], and HCV is associated with intrahepatic elevation of tumor necrosis factor–α levels, insulin resistance, and liver disease [12]. Although initial studies associated the onset of diabetes in PLWHA to ART containing protease inhibitors (PIs) [13, 14], which cause hyperglycemia by preventing the uptake and metabolism of glucose and lipids by adipocytes and hepatocytes [15], findings subsequently pointed toward the nucleoside reverse transcriptase inhibitors (NRTIs) and nonnucleoside reverse transcriptase inhibitors by virtues of their mitochondrial toxicity and apoptosis of adipocytes [9, 16]. However, recent studies have suggested that traditional risk factors for diabetes such as age and body weight are the major predictors of the development of type 2 diabetes mellitus (T2DM), as opposed to medications [6].

We have therefore determined the prevalence of T2DM in ART-naive patients at the time of enrollment into a cohort of newly diagnosed PLWHA, and describe the proportion of patients who developed T2DM within 1 year of ART initiation in a large HIV/AIDS cohort in Jos, Nigeria.

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METHODS

This was a cross-sectional survey of all newly registered patients attending the Prevention Initiative of Nigeria (APIN) adult ART clinic of Jos University Teaching Hospital. The APIN clinic is a regional referral center that provides comprehensive HIV/AIDS services for Plateau State in north-central Nigeria, with about 3 million population. Upon registration, all patients undergo an induction that includes lifestyle advice, clinical and laboratory investigations, and assessment of ART eligibility. Patients are then followed fortnightly, monthly, quarterly, and bianually depending on whether they have symptoms or have initiated ART. Sociodemographic, clinical, and laboratory information is entered into standardized forms and uploaded onto a single electronic database developed in FileMaker Pro (version 10) in computers to ensure data consistency and completeness. The database is cleaned and curated using routine data management training and quality checks. Data errors for the study were further corrected by checking the original patient case notes and the electronic databases.

Data on all patients ≥18 years old registered for treatment, care, and support were retrieved from the database to generate a retrospective cohort of patients initiating ART from 1 January 2011 to 31 December 2013. Patients without baseline plasma glucose records and those who had already initiated ART at the time of enrollment were excluded from the analysis of baseline diabetes. The precision for estimates was approximately ±1% based on 2632 patients who met the selection criteria and an assumed prevalence of diabetes of 3% in Jos [17]. This post hoc precision was calculated using a standard formula [18].

Data retrieved included age, sex, body mass index (BMI), total cholesterol (mmol/L), $CD4^+$ cell count (per μL), HIV RNA load (copies/mL), ART regimen, and the presence of diabetes. ART was categorized as first-line or second-line. The most frequently prescribed first-line regimens were lamivudine + zidovudine + nevirapine (45.9%), and lamivudine or emtricitabine + tenofovir + efavirenz (31.4%). The most readily available first-line regimen was nevirapine-containing ART. The second-line ART contained atazanavir/ritonavir (92%) and lopinavir/ritonavir (8%). Nevirapine-containing ART was generally avoided in patients with liver disease or was switched to efavirenz in those who developed hypersensitivity reactions (hepatotoxicity or skin rash). Efavirenz was also preferred in patients with tuberculosis. However, efavirenz was avoided in individuals with severe mental health issues or in women of childbearing age, except if given with contraception. Second-line regimens were considered if there was suspicion of transmitted resistance (eg, newly infected contacts of PLWHA with known ART resistance), a diagnosis of tuberculosis (as rifabutin was not readily available), Kaposi sarcoma, or adverse effects to the first-line regimens. In our clinic, a switch to second-line ART due to treatment failure is generally considered after 12 months of ART and therefore not a reason for use in this study.

Diabetes was defined as a random plasma glucose level of ≥11.1 mmol/L, fasting plasma glucose of ≥7.0 mmol/L, or self-reported use of hypoglycemic agents [19]. Plasma glucose measurements were repeated if classic osmotic symptoms were not present, to confirm the presence of diabetes. Pregnant women were not included in the database used for this study as pregnant women were monitored in a separate service. Hypercholesterolemia was defined according to the US National Cholesterol Education Program [20]. The estimated glomerular filtration rate (eGFR) was derived by the Cockcroft-Gault formula [21]. A Cobas C311 auto analyzer was used for plasma chemistry, and HCV antibodies were documented by enzyme-linked immunosorbent assay.

The main outcomes were the proportion of ART-naive participants with T2DM at the time of enrollment and the incidence of T2DM among patients without diabetes on enrollment 12 months after initiation of ART.

Ethical approval was obtained from the Liverpool School of Tropical Medicine and the Jos University Teaching Hospital Ethics committees. The identity of all patients was anonymized across the data set by replacing their names with initials and serial numbers.

Statistical analysis was conducted using SPSS software (IBM SPSS, Chicago, Illinois). Continuous variables were expressed as mean ± standard deviation, or median (range). Categorical variables were presented as proportions and compared using χ^2 test. Means were compared using unpaired Student *t* tests. Positively skewed data were $\log_{10}$ transformed. Bivariate analysis was conducted and variables with $P < .25$ were entered into multiple logistic regression models. Results of the bivariate analyses and logistic regressions were presented as odds ratios and adjusted odds ratios (AORs), with 95% confidence intervals (CIs), respectively. A P value <.05 was considered statistically significant.

RESULTS

A total of 2753 patients were recruited in the study period. Of these, 2632 (96%) had the information required to assess the presence of diabetes at baseline and 93% (2452/2632) had new-onset diabetes 1 year after initiation of ART, as shown in Figure 1. The baseline characteristics of the overall cohort are shown in Table 1.

Sixty-one of 2632 patients (2.3% [95% CI, 1.8%–2.9%]) had T2DM on enrollment. Of these, 21 (41%) were unaware of the diagnosis. Patients with T2DM were older and had significantly lower eGFR than patients without T2DM (Table 2). There was no difference in sex distribution, BMI, cholesterol levels, $CD4^+$ count, HIV RNA load, or HCV-positive status. Patients >40 years of age were 3.5 times more likely to have T2DM (AOR, 3.5 [95% CI, 1.9–6.5]; $P < .001$), and patients with T2DM

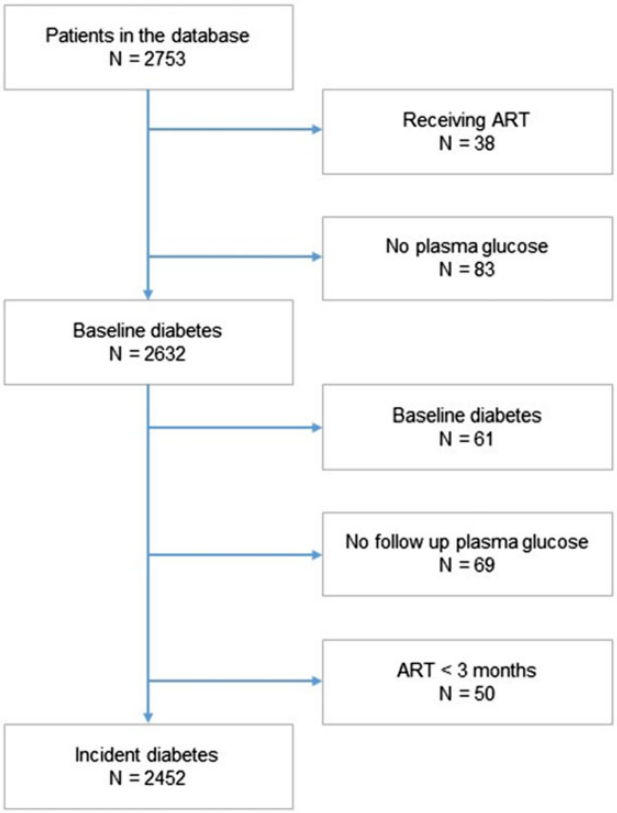

Figure 1. Flowchart of patient selection for the study. Abbreviation: ART, antiretroviral therapy.

Table 1. Overall Characteristics of the Individuals Enrolled in the Cohort (N = 2632)

Variable	No. (%)
Age, y	
Mean (SD)	37.4 ± 9.7
Median (range)	36 (19–79)
Proportion >40 years old	958 (36.4%)
Male/female (% male)	924/1708 (35.1%)
Mean (SD) body mass index, kg/m^2	22.9 (4.8)
Total cholesterol, mean (SD), mmol/L	4.1 (1.3)
Median (range) CD4$^+$ count, cells/μL	190 (2–1837)
Geometric mean (SD) viral load, copies/mL[a]	4.3 (0.9)
Mean (SD) eGFR, mL/min[b]	79.6 (24.8)
HCV antibody present, no./No. (%)[c]	69/1645 (41.9%)
ART regimen[d]	
3TC + ZDV + NVP	1125 (45.9%)
3TC or FTC + TDF + EFV	769 (31.4%)
3TC + NVP + TDF	281 (11.6%)
3TC + ZDV + EFV	59 (2.1%)
ATV/RTV-based PI	64 (2.5%)
LPV/RTV-based PI	4 (0.3%)
Other[e]	150 (6.2%)

Data are presented as No. (%) unless otherwise indicated. Only patients followed up for incident diabetes were exposed.

Abbreviations: 3TC, lamivudine; ABC, abacavir; ART, antiretroviral therapy; ATV, atazanavir; EFV, efavirenz; eGFR, estimated glomerular filtration rate; FTC, emtricitabine; HCV, hepatitis C virus; LPV, lopinavir; NVP, nevirapine; PI, protease inhibitor; RTV, ritonavir; SD, standard deviation; TDF, tenofovir disoproxil fumarate; ZDV, zidovudine.

[a] n = 2140.

[b] n = 2157.

[c] n = 1714.

[d] n = 2452.

[e] Other regimens: ZDV + FTC + TDF, 3TC + NVP + ABC, 3TC + ABC + EFV, 3TC + ZDV + TDF.

were more likely to have reduced eGFR (AOR, 0.99 [95% CI, .97–.98]; $P < .017$).

Of the 2452 patients without T2DM on enrollment, 130 (5.3% [95% CI, 4.2%–6.3%]) developed T2DM within 1 year of initiating ART. If these patients are added to those already identified on enrollment, 191 (7.6%) of the participants had T2DM 1 year after initiating ART.

Patients who developed T2DM after initiation of ART had higher BMI and were more likely to have HCV antibodies on enrollment (12.1% and 3.6% of the patients with and without incident T2DM; $P < .001$). There were no differences in age, sex, cholesterol concentrations, CD4$^+$ count, HIV RNA load, eGFR, or the use of first- or second-line ART among patients with and without incident T2DM (Table 3).

Variables included in the logistic regression model were BMI, cholesterol ≥5.2 mmol/L, CD4$^+$ cells/mL, viral load, eGFR, and the presence of HCV antibodies. Of these, only BMI ≥25 kg/m^2 (AOR, 7.5 [95% CI, 2.9–23.7]; $P < .001$) was independently associated with incident T2DM (Table 3).

DISCUSSION

Our study of a large cohort of HIV-infected Nigerians enrolled for ART showed a baseline diabetes prevalence of 2.3%. This was associated positively with age and inversely with renal function but surprisingly not with BMI. After 12 months of ART, an additional 5.3% had developed T2DM. In this group, diabetes was not associated with age, but was positively associated with BMI and the presence of HCV antibodies on enrollment. Of these, only BMI >25 kg/m^2 was independently associated with newly developed T2DM in multivariate analysis.

The baseline T2DM prevalence is similar to other reports in both ART-naive and -experienced patients [6, 22]. However, in Italy, investigators reported a higher prevalence of 4.1% among ART-experienced patients [5], and in China 10.5% of ART-naive patients had T2DM [7]. Patients in Italy were older (46 vs 37 years) and had significantly higher CD4$^+$ counts than patients in our study (538 vs 206 cells/μL), while the prevalence of diabetes in a Chinese population [23] was higher than in Nigeria, suggesting that prevalence of T2DM may vary with the overall T2DM prevalence in the general population, HIV disease progression, and the disease stage when patients access ART.

Similarly, our 5.3% incidence of T2DM among patients on ART is similar to the 6.0% reported in the United States [23], but lower than a 7.2% 3-year cumulative incidence among

Table 2. Characteristics of Patients With and Without Diabetes at Baseline in a Cohort of People Living With Human Immunodeficiency Virus in Jos, Nigeria (N = 2452)

Characteristics	With Diabetes (n = 61 [2.3%])	Without Diabetes (n = 2571 [97.7%])	OR (95% CI)	*P* Value
Age >40 y	43/61 (70.5%)	915/2571 (35.6%)	4.32 (2.48–7.54)	.0001
Male:female (% male)	25:36 (41%)	899:1656 (35%)	1.29 (.77–2.16)	.330
BMI ≥25 kg/m^2	22 (36.1%)	830 (32.3%)	1.13 (.79–1.65)	.490
Mean (SD) cholesterol, mmol/L	4.1 (1.4)	4.1 (1.3)	1.07 (.94–1.23)	.980
Median (range) CD4$^+$ count, cells/μL	180 (10–867)	190 (2–1837)	1.00 (1.00–1.00)	.938
Log mean (SD) viral load, copies/mL	4.3 (0.9)	4.3 (0.9)	1.00 (1.00–1.00)	.340
Mean (SD) eGFR[a], mL/min	67.5 (22.3)	79.9 (24.8)	0.98 (.97–.99)	.005
Positive HCV antibody	1/40 (2.5%)	68/1674 (4.1%)	0.61 (.08–4.47)	.619

Data are presented as No. (%) unless otherwise indicated.

Abbreviations: BMI, body mass index; CI, confidence interval; eGFR, estimated glomerular filtration rate; HCV, hepatitis C virus; OR, odds ratio; SD, standard deviation.

[a] Variable with $P < .25$ in bivariate analysis.

recipients of early-generation PIs [24]. T2DM development is a progressive condition that may require several years to become established among PLWHA, and longer-term follow-up may be needed to establish total cumulative risk.

The association of age with baseline diabetes in HIV cohorts was reported by Mehta et al [25], who calculated an AOR of 3.5 among patients ≥50 years of age, and by Brar et al [6], who estimated an AOR of 3.0 for every 10-year age increment. The lack of association between age and incident diabetes after ART initiation was also reported by Yoon et al [26]. However, others have reported that there are associations between age and incident diabetes in French and multinational cohorts [8, 9]. These varying findings may be due to differences in study design, and in the duration and type of ART used across studies.

In our study, patients with T2DM at enrollment were more likely to have a lower eGFR, whereas there was no association with incident diabetes. It is possible that those with diabetes at baseline had had the disease for sufficiently long duration to affect kidney function, unlike incident cases who had developed diabetes within <1 year. Although older age, lower CD4$^+$, and higher BMI may reduce eGFR in HIV/AIDS, data on the relationship between eGFR and diabetes in HIV-infected people are scarce. We did not have data on the duration of diabetes before enrollment, but Medapalli et al [27] demonstrated a greater probability for progression to chronic kidney disease in patients with HIV infection and diabetes, compared with HIV infection alone, in a large cohort followed over a 5-year period.

The association between HCV and T2DM has been reported previously [6, 25]. Nevertheless, not all studies have reported this association, as the large Swiss HIV Cohort Study reported that HCV did not increase the risk of diabetes [10]. The presence of HCV antibodies is not synonymous with active infection, and further studies are needed to evaluate whether recent or current infection increases the risk of diabetes.

Unexpectedly, BMI was not associated with baseline diabetes, in contrast with other series [5, 6], but it was associated with newly developed diabetes on ART, as previously reported [8, 9]. The weight loss that may occur with uncontrolled diabetes may be responsible for this lack of association, as 41% of patients were unaware of their T2DM diagnosis. Also, other common HIV-related illnesses causing weight loss (such as diarrhea and tuberculosis) might have masked the association at

Table 3. Bivariate and Multivariate Analysis of Risk Factors of New-Onset Diabetes in a Cohort of People Living With Human Immunodeficiency Virus on Antiretroviral Therapy in Jos, Nigeria (N = 2452)

Characteristic	New-Onset Diabetes (n = 130 [5.3%])	No Diabetes (n = 2322 [94.7%])	OR (95% CI)	AOR (95% CI)	*P* Value
Age >40 y	51 (39.2%)	822 (35.4%)	1.13 (.79–1.61)	1.02 (.99–1.05)	.14
Mean (SD) cholesterol[a], mmol/L	4.2 (1.2)	4.1 (1.3)	1.07 (.94–1.23)	0.88 (.71–1.10)	.23
Median (range) CD4$^+$ count[a], cells/μL	206 (13–968)	188 (2–1837)	0.98 (.90–1.10)	1.00 (1.00–1.02)	.90
Log (SD) mean viral load[a], copies/mL	4.5 (0.89)	4.3 (0.92)	0.91 (.89–1.09)	1.21 (.90–1.64)	.21
Mean (SD) eGFR[a], mL/min	78.9 (25.3)	80.0 (24.8)	1.01 (.99–1.03)	0.99 (.99–1.01)	.85
Positive HCV antibody[a]	12/99 (12.1%)	56/1575 (3.6%)	1.15 (1.03–1.28)	2.46 (.58–10.54)	.22
First-line ART	123/130 (94.6%)	2245/2306 (97.3%)	1.16 (.97–1.39)	NA	. . .

Data are presented as No. (%) unless otherwise indicated.

Abbreviations: AOR, adjusted odds ratio; ART, antiretroviral therapy; CI, confidence interval; eGFR, estimated glomerular filtration rate, HCV, hepatitis C virus; OR, odds ratio; NA, not applicable; SD, standard deviation.

[a] Variables with $P < .25$ in bivariate analysis which were also baseline characteristics adjusted for associations with new diabetes. Hosmer and Lemeshow test: $\chi^2 = 9.242$; $P = .32$.

baseline, and these illnesses were likely to be common in our cohort due to the low CD4 counts of patients on enrollment.

Markers of HIV progression ($CD4^+$ and viral load) did not differ between patients with and without T2DM and incident diabetes, which is in agreement with a previous finding in the United States [6]. The association of $CD4^+$ and viral load with diabetes can be complex, and were not identified in the comparison of a large cohort of HIV-infected and HIV-uninfected veterans [28]. However, Shen et al had reported a significant increase in diabetes risk for every 150-$CD4^+$ cell/μL reduction among ART-naive patients [7].

We did not find associations between the type of ART regimen and diabetes, as reported by Ledergerber et al [10]. De Wit et al reported that although PIs were not associated with diabetes, there was an association with NRTIs [9], with stavudine followed by zidovudine, and didanosine conferring the greatest risk. In our study, the overall number of individuals on second-line ART was small and the majority were on atazanavir-based PI, which does not have a significant effect on glucose metabolism. In addition, ART adherence and the use of medications with adverse glycemic effects were not assessed, and none of the patients received stavudine or didanosine.

Our study has strengths, but also some important limitations. It is probably the largest study providing concurrent data on both baseline and new diabetes on ART in HIV/AIDS patients residing in sub-Saharan Africa. However, our cohort had a relatively short follow-up period of only 1 year, and a longer period of observation would likely reveal additional patients developing diabetes, and possibly stronger risk associations. Furthermore, information such as waist/hip circumference of patients was not routinely measured in the clinic, and metabolic markers were coded into dichotomous variables (eg, diabetes yes/no), precluding further stratification for analysis of data. Also, the study lacks a control cohort of non-HIV-infected subjects and data of PLWHA who did not initiate ART. Last, the absence of data on prediabetes could represent a missed opportunity to estimate and plan diabetes prevention initiatives.

In conclusion, diabetes is common among HIV/AIDS patients on established ART. Traditional risk factors are important, and a higher BMI appears to confer the strongest risk. Body weight is modifiable, and supporting patients to achieve healthy dietary and lifestyle behavior is important, as PLWHA may overcompensate in weight gain to avoid the stigma associated with weight loss. The relationship between diabetes and ART needs further long-term exploration. Patients with HIV initiating ART need to be aware of the risk of developing diabetes, and services should provide integrated services for HIV/AIDS and noncommunicable diseases such as diabetes.

Notes

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