

HIV and risk of type 2 diabetes in a large adult cohort in Jos, Nigeria

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Summary of article's main point: Diabetes is common among HIV/AIDS patients, especially within the first year of antiretroviral therapy. Newly occurring diabetes was associated with a high body mass index, and excessive weight gain should be avoided.

Abstract

Background: HIV infection and the use of anti-retroviral therapy (ART) may increase the risk of type 2 diabetes mellitus (T2DM). However, data from regions with a high burden of HIV/AIDS is 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 re-evaluated after 12 months of ART commencement. The presence of diabetes, demographic, clinical and biochemical data were retrieved from standardized databases. CD4+, HIV viral load, and hepatitis C virus (HCV) status were noted. Bivariate and logistic regressions were used to identify risk factors for T2DM.

Results: Baseline T2DM prevalence was 2.3% (95%CI: 1.8% – 2.9%), and age, but not body mass index (BMI) was a risk factor for diabetes. After 12 months of ART, a further 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 then have a high risk of developing diabetes in the first year of ART. Incident diabetes was associated with a BMI ≥ 25.0 , and excessive weight gain should be avoided.

INTRODUCTION

Diabetes is a major public health concern worldwide and is rapidly increasing in sub-Saharan Africa, where it is projected to affect more than 20 million people by 2030. [1, 2] In Nigeria alone, diabetes affects between 0.6% to 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 health care systems.

Nigeria also has the second largest number of individuals with the Human Immunodeficiency Virus (HIV) in the African continent, with more than 3 million people living with HIV/AIDS (PLWHA) and 600,000 receiving antiretroviral therapy (ART)[4]. PLWHA nowadays have longer survival with the expanding access to ART, and the prevalence of HIV/diabetes co-morbidity 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 dyslipidaemia [11] and HCV is associated with intra-hepatic elevation of TNF- 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 hyperglycaemia by preventing the uptake and metabolism of glucose and lipids by adipocytes and hepatocytes [15], subsequently pointed towards the nucleoside (NRTIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs) 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 naïve patients at the time of enrolment into a cohort of newly diagnosed PLWHA, and describe the proportion of patients

who developed T2DM within one year of ART initiation in a large HIV/AIDS cohort in Jos, Nigeria.

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 (JUTH). The APIN clinic is a regional referral centre 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 life style advice, clinical and laboratory investigations and assessment of ART eligibility. Patients are then followed fortnightly, monthly, quarterly and 6 monthly depending on whether they have symptoms or have initiated ART. Socio-demographic, 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 the 1st January 2011 to the 31st December 2013. Patients without baseline plasma glucose records and those who had already initiated ART at the time of enrolment were excluded from the analysis of baseline diabetes. The precision for estimates was $\approx \pm 1\%$ 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, gender, body mass index (BMI), total cholesterol (mmol/l), CD4+ cell counts (per μ l), HIV viral load (copies/ml), ART regimen and the presence of

diabetes. ART was categorized as 1st or 2nd line. The most frequently prescribed 1st line regimens were: lamivudine + zidovudine + nevirapine (45.9%), and lamivudine or emtricitabine + tenofovir + efavirenz (31.4%). The most readily available 1st line regimen was Nevirapine-containing ART. The 2nd 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 develop 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 child bearing age, except if given with contraception. Second line regimens were considered if there was suspicion of transmitted resistance (e.g. newly infected contacts of PLWHIV with known ART-resistance), a diagnosis of tuberculosis (since Rifabutin was not readily available), Kaposi sarcoma or adverse effects to the 1st line regimens. In our clinic, a switch to 2nd line 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 of ≥ 11.1 mmol/l, fasting plasma glucose of ≥ 7.0 mmol/l; or self-reported use of hypoglycaemic 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 USA National Cholesterol Education Programme [20]. The estimated glomerular filtration rate (eGFR) was derived by the Cockcroft-Gault formula [21]. A Cobas C311 auto analyser was used for plasma chemistry and HCV antibodies were documented by an ELISA method.

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

Ethical approval was obtained from the Liverpool School of Tropical Medicine (LSTM) and the JUTH 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 (Chicago, IL, USA, 2011). Continuous variables were expressed as means \pm standard deviations, or medians with ranges. Categorical variables were presented as proportions and compared using Chi Squared tests. Means were compared using unpaired Student's t tests. Positively skewed data were \log_{10} transformed. Bivariate analysis was conducted and variables with $p < 0.25$ were entered into multiple logistic regression models. Results of the bivariate analyses and logistic regressions were presented as odds ratios (OR) and adjusted odds ratios (AOR), with 95% confidence intervals (CI), respectively. A p-value of < 0.05 was considered statistically significant.

RESULTS

A total of 2,753 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) for new onset diabetes one year after initiation of ART, as shown in Figure 1. The baseline characteristics of the overall cohort are shown in Table 1.

A total of 61 out of 2632 patients (2.3%; 95%CI 1.8%– 2.9%) had T2DM on enrolment. Of these, 21 (41%) were unaware of the diagnosis. Patients with T2DM were older and had significantly lower eGFR than patients without T2DM, as shown in Table 2. There was no difference in the gender distribution, BMI, cholesterol levels, CD4+ count, HIV viral load or HCV positive status. Patients > 40 years were 3.5 times more likely to have T2DM (AOR 3.5, 95% CI 1.9 – 6.5, $p < 0.001$), and patients with T2DM were more likely to have reduced eGFR (AOR 0.99, 95% CI 0.97 – 0.98, $p < 0.017$).

Of the 2452 patients without T2DM on enrolment, 130 (5.3%; 95% CI: 4.2 – 6.3%) developed T2DM within one year of initiating ART. If these patients are added to those

already identified on enrolment, 191 (7.6%) of the participants had T2DM one year after initiating ART.

Patients who developed T2DM after initiation of ART had higher BMI and were more likely to have HCV antibodies on enrolment (12.1% and 3.6% of the patients with and without incident T2DM, $p < 0.001$). There were no differences in age, gender, cholesterol concentrations, CD4+ count, HIV viral load, eGFR or the use of 1st or 2nd line ART among patients with and without incident T2DM, as shown in 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/m² (AOR: 7.5, 95%CI 2.9 – 23.7, $p < 0.001$) was independently associated with incident T2DM, as shown in Table 3.

DISCUSSION

Our study of a large cohort of HIV-positive 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, a further 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 enrolment. Of these, only BMI > 25 kg/m² was independently associated with newly developed T2DM in multivariate analysis.

The baseline T2DM prevalence is similar to other reports in both ART naïve 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 naïve patients had T2DM [7]. Patients in Italy were older (46 vs 37 years) and had a significantly higher CD4 counts than patients in our study (CD4+ counts of 538 vs 206 cells/ul), while the prevalence of diabetes in a Chinese population [23] was higher than in Nigeria; suggesting that

prevalence of T2DM diabetes 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 USA [23], but lower than a 7.2% 3-year cumulative incidence among recipients of early generation PIs [24]. T2DM development is a progressive condition that may require several years to become established among PLWHA, and a 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 old, 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 on enrolment were more likely to have a lower eGFR, while 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 less than one 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 enrolment, but Madapalli 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 a 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 which 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 diarrhoea and tuberculosis) might have masked the association at baseline, and these illnesses were likely to be common in our cohort due to the low CD4 counts of patients on enrolment.

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 USA [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-negative veterans [28]. However Shen et al had reported a significant increase in diabetes risk for every 150 CD4+ cell/ul reductions among ART naïve 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 2nd line ART was small and the majority were on atazanavir based PI which does not have significant effect on glucose metabolism. In addition, ART adherence and the use of medications with adverse glycaemic 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 one year, and a longer period of observation would likely reveal further 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 (e.g. diabetes yes/no), precluding further stratification for analysis of data. Also, the study lacks a control cohort of non-HIV infected population and data of PLWHA who did not initiate ART. Lastly, the absence of data on pre-diabetes 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 behaviour is important, as PLWHA may over compensate 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 non-communicable diseases (NCDs) such as diabetes.

NOTES

Acknowledgements: This study represents work from Dr Isa's MSc dissertation at the Liverpool School of Tropical Medicine. We acknowledge Dr Ralf Weigel who was the Director of Studies for the course. We also wish to thank PEPFAR Harvard and the AIDS Prevention Initiative of Nigeria for permitting the use of data presented in this study.

Sources of funding: The Government of Nigeria through the Tertiary Education Trust Fund and the Liverpool School of Tropical Medicine.

Conflicts of interest statement: The authors declare no conflicts of interest.

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Figure1: Flow chart of patient selection for the study.

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Table 1. The overall characteristics of the 2632 individuals enrolled in the cohort

| Variables | N |
|--|------------------|
| Age | |
| Mean (SD) in years | 37.4±9.7 |
| Median [range] | 36 [19-79] |
| Proportion > years old | 958 (36.4%) |
| Male/Female (male%) | 924/1708 (35.1%) |
| Mean (SD) BMI | 22.9 (4.8) |
| Total Cholesterol (SD) mmol/l | 4.1 (1.3) |
| Median [range] CD4+ cells/mm ³ | 190 [2-1837] |
| Geometrical mean viral load (SD) copies/ml* ¹ | 4.3 (0.9) |
| Mean eGFR (SD) ml/min* ² | 79.6 (24.8) |
| HCV antibody present (%)* ³ | 69/1645 (41.9%) |
| ART regimens * ⁴ | |
| 3TC+AZT+NVP | 1125 (45.9%) |
| 3TC or FTC + TDF + EFV | 769 (31.4%) |
| 3TC+NVP+TDF | 281 (11.6%) |
| 3TC+AZT+EFV | 59 (2.1%) |
| ATZ/RTV based PI | 64 (2.5%) |
| LPV/RTV based PI | 4 (0.3%) |
| Others | 150 (6.2%) |

Abbreviations: ART; anti-retroviral therapy, ABC; abacavir, ATZ; antazanavir, AZT; zidovudine, EFV; efavirenz, FTC; emtricitabine, NVP; nevirapine, PI; protease inhibitor, RTV; ritonavir SD; standard deviation, 3TC; lamivudine, TDF; tenofovir. *Only patients followed up for incidence diabetes were exposed. Others: AZT+FCT+TDF, 3TC+NVP+ABC, 3TC+ABC+EFV, 3TC+AZT+TDF. *¹ N= 2140; *² N = 2157; *³ N = 1714; *⁴ N = 2452.

Table 2. Characteristics of patients with and without diabetes at baseline in a cohort of people living with HIV in Jos, Nigeria

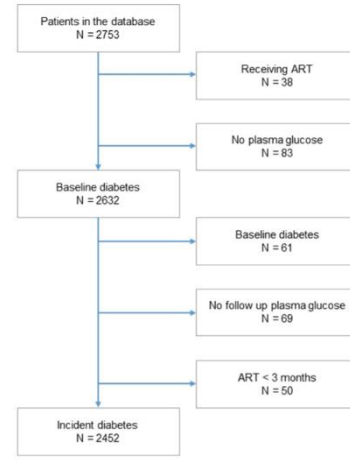
| Characteristics | With diabetes n = 61 (2.3%) | Without diabetes n = 2571 (97.7%) | OR (95%CI) | p-value |
|---|--------------------------------|--------------------------------------|--------------------|---------|
| Age > 40 years | 43/61 (70.5%) | 915/2571 (35.6%) | 4.32 (2.48 – 7.54) | 0.0001 |
| Male:Female (%male) | 25:36 (41%) | 899:1656 (35%) | 1.29 (0.77 – 2.16) | 0.330 |
| BMI ≥25 Kg/m ² | 22 (36.1%) | 830 (32.3%) | 1.13 (0.79 – 1.65) | 0.490 |
| Mean Cholesterol (SD) mmol/L | 4.1 (1.4) | 4.1 (1.3) | 1.07 (0.94 – 1.23) | 0.980 |
| Median CD4+ cells/mm ³ (range) | 180 (10 - 867) | 190 (2 - 1837) | 1.00 (1.00 – 1.00) | 0.938 |
| Log mean viral load (SD) | 4.3 (0.9) | 4.3 (0.9) | 1.00 (1.00 – 1.00) | 0.340 |
| *Mean eGFR in ml/min (SD) | 67.5 (22.3) | 79.9 (24.8) | 0.98 (0.97 – 0.99) | 0.005 |
| Positive HCV antibody | 1/40 (2.5%) | 68/1674 (4.1%) | 0.61 (0.08 – 4.47) | 0.619 |

BMI, body mass index; CD, cluster of differentiation; SD=Standard deviation; CI, confidence interval; eGFR, estimated glomerular filtration rate, HCV, Hepatitis C virus; OR, odds ratio. * variables with p<0.25 in bivariate analysis.

Table 3. Bivariate and multivariate analysis of risk factors of new onset diabetes in a cohort of people living with HIV on antiretroviral therapy in Jos, Nigeria

| Characteristics | New diabetes n = 130 (5.3%) | No diabetes n = 2322 (94.7%) | OR (95% CI) | AOR (95%CI) | p-value |
|--|--------------------------------|---------------------------------|--------------------|---------------------|---------|
| Age > 40 years | 51 (39.2%) | 822 (35.4%) | 1.13 (0.79 – 1.61) | 1.02 (0.99 – 1.05) | 0.14 |
| *Mean Cholesterol (SD) mmol/L | 4.2 (1.2) | 4.1 (1.3) | 1.07 (0.94 – 1.23) | 0.88 (0.71 – 1.10) | 0.23 |
| *MedianCD4+cells/mm ³ (range) | 206 (13 - 968) | 188 (2 - 1837) | 0.98 (0.90 – 1.10) | 1.00 (1.00 -1.02) | 0.90 |
| *Log mean viral load (SD) | 4.5 (0.89) | 4.3 (0.92) | 0.91 (0.89 – 1.09) | 1.21 (0.90 – 1.64) | 0.21 |
| *Mean eGFR in ml/min (SD) | 78.9 (25.3) | 80.0 (24.8) | 1.01 (0.99 – 1.03) | 0.99 (0.99 – 1.01) | 0.85 |
| *Positive HCV antibody | 12/99 (12.1%) | 56/1575 (3.6%) | 1.15 (1.03 - 1.28) | 2.46 (0.58 – 10.54) | 0.22 |
| First Line ART | 123/130 (94.6%) | 2245/2306 (97.3%) | 1.16 (0.97 - 1.39) | NA | - |

AOR, adjusted odds ratio; BMI, body mass index; CD, cluster of differentiation; CI, confidence interval; eGFR, estimated glomerular filtration rate, HCV, Hepatitis C virus; OR, odds ratio; NA, not applicable. *variables with $p < 0.25$ in bivariate analysis which were also baseline characteristics adjusted for associations with new diabetes. Hosmer and Lemeshow test: Chi Square = 9.242; p-value = 0.32



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