Prevalence and predictors of glucose metabolism disorders among People Living with HIV on combination antiretroviral therapy

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Abstract

Objective
We investigated prevalence and predictors of glucose metabolism disorders (GMDs) among People Living with HIV (PLWH) on efavirenz- and atazanavir/ritonavir-based combination antiretroviral therapy (cART).

Methods
This cross-sectional study involved adult PLWH on efavirenz- (n = 240) and atazanavir/ritonavir-based (n = 111) cART. The prevalence of GMDs was determined by fasting serum glucose, insulin, and homeostasis model assessment. A logistic regression model was used to determine predictors.

Results
The overall prevalence of GMDs for all regimens was 27.6% (97/351) [95% CI 23.0–32.6%], with 31.1% (75/240) [95% CI 25.4–37.5%] for efavirenz-based and 19.8% (22/111) [95% CI 12.9–28.5%] for atazanavir/ritonavir-based cART. The prevalence of impaired fasting glycemia was significantly higher (p = 0.026) in the efavirenz- [(15.4%) (37/240); 95%CI (11.1–20.6%)] than atazanavir/ritonavir-based [(7.2%) (8/111), (95%CI (3.2–13.7%)] cART. However, no significant difference was observed in the prevalence of diabetes mellitus and insulin resistance between the two regimens. Age ≥46 years old and specific type of ARV contained in cART, such as TDF, were independent predictors of GMD in both groups. Whereas the male gender and BMI category were predictors of GMDs among EFV-based cART group, AZT- and ABC-containing regimens and triglyceride levels were predictors in the ATV/r-based group.
Conclusions
GMDs were highly prevalent among adults on EFV- than ATV/r-based cARTs. Age ≥46 years and TDF-containing cARTs are common predictors in both regimens. Close monitoring for impaired fasting glucose during long-term EFV-based cART is recommended for early diagnosis of type-2 diabetes and management.

Introduction
HIV/AIDS has remained a public health problem in sub-Saharan Africa [1]. Over the last three decades, HIV-associated mortality and disease transmission rate has progressively declined, mainly because of the rapid expansion and availability of combination Antiretroviral Therapy (cART) [2]. The introduction of cART has changed the complexion of HIV infection from a deadly disease to a chronic manageable disorder that notably changed patients’ quality of life and longevity [3]. It also changed the global epidemiology of transmission, morbidity, and mortality of HIV [2, 4].

Treatment of HIV is lifelong, embracing frequent clinical evaluation and follow-up [5]. During long-term exposure to antiretroviral therapy (ART), individual patients may experience treatment-associated adverse events or drug toxicities [5]. Long-term exposure to ART may increase the risk of metabolic abnormalities such as lactic acidosis, osteopenia, dyslipidemia, and glucose metabolism disorders (GMDs) [6]. GMDs are glucose homeostasis dysregulations that include diabetes mellitus (DM), impaired glucose tolerance (IGT), impaired fasting glycemia (IFG), or insulin resistance (IR) [7].

The literature indicates that the prevalence of IR, IGT, and DM has significantly increased and became a notable clinical concern, as long-term ART [8] and aging-related factors contribute to a higher risk of glucose metabolism abnormalities. DM is now emerging as one of the non-infectious comorbid conditions among People Living with HIV (PLWH) on cART [8]. Previous studies reported that patients on ART were found to be four-fold more prone to DM and associated conditions compared to HIV uninfected individuals [6, 7, 9–11]. Among cART classes, protease inhibitors (PI) use has been commonly reported to have association with GMDs. PIs may cause abnormal glucose metabolism, ranging from IR through IGT & IFG to type 2 diabetes [8, 12]. The PIs, particularly lopinavir and ritonavir, are linked to an increase in IR and to have effect on lipid and glucose metabolism [13, 14]. A cross-sectional study reported a five-to-nine-fold elevated prevalence of type 2 DM among PLWH on PIs [12]. Recently, a high prevalence of cART-associated dyslipidemia, particularly low High-Density Lipoprotein Cholesterol (HDL-c) and hypertriglyceridemia, has also been reported among treatment-experienced HIV-infected children from Ethiopia [15].

In a resource-limited setting, Efavirenz (EFV) and Atazanavir/Ritonavir (ATV/r) serve as a backbone of combination antiretroviral regimens [16]. In Ethiopia, during the study period, the preferred first-line regimen for adults was EFV-based cART, specifically a combination of tenofovir (TDF), lamivudine (3TC), and EFV [17]. ATV/r-based regimens were the mainstay of second-line cART replacing lopinavir/ritonavir (LPV/r) [17].

The magnitude of and risk factors for GMDs are well investigated in developed countries. Several studies from sub-Saharan African countries also reported a high prevalence of glucose-related abnormalities and risk factors. However, regimen-specific prevalence and predicting factors, particularly for EFV- and ATV/r-based regimens, are limited in Ethiopia. Principally, data are almost unavailable concerning glucose metabolism-related alterations of ATV/r-
based regimens, at least in Ethiopia. Moreover, data comparing the incidence of GMDs and the respective risk factors of Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs), including EFV, and new PIs, such as atazanavir (ATV) are sparse. Thus, this study would provide data and generate evidence for interested researchers and clinicians in sub-Saharan Africa in general and in Ethiopia in particular. Therefore, this study aimed to determine the prevalence and predicting factors of GMDs among PLWH on EFV- and ATV/ritonavir (ATV/r)-based cARTs.

Methods

Study design, population, and setting

This is an institution-based cross-sectional study conducted among treatment-experienced PLWH on EFV- or ATV/r-based cART. The study was conducted from August 2019 to March 2020 at the ART clinic of Tikur Anbessa Specialized Hospital (TASH), College of Health Sciences, Addis Ababa University, Addis Ababa, Ethiopia. TASH is the largest tertiary level teaching and referral hospital in Ethiopia. This setting regularly receives referred patients from different parts of the country. With more than 800 beds, it provides various specialized clinical services for more than 500,000 patients each year [18]. The ART clinic at TASH provides HIV/AIDS prevention, patient care, and ART services.

All adult PLWH on EFV- or ATV/r-based ART attending at ART-clinic of TASH formed the study population. Study participants were confirmed PLWH recruited based on the inclusion and exclusion criteria.

Sample size determination and sampling techniques

The sample size was determined using single proportion formula for cross-sectional studies, with a qualitative variable [19]. To estimate the specific prevalence for sample size calculation, the sum of the prevalence of IFG (pre-diabetes) and DM in PLWH on ART were considered from two local cross-sectional studies [20, 21]. Accordingly, a prevalence of 31.2% was calculated. In addition, 90% power to detect a prevalence difference of 10% between the two groups, 95% confidence interval, and 0.05 level of significance was considered for sample size calculation using the single proportion formula.

The calculated sample size needed for the cross-sectional study was therefore about 330 patients. Adding a 10% contingency for the probability of missing data, the total sample size reached to 363.

The overall proportion of patients receiving EFV- and ATV/r-based cART during the study period was 69% and 31%, respectively. Accordingly, 251 participants were recruited from those on EFV-based cART and 112 from those on ATV/r-based cART. A convenient sampling technique was used to recruit study participants based on their consent and inclusion/exclusion criteria.

PLWH aged 18 years and above and on EFV or ATV/r-based cART at least for one year were included. Patients known to have DM, pregnancy, cancer, renal disease, liver disease, uncontrolled hypertension, and heart failure were excluded from the study. Moreover, patients on certain co-administered medications such as antipsychotics, cancer chemotherapy, anti-TB, corticosteroids, hormonal agents, or antidiabetics were excluded.

Data collection

Relevant data including socio-demographic, clinical characteristics, adherence based on self-reported 3 days recall test, in which study participants were asked to report the number of
doses they missed over the last three consecutive days prior to sampling date [22–24], and anthropometric measurement were collected using a semi-structured interview questionnaire, patient medical charts, and prospective laboratory sample analysis. Waist circumference and body weight were measured with participants wearing light clothing and barefooted. Waist circumference was measured at the umbilical level to the nearest 0.1 cm using a tape measure. BMI was computed as weight divided by height square (kg/m$^2$). Waist circumference and BMI were defined according to WHO recommendations [25].

Blood tests were performed after overnight fasting (8 to 12 h). About 5 ml blood was collected from the brachial artery in serum separator tubes and fasting blood glucose (FBG), insulin, and lipid profiles were determined.

**Operational definitions**

- DM was defined as a fasting glucose level of 126 mg/dL or higher [26].
- IFG was defined as a fasting glucose level between 110 and 125 mg/dL [26].
- Normoglycemia was defined as a fasting serum glucose level between 70 and 109 mg/dL [26, 27].
- Hyperglycemia was defined as a fasting glucose level of 110 mg/dL or higher [26, 27].
- IR was diagnosed by either Homeostasis model assessment insulin resistance (HOMA-IR) value of $\geq 3.8$, fasting plasma insulin of $\geq 20 \mu$U/ml, or fasting glucose/insulin ratio of $\geq 4.5$ [28, 29].
- GMDs were defined as the presence of IFG, IR, or DM [7, 30].

**Data management and analysis**

Data were sorted and entered as codes suitable for Statistical Package for Social Science (SPSS) statistical software version 25. Socio-demographic, anthropometric, and clinical as well as laboratory results were presented using descriptive statistics (frequency, mean, median, inter-quartile range). Continuous variables were reported as mean ± standard error of the mean (SEM), while categorical variables were presented as percent proportions. HOMA-IR was calculated to determine IR using FBG level and insulin concentrations. HOMA-IR is given by the product of fasting insulin concentration ($\mu$U/ml) and fasting glucose (mmol/L) level divided by the constant normalizing factor, 22.5 [31].

To determine associations of variables against GMDs, univariate logistic regression analysis was performed for each socio-demographic, anthropometric, and clinical lab variables. Multivariate analysis was performed using backward-stepwise logistic regression analysis and independent predictors of the primary outcome were identified. Variables with a p-value less than 0.05 were considered statistically significant, while variables with p values less than 0.2 in univariate analysis were candidates for multivariate logistic regression analysis.

**Ethical consideration**

Ethical clearance was obtained from the Institutional Review Board of College of Health Sciences, Addis Ababa University (Protocol No. 019/19/SoP) and National Ethical Review Committee, Ministry of Science and Higher Education, Addis Ababa, Ethiopia (Ref. No. MoSHE/RD14.1/9324/20). Written informed consent was obtained from each study participant after a full explanation of the purpose and nature of all procedures used. In cases of severe abnormal
values, participants were contacted through the HIV clinic and referred for a timely clinical evaluation and follow-up at the same hospital.

**Results**

**Baseline characteristics of study participants**

Out of the 363 recruited study participants, 351 had complete clinical laboratory data for FBG fasting serum insulin, and HOMA-IR value, and thus considered for statistical analysis. As depicted in Table 1, there was a female preponderance in the study participants (70.4%), EFV- (68.8%), and ATV/r-based (73.9%) regimens. Majority of the participants (58.4%) belong to the age group of 18–45 years, with 54.6% and 66.7% in EFV- and ATV/r-based cART group, respectively. A large proportion of participants were non-smokers (99.1%), non-khat chewers (98.6%), or non-alcohol users (96.6%). Related to anthropometric characteristics, the overall mean (SEM) lean weight was 62.4 (0.71) kg, waist circumference was 34.11 (0.26) cm, and BMI was 24.0 (0.26) kg/m$^2$.

About 240 (68.4%) of the participants were on EFV-based 1st line cART (Table 1). The overall mean ($\pm$SEM) of baseline and latest CD4 counts were 206 $\pm$18.3 and 464.6 $\pm$13.6, respectively. Unlike the baseline (225.5$\pm$25.6 vs. 163.3$\pm$16.2), a significantly elevated latest (523.5 $\pm$16.4 vs. 336.8$\pm$19.3) CD4 counts were observed in the EFV- than ATV/r-group. Based on the latest medical records, only 31 (8.8%) of the overall study participants experienced virologic failure, with viral loads of $>1000$ copies/ml, out of which a significant majority were on ATV/r-based cART ($p = 0.000$). The EFV group had a significantly longer cumulative time on cART since initiation (123.9$\pm$2.9 months) than the ATV/r-group (112.0$\pm$4.3 months) (Table 1).

Whilst the cumulative time on EFV-based regimen was 101.4$\pm$2.8, it was 34.3$\pm$3.0 months for ATV/r-based cART. Participants on ATV/r-based cART were on 1st-line cART for 90.5$\pm$11.9 months, mainly on Nevirapine (NVP)-based for 33.4$\pm$4.3 months and later, on EFV-based regimens for 40.8$\pm$4.2 months.

Large majority of the participants (339, 96.6%) were adherent to their respective cART based on the self-reported three-day adherence test. Treatment adherence was higher among participants in ATV/r- (97.3%) than EFV-based groups (96.3%), though no statistically significant difference was found ($p = 0.616$). Based on the overall clinical lab analysis, the mean (SEM) FBG was 99.2 (1.5) mg/dL and serum insulin ranged from 0.46 to 160.5 $\mu$U/mL, with a mean (SEM) of 9.6 (0.6) (Table 1). Moreover, the mean (SEM) HOMA-IR value was found to be 2.5 (0.2), ranging from 0.14 to 57.39. Unlike fasting serum insulin and HOMA-IR values, the EFV-based group showed a significantly elevated FBG than ATV/r-based ($p = 0.018$). In general, the clinical lab values were relatively elevated in the EFV- than the ATV/r-based group, except for the triglyceride level. However, only LDL level showed a statistically significant elevation among EFV- than ATV/r-based cART receiving group (Table 1).

**Prevalence of GMDs**

The prevalence of GMDs is shown in Table 2. The overall prevalence of GMDs was found to be 27.6% ($n = 97/351$). Among the overall study participants, about 12.8% (45/351) were with impaired glycemia and 5.7% (20/351) with a diabetic range of fasting serum glucose. IR was detected in about 14.8% ($n = 52/351$) of the study participants. A significantly higher ($p<0.05$) prevalence of GMDs was found in patients taking EFV-based first-line therapy (31.3%) than ATV/r therapy (19.8%). Disaggregating the data revealed that only the prevalence of IFG was detected to be significantly higher ($p<0.05$) in the EFV- (15.4%) than the ATV/r-based group (7.2%). Although the prevalence of DM and IR tended to be higher in the EFV group than the ATV/r group, it did not reach statistical significance (Table 2).
Table 1. Baseline characteristics of study participants on efavirenz-based or ritonavir-boosted combination antiretrovirals.

| Variables | Categories | Overall | EFV-based | ATV/r-based | χ²/F or t | p |
|-----------|------------|---------|-----------|-------------|-----------|---|
|           | n (%)      | n (%)   | n (%)     |             |           |   |
| Age (years) | Median (IQR) | 43.0 (37.0–50.0) | 45.0 (38.0–52.0) | 40.0 (33.0–48.0) | 3.5 | 0.000 |
| Age category | 18≤45 | 205 (58.4) | 131 (54.6) | 74 (66.7) | 4.6 | 0.033 |
|           | ≥46 years | 146 (41.6) | 109 (45.4) | 37 (33.3) | 1.0 | 0.328 |
| Gender | Female | 247 (70.4) | 165 (68.8) | 82 (73.9) | 3.0 | 0.387 |
|           | Male | 104 (29.6) | 75 (31.3) | 29 (26.1) | 66 | 0.747 |
| Marital status | Single | 76 (21.7) | 47 (19.6) | 29 (26.1) | 0.9 | 0.332 |
|           | Married | 127 (36.1) | 93 (38.8) | 34 (30.6) | 1.0 | 0.328 |
|           | Widowed | 86 (24.5) | 59 (24.6) | 27 (24.3) | 0.1 | 0.731 |
|           | Divorced | 62 (17.7) | 41 (17.1) | 21 (18.9) | 5.4 | 0.143 |
| Educational status | Up to primary | 145 (41.3) | 96 (40.0) | 49 (44.1) | 0.9 | 0.332 |
|           | Above primary | 194 (55.3) | 138 (57.5) | 56 (50.5) | 61.7 | 0.000 |
| Khat use (self-report) | Never | 346 (98.6) | 236 (98.3) | 110 (99.1) | 0.3 | 0.573 |
|           | Current or previous | 5 (1.4) | 4 (1.7) | 1 (0.9) | 0.6 | 0.424 |
| Smoking (self-report) | Never | 348 (99.1) | 238 (99.2) | 110 (99.1) | 0.0 | 0.949 |
|           | Current or previous | 3 (0.9) | 2 (0.8) | 1 (0.9) | 1.0 | 0.332 |
| Alcohol use (Self-report) | Never | 339 (96.6) | 231 (96.3) | 108 (97.3) | 0.2 | 0.616 |
|           | Current or previous | 12 (3.4) | 9 (3.8) | 3 (2.7) | 0.2 | 0.616 |
| Treatment adherence (3-day test) | Adhered | 339 (96.6) | 231 (96.3) | 108 (97.3) | 2.5 | 0.114 |
|           | Non-adhered | 12 (3.4) | 9 (3.8) | 3 (2.7) | 0.2 | 0.616 |
| BMI category | ≤18.5 | 40 (11.4) | 25 (10.4) | 15 (13.5) | 5.4 | 0.143 |
|           | 18.6–24.9 | 163 (46.4) | 105 (43.8) | 58 (52.3) | 0.9 | 0.332 |
|           | 25–29.9 | 104 (29.6) | 80 (33.3) | 24 (21.6) | 5.4 | 0.143 |
|           | ≥30 | 34 (9.7) | 24 (10.0) | 10 (9.0) | 1.0 | 0.332 |
| Viral load status(n = 335) | <1000 copies/ml | 31 (8.8) | 3 (1.3) | 28 (25.2) | 61.7 | 0.000 |
|           | ≥1000 copies/ml | 304 (86.6) | 225 (93.8) | 79 (71.2) | 0.1 | 0.731 |
| History of comorbidity (self-reported) | HIV-only | 340 (96.9) | 233 (97.1) | 107 (96.4) | 0.1 | 0.731 |
|           | HIV + comorbidity | 11 (3.1) | 7 (2.9) | 4 (3.6) | 0.1 | 0.731 |
| cART backbone-type | TDF containing | 266 (75.8) | 216 (90.0) | 50 (45.0) | 80.9 | 0.000 |
|           | AZT containing | 71 (20.2) | 24 (10.0) | 47 (42.3) | 45.3 | 0.000 |
|           | ABC containing | 13 (3.7) | - | 13 (11.7) | 29.2 | 0.000 |
| Time since HIV confirmed date (months) | ≤131.14±2.6 | 134.5±3.1 | 123.9±4.9 | 1.9 | 0.062 |
| Cumulative time on cART (month) | ≤120.2±2.4 | 123.9±2.9 | 112.0±4.3 | 2.3 | 0.021 |
| Cumulative time on EFV-based 1<sup>st</sup>-line (month) | ≤82.3±2.7 | 101.4±2.8 | 40.8±4.2 | 12.2 | 0.000 |
| Cumulative time on ATV/r-based 2<sup>nd</sup>-line (month) | ≤11.3±1.3 | 0.7±0.5 | 34.3±3.0 | 115.1 | 0.000 |
| Time on current cART regimen type (month) | ≤74.6±2.5 | 93.7±2.7 | 33.1±2.6 | 16.2 | 0.000 |
| Time on prior cART regimen types (month) | ≤52.4±5.6 | 34.8±5.6 | 90.5±11.9 | 349 | 0.000 |
| Time on NVP-based 1<sup>st</sup>-line (Prior to EFV) (month) | ≤25.4±2.1 | 21.7±2.4 | 33.4±4.3 | 178.7 | 0.018 |
| Time on LPV/r-based 2<sup>nd</sup>-line (prior to ATV/r) (month) | ≤1.4±0.5 | 0.2±0.2 | 4.1±1.6 | 112.6 | 0.018 |
| Waist circumference (cm) | ≤34.1±0.26 | 34.6±0.3 | 33.3±0.4 | 2.4 | 0.016 |
| CD4+ (cells/ul) (baseline) | ≤206.0±18.3 | 225.5±25.6 | 163.3±16.2 | 1.6 | 0.114 |
| CD4+ (cells/ul) (recent) | ≤464.6±13.6 | 523.5±16.4 | 336.8±19.3 | 7.4 | 0.000 |
| Fasting glucose (mg/dL) | ≤99.2±1.5 | 101.7±1.7 | 94.2±2.6 | 2.4 | 0.018 |
| Fasting insulin (uU/ml) | ≤9.6±0.6 | 10.2±0.8 | 8.4±0.6 | 1.4 | 0.150 |
| HOMA-IR (μU/ml) | ≤2.5±0.2 | 2.8±0.3 | 2.0±0.2 | 1.4 | 0.154 |
| Total cholesterol(mg/dL) | ≤200.8±6.9 | 208.5±9.9 | 184.2±4.1 | 1.6 | 0.103 |
We also tried to calculate the prevalence of these variables based on tenofovir (TDF)-, zidovudine (AZT)-, and abacavir (ABC)-containing combinations. The prevalence of GMDs was higher in participants taking AZT- (29.6%) than TDF- (27.3%) and ABC (15.4%) containing combinations. Looking at the individual variables, the AZT-containing combination showed a relatively higher rate for IR (18.3%) and IFG (14%) than TDF- (13.9% for IR and 13.1% for IFG) and ABC- (7.7% for IR and 0% for IFG) containing combinations. By contrast, prevalence of DM was higher for ABC- (7.7%) than TDF- (5.6%), and AZT- (2.8%)-containing combinations.

Predictors of glucose metabolism disorders

Predictors for overall study participants. Univariate analysis revealed that BMI, serum level of triglycerides, age, gender, khat use, comorbid conditions, and history of hypertension were significantly associated with GMDs (Table 3). However, in multivariate logistic regression analysis, age ≥46 years old, male gender, history of comorbid conditions, and serum triglycerides level were found to be independent predictors of GMDs.

Patients with age ≥46 years [AOR = 2.1, 95% CI 1.2–3.6, p < 0.01] and males had a two-fold risk of GMDs [AOR = 2.6, 95% CI 1.1–3.5, p < 0.01]. Likewise, individuals with comorbid conditions had a nearly five-fold risk of GMDs [AOR = 4.7, 95% CI 1.3–18.9, p < 0.05] than those without comorbid conditions. Serum level of triglycerides showed a statistically significant association with the incidence of GMDs. For each unit increase in the level of triglycerides, the likelihood to develop GMDs increased by 0.5% [AOR = 1.005, 95% CI 1.001–1.008], p < 0.05.

On the other hand, cumulative time on ATV/r-based second-line cART conferred a significant protection from GMDs, i.e., a 2% lower incidence of GMD was observed for each month stay on ATV/r-based cART (Table 3). Paradoxically, waist circumference was negatively

Table 1. (Continued)

| Variables | Categories | Overall (n = 351) | EFV-based cART (n = 240) | ATV/r-based cART (n = 111) | \( \chi^2 \) or F or t | p |
|-----------|------------|------------------|------------------------|---------------------------|----------------|---|
| Triglyceride(mg/dL) \( ^\delta \) | 155.9±4.0 | 152.2±5.0 | 163.7±6.4 | 1.3 | 0.179 |
| HDL-C(mg/dL) \( ^\delta \) | 45.3±1.7 | 46.3±1.8 | 43.1±3.6 | 0.9 | 0.370 |
| LDL-C(mg/dL) \( ^\delta \) | 126.1±6.3 | 135.6±9.0 | 105.5±3.4 | 2.2 | 0.026 |

Values are frequencies or \( ^\delta \)mean ± SEM (N = 351), TDF = Tenofovir, AZT = Zidovudine, ABC = Abacavir, HDL-C = High density lipoprotein Cholesterol, LDL-C = Low density Lipoprotein Cholesterol.

\( ^\delta \)Prior regimens in subsequent order of NVP-based, EFV-based, and LPV/r-based before switched to the current ATV/r-based 2nd-line cART.

\( ^\delta \)Few study participants had a switch to 2nd-line between initiation and current 1st-line cART. HIV Comorbidities refer to conditions such as dyslipidemia, hepatitis or asthma based on patients’ report. \( \chi^2 \) = chi-square test for categoric variables, F = F-test for categoric variables with 1 cell expected count < 5 or t = independent t-test for continuous variables.

We also tried to calculate the prevalence of these variables based on tenofovir (TDF)-, zidovudine (AZT)-, and abacavir (ABC)-containing combinations. The prevalence of GMDs was higher in participants taking AZT- (29.6%) than TDF- (27.3%) and ABC (15.4%) containing combinations. Looking at the individual variables, the AZT-containing combination showed a relatively higher rate for IR (18.3%) and IFG (14%) than TDF- (13.9% for IR and 13.1% for IFG) and ABC- (7.7% for IR and 0% for IFG) containing combinations. By contrast, prevalence of DM was higher for ABC- (7.7%) than TDF- (5.6%), and AZT- (2.8%)-containing combinations.

Table 2. Prevalence of glucose metabolism disorders relative to the overall and specific type of combination antiretroviral treatment category among the study participants.

| Variables | Overall (N = 351) | EFV-Based cART (n = 240) | ATV/r-Based cART (n = 111) | \( \chi^2 \) or F or t | p |
|-----------|------------------|------------------------|---------------------------|----------------|---|
| Impaired Fasting Glycemia | 45 (12.8%) | 37 (15.4%) | 8 (7.2%) | 5.0 | 0.026 |
| Diabetes Mellitus | 20 (5.7%) | 17 (7.1%) | 3 (2.7%) | 1.5 | 0.318 |
| Insulin Resistance | 52 (14.8%) | 36 (15%) | 16 (14.4%) | 0.1 | 0.748 |
| Glucose Metabolism Disorders | 97 (27.6%) | 75 (31.3%) | 22 (19.8%) | 4.6 | 0.039 |
Table 3: Predictors of glucose metabolism disorders determined by logistic regression analysis among all study participants (n=97).

| Variables                          | Categories | Univariate | Multivariate |
|-----------------------------------|------------|------------|--------------|
|                                   |            | COR        | P            | AOR          | P             |
| **Age category**                  |            |            |              |              |               |
| <45                               | 1          |            |              | 1            | 0.006         |
| ≥46                               | 2.3(1.4, 3.8) | 0.000   | 2.1(1.2, 3.6) |              |               |
| **Gender**                        |            |            |              |              |               |
| Female                            | 1          |            |              | 1            | 0.001         |
| Male                              | 3.2(2.0, 5.3) | 0.000   | 2.6(1.4, 4.5) |              |               |
| **Educational status**            |            |            |              |              |               |
| Up to Primary                     | 1          |            |              | -            |               |
| Above primary                     | 1.6(0.9, 2.5) | 0.063   |              |              |               |
| **Marital status**                |            |            |              |              |               |
| Single                            | 1          |            |              | -            |               |
| Married                           | 1.0(0.6,2.0) | 0.913   |              |              |               |
| Widowed                           | 0.9(0.4,1.8) | 0.768   |              |              |               |
| Divorce                           | 1.1(0.5,2.3) | 0.856   |              |              |               |
| **Ever khat use (self-report)**   |            |            |              |              |               |
| Never                             | 1          |            |              | 0.034        |               |
| Current or previous               | 10.9(1.2, 98.6) |          |              |              |               |
| **Ever smoking (self-report)**    |            |            |              |              |               |
| Never                             | 1          |            |              | -            |               |
| Current or previous               | 5.3(0.5, 59.4) | 0.174   |              |              |               |
| **Ever alcohol use (Self-report)**|            |            |              |              |               |
| Never                             | 1          |            |              | -            |               |
| Current or previous               | 1.9(0.6, 6.2) | 0.276   |              |              |               |
| **Treatment adherence (3-day test)**|          |            |              |              |               |
| Non-adhered                       | 1          |            |              | -            |               |
| Adhered                           | 4.3(0.5, 34.1) | 0.162   |              |              |               |
| **BMI category**                  |            |            |              |              |               |
| ≥30                               | 1          |            |              | -            |               |
| <18.5                             | 0.13(0.04, 0.43) | 0.001   |              |              |               |
| 18.6–24.9                         | 0.5(0.2, 1.0) | 0.066   |              |              |               |
| 25–29.9                           | 0.4(0.2, 1.1) | 0.074   |              |              |               |
| **CD4 (n = 342) (recent)**        |            |            |              |              |               |
| <350                              | 1          |            |              | -            |               |
| ≥350                              | 0.9(0.6, 1.5) | 0.762   |              |              |               |
| **Viral load status(n = 335)**    |            |            |              |              |               |
| ≥1000 copies/ml                   | 1          |            |              | -            |               |
| <1000 copies/ml                   | 1.3(0.6, 3.2) | 0.524   |              |              |               |
| **History of comorbidity (self-reported)** |          |            |              |              |               |
| HIV-only                          | 1          |            |              | -            |               |
| HIV + comorbidity                 | 4.9(1.4, 17.0) | 0.013   | 4.7(1.2, 18.4) | 0.027        |               |
| **cART backbone-type**            |            |            |              |              |               |
| ATV/r-based                       | 1          |            |              | -            |               |
| EFV-Based                         | 1.8(1.1, 3.1) | 0.027   |              |              |               |
| **Specific ARVs contained in cART**|          |            |              |              |               |
| TDF containing                    | 0.9(0.5, 1.6) | 0.826   |              |              |               |
| AZT containing                    | 1.1(0.6, 2.0) | 0.682   |              |              |               |
| ABC containing                    | 0.5(0.1, 2.1) | 0.325   |              |              |               |
| **Time since HIV confirmed date (months)** | 1.003(0.998, 1.008) | 0.243   |              |              |               |
| **Cumulative time on cART (month)** | 0.993 (0.992, 0.995) | 0.000   |              |              |               |
| **Cumulative time on EFV-based 1st-line (month)** | 0.993(0.990, 0.995) | 0.000 |              |              |               |
| **Cumulative time on ATV/r-based 2nd-line (month)** | 0.966(0.952,0.980) | 0.000 | 0.98(0.96,0.99) | 0.011 |               |
| **Time on current cART regimen type (month)** | 0.992(0.989,0.995) | 0.000 |              |              |               |
| **Time on prior cART regimen types (month)** | 0.989(0.985,0.993) | 0.000 |              |              |               |
| **Time on NVP-based 1st-line (Prior to EFV) (month)** | 0.989(0.984,0.995) | 0.000 |              |              |               |
| **Time on LPV/r-based 2nd-line (prior to ATV/r) (month)** | 1.0(0.98,1.02) | 0.907 |              |              |               |
| **Waist circumference (cm)**      | 1.1(0.99, 1.11) | 0.055   | 0.96(0.94,0.99) | 0.002        |               |
| **Total cholesterol (mg/dL)**     | 1(0.998, 1.002) | 0.972   |              |              |               |
| **Triglyceride (mg/dL)**          | 1.008(1.004, 1.011) | 0.000   | 1.005(1.001, 1.008) | 0.017 |               |
| **HDL-C (mg/dL)**                 | 0.997 (0.987, 1.007) | 0.566 |              |              |               |
| **LDL-C (mg/dL)**                 | 1.001(0.999, 1.002) | 0.587 |              |              |               |

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associated with the incidence of GMD. A 4% lower incidence of GMD was noted with a 1 cm increase in waist circumference.

**Predictors for EFV-based cARTs.** Being age ≥46 years old, male gender, BMI category, and TDF-containing combinations were independent predictors to GMDs (Table 4). A 2.1-fold high risk of GMDs was observed among participants with age ≥46 years old (AOR = 2.1, 95% CI 1.1–4.0, p = 0.02). The male gender had a 4.3 times higher risk of GMDs (AOR = 4.3, 95% CI 2.2–8.3, p = 0.000). Underweights (BMI <18.5) had an 80% lower incidence of GMDs (AOR = 0.2, 95% CI 0.04, 0.7, p = 0.014) than obese participants (BMI ≥30). Likewise, TDF-regimens demonstrated a lower incidence of GMDs by about 70% (AOR = 0.3, 95% CI 0.1, 0.6, p = 0.001) than AZT-containing EFV-based cARTs. This was consistent with chi-square analysis, which found a significant association of GMDs with AZT-containing EFV-based regimen than AZT-containing ATV/r-based cART (χ² = 6.3, p = 0.012).

**Predictors for ATV/r-based cARTs.** Being age ≥46 years old, type of specific ARVs contained in ATV-based cART, and serum triglycerides level were independent predictors of GMDs incidence (Table 4). Participants with age ≥46 years old exhibited a 5.6 times higher risk of GMDs (AOR = 5.6, 95% CI 1.6, 21.3, p = 0.006) than age ≤45 years. A >90% lower incidence of GMDs was recorded for TDF-, AZT-, and ABC-containing than their corresponding non-containing type of ATV/r-based cARTs (Table 4). Concerning triglycerides level, the likelihood to develop GMDs increased by 0.9% (AOR = 1.009, 95% CI 1.002–1.016, p <0.05) for each unit increase.

**Discussion**

Our study aimed at determining the prevalence and predictors of GMDs among EFV and ATV/r-based cART receiving patients. The overall prevalence of GMDs among participants on EFV-based cART was relatively high than ATV/r-based cART. Remarkably, it was shown that EFV-based cART was associated with the occurrence of IFG than ATV/r-based regimen. Our study linked TDF-containing cART as an independent predictor of GMDs in both EFV- and ATV/r-based combination regimens. Our study considered IR along with IFG and DM as a measure of glucose abnormalities unlike other similar studies [9, 21, 32–34]. This may have increased the chance of detecting GMDs in our study while addressing the pathological hierarchy of glucose-related abnormalities, in which most ARVs in cART are implicated.

The prevalence of DM among PLWH on EFV-based cART in the present study (5.7%) is even higher than reported by WHO in 2016 (3.8%) and IDF (3.2%) [35, 36] for the general population of Ethiopia. This finding may be suggestive of a higher prevalence of GMDs among PLWH on cART, especially on NNRTIs like EFV. A comparative study by Levitt et al. [8] reported a prevalence of dysglycemia (26.0%) among PLWH on first-line ART, which is similar to the overall prevalence of GMDs in the present study (27.6%). A relatively close prevalence of GMDs (32.7%) was also reported in a study conducted in Tanzania among HIV-infected patients on ART, though the specific ARV drugs were not indicated [7]. Our study reported lower IFG (12.8% vs. 24%) but a higher DM prevalence (5.7% vs. 2%) than the South African study [37] among EFV-based cART treated participants. In addition, the DM prevalence in this study was slightly lower than reported from North-east (8.8%) [21] and North-west (8.8%) [9] Ethiopia. But it is concordant with that reported from another North-west Ethiopian (5.1%) [33] and Zambian (5%) [38] studies. On the other hand, a lower prevalence of IR was observed in this study as compared to the 21% prevalence reported in a longitudinal study by Araujo et al. [29] and 34.2% by Guillen et al. [10]. In general, a varied prevalence has been reported for IR, IFG and DM across the literature. These discrepancies could be due to variations in methodology. For instance, the above-stated
Table 4. Predictors of glucose metabolism disorders among EFV- (n = 75) and ATV/r-based (n = 22) cART receiving groups.

| Variables | Categories | EFV-based | ATV/r-based |
|-----------|------------|-----------|-------------|
|           |            | Univariate | Multivariate | Univariate | Multivariate |
|           |            | COR p AOR p |            | COR p AOR p |            |
| Age category | ≤45 | 1 | 1 | 1 | 1 | 5.6(1.6,19.3) | 0.006 |
|            | ≥46 | 0.5 (0.3,0.8) | 0.006 | 2.1(1.1, 4.0) | 0.02 | 0.4 (0.2, 1.1) | 0.069 |
| Gender | Female | 1 | 1 | 1 | 1 | 4.6 (2.6,8.4) | 0.000 | 4.3 (2.2, 8.3) | 0.000 | 1.1 (0.4,3.1) | 0.891 |
|            | Male | 0.5 (0.3,0.8) | 0.002 | 0.4 (0.1,0.8) | 0.017 | 0.3 (0.1,0.9) | 0.023 |
| Educational status | Up to primary | 1 | 1 | 1 | 1 | 1.8 (0.99,3.1) | 0.055 | 1.1 (0.4,2.9) | 0.868 |
|            | Above Primary | 0.48 (0.37,0.63) | 0.000 | 0.24 (0.15,0.39) | 0.000 | 0.1 (0.01,0.54) | 0.011 |
| Marital status | Single | 1 | 1 | 1 | 1 | 0.5 (0.3,0.8) | 0.002 | 0.4 (0.1,0.8) | 0.017 | 0.3 (0.1,0.9) | 0.023 |
|            | Married | 0.5 (0.3,0.8) | 0.002 | 0.4 (0.1,0.8) | 0.017 | 0.3 (0.1,0.9) | 0.023 |
|            | Widowed | 0.3 (0.2,0.9) | 0.000 | 0.4 (0.1,0.8) | 0.017 | 0.3 (0.1,0.9) | 0.023 |
|            | Divorce | 0.5 (0.2,0.9) | 0.022 | 0.3 (0.1,0.9) | 0.023 | 0.3 (0.1,0.9) | 0.023 |
| Treatment adherence (3-day test) | Non-adhered | 1 | 1 | 1 | 1 | 0.1 (0.04, 0.46) | 0.001 | 0.2 (0.04,0.7) | 0.014 | 0.1 (0.01,0.54) | 0.011 |
|            | Adhered | 0.48 (0.37,0.63) | 0.000 | 0.24 (0.15,0.39) | 0.000 | 0.1 (0.01,0.54) | 0.011 |
| BMI category | ≥30 | 1 | 1 | 1 | 1 | 0.5 (0.3, 0.6) | 0.002 | 0.4 (0.1,0.5) | 0.000 | 0.2 (0.1,0.4) | 0.000 |
|            | <18.5 | 0.1 (0.04,0.46) | 0.001 | 0.2 (0.04,0.7) | 0.014 | 0.1 (0.01,0.54) | 0.011 |
|            | 18.6–24.9 | 0.7 (0.5,0.99) | 0.042 | 0.8 (0.3,1.7) | 0.499 | 0.3 (0.1,0.5) | 0.000 |
|            | 25–29.9 | 0.4 (0.23,0.62) | 0.000 | 0.5 (0.2,1.1) | 0.096 | 0.3 (0.1,0.7) | 0.008 |
| CD4 (n = 342) (recent) | <350 | 1 | 1 | 1 | 1 | 0.5 (0.3, 0.6) | 0.002 | 0.4 (0.1,0.5) | 0.000 | 0.2 (0.1,0.4) | 0.000 |
|            | ≥350 | 0.4 (0.3,0.6) | 0.000 | 0.2 (0.1,0.4) | 0.000 | 0.1 (0.01,0.54) | 0.011 |
| Viral load status (n = 335) | ≥1000 copies/ml | 1 | 1 | 1 | 1 | 0.5 (0.3, 0.6) | 0.002 | 0.4 (0.1,0.5) | 0.000 | 0.2 (0.1,0.4) | 0.000 |
|            | <1000 copies/ml | 0.5 (0.3, 0.6) | 0.000 | 0.2 (0.1,0.4) | 0.000 | 0.1 (0.01,0.54) | 0.011 |
| History of comorbidity (self-reported) | HIV-only | 1 | 1 | 1 | 1 | 2.5 (0.5,12.9) | 0.273 | 1.0 (0.1,7.1) | 0.008 |
|            | HIV + comorbidity | 0.1 (0.04,0.8) | 0.027 | 0.034 (0.002,0.474) | 0.000 |
| Specific ARVs contained in cART | TDF containing | No | 1 | 1 | 1 | 1 | 1 | 1 | 0.03 |
|            | Yes | 0.4 (0.3,0.6) | 0.000 | 0.3 (0.1,0.6) | 0.001 | 0.2 (0.1,0.5) | 0.000 | 0.101 (0.013,0.802) | 0.000 |
| AZT containing | No | 1 | 1 | 1 | 1 | 0.9 (0.4,2.0) | 0.842 | 0.092 (0.013,0.637) | 0.000 |
|            | Yes | 0.9 (0.4,2.0) | 0.842 | 0.092 (0.013,0.637) | 0.000 |
| ABC containing | No | 1 | 1 | 1 | 1 | 0.9 (0.4,2.0) | 0.842 | 0.092 (0.013,0.637) | 0.000 |
|            | Yes | 0.9 (0.4,2.0) | 0.842 | 0.092 (0.013,0.637) | 0.000 |
| Time since HIV confirmed date (months) | 0.995 (0.993,0.997) | 0.000 | 0.989 (0.986,0.997) | 0.000 | 0.99 (0.98,1.0) | 0.054 |
| Cumulative time on cART (month) 6 | 0.995 (0.993,0.997) | 0.000 | 0.989 (0.985,0.993) | 0.000 |
| Cumulative time on EFV-based 1st-line (month) 6 | 0.994 (0.991,0.996) | 0.000 | 0.984 (0.975,0.992) | 0.000 |
| Cumulative time on ATV/r-based 2nd-line (month) 6 | 1.0(0.97,1.04) | 0.891 | 0.961 (0.946,0.977) | 0.000 |
| Time on current cART regimen type (month) 6 | 0.993 (0.991,0.996) | 0.000 | 0.987 (0.984,0.992) | 0.000 |
| Time on prior cART regimen types (month) 6 | 0.992 (0.986,0.997) | 0.003 | 0.987 (0.981,0.992) | 0.000 |
| Time on NVP-based 1st-line (prior to EFV) (month) 6 | 0.992 (0.986,0.999) | 0.017 | 0.985 (0.977,0.994) | 0.001 |

(Continued)
studies from Northwest Ethiopia, Northeast Ethiopia, and Zambia considered IFG and DM, while our study included IR parameters in addition to IFG and DM to determine the prevalence and risk factors [9, 21, 33, 38]. The sensitivity of kits or equipment used to determine fasting glucose might also differ, accounting for the observed differences (we used the Cobas 6000 (c501) analyzer machine and glucometer was used by the Zambian study). Study designs employed could also contribute to the differences. Araujo et al. [29] determined the prevalence using a prospective cohort study, recruiting participants from different types of cART, unlike ours which used a cross-sectional study design using only EFV- and ATV/r-based regimens.

Several studies suggested that EFV containing cART is linked with elevated blood glucose levels due to mitochondrial toxicity or IR [34, 39, 40]. This notion could explain why a high prevalence of GMDs was observed among EFV- than ATV/r-based cART receiving study participants. In contrast, a cross-sectional study from Tanzania indicated that neither EFV nor other ARVs had an association with GMDs among HIV-infected patients on cART [7]. Nonetheless, several lines of recent evidence implicated NNRTIs in disturbed glucose metabolism. For example, studies reported that increased fasting plasma glucose, insulin levels, and decreased insulin sensitivity were observed in NNRTI-based regimens, particularly with EFV [34, 39, 40].

This is one of the few studies that assessed GMDs among HIV-infected patients on ATV/r-based cART, particularly in Ethiopia. As ATV/r-based therapy is relatively new to most resource-limited health settings, our study may provide baseline evidence concerning GMDs during ATV/r-based regimen use. Thus, the findings could help guide ARV drug selection when switching to PI-based second line is considered, particularly for the high-risk group of HIV patients. Based on the finding of this study, those participants on ATV/r-based therapies had a low prevalence of GMDs (3.6%), which is similar to the DM estimates of the Ethiopian population for 2016 (3.8%) [35].

The findings highlighted that the type of specific ARVs contained in cART could influence the occurrence of GMDs, as participants on TDF-containing regimens had a significantly reduced risk for developing GMDs than those on without TDF. Considering IR as a component of GMDs, our study is consistent with the interpretation of “The Women’s interagency HIV study” that reported a lack of clear elevation or precise association between cumulative exposure to five NRTIs, including AZT, ABC or TDF, and HOMA [11].

Consistent with previous studies, our study demonstrated that patients above 45 years of age are at higher odds of developing GMDs in both regimen types as well as in the overall

| Variables Categories | EFV-based Univariate | ATV/r-based Univariate | EFV-based Multivariate | ATV/r-based Multivariate |
|----------------------|----------------------|------------------------|------------------------|------------------------|
| Time on LPV/r-based 2nd-line (prior to ATV/r) (month) " | COR: 1.7 | p: 1.000 | COR: 1.000 | p: 0.728 |
| Waist circumference (cm) | COR: 0.979 (0.972,0.987) | p: 0.000 | COR: 0.961 (0.948,0.975) | p: 0.000 |
| Total cholesterol (mg/dL) | COR: 0.996 (0.995,0.998) | p: 0.000 | COR: 0.993 (0.990,0.995) | p: 0.000 |
| Triglyceride (mg/dL) | COR: 0.997 (0.996,0.999) | p: 0.001 | COR: 0.994 (0.991,0.996) | p: 0.000 |
| HDL-C (mg/dL) | COR: 0.984 (0.978,0.99) | p: 0.000 | COR: 0.967 (0.955,0.978) | p: 0.000 |
| LDL-C (mg/dL) | COR: 0.996 (0.994,0.998) | p: 0.000 | COR: 0.988 (0.983,0.992) | p: 0.000 |

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study participants. Aging is a well-recognized traditional risk factor for IFG, diabetes or GMDs in general. A rise in the incidence of GMDs might occur among HIV-infected patients because of increased survival or aging in the face of long-term exposure to cART [7, 21, 41]. Our findings also indicated male patients, specifically among EFV-based cART, were at a higher risk of encountering GMDs than females, which is in line with other studies [34, 38, 41–44]. A meta-analysis also found a significantly higher prevalence of IFG in men among the general population of Eastern, Middle, and Southern African countries [45]. It is thus plausible to assume that the same trend might occur in HIV-infected patients on cART. Although direct evidence is lacking, previous studies suggest that in addition to socio-cultural, lifestyle, or behavioral factors; anthropometric, metabolic, and endocrine differences could contribute to the gender disparity in the prevalence of GMDs [46, 47]. It is also suggested that differences in type and composition of fat might have a role in the risk for IFG, IR, or DM between men and women [48].

Study limitations
The use of a one-time sampling to define glycemic status rather than confirmation on a subsequent day as recommended can be considered as one of the limitations. However, determination of fasting glucose was run three times for each sample and the average was reported, which could probably offset this limitation. Despite the exclusion of participants with DM, our study design lacks excluding study participants who may have other GMDs. Moreover, our study lacks assessing casual association between long term-cART and GMDs as the study did not have control groups and prior baseline data. The study may also share the limitations emanating from the study design effect, as we used a single institution, a cross-sectional study, and a consecutive sampling during recruitment. Hence, the findings might not be extrapolated to the general PLWH receiving treatment in Ethiopia. Nevertheless, one should note that the study site is the largest referral hospital in Ethiopia, where patients from different parts of the country are referred to receive care. Despite the limitations, this study generated findings related to higher prevalence of GMDs among HIV-infected adult patients, particularly those on EFV-based cART. However, future studies with large sample size, comparative case-control, and prospective study design comprising these regimens should be conducted to confirm the predictors and determine if there exist casual relationships between GMDs and long-term cART.

Conclusions
In conclusion, we report a high prevalence of GMDs, such as IR, IFG, and DM, among PLWH on EFV-based cART. Age 46 and above and TDF-containing cART were common predictors of GMDs in both EFV- and ATV/r-based treatment groups. The male gender and BMI are predictors of GMDs in EFV-based cART group. AZT- containing and ABC-containing ATV/r-based cARTs as well as elevated serum triglycerides are predictors of GMDs in ATV/r-based cART receiving group. Close monitoring for impaired fasting glucose during long-term efavirenz-based cART is recommended for early diagnosis of type-2 diabetes and management.

Supporting information
S1 Raw data.
(SAV)
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References

1. Dwyer-Lindgren L, Cork MA, Sligar A, Steuben KM, Wilson KF, Provost NR, et al. Mapping HIV prevalence in sub-Saharan Africa between 2000 and 2017. Nature. 2019; 570: 189–193. https://doi.org/10.1038/s41586-019-1200-9 PMID: 31092927

2. Kharsany ABM, Karim QA. HIV Infection and AIDS in Sub-Saharan Africa: Current Status, Challenges and Opportunities. Open AIDS J. 2016; 10: 34–48. https://doi.org/10.2174/1874613601610010034 PMID: 27347270

3. Eggleton JS, Nagalli S. Highly Active Antiretroviral Therapy (HAART). StatPearls. Treasure Island (FL): StatPearls Publishing; 2020. http://www.ncbi.nlm.nih.gov/books/NBK554533/.

4. El Bcheraoui C, Wang H, Charara R, Khalil I, Moradi-Lakeh M, Afshin A, et al. Trends in HIV/AIDS morbidity and mortality in Eastern Mediterranean countries, 1990–2015: findings from the Global Burden of Disease 2015 study. Int J Public Health. 2018; 63: 123–136. https://doi.org/10.1007/s00038-017-1023-0 PMID: 28776249

5. Bueil KG, Chung C, Chaudhry Z, Puri A, Nawab K, Ravindran RP. Lifelong antiretroviral therapy or HIV cure: The benefits for the individual patient. AIDS Care. 2016; 28: 242–246. https://doi.org/10.1080/09540121.2015.1074653 PMID: 26357912

6. Thet D, Sintientong T. Antiretroviral Therapy-Associated Metabolic Complications: Review of the Recent Studies. HIV AIDS (Auckl). 2020; 12: 507–524. https://doi.org/10.2147/HIV.S275314 PMID: 33061662

7. Maganga E, Smart LR, Kailuvya S, Kataraihya JB, Saleh AM, Obeid L, et al. Glucose Metabolism Disorders, HIV and Antiretroviral Therapy among Tanzanian Adults. PLOS ONE. 2015; 10: e0134410. https://doi.org/10.1371/journal.pone.0134410 PMID: 26287742

8. Levitt NS, Peer N, Steyn K, Lombard C, Maartens G, Lambert EV, et al. Increased risk of dysglycaemia in South Africans with HIV; especially those on protease inhibitors. Diabetes Research and Clinical Practice. 2016; 118: 41–47. https://doi.org/10.1016/j.diabres.2016.03.012 PMID: 27423428

9. Gebrie A, Tesfaye B, Gebre T, Adane F, Abie W, Sisay M. Diabetes mellitus and its associated risk factors in patients with human immunodeficiency virus on anti-retroviral therapy at referral hospitals of
10. Guilen MA, Mejia FA, Villena J, Turin CG, Carcamo CP, Tisce R. Insulin resistance by homeostasis model assessment in HIV-infected patients on highly active antiretroviral therapy: cross-sectional study. Diabetol Metab Syndr. 2015; 7. https://doi.org/10.1186/s13098-015-0046-z PMID: 26034512

11. Brown TT. Antiretroviral Therapy and the Prevalence and Incidence of Diabetes Mellitus in the Multicenter AIDS Cohort Study. Arch Intern Med. 2005; 165: 1179. https://doi.org/10.1001/archinte.165.10.1179 PMID: 1591733

12. Santiprabhob J, Tanchaweng S, Maturapat S, Maleesathorn A, Lermankul W, Sricharoenchai S, et al. Metabolic Disorders in HIV-Infected Adolescents Receiving Protease Inhibitors. In: BioMed Research International [Internet]. Hindawi; 15 Feb 2017 [cited 9 Jan 2021] p. e7481597. https://doi.org/10.1155/2017/7481597 PMID: 28293638

13. Noor MA, Flint OP, Maa J-F, Parker RA. Effects of atazanavir/ritonavir and lopinavir/ritonavir on glucose uptake and insulin sensitivity: demonstrable differences in vitro and clinically. AIDS. 2006; 20: 1813–1821. https://doi.org/10.1097/01.aids.0000244200.11006.55 PMID: 16954722

14. d’Ettorre G, Cecarelli G, Zacarelli M, Ascoli-Bartoli T, Bianchi L, Bellelli V, et al. Impact of switching from lopinavir/ritonavir to boosted and un-boosted atazanavir on glucose metabolism: the ATAzanavir & GLUCose metabolism (ATAGLU) study. Int J STD AIDS. 2016; 27: 638–643. https://doi.org/10.1177/0956462415590724 PMID: 26068963

15. Tadesse BT, Foster BA, Chala A, Chaka TE, Bizuayehu T, Ayalew F, et al. HIV and cART-Associated Dyslipidemia Among HIV-Infected Children. Journal of Clinical Medicine. 2019; 8: 430. https://doi.org/10.3390/jcm8040430 PMID: 3092831

16. Muche Belete A, Seifu D, Menon M, Amogne W, Shewa A, Adela Tefera A. Serum Lipid Profiles of Patients Taking Efavirenz-Based Antiretroviral Regimen Compared to Ritonavir-Boosted Atazanavir with an Optimized Background at Zewduit Memorial Hospital, Addis Ababa, Ethiopia. HIV AIDS (Auckl). 2021; 13: 217–227. https://doi.org/10.2147/HIV.S296170 PMID: 33642861

17. Ministry of Health of Ethiopia. National consolidated guidelines for comprehensive HIV prevention, care and treatment. 2018 [cited 23 Oct 2021]. In: WHO | Regional Office for Africa. https://www.afro.who.int/publications/national-consolidated-guidelines-comprehensive-hiv-prevention-care-and-treatment

18. Yifter H, Reja A, Ahmed A, Narayan KMV, Amogne W. Achievement of diabetes care goals at Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia. EMJ. 2020; 58. Available: https://emjema.org/index.php/EMJ/article/view/1702.

19. Charan J, Biswas T. How to calculate sample size for different study designs in medical research? Indian J Psychol Med. 2013; 35: 121. https://doi.org/10.4103/0253-7176.116232 PMID: 24049221

20. Gebreyesus HA. Prevalence of prediabetes in HIV-1 infected adults receiving antiretroviral therapy in Addis Ababa, Ethiopia. Int J Pharm Sci Res. 2015; 6: 440–443. Available: https://scholar.google.com/scholar_lookup?journal=Int+J+Pharm+Sci+Res&title=Prevalence+of+prediabetes+in+HIV+1+infected+adults+receiving+antiretroviral+therapy+in+Addis+Ababa,+Ethiopia&author=HA+Gebreyesus&volume=6&publication_year=2015&pages=440-443

21. Fiseha T, Belete AG. Diabetes mellitus and its associated factors among human immunodeficiency virus-infected patients on anti-retroviral therapy in Northeast Ethiopia. BMC Research Notes. 2019; 12: 372. https://doi.org/10.1186/s13104-019-4402-1 PMID: 3126341

22. Giordano TP, Guzman D, Clark R, Charlebois ED, Bangsberg DR. Measuring Adherence to Antiretroviral Therapy in a Diverse Population Using a Visual Analogue Scale. HIV Clinical Trials. 2004; 5: 74–79. https://doi.org/10.1310/JFXH-G3X2-EYM6-DeUG PMID: 15116282

23. Da W, Li X, Qiao S, Zhou Y, Shen Z. Evaluation of self-report adherence measures and their associations with detectable viral load among people living with HIV (PLHIV) in China. PLOS ONE. 2018; 13: e0203032. https://doi.org/10.1371/journal.pone.0203032 PMID: 3091177

24. Tadesse WT, Mekonnen AB, Tesfaye WH, Tadesse YT. Self-reported adverse drug reactions and their influence on highly active antiretroviral therapy in HIV infected patients: a cross sectional study. BMC Pharmacology and Toxicology. 2014; 15: 32. https://doi.org/10.1186/2050-6511-15-32 PMID: 24957052

25. World Health Organization. Waist circumference and waist:hip ratio: report of a WHO expert consultation, Geneva, 2008 Dec 8–11. [cited 15 Oct 2021]. https://apps.who.intiris/handle/10665/44583.

26. World Health Organization and International Diabetes Federation. Definition and diagnosis of diabetes mellitus and intermediate hyperglycaemia: report of a WHO/IDF consultation. 2008 [cited 15 Oct 2021]. https://apps.who.int/iris/handle/10665/43588.

27. WHO. Indicator Metadata Registry Details. In: World Health Organization [Internet]. 2021 [cited 15 Oct 2021]. https://www.who.int/data/gho/indicator-metadata-registry/imr-details/2380.
28. Jamil AS, Alaal AF, Al-Tawil NG, Al-Shawaf T. A case–control observational study of insulin resistance and metabolic syndrome among the four phenotypes of polycystic ovary syndrome based on Rotterdam criteria. Reproductive Health. 2015; 12: 7. https://doi.org/10.1186/1742-4755-12-7 PMID: 25595199

29. Araujo S, Baños I, Machuca I, Moreno A, Pérez-Elías MJ, Casado JL. Prevalence of insulin resistance and risk of diabetes mellitus in HIV-infected patients receiving current antiretroviral drugs. Eur J Endocrinol. 2014; 171: 545–554. https://doi.org/10.1530/EJE-14-0337 PMID: 25117462

30. Nguyen QM, Srinivasan SR, Xu J-H, Chen W, Berenson GS. Fasting Plasma Glucose Levels Within the Normoglycemic Range in Childhood as a Predictor of Prediabetes and Type 2 Diabetes in Adulthood: The Bogalusa Heart Study. Arch Pediatr Adolesc Med. 2010; 164. https://doi.org/10.1001/archpediatrics.2009.268 PMID: 20124140

31. Muniyappa R, Madan R. Assessing Insulin Sensitivity and Resistance in Humans. In: De Groot LJ, Hillawe EH, Yatsuya H, Kawaguchi L, Aoyama A. Differences by sex in the prevalence of diabetes mellitus, impaired fasting glycaemia and impaired glucose tolerance in sub-Saharan Africa: a systematic review and meta-analysis. Bull World Health Organ. 2013; 91: 671–682D. https://doi.org/10.2471/BLT.12.113415 PMID: 24101783
46. Kautzky-Willer A, Harreiter J, Pacini G. Sex and Gender Differences in Risk, Pathophysiology and Complications of Type 2 Diabetes Mellitus. Endocr Rev. 2016; 37: 278–316. https://doi.org/10.1210/er.2015-1137 PMID: 27159875

47. Floridia M, Giuliano M, Palmisano L, Vella S. Gender differences in the treatment of HIV infection. Pharmacological Research. 2008; 58: 173–182. https://doi.org/10.1016/j.phrs.2008.07.007 PMID: 18708144

48. Borel A-L, Nazare J-A, Smith J, Aschner P, Barter P, Van Gaal L, et al. Visceral, subcutaneous abdominal adiposity and liver fat content distribution in normal glucose tolerance, impaired fasting glucose and/or impaired glucose tolerance. International Journal of Obesity. 2015; 39: 495–501. https://doi.org/10.1038/ijo.2014.163 PMID: 25179244