Biomarkers and prevalence of cardiometabolic syndrome among people living with HIV/AIDS, Addis Ababa, Ethiopia: a hospital-based, observational study.

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Abstract

Background

Although marked improvements in life expectancy have been observed with the rapid expansion of Antiretroviral Therapy (ART), Cardiometabolic Syndrome (CMetS) is becoming a serious challenge for People Living with HIV/AIDS (PLWHA). The present study aimed in determining biomarkers and prevalence of CMetS in PLWHA.

Methods

A hospital-based, observational study was carried out between January 2019 & February 2020 among HIV infected adults (n = 288). Binary logistic regression was used to estimate odds ratio (OR) and corresponding 95% confidence interval (CI) for the association between the outcomes against the predictor variables.

Results

The current study revealed that the prevalence of CMetS was 28.5% (82/288) using the National Cholesterol Education Program (NCEP)-2005 definition; and it was 43.5% (126/288) using the International Diabetes Federation (IDF)-2005. Male gender was less likely to be associated with CMetS (OR = .086, C.I. 0.025–0.292, p < 0.001) using the NCEP-2005 definition. Individuals with longer duration on ART have an increased odds of CMetS using both the NCEP-2005 (OR = 1.024, C.I. 1.005–1.043, p = 0.014) and the IDF-2005 (OR = 1.251, C.I. 1.061–1.472, p = 0.007) definitions. The age at which ART initiated yet have an impact on the outcomes of CMetS (NCEP-2005: OR = 1.27, C.I. 1.031–1.564, p = 0.025), indicating that individuals who started ART treatment at older age are more likely to have CMetS than their younger counterparts. The study further verified that, individuals with increased waist-grid (central adiposity) were more likely to have CMetS using both the NCEP-2005 (OR = 1.21, C.I. 1.029–1.418, p = 0.021) and the IDF-2005 (OR = 1.730 C.I. 1.454–2.058, p < 0.001) definitions. PLWHA with increased in DBP (OR = 1.164, C.I.1.080–1.254, p < 0.001), Triglyceride (OR = 1.027, C.I. 0.015–0.039, p < 0.001), and low density lipoproteins (OR = 1.075, C.I. 0.020–0.134, p = 0.007) were more likely to have CMetS using the NCEP-2005 definition. PLWHA without comorbidity were less likely to have CMetS (NCEP-2005: OR = 0.086, C.I. 0.025–0.292, p < 0.001).

Conclusions

The prevalence of CMetS in the study area was high. Risk factors associated with CMetS were waist circumference, gender, duration on ART; ART initiated age, waist-grid, and comorbidity. Biomarkers that were more likely contributed to the prevalence of CMetS include triglyceride, low density lipoproteins, and systolic blood pressure.

Introduction

People Living with HIV/AIDS (PLWHA) have been greatly benefited from the introduction of Antiretroviral Therapy (ART) in terms of quality of life, lengthen survival and psychological boost. However, medication and disease related problems have put the ART management in jeopardy [1–6]. Cardiometabolic Syndrome (CMetS) is a group of cardiac and metabolic derangement manifested with alteration on common biomarkers such as Impaired Glucose Tolerance (IGT), Insulin Resistance (IR), high serum Triglycerides (TG), low High-Density Lipoprotein Cholesterol (HDL-C) levels, hypertension, central adiposity, high Fasting Blood Sugar (FBS), and diseases involving the cardiac system [6–13].

Several definitions are being used to define CMetS including the Modified National Cholesterol Education Programme Adult Treatment Panel III (NCEP-ATP III)-2005, the International Diabetes Federation (IDF)-2005, the World Health Organization (WHO)-1998, the European Group for the Study of Insulin Resistance (EGIR)-1999, and the American Heart Association and the National Heart, Lung, and Blood Institute (AHA/ NHLBI) definitions [14–16]. Each definition has its distinctive reason and characterization of variable selection and except for the NCEP-ATP III definition, all the rest definition have an absolute requirement, whereas for the NCEP-2005 definition, there is no an absolute requirement. The five requirements are hypertension, hyperglycemia, dyslipidemia type 1 (measuring TGs) and dyslipidemia type 2 (measuring HDL-C), and waist-grid. Fulfilling three out of the five requirements are needed to define CMetS. Microalbuminuria measurement is an optional criterion for the WHO definition [14, 17–20]. The detail is available in annex-1 [14, 17–20].
Biomarkers or biological markers are objective indications of medical state that can be measured accurately and reproducibly [21]. Biomarkers provide a dynamic and powerful approach to understanding the spectrum of disease detection, progression, and monitoring [22]. Historically, biomarker were coined only to biological fluid, tissues, and chemicals that has been related and used to evaluate the disease conditions [23]. Nowadays, the term biomarker can also be used in various aspects outside biological samples as long as it is helpful in diagnosis, measuring, and monitoring disease conditions [21, 24]. HIV guidelines globally are focusing on HIV treatment and disease monitoring, giving less attention to emerging problems like CMetS, makes the standard of ART care imperfect [25–27]. Hence, the present study is aimed at determining the prevalence and biomarkers of CMetS among HIV infected adults on follow-up care.

**Methods**

**Study design, period and setting**

This was a hospital-based, observational study conducted during the period of 25/01/2019 to 25/02/2020 in HIV infected adults on follow-up care at Zewditu Memorial Hospital (ZMH), Addis Ababa, Ethiopia. The study was part of a large cohort study aimed at reporting the prevalence data. ZMH is the first hospital inaugurated as well as initiated ART service in Ethiopia, July 2003 [28, 29].

**Study population**

The study population was all PLWHA attending the ART follow-up care at ZMH. The target population was PLWHA with age ≥ 18 years and willing to participate in the study.

**Sample size determination**

The following equation was used to calculate the sample size:

\[
\text{Sample size } n = \frac{\text{DEFF} \times Np \times (1-p)}{(d^2/z^2) \times (1-\alpha/2 \times (N-1) + p \times (1-p))}
\]

| Population size (for finite population correction factor or FPC) \(N\): | 7674 |
|---|---|
| Hypothesized % frequency of outcome factor in the population \(p\): | 26%±/−5 [30] |
| Confidence limits as % of 100(absolute +/- %) \(d\): | 5% |
| Design effect (for cluster surveys-DEFF): | 1 |
| Confidence Level (%): | 95% |
| Sample Size: | 286 |

Where, \( N (7674) \) is the total HIV infected population registered for follow-up care and \( P \) is the prevalence for CMetS in HIV- infected population obtained from published articles [30]. Considering 10% contingency (lost to follow-up and defaulters), the final sample size of the study became 314.

**Research Questions**

1. Do HIV infected persons in Ethiopia have a higher prevalence of CMetS?
2. What are the biomarkers associated with CMetS in this population?
3. What are the risk factors that predispose HIV-infected individuals for prevalence and progression of CMetS?

**Hypothesis**

The prevalence, biomarkers, and risk factors of CMetS among HIV infected persons in Ethiopia are not different from other similar studies.

**Sampling procedure and enrollment**

A systematic random sampling technique was used to recruit study participants. The sample interval (K) was calculated using the formula \( N/n (7674/314\approx24) \). The first participant was selected using a lottery method.

**Data collection**
Participants’ information was collected in the form of interview and by tracking participants’ charts. The questionnaire for a face-to-face interview was adapted from the structured questionnaire used by the WHO Stepwise approach to non-communicable disease risk factor surveillance (STEPS-2014) [31]. The questionnaire was composed of information related to socio-demographic characteristics and clinical characteristics. Data were collected by two trained data collectors who administered the questionnaire, performed anthropometric measurements, measured BP, and took blood samples for biomedical measurements. Anthropometric measurements including weight (in Kg), Height (in meter), a derived Body Mass Index (BMI = weight in kg/ height in m²), and Waist Grid Circumference/Abdominal Circumference (in inch) were taken.

**Data analysis**

Data was coded, double-entered, and analyzed using IBM SPSS Statistics 25. Descriptive and inferential statistics were used to present data. Binary logistic regression was used to estimate odds ratios (ORs) and corresponding 95% confidence intervals (CIs) for the association between the outcomes against the predictor variables. The mean of the repeated measures were used in cases of Pulse Rate (PR), Systolic Blood Pressure (SBP), and Diastolic Blood Pressure (DBP); whereas, for the other variables, the baseline data was used to determine the effect on the prevalence of CMetS. A 95% C.I was used and the level of significance for statistical analysis was set at less than 0.05.

Height and weight were measured by Type ZT-160 body-weight balance. Biomedical measurements such as PR (per minute), SBP (mmHg), DBP (mmHg), and tests such as FBG (mg/dl), and Fasting Blood Cholesterol (mg/dl) were taken routinely during appointments (every six months). BP and PR were measured by Omron HEM 7203, a fully automatic digital blood pressure monitor (Omron Healthcare Co. Ltd., Kyoto, Japan). The devices were regularly calibrated for proper validation. Mercury sphygmomanometer was used for evaluating the accuracy of the devices. Three BP recordings were obtained from the right arm of the patients with an interval of 5 min and the mean of the three readings was used for the final result. All measurements were taken at baseline and then repeated after 6 months [32, 33].

An absolute CD4 count (AbsCD4) and per cent CD4 (%CD4) were measured by BD FACSPresto™ and BD FACSCalibur™. Viral load was measured using the Abbott RealTime HIV-1 assay. Lipid profiles were measured using SIEMENS (Dimension EXL 200 Integrated Chemistry System) and the Omina Health (CS-T240 Auto-Chemistry Analyzer). The instruments analyze integrated clinical chemistry and immunoassay.

**Operational definition**

Biomarkers: are measurable indicators of some biological state or condition. Includes waist-grid, BMI, BP, Lipid profile, CD4 and VL measurements, and blood sugar measurements.

Risk factor or determinant: is a variable associated with an increased risk of disease or infection. Examples include: Age, Race/ethnicity, Gender, Some medical conditions, Use of certain medications, Poverty and crowding, certain occupations, Pregnancy.

**Results**

In this observational study, although 314 patients were initially enrolled, the final sample size used for analysis was (n = 288) HIV infected persons. Twenty-six patients were out of the analysis for various reasons: two were discontinued from follow-up due to change of addresses, four were due to critical illnesses (one due to HBS, three due to high BP), and the rest 10 were defaulter for unknown reasons (Fig. 1).

The demographic data illustrated that a slight preponderance of female (162, 56.2%), and nearly 1 in 2 were married, half 62 (21.5%) were divorced, 1 in 3 were completed secondary high school of grade 9-12th education, and 1 in 4 were involved in small self-employed with employee business. Almost, 10 % of the population was jobless and 4.5 % were students. Majority 271 (94.1%) were from Addis Ababa (see Table 1).
Table 1
Socio-demographic information of the study participants: counts, percent of total and cumulative percent; Zewditu Memorial Hospital, June 2020, Addis Ababa, Ethiopia.

| Socio-demographic | Counts | % of Total |
|-------------------|--------|------------|
| Gender            |        |            |
| Female            | 162    | 56.3       |
| Male              | 126    | 43.8       |
| Age               |        |            |
| 20–34             | 52     | 18.1       |
| 35–39             | 47     | 16.3       |
| 40–44             | 55     | 19.1       |
| 45–49             | 43     | 14.9       |
| 50–54             | 35     | 12.2       |
| 55–59             | 23     | 8.0        |
| 60–64             | 21     | 7.3        |
| 65–69             | 5      | 1.7        |
| 70–74             | 3      | 1.0        |
| 75–79             | 1      | 0.3        |
| Civil status      |        |            |
| Never married     | 53     | 18.4       |
| Married           | 130    | 45.1       |
| Divorced          | 62     | 21.5       |
| Widowed/r         | 43     | 14.9       |
| Educational status|        |            |
| No formal education| 35  | 12.2       |
| Primary (1-6th grade) | 65 | 22.6       |
| Secondary Junior (7-8th grades) | 27 | 9.4        |
| Secondary High school (9-12th grades) | 96 | 33.3       |
| College/university diploma | 47 | 16.3       |
| College/ University Degree/master or above | 18 | 6.3        |
| Occupational status# |    |            |
| Higher-level professional | 1 | 0.3        |
| Higher-level manager and entrepreneur | 1 | 0.3        |
| Lower level professional | 27 | 9.4        |
| Lower level manager | 3 | 1.0        |
| Clerical routine non-manual worker | 11 | 3.8        |
| Sales and service routine non-manual worker | 1 | 0.3        |

# Classification is based on ISEC (International Socio-Economic Classes) 64.
| Socio-demographic                      | Counts | % of Total |
|---------------------------------------|--------|------------|
| Small self-employed with employee     | 11     | 3.8        |
| Small self-employed without employer  | 71     | 24.7       |
| Skilled manual worker                  | 21     | 7.3        |
| Semi- and unskilled manual worker      | 84     | 29.2       |
| Agricultural laborer                   | 2      | 0.7        |
| Retired                                | 13     | 4.5        |
| Student                                | 13     | 4.5        |
| Jobless                                | 29     | 10.1       |
| Monthly income                         |        |            |
| \(\leq 100\text{USD}                  | 215    | 74.7       |
| \(>100\text{USD}                      | 73     | 25.3       |
| Address                                |        |            |
| Addis Ababa                            | 271    | 94.1       |
| Gulelle                                | 4      | 1.4        |
| Arada                                  | 11     | 3.8        |
| Kolfe                                  | 7      | 2.4        |
| Addis Ketema                           | 4      | 1.4        |
| Nefas Silk Lafto                       | 38     | 13.2       |
| Kirkos                                 | 109    | 37.8       |
| Lideta                                 | 8      | 2.8        |
| Yeka                                   | 16     | 5.6        |
| Bole                                   | 16     | 5.6        |
| Akaki-Kality                           | 58     | 20.1       |
| Out of Addis Ababa                     | 17     | 5.9        |

In view of the clinical background, most 131 (44.8%) were on stage III of the WHO classification and 276 (95.8%) were on T1 classification. Most were on 1st line ART regimen 235 (81.6%), whereas, 129 (44.8%) were changed their initial regimen at least once (Table 2). Half (139, 48.3%) were on 1j (TDF + 3TC + DTG) regimen, (Fig. 2).
Table 2
Clinical information of the study participants: counts, percent of total and cumulative percent; Zewditu Memorial Hospital, June 2020, Addis Ababa, Ethiopia. N = 288.

| Clinical information                              | Counts | % of Total |
|--------------------------------------------------|--------|------------|
| The WHO clinical staging                          |        |            |
| I                                                | 40     | 13.9       |
| II                                               | 68     | 23.6       |
| III                                              | 131    | 45.5       |
| IV                                               | 49     | 17.0       |
| Treatment staging                                 |        |            |
| T1                                               | 276    | 95.8       |
| T2                                               | 1      | .3         |
| T3                                               | 7      | 2.4        |
| T4                                               | 4      | 1.4        |
| ART regimen                                      |        |            |
| First line                                       | 235    | 81.6       |
| Second line                                      | 51     | 17.7       |
| Third line                                       | 2      | .7         |
| Frequency of ART regimen change                  |        |            |
| No change from the baseline                      | 59     | 20.5       |
| changed once                                     | 129    | 44.8       |
| changed twice                                    | 80     | 27.8       |
| changed thrice                                   | 17     | 5.9        |
| changed four times                               | 3      | 1.0        |
| ART regimen                                      |        |            |
| 2NRTIs + 1INSTI                                  | 140    | 48.6       |
| 2NNRTIs + 1NNRTI                                 | 96     | 33.3       |
| 2NRTIs + 1PI                                     | 50     | 17.4       |
| 1NRTI + 1NNRTI + 1INSTI + 1PI                    | 2      | 0.7        |
| CD4 count (cells/mm3)                            |        |            |
| <50                                               | 5      | 1.7        |
| 51–200                                           | 36     | 12.5       |
| 201–500                                          | 142    | 49.3       |
| >500                                              | 105    | 36.5       |
| VL (copies/mL)                                   |        |            |
| LDL ** (< 150)                                   | 219    | 76.0       |
| Low viral load (151–1000)                        | 11     | 3.8        |
| Intermediate viral load (1000-10,000)            | 25     | 8.7        |

**LDL = Low Detection Level**
The overall mean age of the population was 43.51 with standard deviation (SD) of ± 11.273. That is about, 40.7 ± 10.5 for women, and
47.1 ± 11.4 for men. The overall mean age at the time of HIV confirmation was 32.7 ± 11.1, where, 30.2 ± 10.4 were women, and 35.9 ±
11.4 were men. The details of the characteristics of subjects are shown in Table 3.
Table 3
Characteristics of subjects (N = 288) enrolled in the study, overall and by gender, Zewditu Memorial Hospital, June 2020, Addis Ababa, Ethiopia.

| Characteristics | Minimum | Maximum | Median | Mean ± Std. Deviation |
|-----------------|---------|---------|--------|-----------------------|
| Gender          |         |         |        |                       |
| F               | 20.0    | 20.0    | 20.0   |                       |
| M               | 20.0    | 69.0    | 77.0   |                       |
| F + M           | 69.0    | 77.0    | 40.0   | 40.7 ± 10.5           |
| Monthly income (in bir) | 0.00    | 0.00    | 10000  | 40000                 |
| Age@ confirm (year) | 7.00    | 7.00    | 3.00   | 74.2 ± 48.5           |
| Age@ start (year) | 7.00    | 8.00    | 67.0   | 35.2 ± 12.6           |
| Total years on ART | 0.460   | 0.633   | 0.460  | 22.2 ± 13.0           |
| Current weight (Kg) | 33.0    | 39.0    | 120.0  | 120.0                 |
| Current height (in meter) | 1.44    | 1.50    | 1.44   | 1.57 ± 0.133          |
| BMI (kg²/m²)    | 14.5    | 15.1    | 14.5   | 19.1 ± 4.47           |
| Abd. Circ. (inch) | 24.0    | 25.0    | 49.0   | 32.0 ± 3.5            |
| CD4 (cells/mm³) | 74.0    | 6.00    | 1294.0 | 1294.0                |
| VL (copies/mL)  | 0.00    | 0.00    | 0.00   | 0.00 ± 0.6320         |
| PR (heart-beat/minute) | 47.7    | 60.7    | 123.0  | 82.7 ± 11.6           |
| SBP (mmHg)      | 89.3    | 91.3    | 193.0  | 121.0 ± 21.3          |
| DBP (mmHg)      | 54.7    | 61.7    | 117.0  | 118.0 ± 11.2          |
| TC (mg/dL)      | 78.0    | 100.0   | 354.0  | 354.0 ± 48.5          |
| LDL-C (mg/dL)   | 21.0    | 33.0    | 306.0  | 117.0 ± 49.0          |
| TGs (mg/dL)     | 49.0    | 30.0    | 466.0  | 114.0 ± 153.0         |
| HDL-C (mg/dL)   | 21.0    | 21.0    | 69.8   | 46.0 ± 46.0           |
| VLDL-C (mg/dL)  | 14.0    | 7.00    | 229.0  | 22.0 ± 26.0           |
| Non-HDL-C (mg/dL) | 40.0    | 39.0    | 451.0  | 140.0 ± 49.8          |
| Fasting Blood glucose (mg/dL) | 60.0    | 45.0    | 140.0  | 90.0 ± 98.0           |
| Characteristics                      | Minimum | Maximum | Median | Mean ± Std. Deviation |
|-------------------------------------|---------|---------|--------|-----------------------|
| Age@ confirm = Age at Confirmation of HIV; Age@ start = Age during initiation of ART; Abd. Circ.=abdominal circumference; VL = Viral Load; PR = Systolic Blood Pressure; DBP = Diastolic Blood Pressure; TC = Total Cholesterol; LDL-C = Low-Density Lipoprotein; TGs = Triglyceride, HDL-C = High Density Lipoprotein; VLDL-C = Very-Low-Density Lipoprotein. |

Current Birr to USD conversion rate is 0.0251.

The shortest duration that the participant had on ART follow-up care was 0.46 years, whereas the longest duration was 22.2 years. The overall total years on HAART was 9.81 ± 4.67 (mean ± SD). The youngest age at the time of HIV confirmation & HAART initiation was 7 years and the oldest age among participant for HIV confirmation was 63 for women and 65 for men, and for ART initiation, 67 for women and 65 for men (Table 3).

The prevalence of CMetS using the NCEP-2005 definition was 28.5% (82/288); and it was 43.5% (126/288) using the IDF definition (Table 2).

In order to determine the impact of biomarkers, risk factors, related sociodemographic variables on the prevalence of CMetS, two separate binary logistic analyses were performed for each CMetS_NCEP and CMetS_IDF definitions. Hence, twenty three predictor variables were entered to see their impact on the outcome of CMetS using the NCEP-2005 definition: Age, Gender, Family_history, Current_DX, Waist_circumference in inch, SBP in mmHg, DBP in mmHg, Total cholesterol in mg/dL, TG in mg/dL, LDL-C in mg/dL, Current_Tobacco_use (regular with intermittent use vs no use at all), Current_Alcohol_use (regular with intermittent use vs no use at all), Current_Coffee_use (regular with intermittent use vs no use at all), BMI in kg/m2, Duration_with_ART in year, nadir CD4 count in Cells/mm³, weight gained since HAART initiation in Kg, Frequency of ART Change (changed once or more time vs no change at all), Blood Group (A, B, AB, O), Rh Factor (Rh + vs Rh-), HAART_start_age in year.

The full model containing all the predictors was statistically significant \( \chi^2 \) (23; 288) = 191.443, indicating that the model was able to distinguish b/n those with and without CMetS. The total model explained b/n 48.6% (Cox and Snell R squared) and 69.6% (Nagelkereke R Square) of the variance in CMetS and correctly classified 89.6% of the cases. Eleven of the predictor variables (Age, gender, waist circumference, comorbidity, DBP, TG, LDL-C, duration with ART, blood group, and HAART_start_age) made a statistically significant contribution to the model (see Table 4). The strongest predictors were waist circumference, DBP and ART start age, which had an odds ratio of 1.21, 1.16, and 1.27 respectively. Demonstrating for each inch increment on waist circumference the odds of CMetS increases by 1.21 factors (21% more likely to develop CMetS), and similarly the odds of CMetS increases by 1.16 (16%) for each mmHg increment in DBP and also CMetS increases by 1.27 (27%) for each year increment in ART start age.
Table 4
The effect of the cardiometabolic predictors on the outcome of cardiometabolic syndrome using the National Cholesterol Education Program Adult Treatment Panel III (NCEP_ATP III-2005) definition. Data extracted from the cohort study carried out on HIV-infected persons on follow care of Zewditu Memorial hospital, Addis Ababa, Ethiopia, 2020.

| Variables in the Equation | Odds | S.E. | Odds Ratio | 95% C.I. for OR | Wald Statistics | P |
|---------------------------|------|------|------------|----------------|-----------------|---|
| Age                       | - .240 | .111 | .786       | .633            | .977            | .030* |
| Gender (male)             | -2.455 | .625 | .086       | .025            | .292            | .000** |
| Family history (Yes)      | - .141 | .566 | .869       | .286            | 2.635           | .062 |
| Co-morbidity (No)         | -3.126 | 1.196 | .044       | .004            | .457            | .094 |
| Waist circumference (inch)| .189  | .082 | 1.208      | 1.029           | 1.418           | .021* |
| SBP (mmHg)                | -.014  | .018 | .986       | .951            | 1.022           | .447 |
| DBP (mmHg)                | .152  | .038 | 1.164      | 1.080           | 1.254           | .000** |
| TG (mg/dL)                | .027  | .006 | 1.027      | 1.015           | 1.039           | .000** |
| LDL_C (mg/dL)             | .073  | .027 | 1.075      | 1.020           | 1.134           | .007* |
| Current_Tobacco_use (yes)| - 1.984 | 1.120 | .137       | .015            | 1.234           | .076 |
| Current_Alcohol_use (Yes) | - .964 | .865 | .381       | .070            | 2.080           | .265 |
| Current_Coffee_use (Yes) | .471  | .453 | 1.602      | .659            | 3.893           | .298 |
| BMI (kg/m²)               | .110  | .092 | 1.116      | .932            | 1.337           | .233 |
| Duration on ART (year)    | .024  | .010 | 1.024      | 1.005           | 1.043           | .014* |
| nadir cd4 count (cells/mm³)| - .001 | .002 | .999       | .994            | 1.004           | .646 |
| weight gained since HAART initiation (Kg) | .039  | .035 | 1.040       | .971            | 1.114           | .266 |
| Frequency of ART change (Yes) | - .623 | .587 | .536       | .170            | 1.695           | .289 |
| Blood group               | 12.128 |      |            |                 |                 | .007* |
| Blood group(A)            | -1.541 | .589 | .214       | .068            | .679            | .009* |
| Blood group(B)            | .250  | .599 | 1.284      | .397            | 4.153           | .677 |
| Blood group(AB)           | .929  | .704 | 2.533      | .638            | 10.062          | .187 |
| Rh Factor(+ ve)           | 1.030 | .709 | 2.800      | .697            | 11.242          | .147 |
| ART_start_age (year)      | .239  | .106 | 1.270      | 1.031           | 1.564           | .025* |

*Significant values ** P<0.01

a. Variable(s) entered on step 1: Age, Gender, Family history, Current_DX, Waist circumference in inch, AV_SBP, AV,DBP, AV_Total cholesterol, AV_TG, AV_LDL_C, Current_Tobacco_use, Current_Alcohol_use, Current_Coffee_use, BMI = kg/m2, Duration with ART, nadir cd4 count, weight gained since HAART initiation, Frequency of ART change, Blood group, Rh Factor, HAART_start_AGE.

b. Family history: about the confirmation of Cardiometabolic disease by physicians such as hypertension, Diabetes Mellitus, Heart disease, dyslipidemia.

c. nadir cd4 count: the lowest CD4 count recorded while the patient is on ART follow-up clinic.

As age increases the odds of acquiring CMetS decreases by 21.4% (P = 0.03). Furthermore, male gender was less likely to acquire CMetS than female by 91.4% (p < 0.001). For an additional one mg/dL increase in TG or LDL, the odds of CMetS was increased by 1.5% and 2% respectively. Increased in SBP however not determinant for CMetS and in each mmHg increase in SBP 1.4% less likely develop CMetS. For each year increase in duration with ART, the odds of CMetS increases by 2.4%. This is also true for the case of ART start age and as the patient get older to start ART, the odds of CMetS is increased by a factor of 2.23 per year. Blood group 'A' is less likely to be associated with CMetS while 'O' is highly associated.
Similarly, coded and hypothesized variables were also checked for their impact on the CMetS prevalence using the IDF-2005 definition. The full model containing all predictors had a statistically significant association, $\chi^2 (23; 288) = 202.268$, representing that the model was able to distinguish between those with and without CMetS. The total model explained between 50.5% (Cox and Snell R square) and 67.6% (Nagelkereke R Square) of the variance in CMetS and correctly classified 85.1% of the cases. Only five of the predictor variables (Waist Circumference, TG, LDL-C, duration with ART, and Frequency of ART change) had a statistically significant contribution to the model (see Table 5). The strongest predictors were waist circumference and duration with ART. Indicating that for each additional inch in waist circumference, the odds of CMetS is increases by a factor of 1.73 (73%) and in each year increment in duration with ART, the odds of CMetS increases by 6.7%.
Table 5
The effect of the cardiometabolic predictors on the outcome of cardiometabolic syndrome using the International Diabetes Federation (IDF-2005) definition. Data extracted from a cohort study carried out on HIV-infected persons on follow care of Zewditu Memorial hospital, Addis Ababa, Ethiopia, 2020.

| Variables in the Equation | Odds  | S.E.  | Odds Ratio | 95% C.I. for OR | Wald Statistics | P   |
|---------------------------|-------|-------|------------|-----------------|-----------------|-----|
|                           | Lower | Upper |            |                 |                 |     |
| Age                       | - .033| .080  | .968       | .827            | .1.133          | .166| .684|
| Gender                    |       |       |            |                 |                 |     |
| Family history (Yes)      | - .382| .542  | .682       | .236            | 1.975           | .497| .481|
| Co-morbidity (No)         | .568  | .937  | 1.764      | .281            | 11.076          | .367| .545|
| Waist circumference (inch)| .548  | .089  | 1.730      | 1.454           | 2.058           | 38.121| .000**|
| SBP (mmHg)                | .006  | .016  | 1.006      | .975            | 1.039           | .157| .692|
| DBP (mmHg)                | .001  | .029  | 1.001      | .946            | 1.060           | .003| .959|
| TG (mg/dL)                | .015  | .005  | 1.015      | 1.004           | 1.025           | 7.447| .006*|
| LDL_C (mg/dL)             | .062  | .026  | 1.064      | 1.012           | 1.119           | 5.801| .016*|
| Current_Tobacco_use (yes)| .019  | .011  | 1.019      | .997            | 1.042           | 2.799| .094|
| Current_Alcohol_use (Yes)| -1.688| 1.059 | .185       | .023            | 1.473           | 2.541| .111|
| Current_Coffee_use (Yes) | - .857| .737  | .424       | .100            | 1.800           | 1.351| .245|
| BMI (kg/m²)               | .351  | .410  | 1.421      | .636            | 3.175           | .734| .392|
| Duration with ART (year) | .224  | .083  | 1.251      | 1.064           | 1.472           | 7.324| .007*|
| nadir cd4 count (cells/mm³)| .000 | .007  | 1.000      | .987            | 1.014           | .000| .997|
| weight gained since HAART initiation (Kg) | .003 | .002  | 1.003 | .999 | 1.007 | 2.766 | .096|
| Frequency of ART change (Yes) | - .077 | .029 | .926 | .876 | .980 | 7.187 | .007*|
| Blood group               | .677  | .482  | 1.967      | .766            | 5.055           | 1.975| .160|
| Blood group(A)            |       |       |            |                 |                 |     |     |
| Blood group(B)            | .753  | .474  | 2.124      | .838            | 5.382           | 2.520| .112|
| Blood group(AB)           | .424  | .529  | 1.528      | .542            | 4.305           | .643| .423|
| Rh Factor(+ ve)           | .084  | .746  | 1.088      | .252            | 4.695           | .013| .910|
| HAART_start_age (year)    | .802  | .693  | 2.229      | .573            | 8.664           | 1.339| .247|

*Significant values ** P< 0.01

d. Variable(s) entered on step 1: Age, Family history, Current_DX, Waist circumference in inch, AV_SBP, AV,DBP, AV_Total cholesterol, AV_TG, AV_LDL_C, Current_Tobacco_use, Current_Alcohol_use, Current_Coffee_use, BMI = kg/m², Duration with ART, nadir cd4 count, weight gain since HAART initiation, Frequency of ART change, Blood group, Rh Factor, HAART_start_AGE.

e. Family history: about the confirmation of Cardiometabolic disease by physicians such as hypertension, Diabetes Mellitus, Heart disease, dyslipidemia.

f. nadir cd4 count: the lowest CD4 count recorded while the patient is on ART follow-up clinic.

Whereas for waist circumference, for each inch increment there is a 1.73 times more chance of developing CMeTs. Individuals who have changed their initial ART regimens at least once have less likely to develop CMeTS (7.4% less likely), and TG and LDL have also contributed 1.5% and 6.4% odds of CMeTS respectively.

**Discussion**
Antiretroviral treatment has modified the HIV progression, lengthened survival, and improved quality of life among PLWHA [34, 35]. However, this overwhelming benefit is not without limitations. In recent time, PLWHA are at increased risk of cardiometabolic (CMet) derangements [36–39].

The prevalence of CMetS among HIV-infected persons varies from country to country. In our study the prevalence using the NCEP-2005 definition was 28.5% (82/288); and it was 43.5% (126/288) using the IDF definition. A compiled report of studies showed that prevalence of CMetS in HIV infected population was 20.6% using NCEP-2005, and 31.3% using the IDF-2005 [40]. By considering this report as a reference, the chi-square goodness of fit test (X²) result indicated that the prevalence in our study was significantly higher by using both the NCEP-2005 (X² = 121.94, df = 1, p < 0.001), and the IDF-2005 models (X² = 32.99, df = 1, p < 0.001) [40]. However, in comparison to individual study reports, our prevalence falls within the range of previously done studies of [41–44], and in other aspect, it is a bit higher than the Polish [45], SHIVA (France) [46], Australian [47], South Korean [48], the Ethiopian [8, 44, 49], and the global meta analysis [50] studies; while it is lower than those reported from Nigeria [51], and China [52]. This variability could be due to the difference in study design, sample size, population genetics, study duration, duration with HIV and ART, treatment regimen or switch of therapy, and socio-demographic differences.

Several studies reported that sex, age, weight, BMI, sedentary lifestyle, central obesity, and cigarette smoking had an impact on the prevalence, pathogenesis, and progression of CMetS [218–221]. The European AIDS Clinical Society (EACS) guidelines has strongly addressed that the risk of contracting CMetS is age related [49]. In our study, male gender is less likely to be associated with CMetS (OR = 0.86, C.I. 0.025–0.292, p < 0.001) using the NCEP-2005 model; and this is in agreement with the studies reported from Latin America [53, 54] and Ethiopia [55]. However, a study from South Africa reported that the prevalence was higher in males [56].

Individuals with longer duration on ART had an increased odds of CMetS (NCEP-2005: OR = 1.024, C.I. 1.005–1.043, p = 0.014) and (IDF-2005: OR = 1.251, C.I. 1.061–1.472, p = 0.007). This result is similar to the study reported from Malawi where the duration of ART > 3 years was associated with CMetS. Moreover, a Kenyan study reported that a step-up increment in the duration of ART is significantly related to an increased in CMetS [57]. The long-term exposure to ART could transform into considerable persistent metabolic risk [58–60]. However, the increase in age alone is not a determinant for the prevalence of CMetS. As per the result of our study, age increment was less likely to be associated with CMetS (OR = 0.786, C.I. 0.633–0.977, p = 0.03). This could be due to the fact that CMetS is more prevalent in age between 45 to 65 years [61] and the prevalence of CMetS could then decline thereafter [54]. Age 65 and above have fewer CMetS episodes than their younger counterparts for a number of reasons [62], one could be people who developed CMetS earlier than 60 could die prematurely before reaching 65 and above, the other is it could be due to the fact that diet has an impact on CMetS where elders are usual undernourished [63]. A life expectancy of many nations in the world is also under 65 and can affect the outcome [64]. Moreover, the incidence of CMetS is independent of patient age, and it is rather higher in patients who have other risk factors such as smoking [37].

The age at which ART initiated yet had an impact on the outcomes of CMetS (NCEP-2005: OR = 1.27, C.I. 1.031–1.564, p = 0.025), indicates individuals who started ART treatment at older age are more likely to have CMetS than their younger counterparts. Contrary to this finding, the CMet to childhood association was symmetrical in non-HIV infected population [65].

Our study further identified that, an increase in waist-grid (central adiposity) was associated with the prevalence of CMetS using both the NCEP-2005 (OR = 1.21, C.I. 1.029–1.418, p = 0.021) and the IDF-2005 models (OR = 1.730 C.I. 1.454–2.058, p < 0.001). This finding is well-documented in a number of other studies [39, 48, 66–69]. Additionally, central adedosity can also contribute to CMetS due to its positive correlation with the DBP as described elsewhere [70, 71].

Individuals with increased TG were more likely to have CMetS using both the NCEP-2005 (OR = 1.027, C.I. 0.015–0.039, p < 0.001) and the IDF-2005 models (OR = 1.015 C.I. 0.004–0.025, p < 0.001); similarly individuals with increased LDL were more likely to have CMetS using the NCEP-2005 (OR = 1.075, C.I. 0.020–0.134, p = 0.007) as well as the IDF-2005 models (OR = 1.064, C.I. 0.012–0.119, p = 0.016). These result are in harmony with a number of other publications [37, 69, 72, 73]. Studies also indicated that if lipid abnormalities are not treated as aggressively as individuals living without HIV, and this can pose severe management crisis and premature fatalities in PLWHA [74].

Concerning the pattern of ART medication, 48.6% of the participants in our study were on 2NRTIs + 1 INSTI regimen, 33.3% on 2 NRTIs + 1 NRTI, 17.4% on 2NRTIs + 1PI, and 0.7% on 1NRTI + 1NRTI + 1 INSTI + 1 PI regimen. This regimen pattern was similar to a number of other studies [30, 47, 53]. Besides, the role of ART in the development and progression of CMetS has been elucidated in several other studies, but no significant result was obtained in our study [68, 75]. On the other hand, individuals who had changed their baseline ART regimen had less likely to have CMetS (IDF-2005: OR = 0.926, C.I. 0.876–0.980, p = 0.007). This could be the newer ART medications have relatively fewer CMet effect than the orders [76], though this is still a point of debate among the scientific community. Several studies
reported that ART regimens such as PIs and NNRTIs are considered as a significant contributor to the development and progression of CMetS in HIV infected population [77–81].

PLWHA without comorbidity were less likely to have CMetS (NCEP-2005: OR = 0.086, C.I. 0.025–0.292, p < 0.001). Among the comorbidities notably, Type 2 diabetes mellitus (T2DM), heart failure (HF), dyslipidemia and high BP were known to have a direct impact on the emergence of CMetS [82, 83].

**Conclusions**

The prevalence of CMetS using the NCEP-2005 definition was 28.5% (82/288); and it was 43.5% (126/288) using the IDF definition. Risk factors associated with CMetS were waist circumference, gender, duration on ART, ART initiated age, waist-grid, and comorbidity. Biomarkers more likely contributed to the prevalence of CMetS were triglyceride, low density lipoproteins, and systolic blood pressure.

**Recommendations**

A multicentre, multinational study with larger sample size and follow-up period is recommended. Strategies of lowering hypertriglyceridemia and boosting the HDL cholesterols are beneficial for HIV infected individuals and this can be initially guided by lifestyle modifications and appropriate selection of ART medications.

**Abbreviations And Acronyms**

ART: Antiretroviral Therapy; ATP III: Adult Treatment Panel III; CD4: Cluster of Differentiation 4; CMetS: Cardiometabolic Syndrome; CMet: Cardiometabolic; DBP: Diastolic Blood Pressure; EGIR: European Group for the Study of Insulin Resistance; FBS: Fasting Blood Sugar; HDL-C: High-Density Lipoprotein Cholesterol; HIV: Human Immunodeficiency Virus; IDF: International Diabetes Federation; IGF: Insulin-like Growth Factor; IGT: Impaired Glucose Tolerance; IR: Insulin Resistance; LDL-C: Low-Density Lipoprotein Cholesterol; NCEP: National Cholesterol Education Programme; NHLBI: National Heart, Lung, and Blood Institute; NNRTI: Nonnucleoside Reverse Transcriptase Inhibitor; NRTI: Nucleoside Reverse Transcriptase Inhibitor; PI: Protease Inhibitor; PLWHA: People Living with HIV-AIDS; PR: Pulse Rate; SBP: Systolic Blood Pressure; TC: Total Cholesterol; TGs: Triglyceride; T2DM: Type 2 Diabetes Mellitus; VL: Viral Load; WHO: World Health Organization; ZMH: Zewditu Memorial Hospital

**Declarations**

**Ethical statement**

The study was approved by - 1) the Muhimbili University of Health and Allied Sciences, Office of the Director of Research and Publications (Ref. No. 2018-04-23/AEC//Vol. XII/88), Dar el Saalam, Tanzania. 2) Addis Ababa University, School of Pharmacy, Ethical Review Board (ERB/SOP/41/11/2018), Addis Ababa, Ethiopia. 3) Addis Ababa University, College of Health Sciences, Institutional Review Board (IRB, Meeting number 08/2018), Addis Ababa, Ethiopia. 4) City Government of Addis Ababa Health Bureau, Ethical Clearance Committee (Ref no. A/A/HB/344438/227), Addis Ababa, Ethiopia.

**Consent of publication**

Not applicable.

**Availability of data and materials**

Not applicable.

**Competing interests**

The authors declare that they have no competing interests.
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Authors' contribution

MA: Conceptualization, Methodology, Software, Formal analysis, Investigation, Data Curation, Writing - Original Draft, Writing - Review & Editing, Project administration, Funding acquisition; OM: Supervision, Conceptualization, Methodology, Formal analysis, Investigation, Writing - Review & Editing; WS: Supervision, Funding acquisition; AS: Data Curation, Writing - Review & Editing; EE: Supervision, Conceptualization, Methodology, Formal analysis, Investigation, Writing - Review & Editing

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