

# Dyslipidemia and cardiovascular disease risk profiles of patients attending an HIV treatment clinic in Harare, Zimbabwe

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**Abstract:** The chronic inflammation induced by human immunodeficiency virus (HIV) contributes to increased risk of coronary heart disease (CHD) in HIV-infected individuals. HIV-infected patients generally benefit from being treated with antiretroviral drugs, but some antiretroviral agents have side effects, such as dyslipidemia and hyperglycemia. There is general consensus that antiretroviral drugs induce a long-term risk of CHD, although the levels of that risk are somewhat controversial. The intention of this cross-sectional study was to describe the lipid profile and the long-term risk of CHD among HIV-positive outpatients at an HIV treatment clinic in Harare, Zimbabwe. Two hundred and fifteen patients were investigated (females n=165, mean age 39.8 years; males n=50; mean age 42.0 years). Thirty of the individuals were antiretroviral-naïve and 185 had been on antiretroviral therapy (ART) for a mean 3.9±3.4 years. All participants had average lipid and glucose values within normal ranges, but there was a small difference between the ART and ART- for total cholesterol (TC) and high-density lipoprotein (HDL). Those on a combination of D4T or ZDV/NVP/3TC and PI-based ART were on average oldest and had the highest TC levels. Framingham risk showed 1.4% prevalence of high CHD risk within the next ten years. After univariate analysis age, sex, TC/HDL ratio, HDL, economic earnings and systolic BP were associated with medium to high risk of CHD. After multivariate regression analysis and adjusting for age or sex only age, sex and economic earnings were associated with medium to high risk of CHD. There is small risk of developing CHD, during the next decade in HIV infected patients at an HIV treatment clinic in Harare.

**Keywords:** human immunodeficiency virus, coronary heart disease risk, antiretroviral therapy, dyslipidemia

## Introduction

Human immunodeficiency virus (HIV)-infected patients have, like the general population, established cardiovascular risk factors, such as family history, age, male sex, hypertension, hyperlipidemia, and smoking.<sup>1,2</sup> HIV-infected individuals have an increased relative risk of coronary heart disease (CHD), acute myocardial infarction, and peripheral vascular disease compared with the population not infected with HIV.<sup>3-7</sup> The use of antiretroviral therapy (ART) has shown adverse influences on the lipid profile and is associated with a higher risk of diabetes mellitus and CHD.<sup>8-11</sup> In our context, the lipid profiles of low-density lipoprotein (LDL), high-density lipoprotein (HDL), triglycerides, and total cholesterol (TC) are of special interest.

HIV infection has been associated with progression of atherosclerosis.<sup>12</sup> Rasheed et al were the first to show a direct effect of HIV on lipid metabolism.<sup>13</sup> A South African study performed in ART-naïve blacks measured an association between the degree of inflammation and the degree of dyslipidemia.<sup>14</sup> When these patients were followed up

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3 years later, there was a higher degree of dyslipidemia in the treatment-naïve group than in the treatment-experienced group. In contrast, another African study found a significant burden of risk factors for CHD among ART-experienced patients than among their ART-naïve counterparts.<sup>15</sup>

The recommended treatment regimen for HIV today is the combination of three or more antiretroviral drugs to effectively reduce the viral load.<sup>16</sup> In Zimbabwe, the ART regimens mostly used are nucleotide reverse transcriptase inhibitors (NRTIs) such as tenofovir (Gilead Sciences, Foster City, CA, USA) in combination with non-nucleoside reverse transcriptase inhibitors (NNRTIs) such as nevirapine (Boehringer Ingelheim, Ridgefield, CT, USA) or in combination with protease inhibitors such as lopinavir and ritonavir, together known as Kaletra/Alluvia (Abbott Laboratories, North Chicago, IL, USA).<sup>17,18</sup> There is conflicting evidence from studies performed in both African and Western countries as to whether ART induces dyslipidemia and thereby the risk of CHD.<sup>19,20</sup>

A study of patients in a randomized controlled trial (Development of Antiretroviral Therapy in Africa, DART) in Zimbabwe and Uganda reported modest lipid elevations in African patients switching from first-line ART to predominantly ritonavir-boosted lopinavir + NNRTI-based second-line regimens after 48 weeks.<sup>21</sup> However, there is still a paucity of data describing both the state of lipid profiles and cardiovascular risk profiles in the Zimbabwean HIV-positive setting. As both HIV infection and ART regimens might be associated with cardiovascular disease risk, we sought to determine lipid alterations and CHD risk profiles in two groups of HIV-infected patients, one on treatment with ART and the other ART-naïve.

## Materials and methods

### Recruitment of participants and data collection

This cross-sectional observational study was carried out at an HIV treatment clinic in Harare, Zimbabwe. HIV-infected patients attending the clinic for scheduled visits on selected days between March and August 2013 were sequentially approached. The patients were informed about the study, along with its risks and benefits. Those who qualified and were willing to participate gave written consent before being interviewed and measured for weight, height, and blood pressure (BP). A questionnaire-guided interview was used to collect demographic and clinical data such as age, sex, marital status, health status, clinical history, and family

history. The participants were then bled using venipuncture to obtain 5 mL blood samples in one fluoride tube and one plain tube per participant. Blood samples were separated into fluoride plasma and plain serum within 12 hours of collection. Samples were stored at  $-80^{\circ}\text{C}$  until assay. Plasma and serum samples were thawed at room temperature before assaying for glucose (fluoride plasma) and lipids (plain serum).

### Inclusion and exclusion criteria

HIV-infected patients attending the HIV treatment clinic on a regular basis were included. ART-experienced patients were defined as patients who reported prior use of three antiretroviral drugs, whereas ART-naïve patients had never taken antiretroviral drugs. Male and female HIV-infected patients aged 18 years or older were included. Patients with documented history of diabetes, cardiovascular disease, hypertension, and dyslipidemia before being infected with HIV were excluded.

### Sample size calculation

$$\text{Using } N_1 = \frac{[Z\alpha/2 \sqrt{\{(r+1)p^{\wedge}q^{\wedge}\}} + Z\beta \sqrt{\{rp_1q_1 + p_2q_2\}}]^2}{r(p_1 - p_2)}$$

where  $p_1$  (test group) = 43.4% and  $p_2$  (control group) = 15.9%,  $q_1$  = 56.6% and  $q_2$  = 84.1%; ratio of ART experienced: ART-naïve used in the study = 5:1, hence  $r=5$ ;  $N_1$  = minimum sample size for the ART-naïve control group;  $N_2=5 \times N_1$  is the minimum sample size for the ART-experienced test group;  $Z\alpha/2=1.96$  (95% confidence interval);  $Z\beta=0.84$  (power of study).

The minimum sample size was 186, (31 ART-naïve, 155 ART-experienced).

### Quantitative determination of lipids and glucose

Quantization was carried out using a BS120 Mindray<sup>®</sup> machine (Nanshan, People's Republic of China), for which the test principles are described as follows. Lipids (TC, HDL, LDL) are measured enzymatically in serum in a series of coupled reactions that hydrolyze cholesteryl esters and oxidize the 3-OH group of cholesterol.<sup>22,23</sup> One of the reaction byproducts,  $\text{H}_2\text{O}_2$ , is measured quantitatively in a peroxidase-catalyzed reaction that produces a color. Absorbance is measured at 500 nm. The color intensity is proportional to the cholesterol concentration.<sup>22,23</sup> Plasma glucose was determined using the glucose oxidase method, where the

enzyme (glucose oxidase) catalyzes the oxidation of glucose to gluconic acid.<sup>24</sup>

## Cardiovascular risk values

Elevated BP was defined according to the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III), where the systolic BP is  $\geq 140$  mmHg and/or the diastolic BP is  $>90$  mmHg.<sup>25</sup> The NCEP ATP III guidelines were also used to define dyslipidemia and hyperglycemia, ie, elevated TC is defined as  $>200$  mg/dL, elevated LDL as  $>100$  mg/dL, depressed HDL as  $<40$  mg/dL, and elevated glucose as  $>110$  mg/dL.<sup>25</sup> Obesity was defined by body mass index (BMI), using the World Health Organization classification.<sup>26</sup> BMI was stratified into categories as follows:  $<15$ , very severely underweight; 15–16, severely underweight; 16.1–18.5, underweight; 18.6–24.9, normal; 25–29.9, overweight; 30–35, moderately obese; and 36–40, severely obese.<sup>27</sup> Overall CHD risk was calculated using age, sex, TC, HDL, smoking history, and systolic BP on the US National Health Institute Framingham On-line calculator.<sup>28</sup> The Framingham calculator applies NCEP ATP III guidelines as follows: older age (being older than 55 years for women and older than 45 years for men); elevated TC,  $>200$  mg/dL; decreased HDL,  $<40$  mg/dL; and elevated systolic BP,  $>140$  mmHg.<sup>28</sup> Those on treatment for hypertension were categorized as having a slightly higher risk of CHD in the next 10 years than those of the same sex and age, by the Framingham risk calculator.<sup>28</sup> Framingham risk scores were then used to define risk of coronary artery disease or heart attack as low (less than 10% risk), moderate (10%–20% risk), or high (more than 20% risk).

## Statistical analysis

Data were entered into and analyzed using Statistical Package for Social Sciences version 21 (IBM Statistics, Armonk, NY, USA) and Stata version 13 (StataCorp, College Station, TX, USA) software. Shapiro-Wilk test ( $P<0.05$ ) and visual inspection of histograms, normal Q-Q plots, and box-plots were used to check dependent variables for normality.<sup>29</sup> Continuous data were described as the mean  $\pm$  standard deviation in descriptive statistics and analyzed for differences using *t*-tests, with the level of significance set at  $P<0.05$ . Skewed data were reported as medians (interquartile ranges) and compared using *k* median tests. Categorical variables were compared using contingency tables and Pearson's chi-square tests and/or Fisher's exact tests. Known risk factors, such as age, sex, lipid and glucose levels, BMI, economic income,

systolic BP, diastolic BP, history of ART, and duration on ART, were tested for association with risk of future cardiovascular disease using univariate and multivariate logistic regression calculation.

## Results

### Demographics of participants

A total of 300 patients were targeted for inclusion, but only 235 patients were accessed during the study. Of the patients approached at the clinic during their regular visits, 13 declined for various reasons and two did not qualify (one was diabetic and one was below the age of 18 years). Five patients gave consent but were not bled for all the samples needed for the study due to needle discomfort, excessive bleeding, or collapsed veins.

Finally, 215 HIV-infected adults had complete data. Of these, 30 (14.0%) were ART-naïve (Table 1). The mean age for all participants was  $40.13 \pm 10.14$  years; 165 were female (mean age 39.8 years) and 23.3% ( $n=50$ ) were male (mean age 40.2 years). Patients were selected for participation because they did not have current life-threatening illnesses. Almost two thirds ( $n=145$ ) of participants had been diagnosed with HIV due to appearance of AIDS-defining illnesses such as tuberculosis (60%), diarrhea and unexplained weight loss (20%), or other opportunistic infections (20%). About one-third ( $n=60$ ) were diagnosed after undergoing voluntary testing without clinical symptoms. This might explain the difficulty in getting a high number of ART-naïve patients in this study as more than two thirds of patients started ART soon after initial diagnosis due to their illness. The majority of participants were non-smokers (95.8%,  $n=206$ ) and most were married. Those who had a history of elevated BP in the preceding 6 months were classified as hypertensive ( $n=76$ , 35.5%). Forty-four (58%) of these hypertensive participants were diagnosed with high BP for the first time at the point of inclusion into the study, whilst 42% ( $n=32$ ) of the hypertensive participants were on antihypertensive medical treatment upon inclusion.

Our HIV treatment clinic mainly serves low-income patients. Of all the 215 participants, 44.7% ( $n=96$ ) were employed, with mean earnings of USD  $154.30 \pm 214.14$  per month, and approximately 50% of all participants ( $n=103$ ) earned less than USD 50 per month.

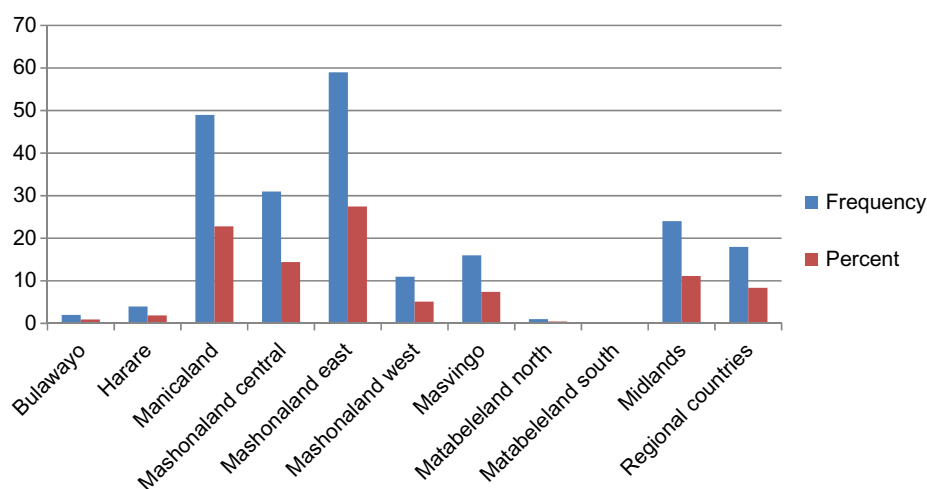
As shown in Figure 1, the participants originated from different parts of Zimbabwe, coming mostly from provinces near Harare and Mutare, whilst 8.4% originated from neighboring Sub-Saharan regional countries (mainly Malawi and

**Table 1** Demographic, clinical, and biochemical parameters by history of antiretroviral therapy

| Demographic characteristic                                                   | ART-naïve (n=30)           | ART-experienced (n=185)     | OR (95% CI)         | P-value |
|------------------------------------------------------------------------------|----------------------------|-----------------------------|---------------------|---------|
| Marital status                                                               |                            |                             |                     |         |
| Married (n=122)                                                              | 18 (60.0%)                 | 104 (56.2%)                 |                     | 0.568   |
| Single (n=32)                                                                | 6 (20.0%)                  | 26 (14.1%)                  |                     |         |
| Widowed (n=42)                                                               | 5 (21.9%)                  | 37 (20.0%)                  |                     |         |
| Divorced (n=19)                                                              | 1 (3.3%)                   | 18 (9.7%)                   |                     |         |
| Sex frequency (%)                                                            |                            |                             |                     |         |
| Males (n=50)                                                                 | 10 (33.3%)                 | 40 (21.6%)                  |                     | 0.159   |
| Females (n=165)                                                              | 20 (66.7%)                 | 145 (78.4%)                 |                     |         |
| Mean $\pm$ SD age, years                                                     | 37.34 $\pm$ 10.60          | 40.83 $\pm$ 9.99            |                     | 0.073   |
| Mean years since diagnosis                                                   | 2.35 (3.13)                | 5.94 (4.03)                 |                     | 0.000   |
| Median (IQR) diastolic BP, mmHg                                              | 79 (69–91)                 | 80 (70–90)                  | 1.04 (0.55–2.07)    | 0.581   |
| Median (IQR) systolic BP, mmHg                                               | 120 (110–131)              | 122 (114–135)               | 1.67 (0.82–3.62)    | 0.798   |
| Blood pressure treatment                                                     |                            |                             |                     |         |
| Yes (frequency/%)                                                            | 2 (6%)                     | 31 (17%)                    | 0.32 (0.036–1.403)  | 0.1193  |
| No (frequency/%)                                                             | 28 (94%)                   | 154 (83%)                   |                     |         |
| Smoking                                                                      |                            |                             |                     |         |
| Yes (frequency/%)                                                            | 1 (3%)                     | 8 (4%)                      | 0.71 (0.12–10.68)   | 0.745   |
| No (frequency/%)                                                             | 29 (97%)                   | 177 (96%)                   |                     |         |
| Heart disease                                                                |                            |                             |                     |         |
| Yes (frequency/%)                                                            | 4 (13%)                    | 5 (3%)                      | 5.086 (0.939–24.95) | 0.109   |
| No (frequency/%)                                                             | 26 (87%)                   | 180 (97%)                   |                     |         |
| Tuberculosis                                                                 |                            |                             |                     |         |
| Yes (frequency/%)                                                            | 4 (13%)                    | 58 (31%)                    | 3.25 (1.06–13.27)   | 0.027   |
| No (frequency/%)                                                             | 26 (87%)                   | 127 (69%)                   |                     |         |
| History of stroke                                                            |                            |                             |                     |         |
| Yes (frequency/%)                                                            | 0 (0%)                     | 10 (5.4%)                   |                     | 0.176   |
| No (frequency/%)                                                             | 30 (100%)                  | 175 (94.6%)                 |                     |         |
| BMI                                                                          |                            |                             |                     |         |
| <15 (very severely underweight)                                              | 0 (0%)                     | 2 (1%)                      |                     | 0.265   |
| 15–16 (severely underweight)                                                 | 0 (0%)                     | 2 (1%)                      |                     |         |
| 16.1–18.5 (underweight)                                                      | 0 (0%)                     | 10 (6%)                     |                     |         |
| 18.6–24.9 (normal)                                                           | 22 (69%)                   | 98 (54%)                    |                     |         |
| 25–29.9 (overweight)                                                         | 3 (6%)                     | 39 (21%)                    |                     |         |
| 30–35 (moderately obese)                                                     | 5 (16%)                    | 28 (14%)                    |                     |         |
| 36–40 (severely obese)                                                       | 0 (0%)                     | 6 (3%)                      |                     |         |
| Economic status by monthly earnings                                          |                            |                             |                     |         |
| <USD50                                                                       | 13 (47%)                   | 88 (48%)                    |                     | 0.694   |
| USD51–200                                                                    | 8 (25%)                    | 56 (31%)                    |                     |         |
| USD201–400                                                                   | 6 (19%)                    | 23 (11%)                    |                     |         |
| USD401+                                                                      | 3 (9%)                     | 18 (10%)                    |                     |         |
| Median (IQR) total cholesterol, mg/dL                                        | 149.03 (124.52–190.73)     | 176.83 (151.35–215.44)      |                     | 0.004   |
| Median (IQR) HDL cholesterol, mg/dL                                          | 38.28 (34.61–47.95)        | 46.79 (39.44–57.62)         |                     | 0.016   |
| Males (n=50)                                                                 | 37.51 (27.07–40.21) (n=10) | 45.05 (35.58–59.94) (n=40)  |                     | 0.077   |
| Females (n=165)                                                              | 38.67 (35.96–48.72) (n=20) | 47.56 (40.60–57.52) (n=145) |                     | 0.116   |
| Median (IQR) LDL cholesterol, mg/dL                                          | 89.125 (53.71–112.38)      | 94.55 (52.70–125.55)        |                     | 0.625   |
| Median (IQR) TC/HDL ratio                                                    | 3.75 (3.17–4.72)           | 3.78 (3.06–4.45)            |                     | 0.916   |
| Median (IQR) BMI                                                             | 22.65 (21.35–27.10)        | 24.30 (21.10–27.20)         |                     | 0.803   |
| Mean $\pm$ SD random blood glucose, mmol/L                                   | 5.25 $\pm$ 0.81            | 5.09 $\pm$ 0.84             | 5.28 $\pm$ 0.80     | 0.247   |
| Percentage of patients with Framingham risk scores >20% (high CHD risk)      | 0% (n=0)                   | 1.64% (n=3)                 |                     | 0.662   |
| Percentage of patients with Framingham risk scores 10%–20% (medium CHD risk) | 3.3% (n=1)                 | 2.2% (n=4)                  |                     | 0.640   |
| Percentage of patients with Framingham risk scores <10% (low CHD risk)       | 96.7% (n=29)               | 96.8% (n=179)               |                     | 0.640   |
| Percentage of patients with Framingham risk scores <1%                       | 15.2% (n=22)               | 84.8% (n=123)               |                     | 0.678   |

**Note:** Level of significance is set at  $P < 0.05$ .

**Abbreviations:** ART, antiretroviral therapy; BMI, body mass index; BP, blood pressure; CHD, coronary heart disease; CI, confidence interval; HDL, high-density lipoprotein; IQR, interquartile range; LDL, low-density lipoprotein; OR, odds ratio; SD, standard deviation; TC, total cholesterol.



**Figure 1** Provinces of origin of participants.

Mozambique). This geographic heterogeneity is apparent across all urban centers of Zimbabwe, as people move across the country in search of opportunities and jobs.

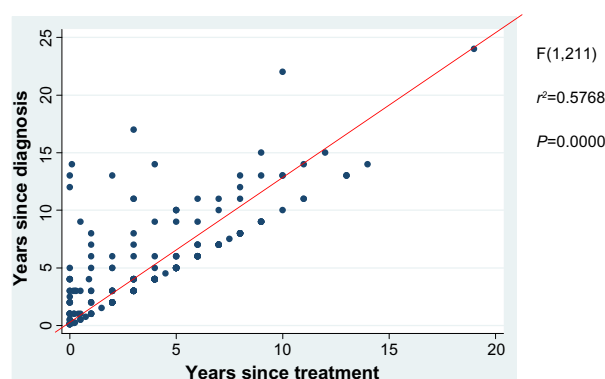
## Diagnosis and treatment history

Participants had been diagnosed for a mean  $5.5 \pm 4.1$  years prior to the study, 38% had been diagnosed within 3–5 years, with 24% of them having been diagnosed less than 2 years or 6–10 years, respectively, before data collection; only 14% of participants had been diagnosed for more than 10 years before the study. ART-experienced participants had been on ART for a mean duration of  $3.9 \pm 3.4$  years. There was a positive correlation between years since diagnosis and years since beginning ART (Figure 2).

## Laboratory parameters

The ART-experienced group as well as the ART-naïve group had normal average values for TC, HDL, LDL, and glucose based on NCEP ATP III guidelines. The majority of

patients (97%,  $n=208$ ) had a low risk of CHD as indicated by Framingham risk scores less than 10%, and only four (1.9%) had moderate risk, ie, Framingham risk scores of 10%–20%. There was a 1.4% ( $n=3$ ) prevalence of participants with a Framingham risk score higher than 20%, indicating a high risk of CHD. Table 1 shows the comparison of demographic, clinical, and biochemical parameters related to ART history. There was a significant difference between ART-experienced and ART-naïve participants for mean years since diagnosis, median TC, and median HDL, but no significant differences for distribution by sex, economic earnings, BMI, median systolic and diastolic BP, median TC/HDL ratio, median LDL, median BMI, mean random blood glucose, and Framingham risk scores. There was a significant difference in prevalence of history of tuberculosis, with those on ART more likely to have suffered from tuberculosis at some time in the past (odds ratio 3.25, confidence interval 1.06–13.27), suggesting that these patients had been more immune-compromised in the past.



**Figure 2** Positive correlation (regression analysis  $r^2=0.5768$ ,  $P=0.0000$ ) between years since diagnosis and years of antiretroviral treatment.

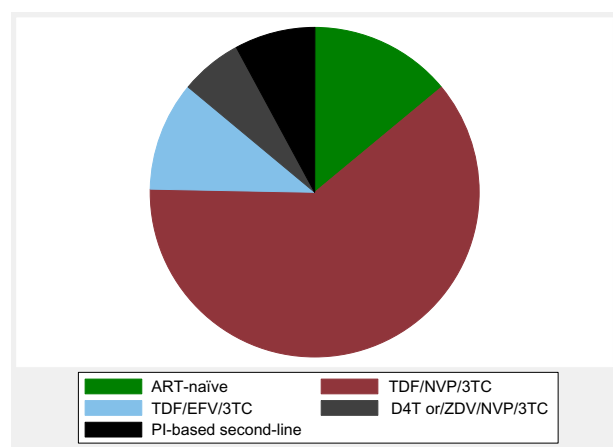
## Body mass index of participants

There was no significant difference in mean BMI between the ART-naïve and ART-experienced participants, although all 14 underweight patients were ART-experienced. However, there was no significant difference in the prevalence of overweight by ART use (odds ratio 1.395, 95% confidence interval 0.591–3.498,  $P=0.416$ ).

## Antiretroviral therapy regimens

Figure 3 shows the ART regimens that were used by the participants. The majority of participants (60.5%,  $n=130$ ) in our study were on a triple combination of tenofovir, nevirapine, and lamivudine (GlaxoSmithKline, Brentford,





**Figure 3** Distribution of ART regimens used by participants.

**Abbreviations:** ART, antiretroviral therapy; PI, protease inhibitor; TDF, tenofovir; NVP, nevirapine; 3TC, lamivudine; EFV, efavirenz; D4T, stavudine; ZDV, zidovudine.

London, UK), 23 (21.1%) were on a tenofovir, efavirenz (Bristol-Myers Squibb, New York City, NY, USA), and lamivudine regimen, and the rest were on either stavudine (Bristol-Myers Squibb) or zidovudine (ViiV Healthcare, Brentford, London, UK) in combination with nevirapine and lamivudine or a protease inhibitor-based second-line therapy.

When patients were stratified by different ART combinations and compared with ART-naïve patients, the distribution of BMI, random blood glucose, LDL, and TC/HDL ratio was all the same. On the other hand, the distribution of age, TC, and HDL was significantly different across categories of ART combinations when compared with the ART-naïve group (Table 4). Those on protease inhibitor-based second-line treatment had on average the highest levels of TC and those on stavudine-based or zidovudine-based first line had the highest levels of HDL.

There was a significant difference across the different combinations for age, with those on a combination of stavudine or zidovudine/nevirapine/lamivudine and protease inhibitor-based therapy being on average oldest (Table 2). There was a significant difference across the ART groups for TC, while there was no significant difference across the groups for HDL, LDL, diastolic BP, systolic BP, BMI, or random blood glucose.

## Framingham risk scores

There was a low (1.4%) prevalence of high risk for future cardiovascular disease when participants were evaluated by Framingham risk scores (Figure 4). The risk of cardiovascular disease ranged from <1% (n=145, 67.4% of participants) to

**Table 2** Results from univariate analysis of various independent variables

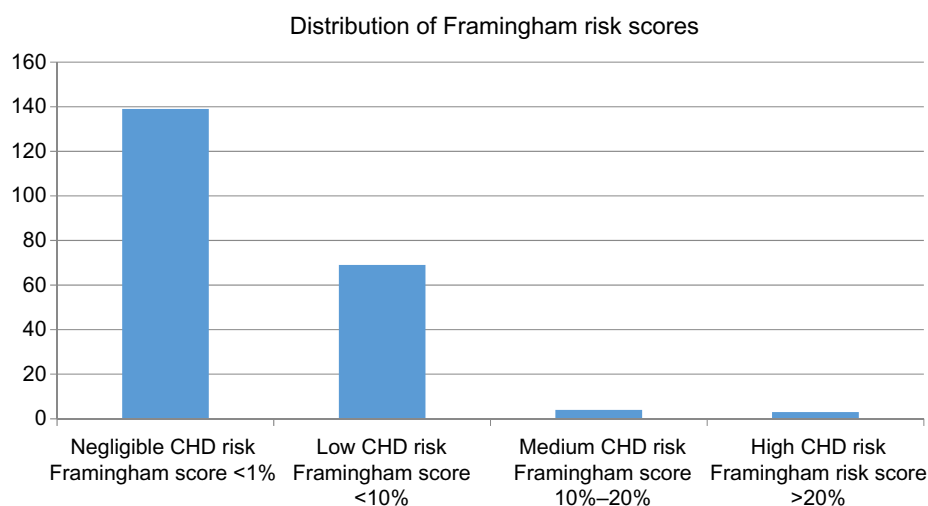
| Variable                  | Patients with low risk of CHD (n=208) | Patients with medium to high risk of CHD (n=7) | P-value          |
|---------------------------|---------------------------------------|------------------------------------------------|------------------|
| Mean (SD) age             | 39.73 (9.77)                          | 57.57 (3.51)                                   | 0.000            |
| Sex                       |                                       |                                                | OR, CI P-value   |
| Males                     | 45                                    | 5                                              | 0.11, 0.10–0.71, |
| Females                   | 163                                   | 2                                              | 0.022            |
| Mean (SD) TC              | 177.00 (44.82)                        | 211.086 (54.68)                                | 0.051            |
| Mean (SD) HDL             | 48.59 (15.16)                         | 36.02 (11.88)                                  | 0.0311           |
| Mean (SD) LDL             | 101.38 (82.58)                        | 127.54 (46.58)                                 | 0.406            |
| Mean (SD) TC/HDL ratio    | 3.90 (1.24)                           | 6.15 (1.43)                                    | 0.000            |
| Mean (SD) glucose         | 94.34 (14.55)                         | 97.97 (13.82)                                  | 0.517            |
| Mean (SD) body mass index | 24.52 (4.97)                          | 24.90 (3.26)                                   | 0.839            |
| Mean (SD) earnings        | 148.09 (206.03)                       | 338.57 (360.67)                                | 0.0203           |
| Mean (SD) systolic BP     | 125.00 (18.56)                        | 143.57 (25.72)                                 | 0.011            |
| Mean (SD) diastolic BP    | 81.45 (16.29)                         | 84.57 (8.46)                                   | 0.615            |
| History of ART            |                                       |                                                | OR, CI, P-value  |
| Experienced               | 179                                   | 29                                             | 0.972, 0.112–    |
| Naïve                     | 6                                     | 1                                              | 46.23, 0.656     |
| Duration on ART           | 3.90 (3.39)                           | 4.71 (3.63)                                    | 0.535            |

**Abbreviations:** ART, antiretroviral therapy; BP, blood pressure; CI, confidence interval; OR, odds ratio; SD, standard deviation; TC, total cholesterol; LDL, low-density lipoprotein; HDL, high-density lipoprotein; CHD, coronary heart disease.

>20% (n=3, 1.4%). There was no difference in the prevalence of medium to high risk of CHD across all categories of ART ( $P=0.134$ ) and no difference when comparing ART-experienced and ART-naïve groups ( $P>0.05$ , Tables 1 and 4). When tested using univariate analysis, the following were associated with medium to high risk of CHD: age, sex, TC/HDL ratio, HDL, economic earnings, and systolic BP (Table 2). However, after multivariate regression analysis and adjusting for age and sex, there was only a statistically significant association between age, sex, and economic earnings with a medium to high risk of CHD (Table 3).

## Discussion

This is the first study describing both the lipid profile and the calculated risk of future cardiovascular disease in HIV-positive Zimbabwean individuals treated with different ART regimens. Although our results indicate a low risk of long-term cardiovascular disease, ART is associated with some changes in lipid metabolism to be taken notice of. When considering serum TC and LDL levels, lipid profiles seemed



**Figure 4** Distribution of future CHD risk using Framingham risk scores amongst the participants.

**Abbreviation:** CHD, coronary heart disease.

more atherogenic in the antiretroviral-treated participants compared with their therapy-naïve counterparts. On the other hand, when classified by HDL or TC/HDL ratio, the ART-naïve participants seem to be at higher risk.

Previous clinical studies have shown that protease inhibitor-based ART is especially associated with highly atherogenic lipid levels, and this peaks 2–3 years after initiating ART.<sup>9,30,31</sup> For example, the Data Collection on Adverse Events of Anti-HIV Drugs (DAD) study group showed evidence of multiple risk factors for cardiovascular disease, including dyslipidemia among HIV-infected persons on NRTIs and protease inhibitors, with an increased risk in older patients; 1.4% of patients in that study had a previous history of cardiovascular disease and 51.5% were cigarette smokers.<sup>32</sup>

In contrast, in our study, less than 5% of the participants had been on a protease inhibitor-based regimen, while more than 80% were on an NNRTI-containing regimen with a mean exposure time of 3.5 years, indicating that even NNRTI-based ART regimens influence lipid metabolism unfavorably, as shown in previous cohorts and clinical trials.<sup>33,34</sup> Most studies have shown

that the level of HDL cholesterol is lower in non-treated HIV patients than in ART-exposed patients, in accordance with our results.<sup>35,36</sup> The DAD study showed a higher risk of cardiovascular disease risk in older patients, ie, 25% of DAD patients were over 50 years of age.<sup>32</sup> Our study population was made up of relatively young adults, with a mean age of  $40.3 \pm 10.1$  years and only 17% of participants being older than 50 years.

In contrast with the DAD study, the Strategies for Management of Antiretroviral Therapy (SMART) study found no associations between rate of cardiovascular disease and cumulative or recent use of NRTIs (zidovudine, stavudine, or lamivudine). However, recent use of specific NRTIs (abacavir and didanosine) was associated with an increased rate of cardiovascular disease, compared with those with no recent use of the two drugs.<sup>37</sup> After adjustment for predicted 10-year risk of CHD, recent use of both didanosine and abacavir remained associated with increased rates of cardiovascular disease.<sup>37</sup> Of note is that the SMART study population had a high rate of cardiac risk factors at baseline, with 39% of participants being current smokers, 36% having ischemic changes on their

**Table 3** Results from multivariate regression analysis

| Variable              | Multivariate analysis results |         |                     |         |                     |         |
|-----------------------|-------------------------------|---------|---------------------|---------|---------------------|---------|
|                       | Unadjusted                    |         | Adjusted by sex     |         | Adjusted by age     |         |
|                       | OR (CI)                       | P-value | OR (CI)             | P-value | OR (CI)             | P-value |
| Age                   | 1.24 (1.10–1.39)              | 0.000   | 1.27 (1.11–1.45)    | 0.001   | –                   | –       |
| Sex                   | 0.11 (0.021–0.588)            | 0.010   | –                   | –       | 0.08 (0.11–0.61)    | 0.015   |
| TC/HDL ratio          | 2.76 (1.59–4.38)              | 0.000   | 2.966 (1.59–5.52)   | 0.001   | 2.35 (1.30–4.23)    | 0.004   |
| Earnings in USD/month | 1.002 (1.0001–1.004)          | 0.037   | 1.002 (1.001–1.003) | 0.05    | 1.004 (1.001–1.005) | 0.04    |
| Systolic BP           | 1.05 (1.01–1.10)              | 0.018   | 1.04 (1.01–1.08)    | 0.016   | 1.03 (0.99–1.07)    | 0.304   |

**Abbreviations:** BP, blood pressure; CI, confidence interval; OR, odds ratio; TC, total cholesterol; HDL, high-density lipoprotein.

**Table 4** Demographic, clinical, and biochemical parameters of study participants on no or different combinations of HAART

|                                      | All (n=215)            | HAART negative (n=30)  | HAART positive (n=185) | TDF/NVP/3TC n=130      | TDF/EFV/3TC n=23       | D4T-ZDV/NVP/3TC n=13   | PI-based 2nd line n=17 | Significance P<0.05 |
|--------------------------------------|------------------------|------------------------|------------------------|------------------------|------------------------|------------------------|------------------------|---------------------|
| <b>Demographic and clinical data</b> |                        |                        |                        |                        |                        |                        |                        |                     |
| Mean ± SD age, years                 | 40.31±10.14            | 37.34±10.60            | 39.4±9.28              | 0.22±0.78              | 40.39±9.93             | 48.38±13.38            | 46.59±8.53             | 0.002               |
| Male:female ratio                    | 0.23:0.77              | 0.31:0.69              | 0.22±0.78              | 0.19±0.81              | 0.19±0.81              | 0.32±0.68              | 0.25±0.75              |                     |
| Mean ± SD diastolic BP mmHg          | 81.55±16.09            | 81.59±16.89            | 81.44±16.65            | 124.80±18.67           | 81.96±14.54            | 130.1±19.7             | 82.3±19.0              | 0.963               |
| Mean ± SD systolic BP mmHg           | 125.61±19.05           | 123.75±16.59           | 124.80±18.67           | 2.7% yes               | 123.96±18.76           | 143.00±32.53           | 134.12±24.99           | 0.601               |
| Smoking history                      | 4.2% yes               | 4.5% yes               | 2.7% yes               | 8% yes                 | 14.6% yes              | 17.9% yes              | 2.8% yes               |                     |
| History of heart disease             | 7.0% yes               | 4.5% yes               | 8% yes                 | 6.2% yes               | 10.7% yes              | 10.7% yes              | 13.9% yes              |                     |
| Tuberculosis history                 | 28.8% yes              | 13.6% yes              | 29.4% yes              | 43.8% yes              | 25.0% yes              | 42% yes                |                        |                     |
| Median (IQR) TC mg/mL                | 173.36 (144.40–208.49) | 149.03 (124.52–176.64) | 175.87 (155.21–210.04) | 179.54 (145.17–227.41) | 174.90 (137.45–246.33) | 188.80 (156.76–222.78) |                        | 0.045               |
| Median (IQR) HDL mg/dL               | 45.63 (37.12–56.46)    | 38.28 (34.61–47.95)    | 46.40 (40.22–56.84)    | 48.72 (38.28–54.52)    | 61.87 (43.70–75.79)    | 43.70 (36.74–54.52)    |                        | 0.055               |
| Median (IQR) LDL mg/dL               | 93.00 (52.70–124.00)   | 89.13 (53.71–112.38)   | 94.55 (58.13–125.55)   | 105.40 (65.10–130.20)  | 91.45 (35.34–137.95)   | 72.85 (30.54–102.30)   |                        | 0.233               |
| Mean ± SD TC/HDL ratio               | 3.97±1.30              | 4.06±1.25              | 3.86±1.13              | 4.27±1.51              | 3.60±0.50              | 4.56±1.78              |                        | 0.219               |
| Median (IQR) BMI                     | 23.30 (21.10–27.20)    | 22.65 (21.35–27.10)    | 23.40 (21.11–27.2)     | 23.60 (20.50–31.00)    | 22.40 (21.40–22.90)    | 23.80 (21.70–26.20)    |                        | 0.211               |
| Mean ± SD random BG mmol/L           | 5.25±0.81              | 5.09±0.84              | 5.32±0.81              | 5.00±0.80              | 4.90±0.57              | 5.30±0.83              |                        | 0.339               |

**Abbreviations:** HAART, highly active antiretroviral therapy; BP, blood pressure; SD, standard deviation; TC, total cholesterol; LDL, low-density lipoprotein; HDL, high-density lipoprotein; BMI, body mass index; BG, blood glucose; IQR, interquartile range; PI, protease inhibitor; TDF, tenofovir; NVP, nevirapine; 3TC, lamivudine; EFV, efavirenz; D4T, stavudine; ZDV, zidovudine.

baseline electrocardiograms, 19% taking antihypertensive agents, and 18% being on lipid-lowering drugs.<sup>37</sup>

Interestingly, an African study performed in newly identified HIV-positive individuals showed that ART improved the dyslipidemic profile found before starting ART.<sup>14</sup> In another study carried out in HIV-infected urban dwellers in Nigeria, the lipid profiles were followed for a period of 15 months in individuals on ART and in treatment-negative asymptomatic HIV-infected patients.<sup>38</sup> When compared with apparently healthy HIV-negative individuals, TC, HDL, LDL, and triglyceride levels in the ART-experienced subjects were not significantly different, while the levels of TC and HDL were significantly lower in the HIV-positive antiretroviral-naïve versus ART-experienced patients.<sup>38</sup> The low levels of HDL observed in antiretroviral-naïve patients seem to be a recurring theme in most studies, including ours, but whether ART contributes to increased cardiovascular risk remains uncertain. The mechanisms of how HIV infection and ART induce these lipid abnormalities are still unknown. Chronic immune activation caused by HIV has been proposed, an activation that persists even after successful treatment with ART.<sup>39</sup> Even if ART induces lipid abnormalities that are classic risk factors for the development of atherosclerosis, ART is of tremendous importance for survival and reduction of morbidities in HIV-positive patients. These patients have longer survival, but are more threatened by cardiovascular disease.

A Nigerian study conducted by Muhammad et al in 100 ART-experienced and 100 ART-naïve patients found a significantly higher burden of some risk factors for cardiovascular disease (hypertension, hypercholesterolemia, obesity, and metabolic syndrome) among ART-treated HIV patients than in their ART-naïve counterparts.<sup>15</sup> Interestingly, in our study, antihypertensive medication was started in 17% of the ART-experienced participants compared with 2% of the ART-naïve participants ( $P<0.001$ ). Prior results exploring the effect of ART on BP are conflicting.<sup>40,41</sup> Previous studies have shown a correlation between sustained hypertension and a nadir CD4 cell count  $<200$  cells/ $\mu$ L, as well as with duration of ART, with an especially high proportion of hypertensive HIV patients having a nadir cell count  $<50$  cells/ $\mu$ L.<sup>42–44</sup> We have no measurements regarding immunodeficiency in our study, but the patients on ART would be expected to have had more advanced immunodeficiency (and hence the lowest nadir CD4 cell counts) in the past than the ART-naïve patients.

The participants in our study had a low risk of developing cardiovascular disease for the next 10 years when evaluated by Framingham risk score. We found risk scores



ranging from <1% (67.5% of patients) to >20% (1.4% of patients); all the higher risk patients (n=3) were found among participants on ART (one on nevirapine and two on protease inhibitors). This is far lower than reported in Europe and developed countries, but is in agreement with studies done elsewhere in Africa.<sup>45-49</sup> In our study, the lipid values were within normal range, but TC and HDL were both higher in the ART-positive group, constituting 85% of all participants. Of note is that the majority of patients in our study were young adults (mean age 40.3 years, with 17% [n=37] being aged older than 50 years), with 75% being women and 96% being non-smokers, contributing to a low risk of future cardiovascular disease. Smoking has been independently associated with cardiovascular disease in HIV-positive patients, and the risk decreases after smoking cessation.<sup>50</sup> We found no differences in the prevalence of cardiovascular disease risk across the different types of ART, and there were no differences when comparing ART-experienced patients with ART-naïve patients (Tables 1 and 4). Interestingly, 70% of the ART-positive patients were treated with lamivudine in combination with tenofovir and non-nucleoside antiretroviral drugs, which has not been associated with an increased risk of myocardial infarction, in contrast with some protease inhibitors and other NRTIs.<sup>51</sup> Multivariate regression analysis (for age, sex, TC/HDL ratio, systolic BP, economic earnings) found an association between higher risk of CHD and monthly earnings, which is a new finding for African countries. Not surprisingly, it tells us that the long-term complications of HIV are influenced by socioeconomic factors.

## Strengths and limits of the study

This study was well powered, and the participants were carefully selected in a randomly manner for participation and were regularly monitored for adherence. However, the study is influenced by the inherent weakness of an observational cross-sectional study design, selection bias (with more females than males due to differences in the health-seeking behaviors of men and women in our setting), lack of HIV-negative controls, and lack of locally generated reference ranges for comparison. Due to lack of CD4 cells and viral load values, each patient's health status was not properly defined, with no HIV staging. The groups of participants were generally small, especially the patient group without ART. The small sample size increases the risk of type II statistical errors. Another major weakness stems from the use of Framingham risk score in HIV-infected patients. It has been proposed that the Framingham risk score may underestimate

the 10-year risk in some subgroups and overestimate this risk in others, depending on risk factors and geographic origin.<sup>52</sup> This warrants further research, for example, using the HIV-specific cardiovascular risk calculator engineered by the DAD study that leaves out antihypertensive therapy but adds in five other factors to the equation, being number of years taking indinavir or lopinavir, current treatment with indinavir, lopinavir, or abacavir, previous smoking, diabetes, and a family history of cardiovascular disease.<sup>52</sup>

## Conclusion

Our main finding is that the risk of future cardiovascular disease is low among outpatients at a Zimbabwean HIV treatment clinic, although there were the worrying aspects of high atherogenic lipid profiles and hypertension. There is still a need to control plasma lipid levels and BP in HIV-positive patients in an attempt to reduce the long-term cardiovascular risk, which is upcoming in HIV-positive patients.

## Acknowledgments

The authors are grateful to: the Letten Foundation, Norway, for funding this research; the academic, technical staff, and students of the University of Zimbabwe, College of Health of Sciences, Department of Medical Laboratory Sciences; Kudzaishe Mateveke, University of Zimbabwe, College of Health of Sciences Research Support Centre for support during the statistical analysis; and to the staff and patients of Newlands Clinic.

## Author contributions

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data, drafting the article, or revising it critically for important intellectual content, gave their approval of the version to be published, and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

## Disclosure

The authors report no conflicts of interest in this work.

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