

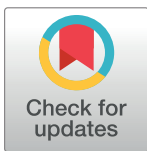
RESEARCH ARTICLE

# Dyslipidemia among rural and urban HIV patients in south-east Malawi

Alemayehu Amberbir<sup>1\*</sup>, Victor Singano<sup>1</sup>, Alfred Matengeni<sup>1</sup>, Zahra Ismail<sup>2</sup>, Gift Kawalazira<sup>3</sup>, Adrienne K. Chan<sup>1,4</sup>, Sumeet D. Sodhi<sup>1,5</sup>, Joep J. van Oosterhout<sup>1,6</sup>

**1** Dignitas International, Zomba, Malawi, **2** Pirititi Rural Hospital, Pirititi, Malawi, **3** District Health Office, Ministry of Health, Zomba, Malawi, **4** Division of Infectious Diseases, Department of Medicine, Sunnybrook Health Sciences Centre, University of Toronto, Toronto, Canada, **5** Toronto Western Hospital, University Health Network, Toronto, Canada, **6** Department of Medicine, College of Medicine, University of Malawi, Blantyre, Malawi

\* [a.amberbir@dignitasinternational.org](mailto:a.amberbir@dignitasinternational.org)



## Abstract

### Background

While dyslipidemia importantly contributes to increased cardiovascular disease risk among patients on antiretroviral therapy (ART), data on lipid patterns among African adults on ART are limited. We describe the prevalence of lipid abnormalities and associated factors in two HIV clinics in Malawi.

### Methods

We conducted a cross-sectional study in 2014 and enrolled adult patients at a rural and an urban HIV clinic in Zomba district, Malawi. We recorded patient characteristics, CVD risk factors and anthropometric measurements, using the WHO STEPS validated instrument. Non-fasting samples were taken for determination of total cholesterol (TC), triglyceride (TG) and HDL-cholesterol (HDL-c) levels. Logistic regression analysis was used to determine factors associated with elevated TC and elevated TC/HDL-c ratio.

### Results

554 patients were enrolled, 50% at the rural HIV clinic, 72.7% were female, the median (IQR) age was 42 years (36–50); 97.3% were on ART, 84.4% on tenofovir/lamivudine/efavirenz, 17.5% were overweight/obese and 27.8% had elevated waist/hip ratio. 15.5% had elevated TC, 15.9% reduced HDL-c, 28.7% had elevated TG and 3.8% had elevated TC/HDL-c ratio. Lipid abnormalities were similar in rural and urban patients. Women had significantly higher burden of elevated TC and TG whereas men had higher prevalence of reduced HDL-c. Waist-to-hip ratio was independently associated with elevated TC (aOR = 1.90; 95% CI: 1.17–3.10,  $p = 0.01$ ) and elevated TC/HDL-c ratio (aOR = 3.50; 95% CI: 1.38–8.85,  $p = 0.008$ ). Increasing age was independently associated with elevated TC level (aOR = 1.54, 95% CI 0.51–4.59 for age 31–45; aOR = 3.69, 95% CI 1.24–10.95 for age >45 years vs.  $\leq 30$  years;  $p$ -trend <0.01).

## OPEN ACCESS

**Citation:** Amberbir A, Singano V, Matengeni A, Ismail Z, Kawalazira G, Chan AK, et al. (2018) Dyslipidemia among rural and urban HIV patients in south-east Malawi. PLoS ONE 13(5): e0197728. <https://doi.org/10.1371/journal.pone.0197728>

**Editor:** Miren Iturriza-Gómara, University of Liverpool, UNITED KINGDOM

**Received:** December 9, 2017

**Accepted:** May 8, 2018

**Published:** May 21, 2018

**Copyright:** © 2018 Amberbir et al. This is an open access article distributed under the terms of the [Creative Commons Attribution License](https://creativecommons.org/licenses/by/4.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

**Data Availability Statement:** The data for this paper included routine programmatic monitoring of Malawi Ministry of Health ART programs. As such, the data is the possession of the Ministry of Health and cannot be posted to an online repository. However, the data can be made available on reasonable request to the Ministry of Health (<https://www.hiv.health.gov.mw>). Such requests would best be made through the corresponding author, Dr. Alemayehu Amberbir, who can facilitate the request for access to the dataset.

**Funding:** The authors received no specific funding for this work.

**Competing interests:** The authors have declared that no competing interests exist.

## Conclusions

We found a moderate burden of dyslipidemia among Malawian adults on ART, which was similar in rural and urban patients but differed significantly between men and women. High waist-hip ratio predicted elevated TC and elevated TC/HDL-c ratio and may be a practical tool for CVD risk indication in resource limited settings.

## Introduction

The wide roll-out of antiretroviral therapy (ART) for people living with HIV (PLHIV) in sub-Saharan Africa [1] has shifted the burden of HIV-related morbidity to chronic conditions including cardiovascular diseases (CVD) [2,3]. Several studies have demonstrated an increased risk of myocardial infarction and stroke in PLHIV compared with uninfected controls [2,4]. High prevalence of classical CVD risk factors such as hypertension, diabetes, smoking and dyslipidemia, as well as chronic inflammation and immune activation associated with HIV infection, contribute to the increased risk of CVD among PLHIV [5,6]. HIV infection and early ART are risk factors for stroke in Malawian adults with the highest attributable risk in younger patients [2]. Individual antiretroviral drugs have also been linked to CVD through elevated markers of atherosclerosis [7,8].

Among risk factors for CVD in PLHIV, dyslipidemia has received limited attention in sub-Saharan Africa. A systematic review and meta-analysis of data from the region found that HIV infection was associated with higher triglyceride (TG) and lower HDL-cholesterol (HDL-c) levels and ART was associated with increased LDL-cholesterol levels [6]. In Ethiopia, patients on ART had higher levels of total cholesterol (TC) and TGs, and lower HDL-c compared to ART-naïve subjects [7]. Studies from the region mainly included patients from urban areas, where a less physically active life style and unhealthy diet may have an unfavorable impact on lipid patterns. Furthermore, earlier studies often enrolled patients on stavudine based regimens, leaving them more prone to the metabolic syndrome, lipodystrophy and dyslipidemia [9].

Patterns of dyslipidemia, its risk factors and the consequences for CVD events among African patients on current ART regimens need to be better understood to determine implications for lipid monitoring in high HIV prevalence and low-income countries. We have therefore described the prevalence of dyslipidemia and associations with patient characteristics in a rural and an urban HIV clinic in south-east Malawi.

## Methods

### Study design and setting

This is an analysis of a larger cross-sectional study that we conducted between July and October 2014. We enrolled consecutive HIV infected adults (aged 18 years or older) in care at the HIV clinics of Pirititi Rural Hospital and Zomba Central Hospital (urban). The first 277 participants at each clinic received a lipid measurement and were included in the current analysis. The clinics are located in Zomba district, southern Malawi, where HIV prevalence is around 14.5% in the 15–49 year age group [10]. During the study period, the urban clinic served an estimated 6,700 HIV infected patients and the rural clinic 3,200. Further details of the study enrolment procedures and methods were reported elsewhere [5]. The study was approved by

the Malawi College of Medicine Research and Ethics Commission (approval number P.02/14/1523). All study participants provided their informed written consent.

## Data collection and measurements

We used adapted, validated WHO STEPS questionnaires to collect information related to CVD risk factors [11]. Information about smoking and alcohol consumption was collected and the level of physical activity was categorized as active and less active [5]. HIV related information was extracted from standard clinic registers and ART master cards. This included ART status, type of ART regimen, ART duration and CD4 count at ART initiation. Anthropometric measurements (weight, height, waist and hip circumferences) were taken by a trained research nurse following the WHO STEPS guide to physical measurements procedure. Body mass index (BMI) was categorized as normal, underweight, overweight and obese using the WHO classification [12]. Central obesity was defined as waist-hip- ratio (waist circumference/hip circumference) of  $\geq 0.90$  for men and  $\geq 0.85$  for women [13]. The Framingham risk score (FRS) score, which includes sex, current smoking status, total cholesterol, HDL-cholesterol, anti-hypertensive drug use and systolic blood pressure was calculated for all patients aged  $\geq 20$  years as recommended [14]. Non-fasting samples were taken for measurement of TC, TG and HDL-c levels, using the point-of-care CardioChek® PA (Polymer Technology Systems, Inc. Indianapolis, USA). TC was elevated if  $> 5.2$  mmol/L, HDL-c was decreased if  $< 1.1$  mmol/L and TG was elevated if  $> 2.9$  mmol/L. The TC/HDL-c ratio was used to indicate a lipid profile prone to atherosclerosis and considered elevated if  $> 5.0$ . [15]

## Statistical analysis

Laboratory and questionnaire data were entered in an Access database, cleaned and analysed using Stata 13 (Statacorp, College Station Texas, USA). Elevated TC and elevated TC/HDL-c ratio were considered as primary markers of increased cardiovascular risk. Lipid data were stratified by urban/rural study site as well as gender. Associations of lipid findings with life-style, metabolic and HIV related risk factors were analyzed using crude odds ratios (ORs) with 95% confidence intervals (CI). Independent predictors of elevated TC and elevated TC/HDL-c ratio were determined with logistic regression analysis adjusting for various confounders. Variables with a p-value of  $\leq 0.1$  in univariate analyses were included in the multivariable logistic regression models. Age, sex and urban/rural site were also included in the model as *a priori* confounders, irrespective of p-values in the univariable analysis. We report overall p-values and p-values for trend for ordinal variables with more than two categories.

## Results

### Description of the study participants

A total of 554 patients were enrolled in the study, 277 (50.0%) were from the rural HIV clinic, 403 (72.7%) were female, the median (IQR) age was 42 years (36–50); 539 (97.3%) were on ART (79.0% for more than 2 years) and 455 (84.4%) were on the standard first line regimen tenofovir/lamivudine/efavirenz. At ART initiation 246 patients (67.0%) had CD4 levels of  $\leq 250$  mm<sup>3</sup> and 207 (38.3%) were in the WHO disease stage III/IV. Ninety seven (17.5%) were overweight/obese, the median (IQR) BMI was 21 (20–24)) and 169 (31.3%) had an elevated waist/hip ratio, median (IQR) (0.82 (0.79–0.88)). The majority (90.6%) reported being active (vs. less active) in terms of physical activity, 63 (11.4%) reported using alcohol in the past 12 months and only 18 (3.3%) said they were current smokers. The Framingham risk

score (FRS) could be determined in 541 patients and the 10-year CVD event risk was  $\geq 10\%$  in 29 patients (5.4%).

### Prevalence of dyslipidemia by rural/urban site and gender

Eighty-six patients (15.5%) had elevated TC, 88 (15.9%) had reduced HDL-c, 159 (28.7%) had elevated TGs, 21 (3.8%) had elevated TC/HDL-c ratio and 283 (51.1%) had completely normal lipid profiles. There were no significant differences in dyslipidemia between rural and urban patients (Table 1). Women had a significantly higher burden of elevated TC (17.6% vs. 9.9%;  $p = 0.026$ ) and elevated TGs (32.3% vs. 19.2%;  $p = 0.002$ ) whereas men had higher prevalence of reduced HDL-c (25.2% vs. 12.4%;  $p < 0.01$ ) (Table 1). Patients with elevated TC levels and with elevated TC/ HDL-c ratio were more likely to have a FRS 10-year CVD risk  $\geq 10\%$  than those with normal TC levels (13.3% vs. 3.9%;  $p = 0.001$ ) and a normal HDL-c/TC ratio (23.8% vs. 4.6%;  $p < 0.001$ ) respectively.

### Factors associated with elevated TC/HDL-c ratio and TC

In multivariable logistic analysis adjusted for various confounders, waist-to-hip ratio (aOR = 1.90; 95% CI: 1.17–3.10,  $p = 0.01$ ), and increasing age (age 31–45: aOR = 1.54, 95% CI 0.51–4.59; age >45 years: aOR = 3.69, 95% CI 1.24–10.95 vs.  $\leq 30$  years;  $p$ -trend <0.001) were independently associated with elevated TC level (Table 2). Only waist-to-hip ratio (aOR = 3.50; 95% CI: 1.38–8.85,  $p = 0.008$ ) was independently associated with elevated TC/ HDL-c ratio (Table 3). There was no significant association between elevated TC/HDL-c ratio or TC and urban/rural study site, gender, diagnosis of diabetes, body mass index, ART status, duration of ART, CD4 levels at ART initiation, levels of physical activity and current use of alcohol (Tables 2 and 3).

**Table 1. Lipid levels among Malawian, adult HIV patients stratified by urban/rural site and by gender.**

Lipid profiles (N = 554)	Total N (%)	Rural n (%)	Urban n (%)	P-value*	Female n (%)	Male n (%)	P-value*
<i>Total cholesterol</i>				0.814			<b>0.026</b>
Elevated	86 (15.5)	44 (15.9)	42 (15.2)		71 (17.6)	15 (9.9)	
Normal	468 (84.5)	233 (84.1)	235 (84.8)		332 (82.4)	136 (90.1)	
<i>Mean total cholesterol (SD)</i>	4.14 (1.02)	4.18 (0.99)	4.10 (1.04)	0.173	4.23 (1.05)	3.89 (0.88)	<0.01
<i>HDL cholesterol</i>				0.642			<0.01
Low	88 (15.9)	46 (16.6)	42 (15.2)		50 (12.4)	38 (25.2)	
Normal	466 (84.1)	231 (83.4)	235 (84.8)		353 (87.6)	113 (74.8)	
<i>Mean HDL cholesterol (SD)</i>	1.60 (0.82)	1.58 (0.74)	1.62 (0.89)	0.682	1.65 (0.84)	1.46 (0.73)	<b>0.006</b>
<i>Total/HDL cholesterol ratio</i>				0.824			0.890
Elevated	21 (3.8)	11 (4.0)	10 (3.6)		15 (3.7)	6 (4.0)	
Normal	533 (96.2)	266 (96.0)	267 (96.4)		388 (96.3)	145 (96.0)	
<i>Mean total/HDL cholesterol (SD)</i>	2.91 (1.04)	2.95 (1.04)	2.87 (1.04)	0.177	2.86 (1.02)	3.02 (1.10)	0.946
<i>Triglycerides</i>				0.159			<b>0.002</b>
Elevated	159 (28.7)	87 (31.4)	72 (26.0)		130 (32.3)	29 (19.2)	
Normal	395 (71.3)	190 (68.6)	205 (74.0)		273 (67.7)	122 (80.8)	
<i>Mean triglycerides (SD)</i>	2.51 (3.57)	2.72 (4.87)	2.31 (1.33)	0.088	2.69 (4.11)	2.03 (1.16)	<b>0.026*</b>

SD, standard deviation; HDL, high density lipoprotein cholesterol

\* P-value based on result of two-way sample t-test with equal variances or chi-square test, as applicable

<https://doi.org/10.1371/journal.pone.0197728.t001>

**Table 2. Multivariate analysis—factors associated with elevated total cholesterol (TC) in Malawi.**

Characteristics	Total n/N (%)	Elevated TC n (%)	Crude Odds Ratio (95% CI)	P-value	Adjusted Odds Ratio (95% CI)	P-value
<i>Study site (N = 554)</i>				0.814		0.696
Urban	277 (50.0)	42 (15.2)	0.95 (0.60, 1.50)		0.91 (0.56, 1.47)	
Rural	277 (50.0)	44 (15.9)	1		1	
<i>Age in years (N = 554)</i>				<0.001* <0.001 <sup>‡</sup>		<0.001* <0.001 <sup>‡</sup>
≤30	51 (9.2)	4 (7.8)	1		1	
31–45	302 (54.5)	35 (11.6)	<b>1.54 (0.52, 4.54)</b>		<b>1.54 (0.51, 4.59)</b>	
>45	201 (36.3)	47 (23.8)	<b>3.59 (1.23, 10.47)</b>		<b>3.69 (1.24, 10.95)</b>	
<i>Sex (N = 554)</i>				<b>0.028</b>		0.064
Male	151 (27.3)	15 (9.9)	<b>0.52 (0.29, 0.93)</b>		0.54 (0.28, 1.04)	
Female	403 (72.7)	71 (17.6)	1		1	
<i>ART Status (N = 554)</i>				-		
On ART	539 (97.3)	86 (16.0)	-			
Pre-ART	15 (2.7)	0 (0.0)	-			
<i>ART regimen (N = 539)</i>				0.501*		
TDF/3TC/EFV	455 (84.4)	69 (15.2)	0.83 (0.23, 2.98)			
AZT/3TC/NVP	67 (12.4)	14 (20.9)	1.23 (0.31, 4.90)			
Other	17 (3.2)	3 (17.7)	1			
<i>ART duration in months (N = 539)</i>				0.138		
<24	114 (21.2)	13 (11.4)	1			
≥24	425 (78.9)	73 (17.2)	1.61 (0.86, 3.03)			
<i>CD4 count at ART initiation (N = 367)</i>				0.117*		
≤250	246 (67.0)	46 (18.7)	1			
>250	121 (32.3)	13 (10.7)	0.52 (0.27, 1.01)			
Missing	187 (33.8)	27 (14.4)	0.73 (0.44, 1.23)			
<i>Diagnosis of diabetes (N = 554)</i>				0.230		
No	524 (94.6)	79 (15.1)	1			
Yes	30 (5.4)	7 (23.3)	1.71 (0.71, 4.13)			
<i>Body mass index (Kg/m<sup>2</sup>) (N = 554)</i>				0.462* 0.338 <sup>‡</sup>		
Normal	389 (70.2)	58 (14.9)	1			
Underweight	68 (12.3)	9 (13.2)	0.87 (0.41, 1.85)			
Overweight/obesity	97 (17.5)	19 (19.6)	1.39 (0.78, 2.47)			
<i>Waist-to-hip ratio (N = 540)</i>				<b>0.003</b>		<b>0.01</b>
Normal	371 (68.7)	46 (12.4)	1		1	
High	169 (31.3)	38 (22.5)	<b>2.05 (1.27, 3.30)</b>		<b>1.90 (1.17, 3.10)</b>	
<i>Physical activity (N = 554)</i>				0.118		
Less active	52 (9.4)	12 (23.1)	1			
Active	502 (90.6)	74 (14.7)	0.58 (0.29, 1.15)			
<i>Alcohol use in the past 12 months (N = 554)</i>				<b>0.041</b>		0.133
No	491 (88.6)	82 (16.7)	1		1	
Yes	63 (11.4)	4 (6.4)	<b>0.34 (0.12, 0.96)</b>		0.44 (0.14, 1.29)	
<i>Current smokers (N = 554)</i>				0.261		
No	536 (96.8)	85 (15.9)	1			

(Continued)

Table 2. (Continued)

Characteristics	Total n/N (%)	Elevated TC n (%)	Crude Odds Ratio (95% CI)	P-value	Adjusted Odds Ratio (95% CI)	P-value
Yes	18 (3.3)	1 (5.6)	0.31 (0.04, 2.38)			

TDF, tenofovir; 3TC, lamivudine; EFV, efavirenz; AZT, zidovudine; NVP, nevirapine

\*P-value based on result of LHR test

†P-value for trend; age, sex and study site were included in the model as *a priori* confounder regardless of degree of association.

<https://doi.org/10.1371/journal.pone.0197728.t002>

## Discussion

In this study of Malawian adults in HIV care, we documented a moderate burden of dyslipidemia. Nearly all (97.3%) were on ART, and a large majority was on a regimen that is the current standard in the region. Most patients (72.7%) were female and the proportion of elevated waist-hip ratio was substantial (27.8%). Half of the patients had a normal lipid spectrum. The burden of abnormal lipid levels was similar in urban and rural patients but differed significantly between men and women. The prevalence of FRS elevated CVD risk, i.e. the probability of a CVD event in the next decade being >10%, was quite low (5.4%) overall but in those with elevated TC and TC/HDL-c ratio it was considerable (13.3% and 23.8% respectively). Elevated waist-to-hip ratio, but not high BMI, was independently associated with elevated TC level and elevated TC/HDL-c ratio.

A systematic review and meta-analysis of cardio-metabolic risk factors, HIV and ART in sub-Saharan Africa included 52 studies from 14 countries of nearly 30,000 individuals found that among PLHIV those on ART had higher LDL-c and HDL-c levels, TG level was not significantly different, while TC was not reported [6]. Many studies in this review were from an era when stavudine and nevirapine containing regimens were used, whereas in our study and in most HIV programmes in sub-Saharan Africa, these drugs have been replaced with tenofovir and efavirenz. Stavudine has particularly unfavorable effects on TC, TG and LDL-c levels [16,17]. Nevirapine may have some benefit over efavirenz in terms of increasing HDL-c and being associated with better surrogate markers of atherosclerosis [17]. This difference with nevirapine may be attributed to a subgroup of efavirenz users with high drug levels, as higher efavirenz levels were associated with moderate increases in TC, TG, HDL-c and LDL-c in a study of 106 South Africans on efavirenz-based ART [18].

Because the composition of standardized first-line ART regimens is relevant to lipid levels, it is important to compare our study with more recent studies from the region. In a study from urban Tanzania that enrolled 354 patients on ART, the burden of dyslipidemia was considerably higher than in our study (elevated TC 71.6%, elevated TG 67.0%, low HDL-c 43.6%), but various, not clearly specified ART regimens were used, more patients were obese and the prevalence of central obesity was also higher [19]. Two hundred fifty Ugandan adults who were on ART for at least two years were enrolled in a cross sectional study of CVD risk factors [20]. Participants had similar gender and age characteristics as ours and comparable median duration on ART. Fifty percent used tenofovir/lamivudine/efavirenz, none were on stavudine. Prevalence of elevated TC was 6.4%, elevated TG 29.6%, low HDL-c 85.6% and elevated TC/HDL-c ratio 22.4%. Another cross sectional study from Uganda investigated 1,024 adults on long-term ART (median duration 9.6 years) but did not specify ART regimens other than protease inhibitor-based or not [21]. Similar to the other Ugandan study [20], being overweight/obese (26.1%) and having abdominal obesity (52.6%) were very common. In this study the prevalence of elevated TC was 30.2%, elevated TG 21.2%, and low HDL-c 37.5% [21]. Among 400 patients on ART from Cameroon, 79.9% were female, the median age was 44 years, 50.8%

**Table 3. Multivariate analysis—factors associated with elevated TC/HDL-c ratio in Malawi.**

Characteristics	Total n/N (%)	Elevated TC/HDL-c ratio n (%)	Crude Odds Ratio (95% CI)	P-value	Adjusted Odds Ratio (95% CI)	P-value
<i>Study site (N = 554)</i>				0.824		0.996
Urban	277 (50.0)	10 (3.6)	0.91 (0.38, 2.17)		1.00 (0.40, 2.48)	
Rural	277 (50.0)	11 (4.0)	1		1	
<i>Age in years (N = 554)</i>				0.736* 0.636 <sup>‡</sup>		0.804* 0.645 <sup>‡</sup>
≤30	51 (9.2)	1 (2.0)	1		1	
31–45	302 (54.5)	12 (4.0)	2.07 (0.26, 16.26)		1.84 (0.23, 14.85)	
>45	201 (36.3)	8 (4.0)	2.07 (0.25, 16.96)		1.92 (0.23, 16.09)	
<i>Sex (N = 554)</i>				0.890		0.799
Male	151 (27.3)	6 (4.0)	1.07 (0.41, 2.81)		1.15 (0.40, 3.31)	
Female	403 (72.7)	15 (3.7)	1		1	
<i>ART Status (N = 554)</i>				-		
On ART	539 (97.3)	21 (3.9)	-			
Pre-ART	15 (2.7)	0 (0.0)	-			
<i>ART regimen (N = 539)</i>				0.780*		
TDF/3TC/EFV	455 (84.4)	20 (4.4)	0.74 (0.09, 5.83)			
AZT/3TC/NVP	67 (12.4)	0 (0.0)	-			
Other	17 (3.2)	1 (5.9)	1			
<i>ART duration in months (N = 539)</i>				0.810		
<24	114 (21.2)	4 (3.5)	1			
≥24	425 (78.9)	17 (4.0)	1.15 (0.38, 3.47)			
<i>CD4 count at ART initiation (N = 367)</i>				0.080*		
≤250	246 (67.0)	12 (4.9)	1			
>250	121 (32.3)	1 (0.8)	0.16 (0.02, 1.26)			
Missing	187 (33.8)	8 (4.3)	0.87 (0.35, 2.18)			
<i>Diagnosis of diabetes (N = 554)</i>				0.893		
No	524 (94.6)	20 (3.8)	1			
Yes	30 (5.4)	1 (3.3)	0.87 (0.11, 6.70)			
<i>Body mass index (Kg/m<sup>2</sup>) (N = 554)</i>				0.202* 0.088 <sup>‡</sup>		
Normal	389 (70.2)	12 (3.1)	1			
Underweight	68 (12.3)	2 (2.9)	0.95 (0.21, 4.35)			
Overweight/obesity	97 (17.5)	7 (7.2)	2.44 (0.94, 6.38)			
<i>Waist-to-hip ratio (N = 540)</i>				<b>0.008</b>		<b>0.008</b>
Normal	371 (68.7)	8 (2.2)	1		1	
High	169 (31.0)	12 (7.1)	<b>3.47 (1.39, 8.65)</b>		<b>3.50 (1.38, 8.85)</b>	
<i>Physical activity (N = 554)</i>				0.133		
Less active	52 (9.4)	4 (7.7)	1			
Active	502 (90.6)	17 (3.4)	0.42 (0.14, 1.30)			
<i>Alcohol use in the past 12 months (N = 554)</i>				0.786		
No	491 (88.6)	19 (3.9)	1			
Yes	63 (11.4)	2 (3.2)	0.81 (0.19, 3.58)			
<i>Current smokers (N = 554)</i>				-		
No	536 (96.8)	21 (3.9)	-			

(Continued)

Table 3. (Continued)

Characteristics	Total n/N (%)	Elevated TC/HDL-c ratio n (%)	Crude Odds Ratio (95% CI)	P-value	Adjusted Odds Ratio (95% CI)	P-value
Yes	18 (3.3)	0 (0.0)	-			

TDF, tenofovir; 3TC, lamivudine; EFV, efavirenz; AZT, zidovudine; NVP, nevirapine

\*LHR test

‡P-value for trend; age, sex and study site were included in the model as *a priori* confounder regardless of degree of association.

<https://doi.org/10.1371/journal.pone.0197728.t003>

were obese, 45.5% had abdominal obesity and 93.3% were on zidovudine/lamivudine plus efavirenz or nevirapine, with a median duration of 3 years [22]. In this population, the prevalence of elevated TC was 6.3%, of elevated TG 7.8% and of low HDL-c 19.5% [22]. The large variation in dyslipidemia observed in these sub-Saharan African studies, including ours, all published in the last four years may be explained by differences in genetic factors, overweight/obesity, central obesity, ART duration, ART regimens and (unmeasured) ART failure rates between the study populations. Very few prospective studies are available and none reported results from regular lipid monitoring and dyslipidemia treatment results. While life style, including physical activity, dietary habits, consumption of alcohol and smoking may vary by geographical setting, we found that lipid abnormalities were not significantly different between rural and urban patients on similar ART regimens. We did not find other studies that compared lipid patterns between urban and rural ART patients.

Women had a 1.8 times higher prevalence of elevated TC and a 1.7 times higher prevalence of elevated TGs. In men, the prevalence of reduced HDL-c was twice as high as in women. In Ugandan ART patients the burden of abnormal TC, TG and HDL-c levels was not significantly different between men and women [20]. The prevalence of dyslipidemia (defined as elevated TC and/or low HDL-c) was also similar in males and females in a study of HIV negative and HIV positive, ART-naive adult Kenyans [23]. Among Ugandans on stable ART, mean HDL-c levels were significantly lower in men and mean TG levels significantly higher in women, but dyslipidemia was not reported by gender [21]. Mean TC and mean HDL-c levels were not significantly different between men and women in a small Zimbabwean study of HIV positive adults who were mostly ART experienced [24]. Contrary to several smaller studies from the region, we may have detected gender differences in dyslipidemia due to our relatively large sample size, but our findings need confirmation in similar settings.

Our study found that waist-to-hip ratio was the only characteristic that predicted both elevated TC/HDL-c ratio and elevated TC. Elevated waist-to-hip ratio resulted in a nearly 2-fold increased probability of elevated TC and a 3.5-fold higher probability of elevated TC/HDL-c ratio. A literature review, not HIV focussed, concluded that both general and abdominal obesity are associated with CVD risk factors and incident CVD events [25]. It further showed that measures of central obesity do not have better discriminatory capacity as predictors of dyslipidaemia and CVD risk than BMI, and that they are not more suitable outside Caucasian populations. The quality of the evidence regarding the latter points was limited, in particular due to the cross sectional nature of most studies [25]. A large pooled analysis >200,000 Asians similarly found that BMI and waist-to-hip ratio were both associated with lipid parameters. The authors concluded that measures of central obesity may help to identify individuals at increased risk of dyslipidaemia [26]. We did not find studies from African HIV populations that reported associations of different measures of obesity with dyslipidaemia and individual lipid parameters. Given the feasibility of measuring central obesity in resource limited settings,



our results, if confirmed, suggest that waist-hip ratio may be utilized for clinical decision making in ART clinics, for instance to select patients for lipid measurements.

Countries in Africa are experiencing a rapid epidemiologic transition, due to population ageing and lifestyle changes (urbanization, diet, tobacco and alcohol consumption and physical inactivity). Such changes together with an increasing burden of obesity could be the drivers of dyslipidemia in this population.[27] In a large population based study in Malawi; we recently found that being overweight and obese are highly prevalent in urban and rural Malawian adults, especially in the 35–54 years age range and in women, and is comparable to that observed in high-income countries.[27] HIV infection itself may play a role on dyslipidemia through endothelial cell injury and local inflammatory response that may impair vessel responsiveness.[3,28]

Our study needs to be interpreted in the light of its limitations. The cross-sectional design precludes causal associations between dyslipidemia and patient characteristics. The study did not include a control group of HIV-uninfected persons which would have provided better insight into the role of HIV infection and antiretroviral drugs. We measured lipid profiles using non-fasting samples but these do not differ significantly from results obtained from fasting samples for clinical interpretation, have similar associations with CVD risk and have recently been recommended in favor of fasting samples due to higher feasibility [29]. We used reference values from western settings that have not been validated in sub-Saharan Africans to classify dyslipidemia, as did other studies from the region. The main strength of this study is our ability to compare gender, urban vs. rural location and other patient characteristics among ART patients on current (tenofovir/lamivudine/efavirenz) regimens and that we included relevant anthropomorphic measures, in particular waist-hip-ratio.

## Conclusions

We found a moderate burden of dyslipidemia among Malawian adults on current ART regimens. Dyslipidemia was similar in patients in rural and urban settings but patterns differed significantly between men and women. Patients with elevated TC and elevated TC/HCL-c ratio had significantly higher FRS predicted CVD risk. Higher age was associated with elevated TC/HCL-c ratio. Elevated waist-to-hip ratio predicted both elevated TC and elevated TC/HCL-c ratio and may be a feasible tool for prediction of dyslipidemia and CVD risk. Future prospective studies with CVD endpoints among African ART patients are needed to determine the role of lipid monitoring and treatment of dyslipidemia.

## Author Contributions

**Conceptualization:** Alemayehu Amberbir, Adrienne K. Chan, Sumeet D. Sodhi, Joep J. van Oosterhout.

**Data curation:** Alemayehu Amberbir, Alfred Matengeni.

**Formal analysis:** Alemayehu Amberbir.

**Investigation:** Victor Singano, Zahra Ismail, Gift Kawalazira.

**Methodology:** Alemayehu Amberbir, Victor Singano, Adrienne K. Chan, Sumeet D. Sodhi, Joep J. van Oosterhout.

**Writing – original draft:** Alemayehu Amberbir, Joep J. van Oosterhout.

**Writing – review & editing:** Alemayehu Amberbir, Victor Singano, Alfred Matengeni, Zahra Ismail, Gift Kawalazira, Adrienne K. Chan, Sumeet D. Sodhi, Joep J. van Oosterhout.

## References

1. Chan AK, Mateyu G, Jahn A, Schouten E, Arora P, Mlotha W, et al (2010) Outcome assessment of decentralization of antiretroviral therapy provision in a rural district of Malawi using an integrated primary care model. *Trop Med Int Health* 15: 90–97. <https://doi.org/10.1111/j.1365-3156.2010.02503.x> PMID: 20586966
2. Benjamin LA, Corbett EL, Connor MD, Mzinganjira H, Kampondeni S, Choko A, et al (2016) HIV, antiretroviral treatment, hypertension, and stroke in Malawian adults: A case-control study. *Neurology* 86: 324–333. <https://doi.org/10.1212/WNL.0000000000002278> PMID: 26683649
3. Nou E, Lo J, Hadigan C, Grinspoon SK (2016) Pathophysiology and management of cardiovascular disease in patients with HIV. *Lancet Diabetes Endocrinol.* Jul; 4(7):598–610. [https://doi.org/10.1016/S2213-8587\(15\)00388-5](https://doi.org/10.1016/S2213-8587(15)00388-5) PMID: 26873066
4. Sagui E (2007) [Stroke in sub-Saharan Africa]. *Med Trop (Mars)* 67: 596–600.
5. Divala OH, Amberbir A, Ismail Z, Beyene T, Garone D, Pfaff C, et al (2016) The burden of hypertension, diabetes mellitus, and cardiovascular risk factors among adult Malawians in HIV care: consequences for integrated services. *BMC Public Health* 16: 1243. <https://doi.org/10.1186/s12889-016-3916-x> PMID: 27955664
6. Dillon DG, Gurdasani D, Riha J, Ekoru K, Asiki G, Mayanja BN, et al (2013) Association of HIV and ART with cardiometabolic traits in sub-Saharan Africa: a systematic review and meta-analysis. *Int J Epidemiol* 42: 1754–1771. <https://doi.org/10.1093/ije/dyt198> PMID: 24415610
7. Gleason RL Jr., Caulk AW, Seifu D, Parker I, Vidakovic B, Getenet H, et al (2015) Current Efavirenz (EFV) or Ritonavir-Boosted Lopinavir (LPV/r) Use Correlates with Elevate Markers of Atherosclerosis in HIV-Infected Subjects in Addis Ababa, Ethiopia. *PLoS ONE* 10: e0117125. <https://doi.org/10.1371/journal.pone.0117125> PMID: 25915208
8. Jamieson L, Evans D, Brennan AT, Moyo F, Spencer D, Mahomed K, et al (2017) Changes in elevated cholesterol in the era of tenofovir in South Africa: risk factors, clinical management and outcomes. *HIV Med.* 18(8):595–603. <https://doi.org/10.1111/hiv.12495> PMID: 28332270
9. Liu Enju, Armstrong Catharina, Spiegelman Donna, Chalamilla Guerino, Njelekela Marina, Hawkins Claudia, et al (2013) First-line Antiretroviral Therapy and Changes in Lipid Levels Over 3 Years Among HIV-Infected Adults in Tanzania. *Clin Infect Dis* 56: 1820–1828. <https://doi.org/10.1093/cid/cit120> PMID: 23449270
10. Jahn A, Harries AD, Schouten EJ, Libamba E, Ford N, Maher D, et al (2016) Scaling-up antiretroviral therapy in Malawi. *Bull World Health Organ* 94: 772–776. <https://doi.org/10.2471/BLT.15.166074> PMID: 27843168
11. World Health Organization (2003) STEPS Q by Q guide for chronic diseases risk factor surveillance -instrument V2.0.
12. de OM, Garza C, Onyango AW, Borghi E (2007) Comparison of the WHO child growth standards and the CDC 2000 growth charts. *J Nutr* 137: 144–148. <https://doi.org/10.1093/jn/137.1.144> PMID: 17182816
13. Waist circumference and waist-hip ratio: report of a WHO expert consultation. Geneva: World Health Organization; 2009.
14. Agostino RB, Vasan RS, Pencina MJ, Wolf PA, Cobain M, Massaro JM, et al (2008) General Cardiovascular Risk Profile for Use in Primary Care. *Circulation* 117: 743. <https://doi.org/10.1161/CIRCULATIONAHA.107.699579> PMID: 18212285
15. Millan J, Pinto X, Munoz A, Zuniga M, Rubies-Prat J, Pallardo LF et al (2009) Lipoprotein ratios: Physiological significance and clinical usefulness in cardiovascular prevention. *Vasc Health Risk Manag* 5: 757–765. PMID: 19774217
16. van Oosterhout JJ, Mallewa J, Kaunda S, Chagoma N, Njalale Y, Kampira E, et al (2012) Stavudine Toxicity in Adult Longer-Term ART Patients in Blantyre, Malawi. *PLoS ONE* 7: e42029. <https://doi.org/10.1371/journal.pone.0042029> PMID: 22848696
17. Menezes CN, Crowther NJ, Duarte R, Van Amsterdam D, Evans D, Dickens C, et al (2014) A randomized clinical trial comparing metabolic parameters after 48 weeks of standard- and low-dose stavudine therapy and tenofovir disoproxil fumarate therapy in HIV-infected South African patients. *HIV Med* 15: 3–12. <https://doi.org/10.1111/hiv.12074> PMID: 23980620
18. Sinxadi PZ, McIlleron HM, Dave JA, Smith PJ, Levitt NS, Haas DW, Met al (2016) Plasma Efavirenz Concentrations Are Associated With Lipid and Glucose Concentrations. *Medicine* (Baltimore). Jan; 95(2):e2385. <https://doi.org/10.1097/MD.0000000000002385> PMID: 26765416
19. Kagaruki GB, Mayige MT, Ngadaya ES, Kimaro GD, Kalinga AK, Kilale AM, et al (2014) Magnitude and risk factors of non-communicable diseases among people living with HIV in Tanzania: a cross sectional

- study from Mbeya and Dar es Salaam regions. *BMC Public Health* 14: 904. <https://doi.org/10.1186/1471-2458-14-904> PMID: 25183300
20. Muyanja D, Muzoora C, Muyingo A, Muyindike W, Siedner MJ (2016) High Prevalence of Metabolic Syndrome and Cardiovascular Disease Risk Among People with HIV on Stable ART in Southwestern Uganda. *AIDS Patient Care Stds* 30: 4–10. <https://doi.org/10.1089/apc.2015.0213> PMID: 26683587
  21. Kazooba P, Kasamba I, Mayanja BN, Lutaakome J, Namakoola I, Salome T, et al (2017) Cardiometabolic risk among HIV-POSITIVE Ugandan adults: prevalence, predictors and effect of long-term antiretroviral therapy. *Pan Afr Med J* 27: 40. <https://doi.org/10.11604/pamj.2017.27.40.9840> PMID: 28761616
  22. Noumegni SRN, Nansseu JR, Ama VJM, Bigna JJ, Assah FK, Guewo-Fokeng M, et al (2017) Insulin resistance and associated factors among HIV-infected patients in sub-Saharan Africa: a cross sectional study from Cameroon. *Lipids Health Dis* 16: 148. <https://doi.org/10.1186/s12944-017-0543-1> PMID: 28797289
  23. Njoroge A, Guthrie BL, Bosire R, Wener M, Kiarie J, Farquhar C (2017) Low HDL-cholesterol among HIV-1 infected and HIV-1 uninfected individuals in Nairobi, Kenya. *Lipids Health Dis* 16: 110. <https://doi.org/10.1186/s12944-017-0503-9> PMID: 28599673
  24. Zhou DT, Kodogo V, Chokuona KFV, Gomo E, Oektedalen O, Stray-Pedersen B (2015) Dyslipidemia and cardiovascular disease risk profiles of patients attending an HIV treatment clinic in Harare, Zimbabwe. *HIV AIDS (Auckl)* 7: 145–155.
  25. Huxley R, Mendis S, Zheleznyakov E, Reddy S, Chan J (2009) Body mass index, waist circumference and waist:hip ratio as predictors of cardiovascular risk—a review of the literature. *Eur J Clin Nutr*. 2010 Jan; 64(1):16–22. <https://doi.org/10.1038/ejcn.2009.68> Epub 2009 Aug 5. PMID: 19654593
  26. Barzi F, Woodward M, Czernichow S, Lee CMY, Kang JH, Janus E, et al (2010) The discrimination of dyslipidaemia using anthropometric measures in ethnically diverse populations of the Asia—Pacific Region: The Obesity in Asia Collaboration. *Obes Rev*. 2010 Feb; 11(2):127–36. <https://doi.org/10.1111/j.1467-789X.2009.00605.x> Epub 2009 Jun 2. PMID: 19493299
  27. Price AJ, Crampin AC, Amberbir A, Kayuni-Chihana N, Musicha C, Tafatatha T et al (2018) Prevalence of obesity, hypertension, and diabetes, and cascade of care in sub-Saharan Africa: a cross-sectional, population-based study in rural and urban Malawi. *Lancet Diabetes Endocrinol* 6: 208–222. [https://doi.org/10.1016/S2213-8587\(17\)30432-1](https://doi.org/10.1016/S2213-8587(17)30432-1) PMID: 29371076
  28. Lars G., Hemkens, Bucher Heiner C. (2014) HIV infection and cardiovascular disease. *Eur Heart J* 35: 1371–1381. <https://doi.org/10.1093/eurheartj/ehu528> PMID: 24408888
  29. Nordestgaard BG, Langsted A, Mora S, Kolovou G, Baum Hr, Bruckert E, et al (2016) Fasting is not routinely required for determination of a lipid profile: clinical and laboratory implications including flagging at desirable concentration cut-points: a joint consensus statement from the European Atherosclerosis Society and European Federation of Clinical Chemistry and Laboratory Medicine. *Eur Heart J* 37: 1944–1958. <https://doi.org/10.1093/eurheartj/ehw152> PMID: 27122601