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# Association between non-high-density lipoprotein cholesterol and non-alcoholic fatty liver disease among people living with HIV on dolutegravir-based antiretroviral therapy: A cross-sectional study in Southwestern Uganda

Charles Nkubi Bagenda<sup>1,2\*</sup>, Carol Nantongo<sup>2,9</sup>, Elastus Ssemwanga<sup>8,13</sup>, Michael Junior Mugisa<sup>1,8</sup>, Jesca Wafwoyo Akoth<sup>1</sup>, Daniel Nzaramba<sup>1</sup>, Rogers Kalyetsi<sup>1</sup>, Elizabeth A. John<sup>5</sup>, Jazira Tumusiime<sup>1</sup>, Blendar Ainebyoona<sup>2</sup>, Shadrach Omara<sup>1</sup>, Vicent Mwesigye<sup>1</sup>, Sylvia Achieng Lumumba<sup>7</sup>, Conrad Lubwama<sup>12</sup>, Benson Musinguzi<sup>6</sup>, Lucas Ampaire<sup>1</sup>, Rose Nassali<sup>2</sup>, Herbert Itabangi<sup>10</sup>, Lawrence Obado Osuwat<sup>4</sup>, Brian Ssenkumba<sup>11</sup> and Ronald Ouma Omolo<sup>3</sup>

## Abstract

**Objective** Non-high-density lipoprotein cholesterol, an aggregate marker of atherogenic lipoproteins, has been implicated in metabolic dysfunction and may predict non-alcoholic fatty liver disease risk. Our study investigated the association between non-high-density lipoprotein cholesterol and non-alcoholic fatty liver disease among people living with Human Immunodeficiency Virus on dolutegravir-based antiretroviral therapy in southwestern Uganda. We conducted a secondary analysis of data obtained from a cross-sectional study of 377 adults who had been on dolutegravir-based antiretroviral therapy for  $\geq 12$  months at Ruhoko Health Centre IV, southwestern Uganda.

**Results** Of the 377 participants, 42(11.1%; 95CI: 8.3–14.8) had non-alcoholic fatty liver disease. We observed a significant association between high non-high-density lipoprotein cholesterol and non-alcoholic fatty liver disease; second tertile (aOR = 3.08, 95% CI: 1.06–8.99,  $p = 0.039$ ) and third tertile (aOR = 4.46, 95% CI: 1.25–15.88,  $p = 0.021$ ). At an optimal cut-off of  $\geq 113.4$  with a sensitivity of 69% and specificity of 48%, non-high-density lipoprotein cholesterol had a significant discriminative ability; AUC = 0.654(95%CI: 0.561–0.747) to distinguish participants with from those without non-alcoholic fatty liver disease. Therefore, High non-high-density lipoprotein cholesterol is a potential predictor for non-alcoholic fatty liver disease.

**Keywords** Non-alcoholic fatty liver disease, Atherogenic lipid, Fatty liver index

\*Correspondence:  
Charles Nkubi Bagenda  
cbagenda@must.ac.ug

Full list of author information is available at the end of the article



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## Introduction

Non-alcoholic fatty liver disease (NAFLD), also termed metabolic dysfunction-associated steatotic liver disease (MASLD), is defined by the accumulation of  $\geq 5\%$  hepatic fat in the absence of significant alcohol intake or other identifiable causes of liver disease [1]. NAFLD is now the most common chronic liver disease worldwide, affecting 25–30% of the global population, and is a leading cause of cirrhosis and hepatocellular carcinoma [2]. Among people living with human immunodeficiency virus (HIV), the prevalence of NAFLD appears even higher; a recent meta-analysis estimated it at 33–43%, exceeding that of the general population [3].

Integrase inhibitor-based antiretroviral therapy (ART), particularly dolutegravir (DTG), which is currently the preferred first-line regimen, has been associated with weight gain, metabolic abnormalities, and increased hepatic steatosis [4–8], potentially heightening NAFLD risk in people living with HIV (PLWH). Epidemiological data indicate that NAFLD prevalence is rising in sub-Saharan Africa, with an estimated regional prevalence of 29.21% [9]. In Uganda, community-based data report MASLD in 14% of women and 8% of men, with slightly higher prevalence among individuals with HIV [10]. This growing burden highlights NAFLD as an emerging challenge within metabolic and chronic disease management in the region.

If left untreated, NAFLD may progress to non-alcoholic steatohepatitis (NASH), advanced fibrosis, cirrhosis, and hepatocellular carcinoma [2]. NAFLD is also an independent risk factor for cardiovascular disease, the leading cause of death among affected individuals [11]. In PLWH, where liver disease and cardiovascular events already constitute major non-AIDS causes of mortality [12], unrecognized NAFLD may substantially worsen clinical outcomes.

Despite the recognized risk of NAFLD in PLWH, the contribution of specific atherogenic lipids remains poorly defined. Non-high-density lipoprotein cholesterol (non-HDL-C), encompassing low density lipoprotein-cholesterol (LDL-C), very low-density lipoprotein-cholesterol (VLDL-C), and intermediate density lipoprotein-cholesterol (IDL-C), is a potent marker of atherogenic cholesterol and cardiovascular risk. Evidence also indicates that elevated non-HDL/HDL-C ratios predict incident NAFLD [13–15]. However, data linking these lipid markers to NAFLD in ART-treated HIV populations are

limited. To the best of our knowledge, no study in southwestern Uganda has specifically examined atherogenic lipid markers in relation to NAFLD among PLWH receiving DTG-based ART. Given DTG's metabolic effects [4] and its widespread use, this study aimed to evaluate the association between non-HDL-C, related lipid ratios, and NAFLD among PLWH on DTG-based ART in southwestern Uganda.

## Materials and methods

### Study design and population

We conducted a secondary data analysis using a dataset generated from a cross-sectional study that investigated the association between low aspartate aminotransferase (AST)/alanine aminotransferase (ALT) ratio and metabolic syndrome (MetS) among 377 PLWH on DTG-based ART in southwestern Uganda [16].

### Sample size determination

For this secondary analysis, the sample size was estimated based on a reported prevalence of liver fibrosis of 15% among adults living with HIV attending rural care clinics in Uganda [17]. Using the Kish–Leslie formula (1965), with a 5% margin of error and a 95% confidence interval, the minimum required sample size was calculated as:

$$n = 1.96^2 * 0.15(1-0.15) / 0.05^2 = 196.$$

The primary study enrolled 377 participants, which exceeded the minimum required sample size. Therefore, the available sample was considered adequate for the secondary data analysis.

### Data collection

The secondary study was conducted between 10 May 2025 and 10 July 2025. In the primary study, patients aged  $\geq 18$  years who had been on DTG-based ART for  $\geq 12$  months and had given informed consent were enrolled systematically. Individuals with missing records, pregnancy, interrupted treatment, acute illness including hepatitis, or using diabetes therapy, lipid-lowering drugs, corticosteroids, or oral contraceptives were excluded.

In this secondary analysis, the primary outcome of interest was NAFLD. NAFLD was assessed using the fatty liver index (FLI) [18] validated algorithm based on body mass index (BMI), waist circumference, serum triglycerides, and gamma-glutamyl transferase ( $\gamma$ -GTP). The FLI was calculated as follows:

$$FLI = \frac{100 \times e^{(0.953 \times \log_e(\text{triglycerides}) + 0.139 \times (\text{BMI}) + 0.718 \times \log_e(\gamma - \text{GTP}) + 0.053 \times (\text{waist circumference}) - 15.745)}}{1 + e^{(0.953 \times \log_e(\text{triglycerides}) + 0.139 \times (\text{BMI}) + 0.718 \times \log_e(\gamma - \text{GTP}) + 0.053 \times (\text{waist circumference}) - 15.745)}}$$

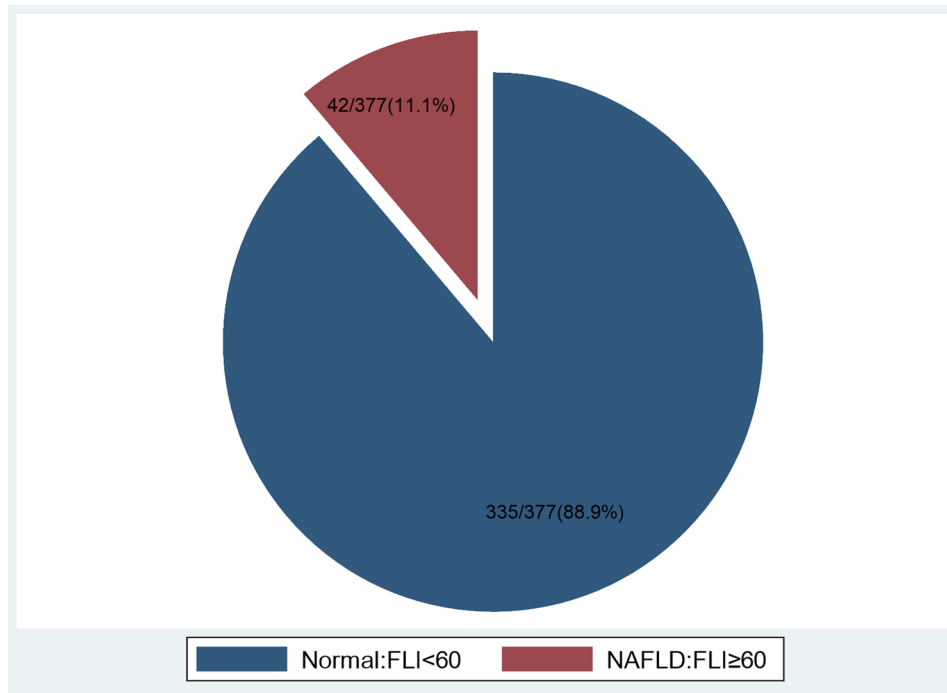
**Table 1** Sociodemographic and clinical characteristics of the study participants stratified by non-alcoholic fatty liver disease status

Variable	Total	Non-alcoholic fatty liver disease		p-value
	N= 377	Absent: FLI < 60 N= 335	Present: FLI ≥ 60 N= 42	
<b>Age(Years):</b> Median (IQR)	44 (30–59)	41 (29–56)	60.5 (44–68)	<0.001
<b>Age group</b>				<0.001
<40	166 (44.0%)	160 (47.8%)	6 (14.3%)	
40–60	124 (32.9%)	109 (32.5%)	15 (35.7%)	
>60	87 (23.1%)	66 (19.7%)	21 (50.0%)	
<b>Sex</b>				0.015
Male	165 (43.8%)	154 (46.0%)	11 (26.2%)	
Female	212 (56.2%)	181 (54.0%)	31 (73.8%)	
<b>Marital status</b>				0.009
Single	161 (42.7%)	151 (45.1%)	10 (23.8%)	
Married	216 (57.3%)	184 (54.9%)	32 (76.2%)	
<b>Education level</b>				0.037
No education	83 (22.0%)	68 (20.3%)	15 (35.7%)	
Primary	68 (18.0%)	60 (17.9%)	8 (19.0%)	
Secondary	75 (19.9%)	65 (19.4%)	10 (23.8%)	
Tertiary	151 (40.1%)	142 (42.4%)	9 (21.4%)	
<b>Residence</b>				0.045
Urban	216 (57.3%)	198 (59.1%)	18 (42.9%)	
Rural	161 (42.7%)	137 (40.9%)	24 (57.1%)	
<b>Religion</b>				0.40
Christian	345 (91.5%)	308 (91.9%)	37 (88.1%)	
Moslem	32 (8.5%)	27 (8.1%)	5 (11.9%)	
<b>Employment status</b>				0.56
Unemployed	60 (15.9%)	52 (15.5%)	8 (19.0%)	
Employed	317 (84.1%)	283 (84.5%)	34 (81.0%)	
<b>Ventilated kitchen</b>				0.15
No	55 (14.6%)	52 (15.5%)	3 (7.1%)	
Yes	322 (85.4%)	283 (84.5%)	39 (92.9%)	
<b>Smoking</b>				0.99
Non smoker	332 (88.1%)	295 (88.1%)	37 (88.1%)	
Ever smoked	45 (11.9%)	40 (11.9%)	5 (11.9%)	
<b>Alcohol status</b>				0.041
Never consumed	143 (37.9%)	121 (36.1%)	22 (52.4%)	
Ever consumed	234 (62.1%)	214 (63.9%)	20 (47.6%)	
<b>Vegetable and fruit intake</b>				1.00
<5 servings per day	367 (97.3%)	326 (97.3%)	41 (97.6%)	
≥5 servings per day	10 (2.7%)	9 (2.7%)	1 (2.4%)	
<b>Poor sleep quality</b>				<0.001
Good quality	275 (72.9%)	255 (76.1%)	20 (47.6%)	
Poor quality	102 (27.1%)	80 (23.9%)	22 (52.4%)	
<b>Sleep duration</b>				0.86
>7	72 (19.1%)	65 (19.4%)	7 (16.7%)	
6–7	251 (66.6%)	221 (66.0%)	30 (71.4%)	
5–6	38 (10.1%)	35 (10.4%)	3 (7.1%)	
<5	16 (4.2%)	14 (4.2%)	2 (4.8%)	
<b>Obstructive Sleep Apnea</b>				<0.001
Low risk of OSA	302 (80.1%)	280 (83.6%)	22 (52.4%)	
High risk of OSA	75 (19.9%)	55 (16.4%)	20 (47.6%)	
<b>High blood pressure</b>				0.038
Absent	145 (38.5%)	135 (40.3%)	10 (23.8%)	
Present	232 (61.5%)	200 (59.7%)	32 (76.2%)	
<b>DTG-ART duration</b>				0.020

**Table 1** (continued)

Variable	Total N= 377	Non-alcoholic fatty liver disease		p-value
		Absent: FLI < 60 N= 335	Present: FLI ≥ 60 N= 42	
≤2years	112 (29.7%)	106 (31.6%)	6 (14.3%)	
>2years	265 (70.3%)	229 (68.4%)	36 (85.7%)	

Data are presented as median (IQR) or n (%). P-values compare groups using appropriate non-parametric or categorical tests. Abbreviations: NAFLD, non-alcoholic fatty liver disease; FLI, Fatty Liver Index; DTG, dolutegravir; OSA, obstructive sleep apnea; IQR, interquartile range.



**Fig. 1** Proportion of study participants with Non-alcoholic fatty liver disease

The index ranges from 0 to 100 and has demonstrated good diagnostic accuracy for detecting NAFLD, with an AUC of 0.84 (95% CI: 0.81–0.87) [19, 20]. A FLI score of < 30 reliably rules out, while a score ≥ 60 rules in hepatic steatosis as confirmed by ultrasonography. Accordingly, in this study, NAFLD was defined as FLI ≥ 60 [21]. At this cut off point, FLI has excellent diagnostic accuracy for detecting fatty liver on ultrasound with sensitivity 96% (95% CI 91.1–98.4%), specificity 92.5% (95% CI 86.7–96.2%), PPV 92.4% (95% CI 86.5–96.2%), NPV 96.1% (95% CI 90.8–98.7%), and accuracy 94.6% (95% CI 91.9–96.6%) [20].

The major independent variables were non-HDL-C, Castelli’s Risk Index (CRI-I), Castelli’s Risk Index (CRI-II), Atherogenic Coefficient (AC) and Residual cholesterol (RC). In this study, High blood pressure (Hypertension) was defined as Systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg [22].

**Parameter calculations**

- (1) Non-HDL-C = TC (mg/dL) – HDL-c (mg/dL) [23].
- (2) Castelli’s Risk Index (CRI-I) = TC/HDL-C [24].
- (3) Castelli’s Risk Index (CRI-II) = LDL-C/HDL-C [24].
- (4) “Atherogenic Coefficient (AC)” = Non-HDL-C/HDL-C [25].
- (5) Residual cholesterol (RC) = TC (mg/dL) – HDL-c (mg/dL) – LDL-c (mg/dL) [26].

**Statistical analysis**

Data were analyzed using STATA software version 17. Continuous variables were assessed for normality using the Shapiro-Wilk normality test. All variables were not normally distributed and therefore were summarized using medians (interquartile range, IQR). The distribution of the variables between participants with and those without NAFLD was compared using Mann-Whitney U test. Categorical variables were summarized

**Table 2** Biochemical parameters and indices of the study participants stratified by non-alcoholic fatty liver disease status

Variable	Total N=377	Non-alcoholic fatty liver disease		p-value
		Absent: FLI < 60 N=335	Present: FLI ≥ 60 N=42	
Fasting plasma glucose	87.40(77.5–101.2.5.2)	87.10(77.30–99.70)	94.30(79–117.3.3)	<b>0.012</b>
Total cholesterol	168 (144–208.8.8)	167.5 (144–208)	176 (154–211)	0.29
Non-HDL cholesterol	115.2 (92.4–134.1.4.1)	113.9 (92.2–132.9.2.9)	121.75 (102.5–146.3.5.3)	0.076
RC	35.4 (26.6–40.2)	34.6 (26.16–39.6)	38.9 (32.4–42.8)	<b>0.014</b>
LDL/HDL-C	1.56(0.99–2.45)	1.56(0.98–2.44)	1.54(1.08–2.83)	0.56
TC/HDL-C ratio	3.36(2.55–4.34)	3.32(2.52–4.29)	3.39(2.60–4.86)	0.43
Non-HDL-C/HDL-C	2.36(1.55–3.34)	2.32(1.52–3.29)	2.39(1.60–3.86)	0.43
AST	21 (15–30)	21.20(16–31)	17 (13–25)	<b>0.004</b>
ALT	23 (17–31)	23 (17–31)	22 (18–31)	0.93
ALP	101 (82–119)	101 (82–117)	106.45 (77–148)	0.32
Na+	137.8 (135.40–141)	137.8 (134.90–141)	138.5 (136.10–142.2.10.2)	0.13
K+	4.03(3.81–4.41)	4.03(3.81–4.42)	4.11(3.82–4.40)	0.91
Na/K ratio	34.22(30.87–36.44)	34.22(30.86–36.44)	33.75(31.26–36.73)	0.75
Cl-	99.40(97.30–102.7.30.7)	99.30(97.30–102.7.30.7)	99.5 (97.70–103.10.70.10)	0.49

Values are reported as median (IQR). P-values indicate between-group comparisons using the Mann-Whitney U test. Abbreviations: NAFLD, non-alcoholic fatty liver disease; FLI, Fatty Liver Index; IQR, interquartile range; RC, remnant cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol.

as frequencies and percentages and their distribution by NAFLD status compared using Chi-square or Fisher's exact tests.

To assess associations between independent variables and the binary outcome variable; NAFLD, logistic regression was performed. Associations were reported as odds ratios with 95% confidence intervals, and statistical significance was set at  $p \leq 0.05$ . Non-HDL-C and the lipoprotein ratios were categorized into tertiles. Variables with  $p$ -values  $\leq 0.05$  at bivariate analysis and those with biological plausibility were included in the multivariate analysis to adjust for possible confounding. To adjust for precision, non-significant variables lacking strong biological plausibility with NAFLD were dropped from the multivariate model without significant loss of model validity. The final chosen reduced model was tested for its suitability to predict the outcome variable using Hosmer-Lemeshow goodness of fit test, and a  $p$ -value  $> 0.05$  indicates good goodness of fit. The final model was

assessed for severe multicollinearity using the mean variance inflation factor (VIF), which was 2.67 (range: 1.07–10.73). A VIF threshold of  $< 5$  was considered acceptable, indicating the absence of severe multicollinearity. A  $p$ -value  $< 0.05$  was considered statistically significant in the final model.

To evaluate the predictive ability of the lipoprotein indices for identifying participants with NAFLD, we performed receiver operating characteristic (ROC) curve analysis. The area under the ROC curve (AUC) was calculated to quantify the overall ability of each lipoprotein index to discriminate between participants with and without NAFLD. An AUC value approaching 1.0 indicates excellent discriminative performance, whereas an AUC of 0.5 reflects no discriminative ability beyond chance. Predictive performance was considered statistically significant when the 95% confidence interval of the AUC did not include the null value of 0.5.

## Results

### Sociodemographic and clinical characteristics of the study participants

A total of 377 participants were included in the study, with a median age of 44 years (IQR: 30–59) as indicated in Table 1. Of the 377 participants, 42 (11.1%) screened positive for NAFLD based on the  $FLI \geq 60$ . Therefore, the overall prevalence of NAFLD was 11.1% with 95% Confidence Interval of 8.3% – 14.8% as indicated in Fig. 1. Participants with NAFLD had a significantly higher median age than those without (60.5 vs. 41 years,  $p < 0.001$ ). Females predominated (56.2%) and were more represented in the NAFLD group (73.8% vs. 54.0%,  $p = 0.015$ ). Married (76.2% vs. 54.9%,  $p = 0.009$ ), less educated ( $p = 0.037$ ), and rural participants (57.1% vs. 40.9%,  $p = 0.045$ ) were significantly more prevalent in the NAFLD group compared to those without the condition. Poor sleep quality (52.4% vs. 23.9%,  $p < 0.001$ ), high risk of obstructive sleep apnea (47.6% vs. 16.4%,  $p < 0.001$ ), high blood pressure (76.2% vs. 59.7%,  $p = 0.038$ ) and longer DTG-based ART duration ( $> 2$  years) (85.7% vs. 68.4%,  $p = 0.020$ ) were also significantly more prevalent among participants with NAFLD than those without (Table 1).

### Biochemical parameters and indices of the study participants

Among biochemical parameters (Table 2), fasting plasma glucose, remnant cholesterol (RC), and aspartate aminotransferase (AST) significantly differed between the two groups. Participants with NAFLD had higher fasting plasma glucose (94.3 vs. 87.1 mg/dL,  $p = 0.012$ ) and RC levels (38.9 vs. 34.6 mg/dL,  $p = 0.014$ ), but significantly lower AST levels (17 U/L vs. 21.2 U/L,  $p = 0.004$ ) than those without NAFLD.

**Table 3** Association of Non-High-density lipoprotein cholesterol with Non-alcoholic fatty liver disease using logistic regression analysis

Predictor variable	NAFLD (1=Present, 0=Absent)			
	Bivariate analysis		Multivariate analysis	
	cOR(95%CI)	P-value	aOR(95%CI)	P-value
<b>Non-HDL-C</b>				
First tertile	1.00		1.00	
Second tertile	1.63(0.68-3.90)	0.278	<b>3.08(1.06-8.99)</b>	<b>0.039</b>
Third tertile	<b>2.33(1.01-5.37)</b>	<b>0.047</b>	<b>4.46(1.25-15.88)</b>	<b>0.021</b>
<b>RC</b>				
First tertile	1.00		1.00	
Second tertile	1.17(0.48-2.86)	0.733	1.25(0.42-3.72)	0.694
Third tertile	<b>2.47(1.11-5.49)</b>	<b>0.026</b>	1.41(0.48-4.09)	0.532
<b>LDL-C/HDL-C ratio</b>				
First tertile	1.00		1.00	
Second tertile	1.07(0.49-2.42)	0.839	0.52(0.09-2.95)	0.462
Third tertile	1.19(0.54-2.61)	0.672	0.34(0.03-4.53)	0.414
<b>TC/HDL-C ratio</b>				
First tertile	1.00		1.00	
Second tertile	0.99(0.44-2.23)	0.983	1.38(0.25-7.49)	0.711
Third tertile	1.29(0.59-2.80)	0.524	0.89(0.09-9.11)	0.924
<b>Non-HDL/HDL-C ratio</b>				
First tertile	1.00			
Second tertile	0.99(0.44-2.23)	0.983		
Third tertile	1.29(0.59-2.80)	0.524		
<b>Age (Years)</b>				
<40	1.00		1.00	
40-60	<b>3.67(1.38-9.75)</b>	<b>0.009</b>	<b>3.91(1.13-13.58)</b>	<b>0.032</b>
>60	<b>8.48(3.28-21.97)</b>	<b>&lt;0.001</b>	<b>6.80(1.43-32.41)</b>	<b>0.016</b>
<b>Sex</b>				
Male	1.00			
Female	2.40(1.17-4.93)	0.017		
<b>Education level</b>				
No education	1.00		1.00	
Primary	0.60(0.24-1.53)	0.286	1.38(0.42-4.55)	0.592
Secondary	0.70(0.29-1.66)	0.417	2.75(0.79-9.74)	0.116
Tertiary	<b>0.29(0.12-0.69)</b>	<b>0.005</b>	1.50(0.40-5.66)	0.551
<b>Residence</b>				
Urban	1.00		1.00	
Rural	<b>1.93(1.01-3.69)</b>	<b>0.048</b>	<b>2.25(1.02-4.99)</b>	<b>0.046</b>
<b>Religion</b>				
Christian	0.65(0.24-1.79)	0.403		
Moslem	1.00			
<b>Employment status</b>				
Unemployed	1.00			
Employed	0.78(0.34-1.78)	0.557		
<b>Ventilated kitchen</b>				
No	0.42(0.12-1.41)	0.159		
Yes	1.00			
<b>Smoking</b>				
Non smoker	1.00			
Ever smoked	1.00(0.37-2.68)	0.995		
<b>Alcohol status</b>				
Never consumed	1.00		1.00	
Ever consumed	<b>0.51(0.27-0.98)</b>	<b>0.043</b>	<b>0.40(0.19-0.88)</b>	<b>0.023</b>

**Table 3** (continued)

Predictor variable	NAFLD (1=Present, 0=Absent)			
	Bivariate analysis		Multivariate analysis	
	cOR(95%CI)	P-value	aOR(95%CI)	P-value
<b>Vegetable and fruit intake</b>				
<5 servings per day	1.13(0.14-9.16)	0.908		
≥5 servings per day	1.00			
<b>Poor sleep quality</b>				
Good quality	1.00		1.00	
Poor quality	<b>3.51(1.82-6.75)</b>	<b>&lt;0.001</b>	<b>2.82(1.20-6.66)</b>	<b>0.018</b>
<b>Sleep duration</b>				
>7	1.00			
6-7	1.26(0.53-3.00)	0.601		
5-6	0.80(0.19-3.27)	0.752		
<5	1.33(0.25-7.08)	0.741		
<b>Obstructive Sleep Apnea</b>				
Low risk of OSA	1.00		1.00	
High risk of OSA	<b>4.63(2.37-9.05)</b>	<b>&lt;0.001</b>	1.73(0.64-4.68)	0.282
<b>High blood pressure</b>				
Absent	1.00		1.00	
Present	<b>2.16(1.03-4.54)</b>	<b>0.042</b>	0.91(0.36-2.32)	0.839
<b>DTG-ART duration</b>				
≤2years	1.00		1.00	
>2years	<b>2.78(1.14-6.79)</b>	<b>0.025</b>	0.56(0.18-1.74)	0.318
Fasting plasma glucose	<b>1.03(1.01-1.05)</b>	<b>0.002</b>	1.02(0.98-1.05)	0.075
Total cholesterol	1.00(1.00-1.01)	0.243		
AST	<b>0.94(0.91-0.98)</b>	<b>0.005</b>	<b>0.92(0.88-0.97)</b>	<b>0.002</b>
ALT	0.99(0.96-1.03)	0.716	1.00(0.95-1.05)	0.973
ALP	1.00(1.00-1.01)	0.140	1.01(1.00-1.01)	0.191
Na <sup>+</sup>	1.04(0.99-1.10)	0.154		
K <sup>+</sup>	0.88(0.51-1.53)	0.653		
<b>Na/K ratio</b>				
First tertile	1.00		1.00	
Second tertile	1.26(0.58-2.75)	0.554	1.54(0.57-4.14)	0.391
Third tertile	1.01(0.45-2.27)	0.983	1.19(0.43-3.28)	0.732
Cl <sup>-</sup>	1.02(0.97-1.08)	0.402		

cOR: Crude Odds ratio, aOR: adjusted Odds ratio, CI: 95% Confidence interval

**Table 4** Predictive performance of lipoprotein ratios for NAFLD

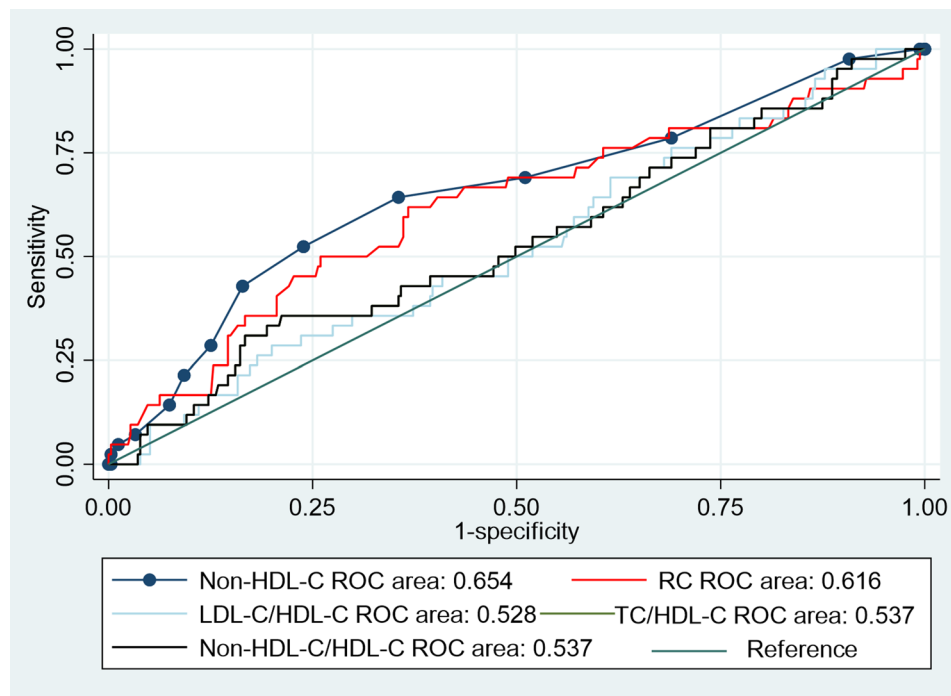
Obesity index	AUC	95% CI	Optimal cutoff	Sensitivity	Specificity	Youden J index
Non-HDL-C	0.654	0.561 0.747	≥ 113.4	69%	48%	0.180
RC	0.616	0.518 0.714	≥ 37.7	62%	63%	0.252
LDL-C/HDL-C	0.528	0.435 0.620	≥ 2.7	29%	80%	0.086
TC/HDL-C	0.537	0.441 0.633	≥ 4.5	36%	79%	0.145
Non-HDL-C/HDL-C	0.537	0.441 0.633	≥ 3.5	36%	79%	0.145

**Association of non-high-density lipoprotein cholesterol with non-alcoholic fatty liver disease**

In the bivariate analysis (Table 3), higher levels of non-HDL-C were positively associated with NAFLD. Participants in the second tertile had higher, though not statistically significant, odds of NAFLD compared to those in the first tertile (cOR=1.63, 95% CI: 0.68–3.90, *p*=0.278). However, those in the third tertile

demonstrated significantly increased odds of NAFLD (cOR = 2.33, 95% CI: 1.01–5.37, *p* = 0.047).

After adjusting for potential confounders in the multivariate analysis (Table 3), the strength of association increased. Participants in the second tertile of non-HDL-C were more than three times as likely to have NAFLD compared to those in the first tertile (aOR = 3.08, 95% CI: 1.06–8.99, *p* = 0.039). Similarly, those in the third tertile



**Fig. 2** Receiver operating characteristic curve showing the predictive performance of lipoprotein ratios for NAFLD

had over four times the odds of NAFLD (aOR = 4.46, 95% CI: 1.25–15.88,  $p = 0.021$ ). At an optimal cut-off of  $\geq 113.4$  with a sensitivity of 69% and specificity of 48%, non-HDL-C had a significant discriminative ability; AUC = 0.654 (95% CI: 0.561–0.747) to distinguish participants with from those without NAFLD as indicated in Table 4; Fig. 2.

## Discussion

In this study, we found a significant and independent association between non-HDL-C and NAFLD among PLWH on DTG-based ART. Higher non-HDL-C tertiles were associated with progressively increased odds of NAFLD, and non-HDL-C demonstrated modest but significant discriminative ability for NAFLD. There have been efforts to determine blood lipid profiles as predictors for NAFLD [27, 28]. Biologically, non-HDL-C aggregates all atherogenic lipoproteins LDL, VLDL, and IDL [29, 30], which are implicated in the pathogenesis of hepatic steatosis through enhanced delivery of cholesterol and triglyceride precursors to the liver and promotion of insulin resistance. The linkage between atherogenic lipids and NAFLD is supported by studies showing that elevated remnant cholesterol and non-HDL components correlate with both steatosis and severity of NAFLD in cross-sectional populations such as NHANES cohorts where non-HDL-based indices were robustly associated with NAFLD prevalence and severity [14, 31].

Our findings are consistent with evidence from general population studies demonstrating that non-HDL-C is a

predictor of NAFLD risk. In a longitudinal cohort, higher baseline non-HDL-C independently predicted incident NAFLD over 7 years (OR = 1.02 per mg/dl increase; 95% CI: 1.01–1.04,  $p = 0.008$ ) [32]. Similarly, epidemiological data show that rising non-HDL-C trajectories are associated with increased NAFLD incidence (adjusted HR = 1.46 [33]). In addition, a recent multidimensional study demonstrated that statin therapy is associated with a reduced prevalence of NASH and liver fibrosis, mediated through reductions in both serum LDL-C and non-HDL-C [34]. However, despite evidence from previous studies indicating that the non-HDL-C/HDL-C ratio predicts NAFLD and its severity more effectively than non-HDL-C alone [14, 35–38], this ratio was not significantly associated with NAFLD in our bivariate analysis. The ratio was initially included in multivariable models because of its biological plausibility but was automatically excluded due to high collinearity with other lipid parameters, indicating overlapping rather than independent predictive information. This discrepancy may be explained by several factors. Non-HDL-C reflects the absolute burden of atherogenic lipoproteins that directly promote hepatic lipid accumulation and may therefore be a more direct marker of NAFLD risk in ART-treated HIV populations characterized by atherogenic dyslipidemia. In addition, statistical collinearity and limited sample size may have further reduced power to detect an independent association. Therefore, further studies with more statistical power to investigate the predictive ability of the lipoprotein indices including non-HDL-C/HDL-C ratio for

NAFLD among PLWH DTG-based ART in Uganda are highly recommended.

### Conclusion

High Non-HDL-C is a potential predictor for NAFLD among PLWH on DTG-based ART. This study indicates the potential application of Non-HDL-C profiling for the detection of risk of NAFLD at an early stage to guide the onset of timely interventions to prevent cardiovascular complications in this vulnerable population.

### Study limitations

This study has some limitations that should be considered when interpreting the findings. First, it provides only a snapshot of the NAFLD prevalence and its association with non-HDL-C, limiting our capacity to establish causality. Additionally, some variables were self-reported and hence susceptible to inaccurate reporting. The small sample size, particularly the limited number of participants with NAFLD, may have reduced statistical power to detect modest associations and contributed to wide confidence intervals for some estimates. Furthermore, NAFLD was defined using the FLI, a validated non-invasive tool with good diagnostic performance, especially at higher cut-offs; however, FLI may underestimate steatosis in certain subgroups of PLWH, such as lean individuals. FLI also does not provide information on disease severity or fibrosis stage and cannot replace imaging or histological assessment. Future studies with larger sample sizes, longitudinal designs, and incorporation of imaging-based or histological methods are warranted to better elucidate the relationship between atherogenic lipid indices and NAFLD in PLWH.

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### Author contributions

C.N.B and C.N participated in the conceptualization of the study. C.N.B performed data analysis and results interpretation. C.N.B, C.N, E.S, M.J.M, J.W.A, D.N, R.K, E.A.J, J.T, B.A, S.O, V.M, S.A.L, C.L, B.M, L.A, R.N, H.J, L.O.O, B.S, R.O.O contributed to writing the first draft of the manuscript with C.L, M.J.M, B.M, R.N, H.J, L.O.O, B.S, R.O.O providing critical revisions. All authors read and approved the final manuscript.

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### Data availability

The datasets used in this study are available from the corresponding author upon reasonable request.

### Declarations

#### Ethics approval and consent to participate

Ethical clearance was obtained from the Research Ethics Committee (REC) of the Mbarara University of Science and Technology (REC number: MUST-2024-1575) on 10 June 2024 to conduct the primary study [16]. All participants provided written informed consent prior to enrollment. The consent forms were translated into the local language (Runyankore) to ensure comprehension. Formally educated participants gave consent by signing the written forms. For participants with no formal education, the written informed consent form was read aloud in Runyankore, followed by administration of the comprehension screening tool approved by the MUST REC. Only participants who demonstrated understanding were allowed to consent by placing a thumbprint on the informed consent form. Participants were also explicitly asked to provide consent for the use of their data in the secondary analysis, for which they approved. This study was conducted in accordance with the Declaration of Helsinki (1975) as revised in 2024. Confidentiality of the study participants was observed by giving each participant a study code that was not traceable to them. To protect patient privacy, all personal identifiers were removed, and the data were fully deidentified before analysis. Permission to perform secondary analysis was also obtained from the principal investigator of the primary study.

#### Consent for publication

Not applicable.

#### Competing interests

The authors declare no competing interests.

#### Author details

<sup>1</sup>Department of Medical Laboratory Science, Faculty of Medicine, Mbarara University of Science and Technology, P.O. Box 1410, Mbarara, Uganda

<sup>2</sup>Department of Medical Laboratory Science, Uganda Institute of Allied Health and Management Sciences, P.O. Box, 34025, Kampala, Uganda

<sup>3</sup>Department of Physiology, Faculty of Medicine, Mbarara University of Science and Technology, P.O. Box 1410, Mbarara, Uganda

<sup>4</sup>Department of Medical Laboratory Science, School of Health Sciences, Soroti University, P.O. Box 211, Soroti, Uganda

<sup>5</sup>Department of Microbiology and Parasitology, School of Medicine and Dentistry, P.O. Box 259, Dodoma, Tanzania

<sup>6</sup>Department of Medical Laboratory Sciences, Faculty of Medicine, Muni University, P.O. Box, 725, Arua, Uganda

<sup>7</sup>Department of Medical Laboratory Sciences, School of Medicine, Technical University of Mombasa, P.O. Box 90420, Mombasa, Kenya

<sup>8</sup>Department of Medical Laboratory Technology, Mayanja Memorial Medical Training Institute, P.O Box 348, Mbarara, Uganda

<sup>9</sup>Department of Medical Laboratory, Joint Clinical Research Centre, PO Box 160, Gulu, Uganda

<sup>10</sup>Department of Microbiology and Immunology, Faculty of Health Sciences, Busitema University, P.O Box 1460, Mbale, Uganda

<sup>11</sup>Department of Pathology, Faculty of Health Sciences, Busitema University, PO Box 1460, Mbale, Uganda

<sup>12</sup>Department of Physiology, Faculty of Health Science, Mountains of the moon University, P.O Box 837, Fort Portal, Uganda

<sup>13</sup>Department of Immunology and Molecular Biology, College of Health Sciences, Makerere University, P.O Box 7072, Kampala, Uganda

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