Risk factors of metabolic dysfunction-associated fatty liver disease in people with HIV receiving antiretroviral therapy

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Objective: This study aimed to identify risk factors associated with the onset and progression of metabolic dysfunction-associated fatty liver disease (MAFLD) in people with human immunodeficiency virus (PWH).

Methods: Clinical and laboratory data were retrospective collected at 6 months, 1, 1.5, 2, and 3 years after ART initiation. Multivariable logistic regression was employed to identify MAFLD risk factors and evaluate ART's influence.

Results: Among the 740 participants (95% male, mean age 36.58 ± 13.93 years), with an average ART duration of 3.33 ± 4.56 years. Laboratory data at 6 months showed a $CD4^+$ cell count of (356.95 ± 98.76) cells/mm^3, body mass index (BMI) of (22.87 ± 7.47) kg/m^2, triglycerides (TG) of (1.53 ± 0.98) mmol/l and low-density lipoprotein cholesterol (LDL-c) of (2.45 ± 0.71) mmol/l. MAFLD detection rates by hepatic steatosis index (HSI) and Zhejiang University indices (ZJU) increased with longer ART duration. Patients with >10% weight gain showed a notable rise from 48.80% at baseline to 87% after 3 years of ART. Independent risk factors for MAFLD included female, type 2 diabetes mellitus (T2DM) prior MAFLD, baseline BMI >24 kg/m^2 and TG ≥1.7 mmol/l, weight gain of 5–10% or >10% within 1 year, BMI ≥24 kg/m^2 and TG ≥1.7 mmol/l at year 1. Protective factors included age >65 years, AZT and 3TC-based therapies.

Conclusion: The prevalence of MAFLD as assessed by the HSI and ZJU indices increases steadily with ART and is strongly related to weight gains. These findings validate the effectiveness of these noninvasive tools for identifying key risk factors and underscore the necessity of continuous weight monitoring in contemporary ART-treated patients.

Graphical abstract: http://links.lww.com/QAD/D734

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Introduction

Acquired immunodeficiency syndrome (AIDS) is no longer a prominent cause of mortality among people with human immunodeficiency virus (PWH) in developed nations thanks to major breakthroughs in HIV therapy over the past three decades. Hepatitis virus co-infections can also be easily eradicated (hepatitis c virus, HCV) or prevented and managed (hepatitis B virus, HBV) [1]. Despite these advancements, metabolic dysfunction-associated fatty liver disease (MAFLD) remains to be considered a substantial threat in HIV monoinfection [2].

In 2020, a revised diagnostic criteria and a terminological shift from fatty liver disease to MAFLD were proposed [3]. While this updated definition and diagnostic criteria provide new guidance for clinical practice and research, there is limited information on the burden of MAFLD in PWH. Until now, only a few research have assessed the burden of disease in PWH [4,5] infected individuals with MAFLD. Long-term use of ART and a weakened immune system may put PWH at higher risk for MAFLD [6]. The burden of MAFLD disease in this population has, however, not received much attention in research. Further investigation and analysis are required to determine the prevalence of MAFLD among PWH, the contributing factors driving it, and the precise effects on patient health.

Furthermore, MAFLD is frequently asymptomatic in its early stages, making it challenging to identify high-risk individuals. Noninvasive diagnostic scoring systems, such as the Zhejiang University (ZJU) score and the hepatic steatosis index (HSI), are especially useful for early screening and evaluation of MAFLD due to their convenience, efficiency, noninvasiveness, accessibility, and repeatability [7]. The ZJU index has validated its consistent validity across populations in large-scale studies and has become a reliable tool for the detection of nonalcoholic fatty liver disease (NAFLD) [8]. HSI likewise serves as a highly effective screening tool to assist healthcare professionals in screening individuals suitable for liver ultrasound and guiding lifestyle modifications, collectively enhancing the efficiency of early diagnosis and management of MAFLD [9].

It's critical to ascertain how ART contributes to the development of MAFLD given the rising number of patients on ART and the elevated prevalence of liver disease among PWH. Therefore, we conducted a retrospective cohort study by using noninvasive liver serology models (ZJU, HSI index) to describe the prevalence characteristics and assess the impact of ART treatment on MAFLD among PWH individuals attended at the infectious department, Zhongnan Hospital of Wuhan University. The purpose of this study was to identify the risk factors associated with the development of MAFLD in PWH to manage individuals at high risk of developing MAFLD at an early stage and ultimately reduce disease burden. The Graphical Abstract was provided in Supplementary Figure 1, Supplemental Digital Content, http://links.lww.com/QAD/D734.

Materials and methods

Study population

A total of 740 PWH who received ART at the Department of Infectious Diseases, Zhongnan Hospital of Wuhan University, between December 2019 and January 2022 were included in the study. The inclusion criteria were: confirmed HIV infection; received ART; had a definite duration time of ART and maintained good compliance; comprehensive clinical data. The exclusion criteria were: persons under the age of 18 or over the age of 70; woman who is pregnant; myelosuppression during ART treatment; had other diseases that induce immune insufficiency besides HIV (such as aplastic anemia, leukemia, multiple myeloma, nephrotic syndrome, Hepatic and renal failure, systemic lupus erythematous, etc.); had a malignant tumor or other underlying illness; using immunosuppressant concurrently; missing anthropometric measurements or laboratory data; HCV and/or HBV infection, determined by HCV antibody testing and HBV surface antigen positivity. In accordance with the inclusive diagnostic criteria for MAFLD [3], study participants were not excluded based on alcohol consumption.

Ethics statement

This study was approved by the Institutional Ethics Committee of Zhongnan Hospital of Wuhan University (Approval No.: 2021022). All patient data were analyzed anonymously and confidentially. At the time of their initial clinical visit, a general informed consent for the use of their de-identified data in future medical research was obtained from all patients. Our study strictly adhered to the terms of this consent.

Laboratory testing and clinical data collection

Blood samples were tested at baseline, 6 months, 1 year, 1.5 years, 2 years, 3 years after initiating of ART. For each patient, the following information was collected: demographic data (age, sex), clinical comorbidities, such as T2DM, time since HIV diagnosis, duration of ART, current ART including nucleoside reverse transcriptase inhibitors (NRTIs), nonnucleoside reverse transcriptase inhibitors (NNRTIs), integrase strand transfer inhibitors (INSTIs) and protease inhibitors (PIs). The lipid profiles comprised TG, TC, high-density lipoprotein cholesterol (HDL-C), and LDL-c. Liver function measures included Alanine aminotransferase (ALT), Aspartate aminotransferase (AST) and albumin (Alb). Renal function measures included creatinine (Cr). Weight and height were measured in routine consultation at baseline, before starting ART, and during follow-up. BMI was calculated automatically using the formula: weight (kg)/height (m^2). These data were collected through clinical records stored at the hospital's electronic platform.

Noninvasive serologic models of HSI and ZJU

Noninvasive serologic models for assessing MAFLD and index calculation formulae:

The HSI values were calculated automatically using the formula: 8 × (ALT/AST ratio) + BMI (+2, if female; +2, if T2DM). The categories considered were MAFLD ruled out with HSI <30.0 and MAFLD detected with HSI >36.0 [9].

ZJU index = BMI (kg/m^2) + FPG (mmol/l) + TG (mmol/l) + 3 × ALT/AST ratio (+2, if female) [8]. The categories considered were MAFLD ruled out with ZJU <32.0 and NAFLD detected with ZJU >38.0.

An individual was deemed screening positive for MAFLD only if both HSI ≥30.0 and ZJU ≥32.0 were met. The prevalence of MAFLD in this study was calculated by dividing the number of participants meeting both criteria by the total number of eligible participants. Through internal validation, this combined approach exhibits the closest match between baseline detection rate (28.7%) and radiological confirmation rate (25.9%), effectively controlling false positives while maintaining high sensitivity (detailed data distributions are provided in Supplementary Table 1, Supplemental Digital Content, http://links.lww.com/QAD/D735).

Statistical analysis

Statistical analysis was conducted using SPSS statistical software (version 27.0, Armonk, New York). All normally distributed data were expressed with means and standard deviations (SD). All nonnormal distribution data were expressed through median (interquartile range). χ^2 analysis was conducted to examine the categorical variables and ANOVA was performed for comparison of means between multiple groups. Univariable and stepwise multivariable logistic regression models were used to calculate odds ratios (ORs) and 95% confidence intervals (CIs) to identify factors associated with MAFLD and selected variables a priori. Variables with a *P*-value <0.10 at the univariable analyses and those with a recognized association with MAFLD were included in the multivariable analyses. The variance inflation factor (VIF) was used to measure multicollinearity, with a value greater than 10 indicating severe multicollinearity. LASSO (Least Absolute Shrinkage and Selection Operator)-penalized logistic regression (R glmnet package) was employed to mitigate parameter estimation instability from sparse data in some strata, while facilitating variable selection and robust modeling (Supplementary Figure 2, Supplemental Digital Content, http://links.lww.com/QAD/D735). For data results, GraphPad Prism 8.0 Statistical analysis was used and differences were considered statistically significant at $P < 0.05$. Persons with missing baseline or follow-up data for the variables needed to calculate each score were excluded from the analysis of the respective score.

Table 1. Baseline demographic, clinical and laboratory characteristics.

Characteristics	All participants (*n* = 740)
Sex (male), '$x \pm s$	706 (95.4)
Age (years), '$x \pm s$	36.6 ± 13.9
Routes of transmission [*n* (%)]	
MSM	551 (74.5)
Heterosexual contacts	189 (25.5)
Comorbidities [*n* (%)]	
T2DM	30 (4.1)
Steatohepatitis	192 (25.9)
Liver fibrosis	38 (5.1)
cART regimen [*n* (%)]	
NRTIs (*n* = 740)	
TDF	508 (68.6)
3TC	549 (74.2)
AZT	42 (5.7)
ABC	17 (2.3)
TAF	20 (2.7)
FTC	20 (2.7)
PIs (*n* = 24)	
LPV-r	24 (100.0)
NNRTIs (*n* = 486)	
EFV	457 (94.0)
NVP	29 (6.0)
INSTIs (*n* = 230)	
DTG	172 (74.8)
BIC	58 (25.2)
Noninvasive tests,'$x \pm s$	
HSI score	29.91 ± 5.27
ZJU score	31.54 ± 5.41
Clinical laboratory tests,'$x \pm s$	
CD4$^+$, cells/mm^3	291.6 ± 98.4
$\log_{10}$(HIV-RNA), copies/ml	4.52 ± 0.80
Weight, kg	65.5 ± 10.8
FPG, mmol/l	5.35 ± 1.48
BMI, kg/m^2	21.91 ± 3.28
ALT, U/l	29.04 ± 25.96
AST, U/l	29.17 ± 25.73
Platelets, 10^9/l	217.44 ± 106.05
Albumin, g/l	42.68 ± 5.05
Cholesterol, mmol/l	3.92 ± 0.85
Triglyceride, mmol/l	1.39 ± 0.87
HDL, mmol/l	0.98 ± 0.27
LDL, mmol/l	2.42 ± 0.69
Creatinine, μmmol/l	75.37 ± 28.21

3TC, lamivudine; ABC, abacavir; ALT, alanine aminotransferase; AST, aspartate aminotransferase; AZT, zidovudine; BIC, bictegravir; BMI, body mass index; cART, antiretroviral therapy; DTG, dolutegravir; FPG, fasting plasma glucose; FTC, mtricitabine; HDL, high-density lipoprotein; INSTIs, integrase strand transfer inhibitors; LDL-c, low-density lipoprotein cholesterol; LPV-r, lopinavir/ritonavir; NNRTIs, nonnucleoside reverse transcriptase inhibitor; NRTIs, nucleoside reverse transcriptase inhibitor; NVP, nevirapine; PIs, protease inhibitor; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.
Fasting plasma glucose (FPG) was measured after at least 8 h of fasting by using glucose oxidase technique.

Results

Characteristics of the study population

As demonstrated in Table 1, 740 PWH were included in our analysis. 95.4% were male and the mean age and standard deviation at baseline was 36.58 ± 13.93 years. The primary routes of HIV transmission were men who have sex with men (MSM) [74.5%(551/740)]. Mean time since HIV diagnosis was 3.68 ± 4.70 years and patients

were on ART for 3.33 ± 4.56 years. The baseline metabolic profile was characterized by a mean BMI of 21.91 ± 3.28 kg/m^2 and a FPG of 5.35 ± 1.48 mmol/l, with 4.1% of participants having comorbid type 2 diabetes. All patients enrolled in our study received ART, with 65.7% receiving NNRTIs-containing regimens, 31.1% receiving INSTIs-containing regimens, and only 24 patients receiving PIs. The noninvasive serum indicators for MAFLD screening revealed HSI and ZJU values of 29.91 ± 5.27 and 31.54 ± 5.41, respectively. Immunovirological results showed a mean CD4$^+$ cell count of 291.6 ± 98.4 cells/mm^3 and an HIV RNA level of 4.52 ± 0.80 $\log_{10}$ copies/ml. TG (1.39 ± 0.87) mmol/l and LDL-c (2.42 ± 0.69 mmol/l) were among the most significant lipid abnormalities.

Characterization of MAFLD detection rates with ART duration

It was clear that MAFLD detection rates gradually increased during ART period, and the differences between groups showed statistical significance ($P <$ 0.05). Specifically as shown in Table 2, MAFLD detection rates were still at a relatively low level evaluated by using the HSI and ZJU indices (approximately 28.7%) prior to the initiation of ART, which gradually raised to nearly 2 times after ART initiation for 3 years. Similarly, HSI and ZJU index scores also showed a similar trend. These findings suggest that extended ART duration is associated with a marked and progressive increase in MAFLD risk among PWH.

Factors associated with MAFLD

As shown in Table 3, univariate and multivariable analyses identified key risk factors for MAFLD. Female, T_2DM, a history of MAFLD, BMI >24 kg/m^2 and TG ≥1.7 mmol/l at baseline; weight changes over 5% within 1 year, BMI ≥24 kg/m^2 and TG ≥1.7 mmol/l at 1 year of ART were strong predictors of significantly elevated risk related to the MAFLD. Particularly noteworthy was the development of obesity (BMI ≥ 24 kg/m^2) after 1 year of treatment, which was associated with a dramatic increase in MAFLD risk (OR = 19.84). Additionally, weight gain exceeding 5% within 1 year also demonstrated an elevated risk trend. Conversely, age >65 years at the time of enrollment and the use of specific antiretroviral agents such as AZT and 3TC showed protective effects had a favorable effect against the progression of liver disease. We did not observe statistically significant associations between AST, platelets (PLT), Alb, TC, LDL-c, Cr, and the presence of MAFLD in our cohort.

Clinically significant weight gain

Baseline characteristics were assessed among various weight gain categories, revealing no significant variations in age, sex, ART regimen, HIV-RNA, fasting blood glucose, or liver function, except for CD4$^+$ cell count, BMI, and weight ($P < 0.01$) (Supplementary Table 2, Supplemental Digital Content, http://links.lww.com/QAD/D735). Building on this, we further analyzed the association between weight gain and MAFLD. As shown in Table 4, we observed a significant increase in all groups during follow-up, except for those who gained weight <5%, the differences between groups for other three groups were statistically significant ($P < 0.05$). A strong association was observed between weight gain magnitude and MAFLD risk, with individuals gaining ≥5% weight having a significantly elevated risk compared to those gaining <5% ($P < 0.05$). The MAFLD detection rate surpassed 85% in patients with 5% or more weight gain after ART initiation for 3 years, which was markedly higher than the 65.8% seen in the group with less than 5% weight gain. A similar trend was observed for the increment in detection rate as illustrated in Fig. 1. Collectively, patients with greater weight gain demonstrated both a higher incidence of MAFLD and a significantly greater increment in detection rate.

Discussion

Widespread use of ART has led to a considerable reduction in the all-cause death rate among PWH. The higher life expectancy of PWH is also expected to increase the risk of MAFLD and other aging-related noncommunicable diseases [10]. Among this group, liver-related complications remain the leading cause of death. With an estimated global frequency of 25% [11], MAFLD is becoming a major public health concern. It worsens more

Table 2. Changes of detection rate of MAFLD in PWHA after different duration of ART.

	ART-naive	At month 6	At year 1	At year 1.5	At year 2	At year 3	F/χ^2	*P*-value
Noninvasive serologic index of MAFLD ($x \pm s$)								
HIS	29.86 ± 5.31	31.48 ± 7.69	31.83 ± 5.72	32.04 ± 6.03	32.69 ± 6.35	33.06 ± 6.51	17.375	0.000
ZJU	31.52 ± 5.41	32.64 ± 8.18	33.27 ± 8.56	34.01 ± 7.47	34.19 ± 8.45	36.16 ± 12.85	2.623	0.022
Detection rate of MAFLD (%)								
HIS	44.6	54.3	58.7	60.5	62.6	64.8	60.910	0.000
ZJU	38.8	45.1	50.7	50.5	53.0	53.5	50.398	0.038
HSI & ZJU[a]	28.7	46.5	52.3	57.7	55.27	57.4	182.06	0.000

HSI, hepatic steatosis index; ZJU, Zhejiang University indices; MAFLD, metabolic dysfunction-associated fatty liver disease.
[a]An individual was deemed screening positive for MAFLD only if both HSI≥30.0 and ZJU≥32.0 were met. The baseline prevalence of fatty liver diagnosed by imaging was 25.9% (192/740) in this study cohort.

Table 3. Multivariable model for risk factors associated with MAFLD.

Characteristics	Univariable analysis					Multivariable analysis				
	β	SE	*Z*	*P*	OR (95% CI)	β	SE	*Z*	*P*	OR (95% CI)
Sex (female)	0.69	0.37	1.83	0.067	1.99 (0.95–4.14)	1.972	0.482	16.776	0.000	7.19 (2.8–18.47)
Age (years)										
<40					1 (reference)					
[41–65)	0.28	0.17	1.61	0.108	1.32 (0.94–1.86)	−0.344	0.258	1.777	0.345	0.72 (0.37–1.42)
≥65	−0.61	0.30	−2.012	0.043	0.54 (0.30–0.98)	−1.008	0.489	4.248	0.039	0.37 (0.14–0.95)
$CD4^+$ (≤200 cells/ul)	0.14	0.17	0.85	0.394	1.15 (0.83–1.60)					
T_2DM	1.58	0.51	3.19	0.001	4.86 (1.84–12.84)	2.064	0.681	9.195	0.002	7.87 (2.08–29.88)
HIV RNA (copies/ml)										
$\leq 10^3$					1 (reference)					
10^3~10^5	0.14	0.35	0.41	0.683	1.15 (0.58–2.29)					
$\geq 10^5$	0.29	0.37	0.77	0.443	1.33 (0.64–2.76)					
Drugs										
TDF	−0.43	0.19	−2.24	0.025	0.65 (0.45–0.95)	0.872	0.567	2.371	0.124	2.39 (0.79–7.26)
EFV	−0.34	0.17	−1.97	0.049	0.71 (0.51–0.99)	0.348	0.482	0.520	0.471	1.42 (0.55–3.64)
BIC	−0.49	0.68	−0.73	0.466	0.61 (0.16–2.30)					
LPV-r	−0.85	0.49	−1.72	0.085	0.43 (0.16–1.12)	−2.158	1.645	1.722	0.643	0.81 (0.33–1.98)
DTG	0.09	0.24	0.39	0.695	1.10 (0.69–1.75)					
NVP	−0.38	0.39	−0.98	0.328	0.69 (0.32–1.46)					
AZT	−0.92	0.32	−2.86	0.004	0.40 (0.21–0.75)	−1.727	0.661	6.826	0.009	0.18 (0.05–0.65)
3TC	−0.72	0.23	−3.21	0.001	0.48 (0.31–0.75)	−1.341	0.629	4.537	0.003	0.26 (0.08–0.90)
ABC	−0.36	0.51	−0.72	0.469	0.70 (0.26–1.85)					
TAF	−0.63	0.44	−1.43	0.154	0.53 (0.22–1.27)					
FTC	−0.52	0.46	−1.15	0.251	0.59 (0.24–1.45)					
Regimens										
PIs					1 (reference)					
NNRTIs	0.60	0.44	1.36	0.172	1.82 (0.77–4.27)	0.044	1.316	0.001	0.973	1.05 (0.08–13.78)
INSTIs	1.06	0.45	2.35	0.019	2.90 (1.19–7.03)	0.022	1.277	0.000	0.987	1.02 (0.08–12.48)
Baseline										
Steatohepatitis, **25.9 (192/740)**	2.81	0.28	9.98	<0.001	16.55 (9.54–28.72)	2.393	0.426	31.531	0.000	10.94 (4.75–25.22)
Liver fibrosis, **5.1 (38/740)**	0.05	0.19	0.25	0.813	1.05 (0.73–1.51)					
BMI≥24 (kg/m2)	3.10	0.34	9.21	<0.001	22.26 (1.49–43.12)	1.843	0.477	14.91	0.036	2.35 (1.06–5.24)
ALT ≥1.5 ULN (U/l)	0.64	0.30	2.13	0.033	1.90 (1.05–3.44)	−0.627	0.493	1.622	0.203	0.53 (0.20–1.40)
AST ≥1.5 ULN (U/l)	0.54	0.35	1.52	0.129	1.71 (0.86–3.41)					
PLT ≤100 (10^9 cells/ml)	−0.51	0.41	−1.28	0.201	0.60 (0.28–1.31)					
Alb ≤30 (g/l)	0.57	0.41	1.39	0.165	1.76 (0.79–3.93)					
TC ≥5.18 (mmol/l)	0.31	0.32	0.96	0.337	1.36 (0.72–2.57)					
TG ≥1.7 (mmol/l)	1.73	0.22	8.01	<0.001	5.64 (3.69–8.62)	1.176	0.338	12.122	0.000	3.24 (1.67–6.29)
LDL ≥3.37 (mmol/l)	0.09	0.31	0.28	0.776	1.09 (0.59–2.03)					
Cr ≥1.5 ULN (μmmol/l)	0.91	1.10	0.82	0.409	2.47 (0.29–21.30)					
ART 1 year										
Wt. change (%)										
<5					1 (reference)					
(5–10)	0.93	0.20	4.61	<0.001	2.54 (1.71–3.79)	0.716	0.347	4.251	0.039	2.05 (1.04–4.04)
≥10	1.14	0.19	5.87	<0.001	3.13 (2.14–4.58)	0.798	0.343	5.431	0.020	2.22 (1.14–4.35)
BMI≥24 (kg/m^2)	4.92	0.72	6.87	<0.001	136.58 (59–555.33)	4.38	0.772	32.179	<0.001	19.84 (9.54–41.23)
ALT ≥1.5 ULN (U/l)	16.97	33.4	0.03	0.975	23.36 (0.00–34.5)					
AST ≥1.5 ULN (U/l)	2.01	0.6	3.33	<0.001	7.43 (2.28–24.23)	1.091	0.732	2.223	0.136	2.98 (0.71–12.5)
PLT ≤00 (10^9 cells/ml)	0.82	0.56	1.46	0.144	2.26 (0.76–6.75)					
Alb ≤30 (g/l)	1.86	0.74	2.52	0.012	6.42 (1.51–27.34)	0.562	1.113	0.255	0.902	0.95 (0.44–2.07)
TC ≥5.18 (mmol/l)	1	0.25	3.93	<0.001	2.72 (1.65–4.47)	−0.049	0.397	0.015	0.002	2.19 (1.32–3.63)
TG ≥1.7 (mmol/l)	1.88	0.23	8.06	<0.001	6.57 (4.16–10.38)	1.46	0.295	24.448	0.665	1.16 (0.59–2.31)
LDL ≥3.37 (mmol/l)	0.59	0.18	3.19	0.001	1.80 (1.26–2.59)	0.312	0.265	1.391	0.238	1.37 (0.81–2.3)
Cr ≥.5 ULN (μmmol/l)	15.9	511.80	0.03	0.975	8056818.64 (0.00-Inf)					

3TC, lamivudine; ABC, abacavir; ALT, alanine aminotransferase; AST, aspartate aminotransferase; AZT, zidovudine; BIC, bictegravir; BMI, body mass index; cART, antiretroviral therapy; DTG, dolutegravir; FPG, fasting plasma glucose; FTC, mtricitabine; HDL, high-density lipoprotein; INSTIs, integrase strand transfer inhibitors; LDL-c, low-density lipoprotein cholesterol; LPV-r, lopinavir/ritonavir; NNRTIs, nonnucleoside reverse transcriptase inhibitor; NRTIs, nucleoside reverse transcriptase inhibitor; NVP, nevirapine; PIs, protease inhibitor; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.

Table 4. Changes of detection rate in MAFLD of each group within the different weight gain categories.

	Detection rate of MAFLD (%)							
	ART-naïve	At month 6	At year 1	At year 1.5	At year 2	At year 3	F/χ^2	*P* value
Weight changes<5%	233/437 (53.3)	130/236 (55.1)	236/406 (58.1)	148/253 (58.5)	131/217 (60.4)	52/79 (65.8)	6.101	0.296
Weight changes (5–10%)	80/138 (58.0)	50/70 (71.4)	79/106 (74.5)	45/61 (73.8)	34/43 (79.1)	23/27 (85.2)	14.532	0.013
Weight changes ≥10%	79/165 (47.9)	63/97 (64.9)	114/146 (78.1)	61/80 (76.3)	48/62 (77.4)	18/21 (85.7)	42.591	0.000
All participants	392/740 (53.0)	243/403 (60.3)	429/658 (65.2)	254/394 (64.5)	213/322 (66.1)	93/127 (73.2)	38.120	0.000

MAFLD, metabolic dysfunction-associated fatty liver disease.

quickly and more severely in PWH. Nevertheless, there is a dearth of thorough information regarding the prevalence of MAFLD in the PWH population. Hence, the goal of this study is to assess the prevalence of MAFLD among PWH using noninvasive serological models and to identify the risk variables related to this condition.

The ZJU and HSI index, as a reliable and efficient tool for NAFLD detection [8,12], has been validated and reaffirmed in previous research. The metabolic anomalies that the HSI and ZJU indices evaluate have a strong correlation with the pathophysiological pathways of MAFLD, despite the fact that they were originally designed for NAFLD [9]. Recent liver biopsy validation studies have also shown that these indices are highly effective in differentiating MASLD (with an AUROC over 0.80) [13]. This evidence supports their suitability for the current investigation, in which extensive preliminary screening and reducing false negatives in a large retrospective cohort were critical methodological priorities. In this study, we discovered that the detection rate of MAFLD progressively rose over the course of the ART period by utilizing both models.

The reported prevalence of MAFLD in PWH ranges from 28% to 48% [14–16]. In our cohort, the prevalence was 28.7% at baseline and rose to 57.4% after three years of

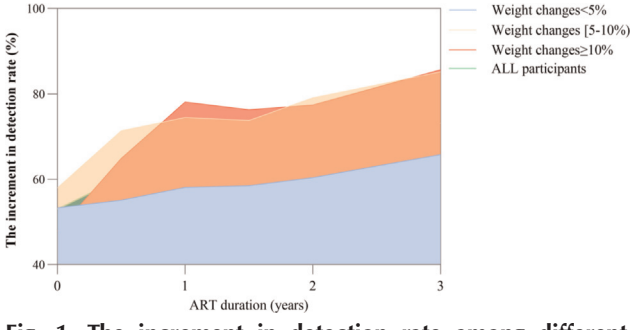

Fig. 1. The increment in detection rate among different weight gains group. The absolute increase in MAFLD detection rate from baseline to each time point is shown. The increment in detection rate of MAFLD was defined as MAFLD detection rate with ART follow-up minus MAFLD detection rate without ART in this study. MAFLD, metabolic dysfunction-associated fatty liver disease.

ART, a trend that aligns with the global annual increase of about 1% in steatosis [17]. Consistent with established risk factors in both HIV and non-HIV populations [18,19], we found MAFLD to be associated with TG >1.7 mmol/l, type 2 diabetes, weight gain, and BMI >24 kg/m^2 after adjusting for confounders. Beyond these factors, we newly identified AZT/3TC-containing therapy as a potential protective factor against MAFLD.

Integrase chain transfer inhibitors (INSTIs) are now recommended as first-line ART for newly diagnosed individuals with HIV due to their rapid viral suppression [20]. However, a study [6] have indicated that long-term exposure to specific ART medicines (such as TAF and INSTIs) may increase the incidence of MAFLD in PWH. Regimens combining INSTIs with TAF have been strongly associated with considerable weight gain [21] and metabolic alterations compared to those based on NNRTIs [6]. Notably, weight gain occurs most quickly, particularly in the first six months following the initiation of ART [22], and this variation may affect the long-term risk of noncommunicable disorders.

INSTI and TAF appear to raise MAFLD risk via several mechanisms. Switching from TDF to TAF raises serum lipids, indicating that TAF lacks TDF's positive impact on appetite control and lipid homeostasis [23]. When used in a combination, they significantly increase insulin resistance [10], impact adipocyte differentiation, thermogenesis, and estrogen-dependent metabolic pathways, as well as stimulate appetite [24,25] by blocking melanocortin and leptin signaling activation. Furthermore, INSTI might cause intestinal microbiota abnormalities and alter the concentration of fatty acid binding proteins (FABPs), which are indicators of increased visceral fat and weight gain, resulting in metabolic dysfunction and weight gain [10]. Besides, women and black individuals, lower baseline BMI, higher HIV-1 RNA levels, lower CD4$^+$ cell count and comorbidities [22] are also associated with greater weight increase after ART initiation [24].

Although INSTI and TAF have been linked to an increased risk of MAFLD, our study did not find a significant correlation. This disparity could be explained by our cohort's small sample size receiving TAF and

DTG/BIC regimens, which decreased statistical power and comparability. Furthermore, the metabolic effects of ART frequently take a long time to manifest [10]. Thus, the observation period in this study may have been insufficient to detect such long-term risks, underscoring the need for further research with larger cohorts and extended follow-up periods to explore the potential correlations and mechanisms thoroughly.

Some aspects of the pathogenesis of MAFLD in PWH are the adverse effects of ART, which may contribute to the development of hepatic steatosis [6]. First-generation NRTIs (zalcitabine (ddC), ddI, d4T, and AZT) exhibit significant mitochondrial toxicity, increasing lactate production and abnormal lipid oxidation in the liver, leading to steatosis and other lipid disorders [26]. The AZT/3TC regimen appeared protective in terms of certain metabolic metrics in our study. We thought that the observed protective association of AZT/3TC against MASLD is most plausibly explained by less weight gain compared to INSTI-based regimens. Therefore, the "protective" effect of AZT/3TC is likely not a direct hepatoprotective effect, but rather a relative advantage conferred by the absence of the strong weight-promoting effects characteristic of INSTI-based regimens. This aligns perfectly with the pathophysiological link between weight gain and MASLD discussed by Biały *et al.* [10]. The lamivudine plus dolutegravir (3TC/DTG) regimen is associated with long-term metabolic protection, manifested by increased HDL-C and the optimization of renal safety [27,28], suggesting that different nucleoside drug backgrounds may affect patients' long-term metabolic risks through distinct pathways. Overall, the protective effect of AZT/3TC appears not from an ideal metabolic state, but from weight gain suppression. The hepatotoxicity of individual ART drugs is difficult to ascertain due to multi-NRTI exposure, highlighting the need for further multiethnic studies on ART optimization.

Our findings support weight monitoring, as weight gains and increasing BMI are substantially linked with an increase in MAFLD as measured by HSI/ZJU. The burgeoning prevalence of overweight and obesity poses a significant challenge to global health, resulting in significant morbidity and mortality from cardiovascular disease, diabetes, chronic renal disease, nonalcoholic steatohepatitis and cancer. Nearly half of the PWH in the ART population may develop MAFLD, according to a single-center study based on transient elastography, which also found a link between weight increase and MAFLD [29]. In clinical trials beginning ART, weight increase is frequently observed and is multifaceted, involving HIV-related factors, demographic factors, and the composition of the ART regimen [30].

The frequency of overweight and obesity among PWH is increasing, with the initiation of ART frequently resulting in weight increase [31]. One theory for the weight increase linked to ART is the phenomenon known as "return to health," which happens once an individual's weight rebounds to its preillness level, particularly in cases of advanced HIV disease [32]. Grant *et al.* [33] related the phenomenon to early weight gain following initiating ART, demonstrating that PWH, especially those with lower baseline $CD4^+$ T cell count and BMI, showed substantial rises in lean body mass and fat mass during the first 96 weeks. These improvements represent physiological benefits from immunological reconstitution and reduced inflammation [34]. However, long-term excessive weight gain considerably increases the risk of noncommunicable diseases as MAFLD [35,36]. A large-scale cohort research discovered that after three years of ART treatment, a significant number of patients progressed from normal weight to overweight or obese [37]. Consistent with the study by Grant *et al.* [33], they found the unfavorable shift in body composition raises the risk of metabolic disorders, which may be influenced by adipocyte differentiation, appetite regulation, gut microbiota, and resting energy expenditure [10]. Thus, while evaluating the impact of ART on MAFLD, it is critical to distinguish between the beneficial "return to health" in the early treatment period and the adverse weight gains associated with subsequent therapy.

Taken together, our results highlight the need for continuous monitoring of MAFLD in PWH, including weight/obese patients, and for further exploration of additional risk factors, as well as the mechanism leading to metabolic changes in this population. It is critical for tracking the progression of body composition abnormalities and their metabolic implications throughout the prolonged course of treatment PWH.

Overall, this study had several noteworthy findings. Firstly, we investigated the prevalence and factors associated with MAFLD in a well characterized cohort of PWH under ART in resource-limited area, and we were able to include 740 of eligible patients. The first-line clinical data from the real world on clinical parameters, laboratory values, and liver metabolic risk factors allowed us to perform one of the comprehensive assessments of the determinants of MAFLD among PWH. Then, this study identified the risk of MAFLD beneath the surface "disease improvement" phenomenon of weight increase among PWH, and stratified analysis of weight changes can provide more detailed reference data for targeted weight management of PWH during ART. Third, our study employs a straightforward, affordable, and noninvasive serological model for MAFLD recognition that eliminates the requirement for liver biopsies. Which helps to facilitate early detection, treatment, and the decrease of disease burden by precisely identifying participants in clinical trials who are at risk for MAFLD.

However, this study does have several flaws, which cannot be denied. Firstly, the single-center, retrospective

design of our study may limit the generalizability of our findings. Future multicenter, prospective studies are warranted to validate our results in broader and more diverse populations of people living with HIV/AIDS. Secondly, the absence of a matched HIV-negative control group precludes direct comparisons to delineate the specific contribution of HIV-related factors, such as chronic inflammation and ART, from traditional metabolic risk factors for MAFLD. Future case-control or cohort studies specifically designed with matched HIV-negative controls are essential to definitively clarify the independent risk imposed by HIV/ART. Thirdly, we used noninvasive indices at their lower exclusion thresholds to estimate MAFLD prevalence, which may overstate actual prevalence due to their sensitivity and specificity falling short of imaging or liver biopsy. Nevertheless, these findings serves as a crucial first step for identifying individuals warranting further confirmatory investigation. Fourthly, while the 3-year follow-up remains inadequate for long-term outcomes, nevertheless, the study successfully identified ART-related weight gain as a key modifiable risk factor for MAFLD, pinpointing a critical window for early intervention. Future studies with extended follow-up are needed to evaluate long-term cardiometabolic and hepatic sequelae. As a preliminary investigation of MAFLD screening among PWH, future studies should incorporate fibrosis assessment tools to enable more comprehensive disease stratification.

Conclusion

In conclusion, this study used a serological model to track the status of MAFLD in PWH during ART and discovered that the longer the ART duration, the greater the MAFLD detection rate, supporting the strong relationship between long-term ART and MAFLD risk. The risk variables for MAFLD among PWH were discovered using multivariate analysis. It reaffirmed the strong relationship between weight gains and MAFLD. This study emphasizes the important necessity for weight monitoring among PWH during ART, which has significant practical implications for optimizing disease surveillance for PWH.

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Availability of data and materials: The data that support the findings of this study are not openly available due to reasons of sensitivity and are available from the corresponding author upon reasonable request. Data are located in controlled access data storage at the Center for AIDS Research, Wuhan University.

Ethics statement: This study was approved by the Ethics Committee of Zhongnan Hospital of Wuhan University, and all individuals signed an informed consent form.

Author contributions statement: R.R.Y. and Y.X. conceived of and designed the study. R.Y., Y.J.Y., L. P.D. and F.L. collected and analyzed the data. Q.H.C. collected samples. XEG provided suggestions. All authors contributed to the study and approved the submitted version.

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Conflicts of interest

The authors declare no conflicts of interest.

References

1. Mauss S, Boesecke C. **Communicable and noncommunicable liver disease in HIV**. *Curr Opin HIV AIDS* 2021; **16**:152–155.
2. Younossi Z, Anstee QM, Marietti M, Hardy T, Henry L, Eslam M, *et al*. **Global burden of NAFLD and NASH: trends, predictions, risk factors and prevention**. *Nat Rev Gastroenterol Hepatol* 2018; **15**:11–20.
3. Eslam M, Sanyal AJ, George J. **International Consensus Panel. MAFLD: a consensus-driven proposed nomenclature for metabolic associated fatty liver disease**. *Gastroenterology* 2020; **158**: 1999–2014. e1.
4. Younossi ZM, Rinella ME, Sanyal AJ, Harrison SA, Brunt EM, Goodman Z, *et al*. **From NAFLD to MAFLD: implications of a premature change in terminology**. *Hepatology* 2021; **73**: 1194–1198.
5. Liu D, Shen Y, Zhang R, Xun J, Wang J, Liu L, *et al*. **Prevalence and risk factors of metabolic associated fatty liver disease among people living with HIV in China**. *J Gastroenterol Hepatol* 2021; **36**:1670–1678.
6. Bischoff J, Gu W, Schwarze-Zander C, Boesecke C, Wasmuth JC, van Bremen K, *et al*. **Stratifying the risk of NAFLD in patients with HIV under combination antiretroviral therapy (cART)**. *EClinicalMedicine* 2021; **40**:101116.
7. Castera L, Friedrich-Rust M, Loomba R. **Noninvasive assessment of liver disease in patients with nonalcoholic fatty liver disease**. *Gastroenterology* 2019; **156**:1264–1281. e4.
8. Wang J, Xu C, Xun Y, Lu Z, Shi J, Yu C, *et al*. **ZJU index: a novel model for predicting nonalcoholic fatty liver disease in a Chinese population**. *Sci Rep* 2015; **5**:16494.
9. Lee JH, Kim D, Kim HJ, Lee CH, Yang JI, Kim W, *et al*. **Hepatic steatosis index: a simple screening tool reflecting nonalcoholic fatty liver disease**. *Dig Liver Dis* 2010; **42**:503–508.
10. Biały M, Czarnecki M, Inglot M. **Impact of combination antiretroviral treatment on liver metabolic health in HIV-infected persons**. *Viruses* 2023; **15**:2432.
11. Younossi ZM. **Nonalcoholic fatty liver disease – a global public health perspective**. *J Hepatol* 2019; **70**:531–544.
12. Fu CP, Ali H, Rachakonda VP, Oczypok EA, DeLany JP, Kershaw EE. **The ZJU index is a powerful surrogate marker for NAFLD in severely obese North American women**. *PLoS One* 2019; **14**: e0224942.

13. Kouvari M, Valenzuela-Vallejo L, Guatibonza-Garcia V, Polyzos SA, Deng Y, Kokkorakis M, *et al*. **HSI-Liver biopsy-based validation, confirmation and comparison of the diagnostic performance of established and novel noninvasive steatotic liver disease indexes: Results from a large multicenter study**. *Metab Clin Exp* 2023; **147**:155666.
14. Perazzo H, Cardoso SW, Yanavich C, Nunes EP, Morata M, Gorni N, *et al*. **Predictive factors associated with liver fibrosis and steatosis by transient elastography in patients with HIV mono-infection under long-term combined antiretroviral therapy**. *J Int AIDS Soc* 2018; **21**:e25201.
15. Boursier J, Zarski JP, De Ledinghen V, Rousselet MC, Sturm N, Lebail B, *et al*. **Determination of reliability criteria for liver stiffness evaluation by transient elastography**. *Hepatology* 2013; **57**:1182–1191.
16. Vuille-Lessard É, Lebouché B, Lennox L, Routy JP, Costiniuk CT, Pexos C, *et al*. **Nonalcoholic fatty liver disease diagnosed by transient elastography with controlled attenuation parameter in unselected HIV monoinfected patients**. *AIDS* 2016; **30**: 2635–2643.
17. Le MH, Yeo YH, Li X, Li J, Zou B, Wu Y, *et al*. **2019 Global NAFLD Prevalence: a systematic review and meta-analysis**. *Clin Gastroenterol Hepatol* 2022; **20**:2809–2817. e28.
18. Morse CG, McLaughlin M, Matthews L, Proschan M, Thomas F, Gharib AM, *et al*. **Nonalcoholic steatohepatitis and hepatic fibrosis in HIV-1-monoinfected adults with elevated aminotransferase levels on antiretroviral therapy**. *Clin Infect Dis* 2015; **60**:1569–1578.
19. Guaraldi G, Squillace N, Stentarelli C, Orlando G, D'Amico R, Ligabue G, *et al*. **Nonalcoholic fatty liver disease in HIV-infected patients referred to a metabolic clinic: prevalence, characteristics, and predictors**. *Clin Infect Dis* 2008; **47**: 250–257.
20. Nance RM, Delaney JAC, Simoni JM, Wilson IB, Mayer KH, Whitney BM, *et al*. **HIV viral suppression trends over time among HIV-infected patients receiving care in the United States, 1997 to 2015: a cohort study**. *Ann Intern Med* 2018; **169**:376–384.
21. Cahn P, Madero JS, Arribas JR, Antinori A, Ortiz R, Clarke AE, *et al*. **Durable efficacy of dolutegravir plus lamivudine in antiretroviral treatment–naive adults with HIV-1 infection: 96-week results from the GEMINI-1 and GEMINI-2 randomized clinical trials**. *J Acquir Immune Defic Syndr* 2020; **83**:310–318.
22. Ruderman SA, Crane HM, Nance RM, Whitney BM, Harding BN, Mayer KH, *et al*. **Brief report: weight gain following ART initiation in ART-naïve people living with HIV in the current treatment era**. *J Acquir Immune Defic Syndr* 2021; **86**:339–343.
23. Venter WDF, Moorhouse M, Sokhela S, Fairlie L, Mashabane N, Masenya M, *et al*. **Dolutegravir plus two different prodrugs of tenofovir to treat HIV**. *N Engl J Med* 2019; **381**:803–815.
24. Bourgi K, Jenkins CA, Rebeiro PF, Shepherd BE, Palella F, Moore RD, *et al*. **Weight gain among treatment-naïve persons with HIV starting integrase inhibitors compared to nonnucleoside reverse transcriptase inhibitors or protease inhibitors in a large observational cohort in the United States and Canada**. *J Int AIDS Soc* 2020; **23**:e25484.
25. Eckard AR, McComsey GA. **Weight gain and integrase inhibitors**. *Curz Opin Infect Dis* 2020; **33**:10–19.
26. Gervasoni C, Cattaneo D, Filice C, Galli M. **Gruppo Italiano Studio-NASH in malattie infettive. Drug-induced liver steatosis in patients with HIV infection**. *Pharmacol Res* 2019; **145**: 104267.
27. Yang J, Wang L, Zhang X, Liu L, Shen Y, Qi T, *et al*. **Safety and efficacy of lamivudine/dolutegravir vs. bictegravir/emtricitabine/tenofovir alafenamide in antiretroviral-naive adults with HIV-1 infection in Shanghai, China: a single-centre retrospective study**. *J Med Microbiol* 2025; **74**:001949.
28. Osiyemi O, De Wit S, Ajana F, Bisshop F, Portilla J, Routy JP, *et al*. **Efficacy and safety of switching to dolutegravir/lamivudine versus continuing a tenofovir alafenamide-based 3 or 4-drug regimen for maintenance of virologic suppression in adults living with human immunodeficiency virus type 1: results through week 144 from the phase 3, noninferiority TANGO randomized trial**. *Clin Infect Dis* 2022; **75**:975–986.
29. Riebensahm C, Berzigotti A, Surial B, Günthard HF, Tarr PE, Furrer H, *et al*. **Factors associated with liver steatosis in people with human immunodeficiency virus on contemporary antiretroviral therapy**. *Open Forum Infect Dis* 2022; **9**:ofac538.
30. Sax PE, Erlandson KM, Lake JE, Mccomsey GA, Orkin C, Esser S, *et al*. **Weight gain following initiation of antiretroviral therapy: risk factors in randomized comparative clinical trials**. *Clin Infect Dis* 2020; **71**:1379–1389.
31. Filip I. **Short-term weight gain after antiretroviral therapy initiation may have long-term consequences**. *AIDS* 2024; **38**: N1–N2.
32. Sharma A, Hoover DR, Shi Q, Gustafson D, Plankey MW, Hershow RC, *et al*. **Relationship between body mass index and mortality in HIV-infected HAART users in the Women's Interagency HIV Study**. *PLoS One* 2015; **10**:e0143740.
33. Grant PM, Kitch D, McComsey GA, Collier AC, Bartali B, Koletar SL, *et al*. **Long-term body composition changes in antiretroviral-treated HIV-infected individuals**. *AIDS* 2016; **30**:2805–2813.
34. Kumar S, Samaras K. **The impact of weight gain during HIV treatment on risk of prediabetes, diabetes mellitus, cardiovascular disease, and mortality**. *Front Endocrinol* 2018; **9**:705.
35. Herrin M, Tate JP, Akgün KM, Butt AA, Crothers K, Freiberg MS, *et al*. **Weight gain and incident diabetes among HIV-infected veterans initiating antiretroviral therapy compared with uninfected individuals**. *J Acquir Immune Defic Syndr* 2016; **73**: 228–236.
36. McCutchan JA, Marquie-Beck JA, FitzSimons CA, Letendre SL, Ellis RJ, Heaton RK, *et al*. **Role of obesity, metabolic variables, and diabetes in HIV-associated neurocognitive disorder**. *Neurology* 2012; **78**:485–492.
37. Koethe JR, Jenkins CA, Lau B, Shepherd BE, Justice AC, Tate JP, *et al*. **Rising obesity prevalence and weight gain among adults starting antiretroviral therapy in the United States and Canada**. *AIDS Res Hum Retroviruses* 2016; **32**:50–58.