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FIB-4 Fails to Identify Significant Liver Fibrosis in People With HIV: A Large Multinational Screening Study

Short title: Fibrosis screening in HIV

Felice Cinque MD[1,2], Sahar Saeed PhD[3], Francesca Farina MD[1,4], Dana Kablawi MD[1], Jihoon Lim PhD[5], Antonio Cascio MD[6], Claudia Gioè MD[6], Emmanuel Tsochatzis MD[7], Rosa Lombardi MD[2,8], Ahmed Cordie MD[9], Rahma Mohamed MD[9], Ahmed M. Kamel MD[10], Gamal Esmat MD[9,11], Alessandra Bandera MD[2,12], Jovana Milic MD[13], Dominik Benke MD[14], Fauzi Elamouri MD[14], Jürgen K. Rockstroh MD[14], Giovanni Guaraldi MD[13*], Giada Sebastiani MD[1,5,15*]
*GG and GS share senior authorship.

[1]Chronic Viral Illness Service, McGill University Health Centre, Montreal, Canada
[2]Department of Pathophysiology and Transplantation, Università degli Studi di Milano, Milan, Italy
[3]Public Health Sciences, Queen's University, Kingston, ON, Canada
[4]San Raffaele Hospital, Milan, Italy
[5]Center for Outcomes Research and Evaluation, Research Institute of the McGill University Health Centre, Montreal, Canada
[6]Department of Health Promotion Sciences and Mother and Child Care “Giuseppe D’Alessandro”, University of Palermo, Palermo, Italy
[7]UCL Institute for Liver and Digestive Health, Royal Free Hospital and UCL, London, UK
[8]SC Medicina Indirizzo Metabolico, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico di Milano, Milan, Italy
[9]Endemic Medicine Department, Cairo University Hospitals, Cairo, Egypt
[10]Clinical Pharmacy Department, Faculty of Pharmacy, Cairo University, Cairo, Egypt

[11]Research Center, Badr University in Cairo, Badr City, Egypt
[12]Infectious Diseases Unit, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy
[13]Department of Medical and Surgical Sciences, University of Modena and Reggio Emilia, Modena, Italy
[14]Department of Internal Medicine I, Venusberg Campus 1, University Hospital Bonn, Bonn, Germany
[15]Division of Gastroenterology and Hepatology, Royal Victoria Hospital, McGill University Health Centre, Montreal, Canada
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Author contributions

F. Cinque, G. Guaraldi, G. Sebastiani contributed to study concept and design, acquisition and interpretation of data, drafting of manuscript, and critical revision of the manuscript. F. Farina, D. Kablawi, A. Cascio, E. Tsochatzis, R. Lombardi, A. Bandera, A. Cordie, R. Mohamed, A. M. Kamel, G. Esmat, D. Benke, F. Elamouri, J. Milic, J.K. Rockstroh, and G. Guaraldi contributed to acquisition and interpretation of data, and critical revision of the manuscript. S. Saeed and J. Lim contributed to methodological support and statistical analysis. All authors participated in the preparation of the manuscript and approved the final version. G. Guaraldi and G. Sebastiani are the guarantors.

Address for Correspondence

Dr Giada Sebastiani, MD FAASLD
Division of Gastroenterology and Hepatology
Chronic Viral Illness Service
Royal Victoria Hospital, McGill University Health Centre
1001 Blvd. Décarie
Montreal, QC H4A 3J1, Canada
Phone: +1 514-8431616; Fax: +1 514-8431421
Email: giada.sebastiani@mcgill.ca

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Conflicts of interest

Sahar Saeed consults for Novo Nordisk. Emmanuel Tsochatzis consults for and is on the speakers' bureau for Novo Nordisk, Siemens, and Boehringer Ingelheim. He consults for Madrigal and MSD. He is on the speakers' bureau for Echosens, Orphalan, Alexion, AbbVie, AstraZeneca, and Gilead. Rosa Lombardi received grants from Gilead. Ahmed Cordie consults for, advises, is on the speakers' bureau for, and received grants from EVA Pharma. He consults for, advises, and is on the speakers' bureau for Gilead, MSD, and GSK. He received grants from Roche. Gamal Esmat consults for and advises AstraZeneca. He consults for EVA Pharma, GSK, Roche, and MSD. Alessandra Bandera advises, is on the speakers' bureau, and received grants from Gilead. She advises and is on the speakers' bureau for AstraZeneca, bioMérieux, Janssen, Nordic, Pfizer, Qiagen, SOBI, Takeda, and ViiV. Jovana Milic is on the speakers' bureau for Gilead and ViiV. Jürgen K. Rockstroh consults for and is on the speakers' bureau for MSD. He consults for Boehringer Ingelheim and Provirex. He is on the speakers' bureau for Gilead, Abbott, AbbVie, Janssen, and ViiV. Giovanni Guaraldi advises, is on the speakers' bureau for, and received grants from ViiV, Merck, and Gilead. He is on the speakers' bureau for and received grants from Janssen. He received grants from Pfizer. Giada Sebastiani consults for, advises, is on the speakers' bureau for, and received grants from Novo Nordisk. She advises and is on the speakers' bureau for Gilead. She advises GSK. She is on the speakers' bureau for Merck, AbbVie, Eli Lilly, Boehringer Ingelheim, and Lupin. The remaining authors have no conflicts to report.

List of Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; APRI, aspartate aminotransferase to platelet ratio index; ART, antiretroviral therapy; AST, aspartate aminotransferase; AUROC, area under the receiver operating characteristic curve; BMI, body mass index; CAP, controlled attenuation parameter; CD4, cluster of differentiation 4; CD8, cluster of differentiation 8; CI, confidence interval; D-drugs, dideoxynucleoside analogues; FIB-4, fibrosis-4

index; GGT, gamma-glutamyl transferase; HbA1c, glycated hemoglobin; HBV, hepatitis B virus; HCV, hepatitis C virus; HDL, high-density lipoprotein cholesterol; HIV, human immunodeficiency virus; HOMA-IR, homeostatic model assessment of insulin resistance; HR, hazard ratio; IDI, integrated discrimination improvement; IDU, injection drug use; INSTI, integrase strand transfer inhibitor; LDL, low-density lipoprotein cholesterol; LHIVPA, Liver pathologies in HIV in Palermo; LIVEHIV, LIVEr disease in HIV; LSM, liver stiffness measurement; MASLD, metabolic dysfunction-associated steatotic liver disease; MASH, metabolic dysfunction-associated steatohepatitis; MetALD, metabolic dysfunction-associated alcohol-related liver disease; MHMC, Modena HIV Metabolic Clinic; MSM, men who have sex with men; MUHC, McGill University Health Centre; NNRTI, non-nucleoside reverse transcriptase inhibitor; NPV, negative predictive value; NRI, net reclassification improvement; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; PPV, positive predictive value; PWH, people with HIV; RR, risk ratio; SLD, steatotic liver disease; T2D, type 2 diabetes; TE, transient elastography.

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Data availability statement

The original contributions presented in this study are included in the article and supplementary material, http://links.lww.com/HEP/K479. According to stipulations of the patient consent form signed by all study participants, ethical restrictions imposed by our Institutional Ethics review boards (Ethics Review Board Biomedical B of the McGill University Health Centre), and legal restrictions imposed by Canadian law regarding clinical trials, anonymized data are available upon reasonable request. Please send data access requests to Biomedical B (BMB) Research Ethics Board (REB) Coordinator Center for Applied Ethics, 5100, boul. de Maisonneuve Ouest, 5th floor, Office 596, Montréal, Québec, H4A 3T2, Canada. Further inquiries can also be directed to the corresponding author.

Graphical Abstract

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Abstract

Background and Aims

Steatotic liver disease (SLD) and liver fibrosis are major comorbidities in people with HIV (PWH). Guidelines recommend stepwise screening using the Fibrosis-4 (FIB-4) index followed by transient elastography (TE), yet its accuracy and the extent of FIB-4 misclassification in PWH remain uncertain. We evaluated the diagnostic performance of FIB-4 against TE, quantified missed fibrosis, and assessed whether metabolic and HIV-specific factors improve risk prediction.

Approach and Results

We conducted a multinational study of 4,917 PWH without viral hepatitis coinfection or hazardous alcohol intake undergoing TE screening across seven centers. SLD was defined by controlled attenuation parameter >275 dB/m and classified as metabolic dysfunction-associated SLD (MASLD) or metabolic dysfunction-associated alcohol-related liver disease (MetALD). Significant fibrosis (liver stiffness measurement [LSM] ≥8 kPa) was present in 12.6% of participants, advanced fibrosis (LSM >11 kPa) in 6.1%, and SLD in 21.7% (20.6% MASLD, 1.1% MetALD). FIB-4 showed modest accuracy for significant fibrosis (AUROC 0.69, 95% CI 0.67–0.72) and misclassified 36% of fibrosis cases as low risk (FIB-4 <1.3). Performance was poorer in MASLD than in non-MASLD (AUROC 0.60 vs 0.76; p<0.001). Participants with false-negative FIB-4 exhibited a more metabolic phenotype, including higher BMI and steatosis. Incorporating metabolic and HIV-specific factors improved discrimination and reclassification and enabled development of the FIB-HIV score, which outperformed FIB-4 (AUROC 0.78 vs 0.69; p<0.001).

Conclusions

In PWH, liver fibrosis is common and frequently missed by FIB-4, particularly in MASLD. TE-centered screening strategies augmented by metabolic and HIV-specific indicators may improve early fibrosis detection and risk stratification.

Introduction

Steatotic liver disease (SLD) is the most common cause of chronic liver disease worldwide, affecting one in three adults and representing a major public health challenge. SLD encompasses a disease spectrum ranging from simple steatosis, including metabolic dysfunction-associated SLD (MASLD) and metabolic dysfunction-associated alcohol-related liver disease (MetALD), to metabolic dysfunction-associated steatohepatitis (MASH), fibrosis, cirrhosis, and hepatocellular carcinoma. The condition is strongly associated with type 2 diabetes (T2D), obesity, and dyslipidemia, which promote hepatic fat accumulation and fibrogenesis through insulin resistance, oxidative stress, and lipotoxicity[1].

With the success of direct-acting antiviral agents for hepatitis C virus (HCV) infection, improved control of chronic hepatitis B virus (HBV) infection, and the near-elimination of severe AIDS-related hepatic complications in the modern antiretroviral therapy (ART) era, SLD has emerged as a leading cause of liver morbidity and mortality among people with HIV (PWH)[2–4]. Reported SLD prevalence in PWH varies widely, from 20% to 39% in studies excluding alcohol misuse and viral hepatitis coinfection, reflecting heterogeneity in study populations and diagnostic methods[5]. However, the burden of MASH and liver fibrosis appears disproportionately higher in PWH, with a recent meta-analysis estimating pooled prevalence at 48% and 12%, respectively[5]. This heightened susceptibility reflects both classical metabolic risk factors and HIV-specific mechanisms. Lifelong exposure to dideoxynucleoside analogues (D-drugs), such as stavudine and didanosine, can induce mitochondrial toxicity, dyslipidemia, and insulin resistance, promoting hepatic steatosis and accelerating fibrosis progression independent of metabolic dysfunction[6]. Persistent immune activation, microbial translocation, and chronic low-grade inflammation further amplify hepatic injury and fibrogenesis. HIV infection also alters adipose tissue distribution, leading to visceral adiposity and ectopic fat deposition, both strongly associated with SLD severity[7]. Furthermore, PWH more frequently exhibit prior HCV infection and alcohol use, which may synergistically worsen liver injury[8]. International societies recommend routine liver fibrosis screening in PWH with metabolic comorbidities, steatosis on imaging, elevated liver transaminases, or prior exposure to D-drugs[9], using the Fibrosis-4 (FIB-4) index as a first-line non-invasive test. Recent multicenter North American data suggest that FIB-4 provides moderate discrimination for advanced fibrosis (area under the receiver operating characteristic curve [AUROC] 0.70) with high negative predictive value (NPV), supporting its role as a rule-out tool[10]. However, its performance is lower for detecting significant fibrosis, and the extent and clinical features of false-negative misclassification remain poorly defined in contemporary HIV populations. In addition, data on the

burden of fibrosis and its metabolic and HIV-specific determinants in large, contemporary cohorts of unselected PWH remain limited.

Population-level transient elastography (TE) screening provides a unique opportunity to evaluate fibrosis burden and assess the real-world performance of simple first-line tests such as FIB-4 in routine HIV care. Therefore, the primary objective of this study was to evaluate the diagnostic performance of the FIB-4 index for detecting significant and advanced liver fibrosis in PWH monoinfection undergoing TE-based liver screening. Secondary objectives were to: (1) quantify and characterize FIB-4 misclassification, with a particular focus on false-negative cases; (2) evaluate whether combining the aspartate aminotransferase (AST)-to-platelet ratio index (APRI) with FIB-4 improves rule-out performance and reduces false-negative classification; and (3) identify metabolic and HIV-specific determinants of significant fibrosis and assess whether incorporating these factors into prediction models improves discrimination and clinical risk stratification beyond FIB-4 alone.

Methods

Study design and population

We conducted a multinational study including seven prospective cohorts of PWH undergoing systematic screening for SLD and liver fibrosis. Participating cohorts included the LIVEr disease in HIV (LIVEHIV) at the McGill University Health Centre (MUHC), the Modena HIV Metabolic Clinic (MHMC), Bonn University Hospital, Liver pathologies in HIV in Palermo (LHIVPA), the University of Milan, Cairo University Hospital, and the Royal Free Hospital in London[11,12]. Between January 2015 and January 2025, we included consecutive patients aged ≥18 years with confirmed HIV infection on ART for ≥6 months and available TE with both liver stiffness measurement (LSM) and controlled attenuation parameter (CAP). During this period, all participating centers implemented annual TE-based liver screening as part of routine HIV care. Relevant clinical and biochemical data collected within six months of TE were required for inclusion. Exclusion criteria were: (i) positive hepatitis B surface antigen or active HCV infection, defined as anti-HCV positivity with detectable serum HCV RNA within 3 years prior to enrollment; (ii) other known liver diseases (autoimmune, cholestatic, genetic, or drug-induced); (iii) excess alcohol intake, defined as >50 g/day for women or >60 g/day for men; (iv) history of hepatocellular carcinoma or liver transplantation; (v) contraindication to TE (pregnancy, pacemaker); (vi) TE failure or unreliable examination. After applying eligibility criteria (Supplementary Figure S1, http://links.lww.com/HEP/K479), the combined cohort of 4,917 PWH included 2,348 (47.8%) patients from the MHMC cohort, 830 (16.9%) from the LIVEHIV cohort, 813 (16.5%) from Cairo

University Hospital, 422 (8.6%) from Bonn University Hospital, 339 (6.9%) from the LHIVPA cohort, 110 (2.2%) from the University of Milan, and 55 (1.1%) from the Royal Free Hospital.

Ethics

All patients provided written informed consent to participate in their respective cohorts. The study was approved by the Research Ethics Board of the Research Institute of the MUHC (study code 14-182-BMD) and local ethics committees at participating centers. The study was conducted in accordance with the Declaration of Helsinki, and this manuscript was prepared according to the STROBE guidelines for observational studies.

Clinical and biological parameters

Data collected included demographic characteristics, HIV and medication history, comorbidities, liver biochemistry, lipid profile, hematological and immunovirological parameters. An undetectable HIV viral load was defined as <50 copies/mL. Prior HBV infection was defined as presence of hepatitis B core antibodies with or without hepatitis B surface antibodies and in the absence of hepatitis B surface antigen, while prior HCV infection was defined as positive HCV serology in absence of detectable HCV-RNA. Alcohol intake was assessed using structured patient self-report. Intake was converted to grams per day using standard drink equivalents and categorized by average daily consumption as light (≤20 g/day in women, ≤30 g/day in men) or moderate (>20–50 g/day in women and >30–60 g/day in men). Overweight was defined as a BMI of 25–29.9 kg/m² (23–27.4 in Asians) and obesity as a BMI ≥30 kg/m² (>27.5 in Asians). A high waist circumference was defined as >88 cm in women and >102 cm in men. Prediabetes was defined as fasting serum glucose >100 mg/dL or glycated hemoglobin (HbA1c) >5.7%. T2D was defined as HbA1c ≥6.5%, current use of antihyperglycemic treatment, or a prior clinical diagnosis. Dyslipidemia was defined as triglycerides >150 mg/dL, high-density lipoprotein cholesterol <40 mg/dL in men or <50 mg/dL in women, or lipid-lowering therapy. MASLD was defined as hepatic steatosis (CAP >275 dB/m) in the absence of alcohol intake >20 g/day in women and >30 g/day in men, plus >1 cardiometabolic risk factor[13]. MetALD was defined as SLD with moderate alcohol consumption (20–50 g/day in women and 30–60 g/day in men), and no primary diagnosis of alcohol-related liver disease[13]. A FIB-4 value <1.3 was used as the low-risk threshold prompting no further fibrosis evaluation, whereas values ≥1.3 prompted second-line assessment with TE, in accordance with current guidelines[9,14]. FIB-4 values of 1.3–2.67 were considered indeterminate, and values ≥2.67 suggestive of advanced fibrosis[9,14]. APRI was calculated using the standard formula and categorized as <0.5 (rule-out for advanced fibrosis), 0.5–1.5 (indeterminate), and >1.5 (rule-in for advanced

fibrosis)[14,15]. Physical activity was assessed using the International Physical Activity Questionnaire and expressed as metabolic equivalents of task[16]. Daily caloric intake was assessed using a standardized three-day food diary and analyzed by a dietician with the aid of a pictorial food atlas to estimate portion sizes. Total mean caloric intake was compared with physical activity intensity[17].

Outcome measures

The primary outcome was the diagnostic performance of the FIB-4 index for detecting significant and advanced liver fibrosis, defined as LSM ≥8 kPa[9,14] and LSM >11 kPa[10], respectively. Secondary outcomes included: (1) the proportion of individuals with significant fibrosis misclassified as low risk by FIB-4 (false negatives) and clinical, metabolic, and HIV-specific factors associated with this misclassification; (2) the diagnostic performance of a combined FIB-4/APRI rule-out strategy; and (3) the identification of metabolic and HIV-specific determinants of significant fibrosis and the incremental value of incorporating these variables into prediction models beyond FIB-4, including improvements in discrimination, reclassification, and clinical utility and the development of a composite clinical risk score.

Transient elastography

Vibration-controlled TE (FibroScan®, Echosens, Paris, France) was performed after a 4-hour fast by one of two experienced operators per center (each with >500 prior examinations)[18]. The standard M probe was used in all patients. The XL probe was applied if the M probe failed or BMI >30 kg/m^2. LSM results were considered reliable when >10 validated measurements were obtained, with an interquartile range <30% of the median.

Longitudinal FIB-4 assessment

In participants from the MHMC and LIVEHIV cohorts with available follow-up laboratory data, FIB-4 was reassessed at 12 and 24 months after baseline. This analysis was performed to explore whether repeat FIB-4 measurement during routine follow-up could reduce false-negative classification among individuals initially categorized as low risk. FIB-4 values were categorized using established clinical thresholds (<1.3, 1.3–2.67, and >2.67)[9,19].

Statistical analysis

We estimated the prevalence of significant liver fibrosis among PWH undergoing routine SLD screening and described the prevalence of advanced liver fibrosis and by SLD phenotype (MASLD, MetALD, and no SLD). The diagnostic performance of FIB-4 was assessed against TE (LSM >8

and LSM >11) using sensitivity, specificity, positive predictive value (PPV), NPV, and AUROC, with subgroup comparisons by MASLD status using the DeLong test[14]. Factors associated with false-negative FIB-4 classification and with significant fibrosis by LSM >8 were examined using modified Poisson regression to estimate risk ratios (RR) with 95% confidence intervals (CI). Covariates were selected a priori for clinical relevance and considered for inclusion if $p<0.10$ in univariable analyses. Adjusted models included sex and center. Nonlinear associations were explored with restricted cubic splines and tested using likelihood-ratio tests. False-negative cases (FIB-4 <1.3 with LSM ≥8 kPa) were compared with true-positive cases (FIB-4 >1.3 with LSM ≥8 kPa) to identify determinants of misclassification. Reclassification across FIB-4 risk categories over time was summarized using transition matrices to evaluate the stability of baseline classification. The proportion of individuals transitioning from low risk (<1.3) to indeterminate (1.3–2.67) or high risk (>2.67) categories at follow-up was calculated to assess whether repeat FIB-4 testing reduced baseline false-negative classification. The diagnostic performance of APRI was evaluated alone and in combination with FIB-4 for detecting significant (LSM ≥8 kPa) and advanced fibrosis (LSM ≥11 kPa). Diagnostic performance was estimated across APRI categories, and a dual rule-out strategy (FIB-4 <1.3 and APRI <0.5) was examined to determine whether this approach reduced false-negative misclassification. Discrimination was quantified using AUROC with 95% CI. To assess incremental value beyond FIB-4, we compared nested models (base, metabolic, and HIV-augmented) using the Integrated Discrimination Improvement (IDI) and Net Reclassification Improvement (NRI) with 10-fold cross-validation. For the derived composite risk score, the optimal operating threshold was determined using the Youden index, defined as the maximum value of sensitivity + specificity –1. Clinical utility was evaluated using decision-curve analysis across clinically relevant risk thresholds. All analyses were conducted using a complete-case approach, and two-sided tests with $\alpha = 0.05$ were applied. Analyses were conducted in R version 4.5.1 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Cohort characteristics

Among the 4,917 participants, the mean age was 50.3 years, 26% were women, 33% reported light-to-moderate alcohol use, and 87.5% had an undetectable HIV viral load. Participants exhibited a high burden of metabolic comorbidities (Table 1). Significant fibrosis and advanced fibrosis were present in 622 (12.6%) and 298 (6.1%) individuals, respectively. The mean FIB-4 was 1.4 (SD 1.6), and 2,950 individuals (60.0%) had FIB-4 <1.3. The mean APRI was 0.4 (SD 0.5), and 4,032 individuals (82.0%) had APRI <0.5. SLD was detected in 21.7% of participants (20.6% MASLD;

1.1% MetALD), with some variation across centers (Supplementary Table S1, http://links.lww.com/HEP/K479). Significant fibrosis was more frequent among individuals with MASLD (25.0%) and MetALD (26.9%) than among those without SLD (8.6%; p<0.001). A similar gradient was observed for advanced fibrosis, which occurred more commonly in individuals with MASLD (11.1%) and MetALD (13.5%) compared with those without SLD (4.1%).

Performance of FIB-4

The diagnostic performance of the continuous FIB-4 index for detecting significant fibrosis (LSM >8 kPa) was modest (AUROC 0.69, 95% CI 0.67–0.72) (Figure 1a). Using the guideline-recommended rule-out threshold (FIB-4 <1.3), sensitivity was 0.64 and specificity 0.66, with a PPV of 0.21 and NPV of 0.92. Within the indeterminate range (FIB-4 1.3–2.67), sensitivity was 0.38 and specificity 0.70, with PPV 0.15 and NPV 0.89. At the rule-in threshold (FIB-4 ≥2.67), specificity increased to 0.96 and PPV to 0.46, whereas sensitivity decreased to 0.24 (NPV 0.90). Diagnostic performance differed significantly according to MASLD status (Figure 1a). Discrimination was lower among individuals with MASLD compared with those without MASLD (AUROC 0.60 vs 0.76, DeLong p<0.001). Complete diagnostic metrics across FIB-4 thresholds are reported in Supplementary Table S2, http://links.lww.com/HEP/K479.

For advanced fibrosis (LSM >11 kPa), overall discrimination improved (AUROC 0.76, 95% CI 0.73–0.79) (Figure 1b). Performance again differed by MASLD status, with lower discrimination among individuals with MASLD compared with those without MASLD (AUROC 0.67 vs 0.83, DeLong p<0.001). Diagnostic metrics across FIB-4 thresholds and MASLD strata are reported in Supplementary Table S2, http://links.lww.com/HEP/K479.

FIB-4 misclassification

Among the 622 individuals with significant fibrosis, 224 (36%) had FIB-4 <1.3 and would therefore have been misclassified as low risk using a FIB-4–based algorithm. Compared with true positives, false-negative individuals were younger, more frequently Hispanic, less likely to have prior HCV or HBV infection, and exhibited a more pronounced metabolic phenotype (Table 1). Their biochemical profile suggested milder liver injury, with lower AST and higher platelet counts, resulting in lower FIB-4 scores. Regarding HIV-specific characteristics, false-negative cases were less likely to have undetectable HIV viral load, had shorter time since HIV diagnosis, higher nadir CD4 counts, and

lower prevalence of prior D-drug exposure. In multivariable analysis adjusted for sex and clinical site, hepatic steatosis and higher BMI remained independently associated with greater risk of false-negative classification, whereas prior HCV infection and prior D-drug exposure were associated with lower risk of misclassification (Table 2).

Factors associated with significant liver fibrosis

Compared with PWH without significant fibrosis, individuals with significant fibrosis were older and more frequently male and Hispanic, more likely to have prior HCV or HBV infection, more likely to report injection drug use, and were less physically active. They also exhibited a more adverse metabolic profile and greater liver injury (Supplementary Table S3, http://links.lww.com/HEP/K479). MASLD and MetALD were more common among individuals with fibrosis. HIV-specific factors associated with fibrosis included longer duration of HIV infection, nadir CD4 <300 cells/μL, and greater prior D-drug exposure. Multivariable results are reported in Supplementary Table S4, http://links.lww.com/HEP/K479. A lean fibrosis phenotype, defined as significant fibrosis in the absence of SLD or metabolic comorbidities, accounted for 13% of fibrosis cases. Compared with metabolically driven fibrosis, lean fibrosis occurred at younger age and more frequently in Hispanic individuals, and was associated with prior HCV or HBV infection, smoking, and light-to-moderate alcohol intake (Supplementary Tables S5–S6, http://links.lww.com/HEP/K479).

Longitudinal reclassification of FIB-4

Among 3,235 participants from the MHMC and LIVEHIV cohorts, follow-up data for FIB-4 reassessment were available for 453 individuals at 12 months and 260 individuals at 24 months (Supplementary Figure S2A, http://links.lww.com/HEP/K479). Among those classified as low risk at baseline (FIB-4 <1.3), the majority remained in the low-risk category at follow-up (106 [65.4%] at 12 months and 81 [73.0%] at 24 months). At 12 months, 54 (33.3%) shifted to the indeterminate category and 2 (1.2%) to the high-risk category; at 24 months, 27 (24.3%) shifted to the indeterminate category and 3 (2.7%) to the high-risk category. Importantly, among participants who remained classified as low risk over time, significant fibrosis (LSM ≥8 kPa) was present in 16 (15.1%) at 12 months and 10 (12.3%) at 24 months, while advanced fibrosis (LSM ≥11 kPa) was present in 4 (3.8%) and 5 (6.2%), respectively (Supplementary Figure S2B, http://links.lww.com/HEP/K479).

APRI and combined FIB-4/APRI performance

APRI alone demonstrated moderate discrimination for significant fibrosis (LSM ≥8 kPa) (AUROC 0.69, 95% CI 0.67–0.72). At the threshold of <0.5, sensitivity was 0.43 and specificity 0.86, while higher thresholds yielded high specificity but low sensitivity. For advanced fibrosis (LSM ≥11 kPa), APRI showed slightly higher discrimination (AUROC 0.76, 95% CI 0.74–0.80) with sensitivity 0.56 and specificity 0.85 at the <0.5 threshold. A combined rule-out strategy requiring FIB-4 <1.3 and APRI <0.5 slightly improved sensitivity compared with FIB-4 alone, reaching 0.65 for significant fibrosis (NPV 0.93; AUROC 0.70) and 0.76 for advanced fibrosis (NPV 0.98; AUROC 0.77) (Supplementary Table S7, http://links.lww.com/HEP/K479).

Model performance, optimization, and clinical utility

Restricted cubic spline analyses were used to assess potential nonlinear associations between predictors and outcomes (Figure 2; Supplementary Figure S3, http://links.lww.com/HEP/K479). For significant fibrosis, alanine aminotransferase (ALT), CAP, and CD4 count demonstrated nonlinear relationships, whereas BMI, waist circumference, HbA1c, nadir CD4 count, and duration of D-drug exposure were modeled as linear terms (Table 3). Among individuals classified as low risk by FIB-4 (FIB-4 <1.3), adding metabolic predictors improved discrimination (IDI = 0.05) and reclassification (NRI = 0.27). Further improvement occurred after incorporating HIV-specific variables (NRI = 0.12) (Table 4). Among individuals with indeterminate FIB-4 (1.3–2.67), both metabolic and HIV-augmented models improved discrimination and reclassification compared with the base model. In contrast, minimal incremental improvement was observed among those with high FIB-4 (≥2.67). Decision-curve analysis demonstrated greater net benefit for both enriched models compared with FIB-4 alone across clinically relevant risk thresholds (5–20%), with the HIV-augmented model performing best overall (Figure 3). For lean fibrosis, net benefit was limited: enriched models outperformed FIB-4 only at low thresholds (~8–12%) and lost this advantage at higher thresholds (~12–15%) (Supplementary Figure S4, http://links.lww.com/HEP/K479).

Development and performance of the FIB-HIV score

To translate these findings into a clinically applicable tool, we derived a composite score extending the FIB-4 components with metabolic (BMI, T2D, dyslipidemia, hypertension) and HIV-specific variables (CD4 count, HIV viral load detectability, prior D-drug exposure). This model, termed the FIB-HIV score, estimates the probability of significant fibrosis according to the following logistic equation:

logit(p) = −4.9619 + 0.0208×Age − 0.0005×ALT + 0.0235×AST − 0.0079×Platelets + 0.1513×Male + 0.0876×BMI + 0.5381×T2D + 0.1807×Dyslipidemia + 0.3795×Hypertension + 0.0002×CD4 − 0.2031×Undetectable HIV viral load + 0.6147×Prior D-drug.
where the predicted probability is calculated as: p = 1 / (1 + e^(−logit(p)))

Compared with FIB-4 alone, the FIB-HIV score significantly improved discrimination for significant fibrosis (AUROC 0.78 vs 0.69; DeLong p<0.001) (Figure 4). The optimal operating threshold was 0.146, corresponding to 0.64 sensitivity and 0.79 specificity, with 0.29 PPV and 0.94 NPV. Full model coefficients are reported in Supplementary Table S8, http://links.lww.com/HEP/K479.

Discussion

This large multinational screening study of nearly 5,000 PWH without active viral hepatitis or hazardous alcohol use demonstrates that liver fibrosis is common, clinically silent, and frequently missed by current screening algorithms. By directly evaluating the guideline-endorsed FIB-4 pathway[9,13], we demonstrate suboptimal diagnostic performance in this high-risk population, with more than one-third of fibrosis cases incorrectly categorized as low risk. Incorporating metabolic and HIV-specific factors improved risk prediction and enabled development of the FIB-HIV score, a clinically applicable tool that may better stratify PWH for TE referral. These findings highlight important limitations of current screening strategies and support refinement of fibrosis detection pathways in PWH.

These observations are particularly relevant in the context of the evolving epidemiology of HIV. As ART has transformed HIV into a chronic condition, nearly half of PWH in high-income settings are now older than 50 years, and metabolic comorbidities have surged. Liver disease remains among the leading causes of mortality in PWH and, unlike many other comorbidities, has not declined in older individuals[20]. With HCV and HBV increasingly controlled, metabolic dysfunction, hepatic steatosis, and progressive fibrosis now represent the dominant drivers of liver disease in PWH[2,4,8]. The broader SLD framework is particularly relevant in PWH, where metabolic risk factors often coexist with HIV-specific mechanisms such as chronic immune activation, long-term ART exposure, microbial translocation, visceral adiposity, and social vulnerabilities[21]. In our screened cohort, MASLD prevalence was 20.6%, somewhat lower than estimates from clinic-based studies and recent meta-analyses[5]. This difference likely reflects our consecutive screening protocol and the use of a CAP threshold >275 dB/m, which prioritizes specificity in line with AASLD

recommendations for imaging-based steatosis assessment[14]. Despite this moderate prevalence of steatosis, the burden of fibrosis was substantial, suggesting that PWH may not necessarily have higher MASLD prevalence than the general population but may experience more severe liver disease once steatosis develops. These findings reinforce the need for fibrosis screening strategies that are not limited to overt metabolic disease or elevated transaminases[22].

FIB-4 demonstrated modest discrimination for detecting significant fibrosis (AUROC 0.69) while maintaining a high NPV, consistent with its established role as a rule-out tool in low-prevalence settings. Notably, diagnostic performance was better for advanced fibrosis (AUROC 0.76) than for significant fibrosis, the threshold typically used in clinical pathways to trigger referral for TE. In our cohort—characterized by a relatively high fibrosis burden—this apparent rule-out performance masked limited sensitivity, with 36% of individuals with significant fibrosis misclassified as low risk. This limitation is clinically relevant because current guidelines recommend FIB-4 as the first-line gatekeeper determining which patients do not require TE or hepatology referral. Diagnostic performance was notably worse among individuals with MASLD (AUROC 0.60), consistent with the fact that FIB-4 was originally derived in viral hepatitis cohorts and primarily validated in lower-prevalence populations[23]. Prior histology-based studies in PWH have reported AUROC values ranging from 0.64 to 0.81, depending on population characteristics and threshold selection[24–26]. Similarly, a TE-based study of 437 PWH without viral hepatitis reported an AUROC of 0.74 for FIB-4[27], while a North American cohort of 1,065 PWH showed a high NPV but sensitivity as low as 54%[10]. Collectively, these data suggest that although FIB-4 retains rule-out value, its performance declines in populations with higher fibrosis prevalence and prominent metabolic disease. Similar limitations have been observed in MASLD outside HIV, where incorporating metabolic variables may improve diagnostic accuracy beyond FIB-4 alone[28,29].

Risk-factor analyses in our study emphasize the multidimensional pathogenesis of liver fibrosis in HIV. Obesity, T2D, and steatosis were strongly associated with fibrosis, yet HIV-specific and legacy factors, including nadir CD4 <300 cells/μL, prior exposure to D-drugs, and sequelae of prior HCV infection, also played a role. The enduring impact of early ART regimens, particularly D-drugs, is reflected in persistent fibrosis risk long after drug discontinuation[6]. These findings suggest lasting hepatic consequences of early ART regimens and immune dysfunction[30]. This supports a combined metabolic–immune–viral model, integrating persistent immune activation, monocyte/macrophage dysregulation, residual lipodystrophy, and ART-related mitochondrial stress[21]. The association with Hispanic ethnicity, potentially reflecting Patatin-like phospholipase

domain-containing protein 3 variants, further highlights genetic–HIV interactions[31]. We also identified a clinically relevant lean fibrosis phenotype, representing 13% of fibrosis cases and occurring in the absence of steatosis or metabolic comorbidities. This phenotype would be inherently missed by screening algorithms triggered by metabolic indicators alone, supporting broader screening strategies in PWH[9].

Given the high false-negative rate of a single FIB-4 measurement, we examined whether repeat testing could mitigate baseline misclassification. This question is particularly relevant given prior studies in MASLD populations showing that longitudinal FIB-4 assessment improves risk stratification and prognostic accuracy[19,32,33]. In our cohort, although approximately one-third of individuals initially classified as low risk transitioned to higher FIB-4 categories within 12 months, most remained persistently classified as low risk even after two years despite the presence of significant fibrosis. Importantly, significant fibrosis persisted in a non-negligible proportion of individuals who remained classified as low risk (FIB-4 <1.3), with prevalences of 15% at 12 months and 12% at 24 months. Serial FIB-4 testing may therefore provide only limited improvement in identifying missed cases. We also explored whether combining FIB-4 with APRI could reduce false-negative classification. However, requiring both FIB-4 <1.3 and APRI <0.5 produced only marginal gains in sensitivity and minimal reduction in false-negative misclassification. These findings suggest that dual biomarker strategies based solely on routine laboratory indices offer limited incremental value in this population.

To address these limitations, we developed enhanced prediction models incorporating metabolic (BMI, T2D, CAP-defined steatosis, dyslipidemia, hypertension, waist circumference) and HIV-specific (CD4 cell count, HIV viral load detectability, CD4:CD8 ratio, prior D-drug exposure) variables. Addition of metabolic predictors improved discrimination by 5%, representing a moderate-to-strong gain, and improved reclassification by 27% compared with FIB-4 alone. The addition of HIV-specific variables yielded an additional 12% reclassification improvement, resulting in a cumulative 39% gain. Decision-curve analysis confirmed that these enriched models provided greater clinical utility than FIB-4 across screening-relevant risk thresholds (5–20%), with the HIV-augmented model yielding the greatest net benefit. These findings reinforce evidence from studies outside the HIV setting[28,29] showing that incorporation of metabolic risk factors improves fibrosis prediction beyond FIB-4. Our study extends this concept to HIV by integrating key HIV-specific determinants that capture immune dysregulation and persistent inflammation contributing to fibrosis progression in PWH. Spline analyses further support these findings, with linear,

clinically relevant associations for BMI and waist circumference, while ALT and CD4 exhibited nonlinear patterns. Together, these observations support routine TE-based screening in PWH, especially in those with metabolic dysfunction or suboptimal immune recovery, even when ALT levels are normal.

Access to TE for PWH remains uneven, particularly in resource-limited settings where systematic screening may not be feasible. In such contexts, reliance on FIB-4 alone as a gatekeeping strategy may lead to substantial under-detection of fibrosis, especially among individuals with MASLD, metabolic risk factors, or suboptimal immune recovery. Guided by the observed improvements in discrimination and reclassification, we derived the FIB-HIV score, a composite index integrating the FIB-4 components with sex and additional metabolic (BMI, T2D, dyslipidemia, hypertension) and HIV-specific variables (CD4 count, viral load detectability, and prior D-drug exposure). This index demonstrated significantly improved discrimination for significant fibrosis compared with FIB-4 alone (AUROC 0.78 vs 0.69). FIB-HIV is based on routinely available clinical variables and may therefore improve triage for TE referral and optimize allocation of limited diagnostic resources. Importantly, the score is not intended to replace TE but rather to refine patient selection for second-line non-invasive assessment.

The substantial fibrosis burden observed in our cohort also underscores the need for effective preventive and therapeutic strategies. Higher physical activity was independently associated with lower fibrosis rates, consistent with evidence from MASLD populations and emerging interventional studies, supporting the integration of structured lifestyle interventions into routine HIV care[34]. Nevertheless, therapeutic gaps remain: despite early evidence that glucagon-like-peptide-1 receptor agonists such as semaglutide reduce hepatic fat in PWH[35], this population remains largely excluded from pivotal MASH trials, limiting access to emerging antifibrotic therapies[36].

Our study has several strengths. These include the large multinational cohort of consecutively screened PWH, standardized TE across centers, and detailed phenotyping of metabolic and HIV-specific factors. Advanced statistical modelling enabled robust evaluation of predictive performance and clinical utility. Importantly, the study extends beyond diagnostic evaluation by deriving the FIB-HIV score that integrates metabolic and HIV-related variables to improve fibrosis risk stratification. However, several limitations should be acknowledged. The cross-sectional design, lack of histological confirmation, and absence of measures of visceral adiposity or inflammatory

biomarkers preclude further elucidation of mechanisms underlying fibrosis in HIV. Self-reported alcohol intake, together with earlier non-alcoholic fatty liver disease-based screening criteria that excluded individuals with moderate alcohol consumption, likely resulted in underdiagnosis of MetALD. In addition, the ethnic composition of the cohort may limit generalizability to populations with higher proportions of Hispanic and Black individuals. Longitudinal data were available only for a subset of participants, and therefore the analyses evaluating repeat FIB-4 assessment over time should be considered exploratory. Finally, the FIB-HIV score was internally derived and requires external validation in independent cohorts before clinical implementation.

In conclusion, this multinational study demonstrates that liver fibrosis is common and frequently missed in PWH when relying on FIB-4-based screening pathways. High false-negative rates and the presence of a lean fibrosis phenotype highlight the need for HIV-adapted screening frameworks. Integrating metabolic and HIV-specific factors improves fibrosis risk prediction beyond FIB-4 and supports development of a clinically applicable tool to better stratify patients and prioritize for TE referral. These findings have direct implications for screening guidelines and support prospective studies to refine TE-based pathways, elucidate non-traditional mechanisms of fibrosis, and evaluate targeted lifestyle and metabolic interventions. Importantly, the substantial fibrosis burden reinforces the need to include PWH in future antifibrotic and MASH therapeutic trials.

Acknowledgments

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Figure 1. AUROC of FIB-4 for: (a) detecting significant fibrosis (LSM ≥8 kPa); (b) detecting advanced fibrosis (LSM ≥11 kPa), overall and stratified by MASLD status.

AUROC, area under the receiver operating characteristic curve; FIB-4, fibrosis-4 index; LSM, liver stiffness measurement; MASLD, metabolic dysfunction-associated steatotic liver disease.

Figure 1A

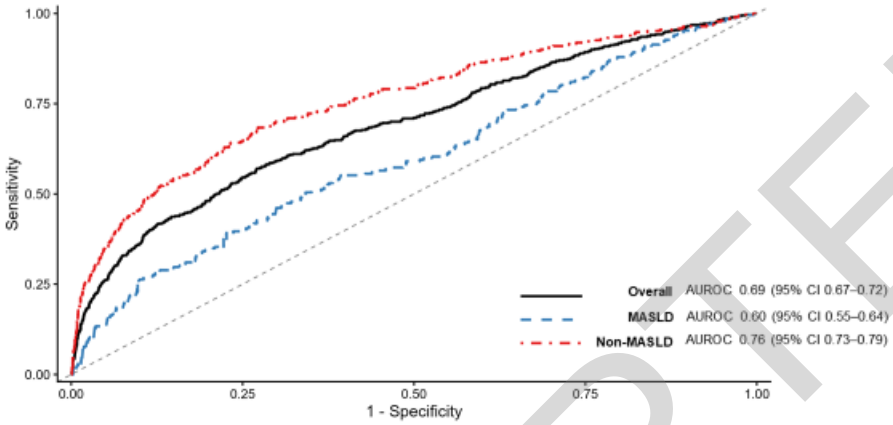

Figure 1B

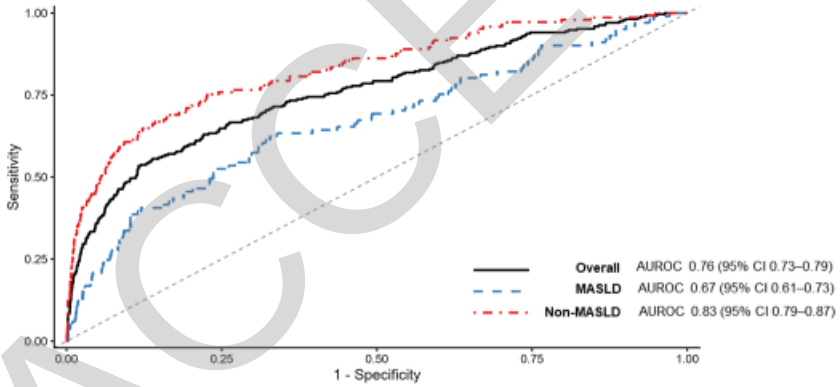

Figure 2. Restricted cubic spline models (3 knots) evaluating nonlinear associations between: (a) clinical risk factors and significant liver fibrosis; (b) clinical risk factors and false-negative classification.

ALT, alanine aminotransferase; CAP, controlled attenuation parameter; HbA1c, glycated hemoglobin; LSM, liver stiffness measurement; PWH, people with HIV.

Figure 2A

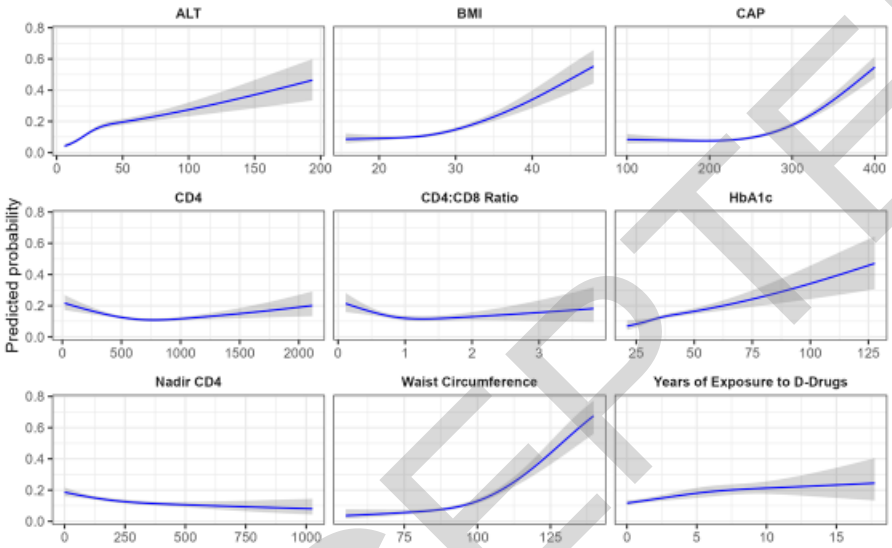

Figure 2B

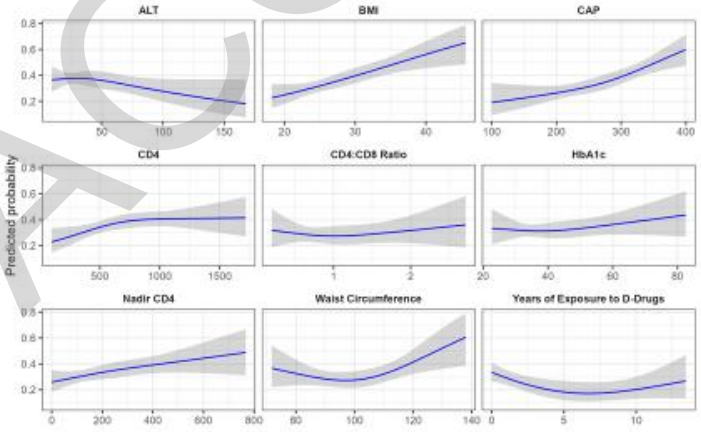

Figure 3. Decision curve analysis evaluating the prediction of significant liver fibrosis. The base model included FIB-4 index and male sex; the metabolic model had base model + BMI, type 2 diabetes, steatosis, dyslipidemia, hypertension, and waist circumference; the HIV model had metabolic model + nadir CD4 count, viral load detectability, CD4:CD8 ratio, and prior D-drug exposure.

FIB-4, fibrosis-4 index; HIV, human immunodeficiency virus.

Figure 3

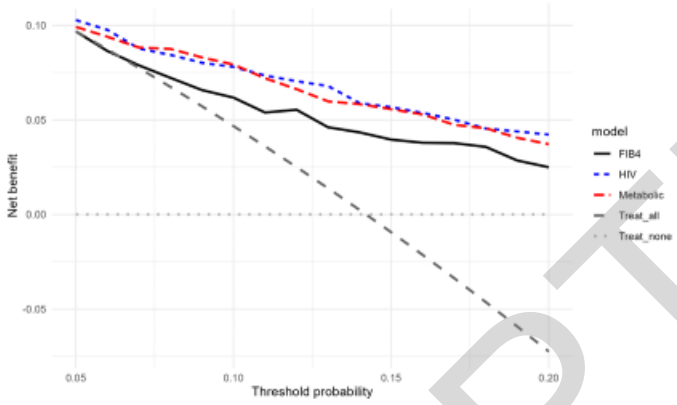

Figure 4. AUROC comparison between the FIB-HIV score and FIB-4 index for detecting significant fibrosis (LSM ≥8 kPa).

AUROC, area under the receiver operating characteristic curve; FIB-4, fibrosis-4 index; FIB-HIV, Fibrosis-HIV score; LSM, liver stiffness measurement.

Figure 4

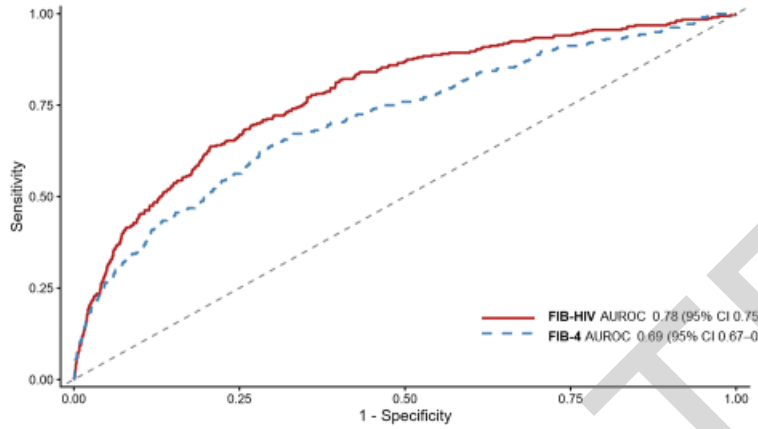

Table 1. Characteristics of the whole multinational cohort (n=4,917) and of patients with significant liver fibrosis by missed significant fibrosis status using FIB-4 (n=622).

Variable	**Whole cohort** (n=4,917)	**True Positive (LSM ≥8 & FIB-4 ≥1.3)** (n=398)	**False Negative (LSM ≥8 & FIB-4 <1.3)** (n=224)	**p-value**
Demographics & Lifestyle				
Age (years)	50.3 (12.1)	57.4 (8.0)	49.3 (11.3)	<0.001
Male sex (%)	3640 (74.0)	318 (79.9)	169 (75.4)	0.155
Hispanic ethnicity (%)	465 (9.5)	41 (10.3)	40 (17.9)	0.017
Previous HCV infection (%)	842 (17.1)	206 (51.8)	36 (16.1)	<0.001
Previous HBV infection (%)	192 (3.9)	37 (9.3)	9 (4.0)	0.024
MSM (%)	2252 (45.8)	116 (29.1)	82 (36.6)	0.058
IDU (%)	949 (19.3)	199 (50.0)	59 (26.3)	<0.001
Smoking (%)	1711 (34.8)	153 (38.4)	84 (37.5)	0.87
Alcohol use (%) - None - Light - Moderate	 3296 (67.0) 1400 (28.5) 221 (4.5)	 253 (63.6) 114 (28.6) 30 (7.5)	 156 (69.6) 59 (26.3) 9 (4.0)	0.28
Adherence to physical activity* (%)	1381 (56.5)	103 (46.4%)	31 (36.5%)	0.150
Adherence to diet* (%)	1818 (84.8)	166 (81.8%)	63 (82.9%)	0.966
Anthropometry				
BMI (kg/m²)	25.7 (5.0)	26.8 (5.8)	29.5 (7.1)	<0.001
Waist circumference (cm)*	92.3 (13.0)	99.1 (13.8)	102.3 (17.8)	0.100
High waist circumference* (%)	1674 (54.2)	156 (70.3%)	78 (72.9%)	0.51
Metabolic comorbidities				
Overweight (%)	1661 (33.8)	134 (33.7)	77 (34.4)	0.84
Obesity (%)	796 (16.2)	96 (24.1)	88 (39.3)	<0.001

Prediabetes or diabetes (%)	1554 (31.6)	200 (50.3)	110 (49.1)	0.78
Hypertension (%)	994 (20.2)	126 (31.7)	72 (32.4)	0.73
MASLD (%)	1012 (20.6)	130 (32.7)	125 (55.8)	<0.001
MetALD (%)	55 (1.1)	10 (2.5)	6 (2.7)	1.000
Laboratory				
AST (U/L)	24 (20–30)	32 (25–44)	24 (19–30)	<0.001
ALT (U/L)	23 (17–32)	28 (20–44)	26 (20–41)	0.300
GGT (U/L)	23 (16–36)	36 (24–63)	36 (22–68)	0.800
ALP (U/L)	71 (57–87)	74 (61–91)	77 (61–93)	0.500
Bilirubin (mg/dL)	0.5 (0.4–0.8)	0.67 (0.49–0.99)	0.54 (0.37–0.82)	<0.001
Albumin (g/dL)	4.4 (4.2–4.6)	4.30 (4.00–4.60)	4.30 (4.10–4.60)	0.200
Platelets (10^9/L)	221 (181–262)	160 (118–190)	256 (222–296)	<0.001
Glucose (mg/dL)	91 (83–103)	101 (86–115)	97 (84–114)	0.200
HbA1c (mmol/mol)	35 (32–38)	37 (32–42)	36 (33–42)	0.800
HOMA-IR index*	2.2 (1.3–3.6)	3.4 (2.2–5.7)	3.9 (2.2–5.8)	0.600
Total cholesterol (mg/dL)	179 (152–209)	162 (138–189)	183 (152–215)	<0.001
Triglycerides (mg/dL)	111 (80–164)	123 (92–186)	148 (96–229)	0.004
HDL (mg/dL)	47 (40–57)	44 (37–53)	43 (36–52)	0.500
LDL (mg/dL)	110 (85–135)	94 (72–121)	110 (79–136)	<0.001
Non-invasive tests				
LSM (kPa)	5.1 (4.2–6.4)	11.4 (9.1–17.5)	9.8 (8.6–11.8)	0.009
CAP (dB/m)	237.4 (58.9)	259.2 (69.3)	290.3 (70.1)	<0.001
HIV-specific				
Time since HIV diagnosis (years)	16.6 (13.3)	25.4 (12.1)	16.7 (13.3)	<0.001
Undetectable HIV viral load (%)	4302 (87.5)	358 (89.9)	174 (77.7)	0.004
CD4 count (cells/µL)	680.1 (328.2)	638 (371)	709 (348)	0.025
Nadir CD4 (cells/µL)	237.3 (183.0)	188 (160)	230 (199)	0.019
Nadir CD4 <300 (%)	3463 (70.4)	320 (80.4)	171 (76.3)	0.288
CD4:CD8 ratio <1 (%)	2755 (56.1)	227 (57.0)	147 (65.6)	0.335
Current NRTI (%)	3855 (78.4)	287 (72.1)	175 (78.1)	0.184

Current NNRTI (%)	1333 (27.1)	114 (28.6)	48 (21.4)	0.059
Current INSTI (%)	3307 (67.3)	268 (67.3)	153 (68.3)	0.920
Current PI (%)	985 (20.0)	99 (24.9)	57 (25.4)	0.937
Prior D-drug exposure (%)	1284 (26.1)	198 (49.7)	55 (24.6)	<0.001

Continuous variables are expressed as mean (standard deviation) or median (interquartile range), as appropriate, and categorical variables are expressed as frequencies (%). The p-values refer to Student t-test or Wilcoxon rank-sum test for continuous variables, and χ^2 test or Fisher's exact test for categorical variables between True Positive and False Negative. *Adherence to physical activity (n=2,446), adherence to diet (n=2,169), waist circumference (n=3,089), and HOMA-IR index (n=1,699) were calculated among participants with available data due to missingness.
ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CAP, controlled attenuation parameter; D-drugs – dideoxynucleoside analogues; FIB-4, fibrosis-4 index; GGT, gamma-glutamyl transpeptidase; HbA1c, glycated hemoglobin; HBV, hepatitis B virus; HCV, hepatitis C virus; HDL, high-density lipoprotein; HIV, human immunodeficiency virus; HOMA-IR, homeostatic model assessment of insulin resistance; IDU, injection drug use; INSTI, integrase strand transfer inhibitor; LDL, low-density lipoprotein cholesterol; LSM, liver stiffness measurement; MSM, men who have sex with men; MASLD, metabolic dysfunction-associated steatotic liver disease; MetALD, metabolic dysfunction–associated alcohol-related liver disease; NNRTI, non-nucleoside reverse transcriptase inhibitors; NRTI, nucleoside reverse transcriptase inhibitors; PI, protease inhibitors.

Table 2. Multivariable analysis of factors associated with missed significant fibrosis using FIB-4 (n=622).

Variable	**Risk Ratio (95% CI)**
Hispanic (yes vs. no)	0.80 (0.53-1.20)
Previous HCV (yes vs. no)	0.31 (0.20-0.47)
Previous HBV (yes vs. no)	0.48 (0.21-1.10)
Hepatic steatosis (yes vs. no)	1.96 (1.46-2.62)
BMI (per Kg/m^2)	1.04 (1.02-1.06)
Nadir CD4 <300 (yes vs. no)	0.69 (0.46-1.04)
Undetectable HIV viral load (yes vs. no)	0.46 (0.32-0.64)
Prior D-drugs exposure (yes vs. no)	0.80 (0.53-1.20)

Multivariable analysis was performed using modified Poisson regression models, reporting risk ratios with 95% confidence interval (CI). Models were adjusted for sex and study site. Covariates were selected a priori based on clinical relevance and retained if $p<0.10$ in the univariable analyses. The model was adjusted for sex and center.

D-drugs – dideoxynucleoside analogues; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus.

Table 3. Test of non-linearity comparing restricted cubic spline models vs. linear models for significant liver fibrosis.

	Significant Liver Fibrosis		**Lean Fibrosis**		**False Negatives**	
Variable	**LR χ^2**	**P-value**	**LR χ^2**	**P-value**	**LR χ^2**	**P-value**
BMI (Kg/m^2)	1.74	0.188	0.38	0.538	0.28	0.595
Waist circumference (cm)	0.09	0.769	1.98	0.159	2.14	0.1434
ALT (U/L)	50.13	< 0.001	7.56	0.006	0.50	0.479
HBA1c (mmol/mol)	3.36	0.067	0.42	0.518	0.23	0.631
CAP (dB/m)	23.21	< 0.001	28.95	< 0.001	0.04	0.834
CD4 count (cells/µL)	15.87	< 0.001	0.63	0.427	1.64	0.201
Nadir CD4 (cells/µL)	1.65	0.199	1.97	0.160	0.21	0.651
CD4:CD8 ratio	6.37	0.016	0.78	0.377	0.32	0.574

Non-linear relationships between continuous predictors and outcomes using restricted cubic splines and compared spline and linear models using likelihood-ratio tests to assess non-linearity.
ALT, alanine aminotransferase; CAP, controlled attenuation parameter; HbA1c, glycated hemoglobin; LR, likelihood ratio.

Table 4. Model performance assessed by Integrated Discrimination Improvement and Net Reclassification Improvement for significant fibrosis, lean fibrosis, and false-negative FIB-4 classification.

	Integrated Discrimination Improvement	**Net Reclassification Improvement**
Significant Liver Fibrosis[1]		
FIB-4 <1.3		
Metabolic vs. Base	0.05 (0.04, 0.08)	0.27 (0.18, 0.37)
HIV vs. Metabolic	0.006 (-0.002, 0.01)	0.12 (0.07, 0.18)
FIB-4 1.3–2.67		
Metabolic vs. Base	0.05 (0.02, 0.08)	0.24 (0.10, 0.37)
HIV vs. Metabolic	0.01 (0.00, 0.02)	0.11 (0.02, 0.19)
FIB-4 >2.67		
Metabolic vs. Base	0.06 (-0.01, 0.10)	0.08 (-0.05, 0.21)
HIV vs. Metabolic	-0.01 (-0.03, 0.02)	0.05 (-0.08, 0.17)
Lean Fibrosis[2]		
HCV vs. Base	0.002 (-0.02, 0.02)	-0.08 (-0.31, 0.10)
HIV vs. HCV	-0.02 (-0.06, -0.00)	-0.10 (-0.46, 0.22)
False Negative[3]		
Metabolic vs. Base	0.07 (0.02, 0.12)	0.21 (-0.03, 0.43)
HIV vs. Metabolic	0.04 (-0.01, 0.10)	0.21 (0.05, 0.38)

[1]The base model had FIB-4 score and male; the metabolic model had base model + BMI, type 2 diabetes, MASLD, dyslipidemia, hypertension, and waist circumference; the HIV model had metabolic model + CD4 count, viral load detectability, CD4:CD8 ratio, and prior D-drug exposure. [2]The base model had FIB-4 score and male; the metabolic model had base model + previous history of HCV; the HIV model had HCV model + CD4 count, viral load detectability, CD4:CD8 ratio, and prior D-drug exposure. [3]The base model had male and age; the metabolic model had base model + BMI, type 2 diabetes, steatosis, dyslipidemia, hypertension, and waist circumference; the HIV model had metabolic model + CD4 count, viral load detectability, CD4:CD8 ratio, and prior D-drug exposure.

HCV, hepatitis C virus; HIV, human immunodeficiency virus.