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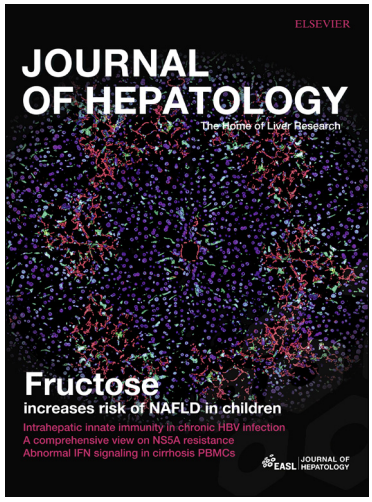

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Hepatic steatosis progresses faster in HIV mono-infected than HIV/HCV co-infected patients and is associated with liver fibrosis

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Short title: Hepatic steatosis in HIV infection

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Conflict of interest

BL has acted as a consultant for ViiV, Gilead, and Merck and received research funding from Merck, Gilead and Abbvie. MD has served as an advisory board member for Merck, Janssen, Gilead. PW has acted as consultant for BMS, Gilead, Merck, Novartis. PG has acted as consultant for Merck and Gilead. MBK has acted as a consultant for ViiV, Gilead, Janssen and Merck and received research funding from Merck and ViiV. GS has acted as speaker for Merck, BMS, Gilead, Abbvie, served as an advisory board member for Merck and BMS and has received research funding from Merck.

TP, AB, MS, AH, EVL, CP have nothing to disclose.

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Authors contributions

TP contributed to study design, data, interpretation of the data and first draft of the article. BL, MS, PG, PW, MD, AH and EVL contributed to data and interpretation of data. AB and CP contributed to data. MBK contributed to conception, study design, data and interpretation of the data. GS contributed to conception, study design, data and interpretation of the data, statistical analysis and first draft of the manuscript. All authors approved the final version of the article.

Abstract

Background & Aims: Hepatic steatosis (HS) seems common in patients infected with human immunodeficiency virus (HIV). However, the relative effect of HIV, as well as hepatitis C virus (HCV) in those co-infected, and the influence of HS on liver fibrosis progression are unclear.

Methods: The LIVEr disease in HIV (LIVEHIV) is a Canadian prospective Cohort using transient elastography and associated controlled attenuation parameter (CAP) to screen for HS and liver fibrosis in unselected HIV-infected adults. HS progression was defined as development of any grade HS (CAP ≥248 dB/m), or transition to severe HS (CAP ≥292 dB/m) for those with any grade HS at baseline. Fibrosis progression was defined as development of significant liver fibrosis (liver stiffness measurement [LSM] ≥7.1kPa), or transition to cirrhosis (LSM ≥12.5kPa) for those with significant liver fibrosis at baseline. Cox regression analysis was used to assess predictors of HS and fibrosis progression.

Results: A prospective cohort study was conducted, which included 726 HIV-infected patients (22.7% HCV co-infected). Prevalence of any grade HS did not differ between HIV mono-infected and HIV/HCV co-infected patients (36.1% vs 38.6%, respectively). 313 patients were followed for a median of 15.4 (interquartile range 8.5-23.0) months. The rate of HS progression was 37.8 (95% confidence interval [CI] 29.2-49.0) and 21.9 (95% CI 15.6-30.7) per 100 person-years in HIV mono-infection and HIV/HCV co-infection, respectively. HCV co-infection was an independent negative predictor of HS progression (adjusted hazard ratio [aHR] 0.50, 95% CI 0.28-0.89). HS predicted liver fibrosis progression in HIV mono-infection (aHR 4.18, 95% CI 1.21-14.5), but not in HIV/HCV co-infection.

Conclusion: HS progresses faster and is associated with liver fibrosis progression in HIV mono-infection but not in HIV/HCV co-infection.

Lay summary

Fatty liver is the most frequent liver disease in Western countries. People living with HIV seems at high risk for fatty liver due to frequent metabolic disorders and long-term effect of antiretroviral therapy. However, due to the invasiveness of liver biopsy, the traditional way to diagnose fatty liver, there are few data about its frequency in people living with HIV. In this work, we used a non-invasive diagnostic tool to study epidemiology of fatty liver in 726 HIV+ patients. We observed that fatty liver affects over one third of people living with HIV. When followed over time, we found that HIV+ patients without co-infection with HCV develops more frequently fatty liver than those co-infected with HCV.

Introduction

Hepatic steatosis (HS) is an accumulation of fat into the liver, which may eventually progress to steatohepatitis, a pathologic inflammatory response leading to fibrosis, cirrhosis and liver failure.[1] HS is particularly common in hepatitis C virus (HCV)-infected patients with human immunodeficiency virus (HIV) co-infection, with reported frequencies ranging between 30 and 70%.[2-6] HCV may induce HS through several mechanisms, including altered lipid metabolism, metabolic risk factors in non-genotype 3 infections and a direct steatogenic effect of HCV genotype 3.[7] Longitudinal studies are not consistent in implicating HS with faster liver fibrosis progression in HIV/HCV co-infection.[8, 9]

Data on HS in HIV mono-infected patients without HCV are scarce. HIV mono-infection is a risk factor for HS through several postulated mechanisms, including frequent metabolic disorders and hepatotoxic effect of antiretroviral therapy (ART).[3] Moreover, HIV itself is associated with chronic inflammation and immune activation, which further contribute to the development of progressive HS and steatohepatitis.[10, 11] Cross-sectional studies reported a prevalence of HS higher in HIV-infected patients than in the general population.[2-5] However, a recent report employing magnetic resonance imaging (MRI) and spectroscopy suggested that HS is more frequent in uninfected adults than in HIV mono-infected and HIV/HCV co-infected patients.[7] These contradictory results may derive from different definitions and techniques used to diagnose HS, from the cross-sectional study design and the possibility of survivorship bias. Given that HS a chronic process, longitudinal studies evaluating the dynamics of HS and its effect on liver

fibrosis progression in HIV-infected patients, particularly if HIV mono-infected, are needed. However, liver biopsy, the gold standard to diagnose HS and fibrosis, carries significant risks and it is not well suited to implement in large-scale screening programs.[12] Moreover, due to the lack of a clear clinical indication, biopsy-based studies with repeated measures over time are very difficult to conduct, particularly in HIV mono-infected patients, without incurring selection biases.

The introduction of transient elastography (TE), a non-invasive tool which measures liver stiffness as a surrogate of liver fibrosis, provides new possibilities for undertaking this research. The controlled attenuation parameter (CAP) measures the degree of ultrasound attenuation by hepatic fat at the central frequency of the FibroScan (Echosens, Paris, France), simultaneously with liver stiffness measurement (LSM). TE and CAP have been validated to diagnose HS and liver fibrosis in HIV-infected patients.[13]

We have initiated the LIVEr disease in HIV (LIVEHIV) Cohort, which is the first North American prospective cohort designed to characterize the epidemiology, dynamics and the effect on liver fibrosis of HS in HIV-infected adults undergoing a routine screening program with TE and associated CAP. The aims of the present study were: 1) To investigate prevalence and associated cofactors of HS and significant liver fibrosis; and 2) To investigate incidence and predictors of HS and liver fibrosis progression in HIV-infected patients, with or without HCV co-infection.

Patients and methods

Study design and population

The LIVEHIV Cohort is a prospective routine screening program for HS and liver fibrosis established in September 2013 at McGill University Health Centre (MUHC), Montreal, Canada. As of September 2016, 1,173 patients have been enrolled in the LIVEHIV Cohort and underwent screening for liver disease, including HCV and hepatitis B virus (HBV) serology, Alcohol Use Disorders Identification Test (AUDIT-C) questionnaire,[14] yearly TE with CAP.

The patients included in the present analysis fulfilled the following criteria: 1) age ≥18 years; 2) HIV infection, as documented by positive enzyme-linked immunosorbent assay [ELISA] with Western blot confirmation; 3) availability of relevant clinical and biochemical parameters; 4) at least one valid LSM with CAP. Exclusion criteria were: 1) evidence of other liver disease (auto-immune hepatitis, haemochromatosis, Wilson's disease); 2) hazardous alcohol intake (AUDIT-C score ≥7 [14]); 3) history or evidence at entry of hepatocellular carcinoma (HCC) or liver transplantation; 4) failure of TE examination or unreliable LSM; 5) contraindications to TE examination (pregnancy; pacemaker insertion). Informed consent was obtained by study participants. The Research Ethic Board of the Research Institute of the MUHC approved the study (code 14-181-BMD), which was conducted according to the Declaration of Helsinki.

Outcome measures and definition of study groups

The primary study outcomes were: (1) prevalence and associated cofactors of any grade HS and significant liver fibrosis; (2) incidence and predictors of HS progression and of liver fibrosis progression. Based on a recent meta-analysis and on previous literature, any grade HS (involving >10% of hepatocytes) and severe HS (involving >66% of hepatocytes) were defined as CAP ≥248 and CAP ≥292 decibel per meter (dB/m), respectively [15, 16]. "HS progression" was defined as development of any grade HS, or transition to severe HS for those with CAP <292dB/m at baseline. "Liver fibrosis progression" was defined as development of significant liver fibrosis (stage F2-4, defined as LSM ≥7.1 kPa), or transition to cirrhosis (stage F4, defined as LSM ≥12.5 kPa) for those with LSM ≥7.1 but <12.5 kPa at baseline.[17] Secondary outcomes were prevalence of severe HS and of cirrhosis.

The study cohort was divided into two groups: (i) the prevalence cohort (whole study cohort) of 726 patients with one valid TE examination and the initial study visit between September 2013 and September 2016; (ii) the incidence cohort included 313 patients with more than one TE with CAP measurement in the same study period (Fig. 1).

Transient elastography examination

The examination was performed on a 4-hours fasting patient. Two experienced operators (>500 examinations before the study) performed 10 valid acquisitions, as previously described.[2] The standard M probe was used in all patients. The XL probe was used in case of failure with M probe and if body mass index (BMI) >30 Kg/m^2. Examinations with no successful measurements after at least 10 attempts were deemed failures. The following criteria were applied to define the result of the examination as reliable: at least

10 validated measures, an interquartile range (IQR) <30% of the median, and >60% success rate [18]. Patients with known risk factors for a false positive LSM were also excluded.[18] The thresholds for liver fibrosis were decreased by -1.5 kPa to interpret the result with the XL probe.[19]

Clinical and biological parameters

Relevant data were collected within 3 months from the TE examination. Clinical parameters included age, gender, ethnicity, BMI, history of hypertension or type 2 diabetes mellitus, risk factors for HIV infection, time since HIV diagnosis, exposure to ART. ART drugs were classified in: protease inhibitors (PIs), non-nucleoside reverse-transcriptase inhibitors (NNRTIs), nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs) and integrase inhibitors. Biological parameters included: CD4 cell count, HIV viral load (Roche Cobas Amplicor assay, Roche Diagnostics, Hoffmann-La Roche Ltd, lower limit of detection 40 copies/mL), HCV RNA (Roche Cobas Amplicor HCV Test, version 2.0, Roche Diagnostics, Hoffmann-La Roche Ltd), HCV genotype, aspartate-aminotransferase (AST), alanine-aminotransferase (ALT), platelet count, total cholesterol, low-density lipoprotein cholesterol (LDL), high-density lipoprotein cholesterol (HDL), triglycerides. Insulin resistance was determined using the homeostasis model for assessment of insulin resistance (HOMA-IR) index [fasting insulin (mIU/l) X fasting glucose (mmol/l) / 22.5].[20]

Statistical analysis

Baseline (time zero) corresponded to the first visit after September 1st, 2013 when TE examination was performed. We compared characteristics of participants at baseline by outcome status using Student's *t* test for continuous variables and Pearson's χ^2 or Fisher's exact test for categorical variables. Multivariable logistic regression models were built to identify cofactors independently associated with any grade HS and significant liver fibrosis in the prevalence cohort. Results were reported as adjusted odds ratios (aOR) with 95% confidence interval (CI). Patients in the incidence cohort were observed until September 2016 or were censored either when they died or at their last clinic visit. We estimated incidence rates of HS and liver fibrosis progression by dividing the number of participants developing the outcome by the number of person-years (PY) of follow-up. Poisson count models were used to calculate CIs for incidence rates. Kaplan-Meier plots and log-rank tests were used to illustrate time to HS and fibrosis progression. Multivariable time-dependent Cox regression models were constructed to assess predictors of HS and fibrosis progression. Results were reported as adjusted hazard ratios (aHR) with 95% CI. Robust variance estimation was used in all Cox regression analyses to account for the correlation of data contributed by the same participant at multiple visits. Multivariable models included covariates that were determined *a priori* to be clinically important, namely age, Black ethnicity, HCV co-infection status, time since HIV diagnosis, BMI, detectable HIV viral load, detectable HCV RNA, ALT, triglycerides, CAP. A complete case analysis was used for the multivariable models and the percentage of missing data was less than 15%, unless specified. All tests were 2-tailed and with a significance level of alpha=0.05. Statistical analyses were performed using STATA 13.1 (STATA Corp. LP, College Station, Texas, USA).

Results

After applying exclusion criteria (Fig. 1), 726 HIV-infected patients were included in the prevalence group. The failure rate of TE examination (19.2%) was in line with previous studies [18]. The XL probe was used in 159 (22%) cases, while the standard M probe was applied in the remaining patients. The characteristics of the prevalence (whole) cohort and of the incidence cohort are summarized in Table 1. In the prevalence cohort, alcohol consumption was distributed as follows: 208 (28.7%) were abstinent (AUDIT-C=0), 359 (49.4%) had low alcohol intake (AUDIT-C=1-3) and 159 (21.9%) had moderate alcohol intake (AUDIT-C=4-6). Most patients (92.0%) were on ART. Eleven (1.5%) and 6 (1.9%) patients were HIV/HBV and HIV/HCV/HBV co-infected, respectively. Supplemental Table 1 depicts the main characteristics of the prevalence (whole) cohort by HCV co-infection status. Among those HIV/HCV co-infected, HCV RNA was detectable in 105 cases (63.6%), while 30 (18.2%) were infected with HCV genotype 3.

Prevalence and associated cofactors of HS and liver fibrosis in the prevalence cohort

The results of the cross-sectional screening phase of the LIVEHIV Cohort are reported in Fig. 2. Overall, 264 (36.4%) and 212 (29.2%) had any grade HS and significant liver fibrosis, respectively. There was no significant difference in prevalence of any grade HS or severe HS between HIV mono-infected and HIV/HCV co-infected patients. Supplemental Fig. S1a reports the median CAP value in the prevalence cohort by HCV co-infection status. Table 2 shows the result of a multivariable analysis of cofactors associated with any grade HS and significant liver fibrosis in the prevalence cohort. After adjustments, higher BMI and triglycerides were independently associated with any grade

HS. Independent cofactors of significant liver fibrosis were higher BMI, HCV co-infection, longer time since HIV diagnosis, detectable HIV viral load, higher ALT and higher triglycerides. The adjunction of HOMA-IR to the two models did not change the result and we decide not to include it due to missingness.

Incidence and predictors of HS progression in the incidence cohort

Eighty-one (25.9%) patients from the incidence cohort were excluded from the analysis for having the outcome (severe HS) at baseline. The remaining 232 were followed for a median of 15.4 (IQR 8.5-23.0) months. Supplemental Fig. S1b reports the median CAP value in the incidence cohort by HCV co-infection status during the follow-up period. Overall, 97 (41.8%) had HS progression, accounting for an incidence rate of 29.7 per 100 PY (95% CI, 24.2–36.5). HIV mono-infected patients had higher rates of HS progression (37.8 per 100 PY, 95% CI 29.2-49.0) as compared to HIV/HCV co-infected patients (21.9 per 100 PY, 95% CI 15.6-30.7; Fig. 3a). There was no difference in rates of HS progression by detectable HCV RNA status or HCV genotype 3 (Supplemental Fig. S2a and S2b, respectively). In order to provide insights into the magnitude of HS dynamics over time, we also looked at HS progression of more than one grade and HS regression. Fig. S3a depicts changes in HS by HCV co-infection status. After adjustments, HS progression was predicted by higher baseline BMI, while anti-HCV positivity was a negative predictor (Table 3). Longer time since HIV diagnosis and higher triglycerides also appeared to be associated, but did not reach statistical significance.

Incidence and predictors of liver fibrosis progression in the incidence cohort

Thirty-nine (12.5%) patients from the incidence cohort were excluded from the analysis for having the outcome (cirrhosis) at baseline. Of the remaining 274 cases, 53 (19.3%) had fibrosis progression, accounting for an incidence rate of 12.7 per 100 PY (95% CI, 9.5–17.1). There was no significant difference in fibrosis progression in patients with and without any grade HS. However, when only HIV mono-infected patients were analyzed, presence vs. absence of any grade HS was associated with higher rates of fibrosis progression (20.4 per 100 PY, 95% CI 13.2-31.6 vs. 5.8 per 100 PY, 95% CI 2.6-13.0; Fig. 3b). Supplemental Fig. S3b and S3c depicts changes in liver fibrosis by HS status in HIV mono-infected and HIV/HCV co-infected patients, respectively. In HIV mono-infected cases, fibrosis progression was independently associated with longer time since HIV diagnosis and any grade HS at baseline (Table 4). In HIV/HCV co-infected patients, detectable HCV RNA and higher ALT were independent predictors of fibrosis progression.

Discussion

Using a large prospective cohort of consecutive HIV-infected patients undergoing a routine screening program, we found that HS diagnosed by TE with CAP is a frequent comorbidity. Contrary to previous reports, HS was not more prevalent in HIV/HCV co-infected compared to HIV mono-infected patients.[8, 9] Furthermore, HS progresses faster in HIV mono-infected than in HIV/HCV co-infected patients, particularly in those who are overweight. This finding underscores the importance of following the evolution of a liver disease over time that fosters evaluation of incidence, dynamics and predictors, rather than relying on a snapshot to characterize its epidemiology. HS predicted liver fibrosis progression in HIV mono-infected, but not in HIV/HCV co-infected patients, likely reflecting the profound pathophysiological difference (metabolic vs. virus-induced) in the fibrogenetic process between the two clinical populations.

A broad range of prevalence of HS in HIV mono-infection and HIV/HCV co-infection has been reported. Studies with low prevalence of HS (11-19%) had greater proportions of women and patients with abstinence or minimal alcohol intake.[7, 9] In contrast, studies reporting high prevalence of HS in HIV-infected patients (60-73%) included mostly male or patients who drank alcohol to excess.[6, 8] These studies were prone to selection bias since they assessed HS by liver biopsy or included only patients with elevated transaminases. Our reported prevalence of 36.1% HS in HIV mono-infection and 38.6% in HIV/HCV co-infection is in keeping with previous studies with low levels of alcohol excess and typical proportions of men (~70%) in the HIV positive population in Western countries.[3, 5, 21] Moreover, these figures are higher than the Canadian general

population, where the prevalence of HS is 20–25%.[22] Importantly, although previous studies suggested a higher prevalence of HS in HIV/HCV co-infected vs HIV mono-infected patients, in our routine screening program we did not find such a difference. Instead, our data corroborates recent findings from Price et al.[7] HS in HIV mono-infection can be induced by several postulated mechanisms, including direct viral effects on lipogenesis, long-standing exposure to ART, metabolic dysfunction and chronic inflammation.[10, 23] As for HIV/HCV co-infected patients, genotype 3 HCV infection is directly steatogenic,[24, 25] and HS improves with viral eradication.[26, 27] The mechanisms responsible for HS in non-genotype 3 HCV infection are related to metabolic factors, similarly to HIV mono-infection.[28, 29] As a confirmation of the critical role of metabolic dysfunction in inducing HS in the context of HIV-infection, the main factors associated with prevalent HS were higher BMI and triglycerides. These were also independent predictors of prevalent significant liver fibrosis, together with other expected factors, namely HCV co-infection, longer time since HIV diagnosis and higher ALT. We and others found that BMI is the main predictor of prevalent HS in HIV-infected patients,[2, 30] thus suggesting the importance of targeting normal weight. Another relevant finding of the cross-sectional phase of the LIVEHIV Cohort was that significant liver fibrosis and cirrhosis are very frequent in consecutive HIV mono-infected patients undergoing a routine screening program. Our data confirm those from smaller studies in Western countries.[2, 4] This should raise awareness among clinicians of the emerging burden of liver disease in HIV mono-infected patients due to aging, metabolic dysfunction and associated fatty liver disease.

Surprisingly, HIV mono-infected individuals had significantly higher rates of HS progression than patients with HIV/HCV co-infection. Longitudinal studies assessing incidence rates of HS in the context of HIV-infection are scarce, particularly for HIV mono-infected patients. In a study of 146 HIV/HCV co-infected patients with paired liver biopsies, progression to HS was observed in 40% of the patients over a median follow-up period of 3.3 (2.0-5.2) years, which is in line with our data.[8] However, no prospective study assessed dynamics of HS in HIV mono-infected patients. The mechanistic explanation underlying our finding is likely multifactorial. HIV mono-infected patients had different clinical characteristics at baseline as compared to HIV/HCV co-infected cases, particularly a higher frequency of metabolic dysfunction and a higher BMI, which was the strongest predictor of HS progression. Moreover, HIV/HCV co-infected patients had a different lipid profile than those HIV mono-infected, including lower levels of total, HDL and LDL cholesterol. The term "lipid paradox" has been recently coined for HIV/HCV co-infected patients, that is, despite the upregulation in HIV/HCV co-infection of proproteins which generally lead to higher serum LDL, LDL levels remain low in these patients.[31] This is likely due to the profound chronic inflammatory state characterizing HIV/HCV co-infection, which may affect the ability of the liver to synthesize lipoproteins. Finally, given that liver fibrosis progresses faster in HIV/HCV co-infected patients, a slower HS progression could be partly explained by fat loss due to higher rates of advanced fibrosis.[32] On multivariable analysis, BMI and HIV mono-infection were the only independent predictors of HS progression. The influence of BMI in HS dynamics measured by CAP has already been suggested by Macias and colleagues.[21] However, the follow-up period was shorter than in our study and most of

the included patients (74%) were HIV/HCV co-infected, so a direct comparison with HIV mono-infected individuals was not carried out.

The longitudinal phase of the study on the LIVEHIV Cohort allowed us to characterize the influence of HS upon liver fibrosis. Three other studies reported incidence rates and predictors of liver fibrosis in HIV mono-infected patients. However, they all used simple serum biomarkers, which have inferior diagnostic accuracy than TE.[18] Moreover, none of them reported the effect of HS on liver fibrosis progression.[33-35] Our data demonstrate that HS and length of exposure to HIV are independent predictors of fibrosis progression in HIV mono-infection. In contrast, HS was not related to fibrosis progression in HIV/HCV co-infected patients. Viral-induced fibrogenesis and necroinflammation had the major impact in this setting, as demonstrated by the fact detectable HCV RNA and elevated ALT were predictive of fibrosis progression. This is in keeping with previous data demonstrating that steatohepatitis, but not HS, and necroinflammation are associated with fibrosis progression in HIV/HCV co-infected patients.[8] Indeed, HIV/HCV patients derive the greatest benefit from HCV eradication with antiviral therapy.[26, 27]

Our study has several strengths. To our knowledge, it is the first prospective study that captures dynamics of HS and demonstrates its association with fibrosis progression in HIV mono-infected patients. Moreover, we included only consecutive patients as part of an ongoing screening program at our center. This study design minimizes the risk of

selection bias, which may have occurred in previous studies selecting patients with elevated transaminases.

Several limitations of our study must be acknowledged. First, we did not include controls from the general Canadian population for a direct comparison. Second, we did not include histology or MRI spectroscopy to confirm HS. However, it would not be justifiable to screen an asymptomatic population with liver biopsy. MRI spectroscopy is unsuitable for screening large cohorts and is not recommended for routine clinical use.[36] Third, TE may overestimate fibrosis in the setting of severe HS.[37] However, following correction of the small number of cases at risk of inaccuracy, there was no change in our results (data not shown). On the same line, when we perform the adjustments to CAP values suggested by Karlas *et al*, the median CAP did not change significantly and only 6% of the whole cohort increased or decreased HS grade.[16] Fourth, due to the relative short follow-up period, we were not able to study the influence of specific ART drugs on HS and liver fibrosis. Finally, we could not identify those patients with NASH, which is the evolutive counterpart of HS. Accurate non-invasive methods capable of diagnosing NASH are still lacking, and this should be a focus for future research.

In summary, this study demonstrates that HS is a frequent comorbidity in HIV-infected patients. HIV mono-infected patients have faster HS progression than those HIV/HCV co-infected. In HIV mono-infected, but not HIV/HCV co-infected patients, HS is associated with fibrosis progression. Those with a higher BMI are at particularly high risk

of HS progression and should be targeted for potential interventions. Further long-term studies to evaluate the effect of HS and liver fibrosis on clinical outcomes are warranted.

Table 1. Characteristics of the prevalence and incidence cohorts.

Variable	**Prevalence (whole) cohort** (n=726)	**Incidence cohort** (n=313)
Age (years)	50 (42-56)	50 (43-54)
Male gender (%)	547 (75.3)	240 (76.7)
Ethnicity (%)		
White/Caucasian	378 (52.1)	194 (62.0)
Black non Hispanic	232 (32.0) **	67 (21.4) **
Hispanic	73 (10.1)	25 (8.0)
South Asian	30 (4.1)	15 (4.8)
Other	13 (1.7)	12 (3.8)
MSM (%)	233 (32.1)	104 (33.2)
IDU (%)	98 (13.5) **	78 (24.9) **
HIV endemic country (%)	127 (17.5)	40 (12.8)
Diabetes (%)	182 (25.1)	88 (28.1)
Hypertension (%)	128 (17.6)	59 (18.9)
BMI (Kg/m²)	25.4 (23.0-28.6)	25.8 (22.6-28.8)
Time since HIV diagnosis (years)	13 (7-20) **	15 (8-22) **
Anti-HCV pos (%)	165 (22.7) **	140 (44.7) **
HBsAg pos (%)	23 (3.2)	15 (4.8)

HIV viral load >40 cp/mL (%)	190 (26.2) *	104 (33.2) *
CD4 count (cells/µL)	544 (373-735)	540 (356-723)
Nadir CD4 count (cells/µL)	197 (96-328)	169 (90-292)
Current ART regimen (%)		
PI	321 (44.2) *	171 (54.6) *
NNRTI	223 (30.7)	94 (30.0)
NRTI	590 (81.3)	269 (85.9)
Integrase inhibitor	202 (27.8)	70 (22.4)
Past stavudine use (%)	166 (22.9)	69 (22.0)
Past didanosine use (%)	91 (12.5)	35 (11.2)
Platelets (10^9/L)	195 (158-240)	190 (149-235)
AST (IU/L)	27 (21-37) *	31 (23-49) *
ALT (IU/L)	28 (20-44) *	35 (23-58) 8
Albumin (g/L)	41 (39-44)	41 (38-43)
HOMA-IR	2.3 (1.5-3.6)	2.4 (1.5-5.6)
Total cholesterol (mmol/L)	4.4 (3.8-5.2)	4.2 (3.7-5.1)
HDL cholesterol (mmol/L)	1.1 (0.9-1.4)	1.1 (0.9-1.3)
LDL cholesterol (mmol/L)	2.5 (1.9-3.2)	2.3 (1.7-3.0)
Triglycerides (mmol/L)	1.4 (0.9-2.2)	1.6 (1.0-2.3)
LSM (kPa)	5.3 (4.1-7.8) *	6.1 (4.7-10.6) *
CAP (dB/m)	233 (196-263) *	246 (208-284) *

Continuous variables are expressed as median (IQR) and categorical variables as numbers (%). *p <0.05; **p <0.001. The p-values refer to t test or χ^2 test between the prevalence (whole) cohort and the incidence cohort. HOMA-IR was evaluated in 335 patients of the prevalence cohort and in 183 patients of the incidence cohort.

Abbreviations: ALT, alanine aminotransferase; ART, antiretroviral therapy; AST, aspartate aminotransferase; BMI, body mass index; dB/m, decibels per meter; CAP, controlled association parameter; HCV, hepatitis C virus; HDL, high-density lipoprotein; HIV, human immunodeficiency virus; HOMA-IR, homeostasis model for assessment of insulin resistance; HS, hepatic steatosis; IDU, injection drug use; IU, international unit; LDL, low-density lipoprotein; LSM, liver stiffness measurement; MSM, men who have sex with men; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor.

Table 2. Multivariable analysis of factors associated with HS and significant liver fibrosis in the prevalence cohort (n=726).

Variable	Any grade HS		Significant liver fibrosis	
	OR	**aOR**	**OR**	**aOR**
Age (per 10 years)	1.14 (0.96-1.34)	0.98 (0.71-1.35)	1.19 (1.02-1.39) *	1.03 (0.74-1.42)
Male gender (yes vs. no)	1.47 (0.96-2.26)		1.26 (0.86-1.84)	
Black ethnicity (yes vs. no)	0.51 (0.33-0.78) *	0.86 (0.42-1.77)	0.18 (0.11-0.31) **	0.48 (0.21-1.12)
MSM (yes vs. no)	1.26 (0.86-1.83)		0.83 (0.59-1.18)	
IDU (yes vs. no)	0.78 (0.35-1.74)		4.49 (2.89-6.99) **	
Diabetes (yes vs. no)	1.79 (1.19-2.69) *	1.60 (0.84-3.03)	1.11 (0.77-1.59)	
Hypertension (yes vs. no)	1.99 (1.26-3.14) *		1.03 (0.68-1.56)	
BMI (per Kg/m^2)	1.15 (1.09-1.21) **	1.16 (1.08-1.25) **	1.03 (0.99-1.06)	1.14 (1.07-1.21) **
HCV co-infection	1.11 (0.59-2.10)	0.54 (0.16-1.79)	8.01 (5.46-11.76)	7.20 (3.67-14.12) **
Time since HIV	1.17	1.17	1.89	2.30

diagnosis (per 10 years)	(0.94-1.47)	(0.75-1.80)	(1.52-2.36) **	(1.48-3.58) **
HIV viral load >40 cp/mL (yes vs. no)	1.10 (0.67-1.51)	0.93 (0.48-1.83)	0.98 (0.68-1.42)	1.87 (1.01-3.47) *
CD4 count (per cells/µL)	1.00 (0.99-1.00)		1.00 (0.99-1.00)	
Currently on PI (yes vs. no)	1.19 (0.83-1.72)		1.41 (1.03-1.92) *	1.41 (0.82-2.41)
Currently on NNRTI (yes vs. no)	0.76 (0.52-1.11)		0.68 (0.47-0.97) *	
Currently on NRTI (yes vs. no)	0.52 (0.34-0.81) *	0.41 (0.15-1.14)	0.63 (0.43-0.94) *	
Currently on Integrase inhibitor (yes vs. no)	1.17 (0.80-1.71)		0.84 (0.59-1.21)	
Platelets (per 10^9/L)	1.00 (0.99-1.00)		0.99 (0.98-0.99) **	
ALT (per 10 IU/L)	1.08 (1.01-1.15) *	1.08 (0.95-1.22)	1.32 (1.23-1.41) **	1.13 (1.04-1.24) *
HOMA-IR (per unit)	1.03 (0.94-1.13)		1.11 (1.04-1.18) *	
HDL cholesterol (per mmol/L)	0.33 (0.18-0.60) **		0.25 (0.15-0.44) **	
Triglycerides (per mmol/L)	1.39 (1.17-1.64) **	1.43 (1.09-1.89) *	1.24 (1.10-1.41) *	1.32 (1.07-1.64) *

Odds ratios (OR) and 95% confidence intervals are shown for each variable analyzed in univariable and multivariable logistic regression analysis. *p <0.05; **p <0.001. HOMA-IR was evaluated in 335 patients.

Abbreviations: ALT, alanine aminotransferase; BMI, body mass index; HCV, hepatitis C virus; HDL, high-density lipoprotein; HIV, human immunodeficiency virus; HOMA-IR, homeostasis model for assessment of insulin resistance; HS, hepatic steatosis; IDU, injection drug use; IU, international unit; MSM, men who have sex with men; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; aOR, adjusted odds ratio; PI, protease inhibitor.

Table 3. Multivariable analysis of predictors of HS progression in the incidence cohort after exclusion of 81 patients with severe HS at baseline.

Variable	Unadjusted HR	aHR
Age (per 10 years)	1.06 (0.86-1.31)	1.12 (0.84-1.50)
Black ethnicity (yes vs. no)	1.36 (0.82-2.23)	1.08 (0.54-2.16)
BMI (per Kg/m^2)	1.09 (1.04-1.14) **	1.09 (1.03-1.17) *
Time since HIV diagnosis (per 10 years)	1.01 (0.86-1.18)	1.16 (0.99-1.37)
HCV co-infection (yes vs. no)	0.55 (0.36-0.85) *	0.51 (0.27-0.96) *
HIV viral load >40 cp/mL (yes vs. no)	1.00 (0.57-1.77)	1.07 (0.51-2.27)
ALT (per 10 IU/L)	1.01 (0.96-1.06)	1.04 (0.97-1.11)
Triglycerides (per mmol/L)	1.17 (1.02-1.33) *	1.15 (0.96-1.38)
Baseline CAP (per 10 dB/m)	1.08 (1.03-1.14) *	1.03 (0.97-1.10)

Hazard ratios (HR) and 95% confidence intervals are shown for each variable analyzed in multivariable Cox regression analysis. *$p < 0.05$; **$p < 0.001$.

Abbreviations: ALT, alanine aminotransferase; BMI, body mass index; CAP, controlled attenuation parameter; dB/m, decibel/meter; HIV, human immunodeficiency virus; HCV, hepatitis C virus; aHR, adjusted hazard ratio; IU, international unit.

Table 4. Multivariable analysis of predictors of liver fibrosis progression by HCV co-infection status in the incidence cohort after exclusion of 39 patients with cirrhosis at baseline.

Variable	Unadjusted HR	aHR
HIV mono-infected		
Black ethnicity (yes vs. no)	0.58 (0.19-1.76)	0.90 (0.22-3.70)
BMI (per Kg/m^2)	1.03 (0.92-1.15)	0.96 (0.84-1.09)
Time since HIV diagnosis (per 10 years)	1.52 (1.29-1.78) **	1.43 (1.02-2.12) *
HIV viral load >40 cp/mL (yes vs. no)	1.72 (0.51-5.86)	1.31 (0.30-5.69)
ALT (per 10 IU/L)	1.02 (1.01-1.03) *	1.20 (0.96-1.47)
Any grade HS (yes vs. no)	3.90 (1.62-9.37) *	4.18 (1.21-14.5) *
HCV co-infected		
Time since HIV diagnosis (per 10 years)	0.64 (0.31-1.33)	0.85 (0.42-1.74)
HIV viral load <40 cp/mL (yes vs. no)	1.99 (0.66-6.00)	1.89 (0.57-6.25)
Detectable HCV RNA (yes vs. no)	11.3 (2.51-50.8) *	5.98 (1.28-27.9) *

ALT (per 10 IU/L)	1.01 (1.00-1.01) **	1.05 (1.00-1.09) *
Any grade HS (yes vs. no)	0.51 (0.17-1.54)	0.79 (0.22-2.81)

Hazard ratios (HR) and 95% confidence intervals are shown for each variable analyzed in multivariable Cox regression analysis. *p <0.05; **p <0.001.

Abbreviations: HS, hepatic steatosis; ALT, alanine aminotransferase; BMI, body mass index; HCV, hepatitis C virus; HIV, human immunodeficiency virus; aHR, adjusted hazard ratio; IU, international unit.

Figure legends

Figure 1. Flow chart displaying the selection of study participants and the two study cohorts (prevalence and incidence).

Figure 2. Prevalence of hepatic steatosis (HS) and liver fibrosis in the cross-sectional screening phase of the LIVEHIV Cohort (prevalence cohort) by HCV co-infection status. **p <0.001. The p-values refer to χ^2 test between HIV mono-infected and HIV/HCV co-infected patients.

Figure 3. a) Hepatic steatosis (HS) progression in the incidence cohort by HCV co-infection category (HIV mono-infection vs. HIV/HCV co-infection); b) Liver fibrosis progression in HIV mono-infected patients by any grade HS category (present vs. absent). The p-values refer to log-rank test.

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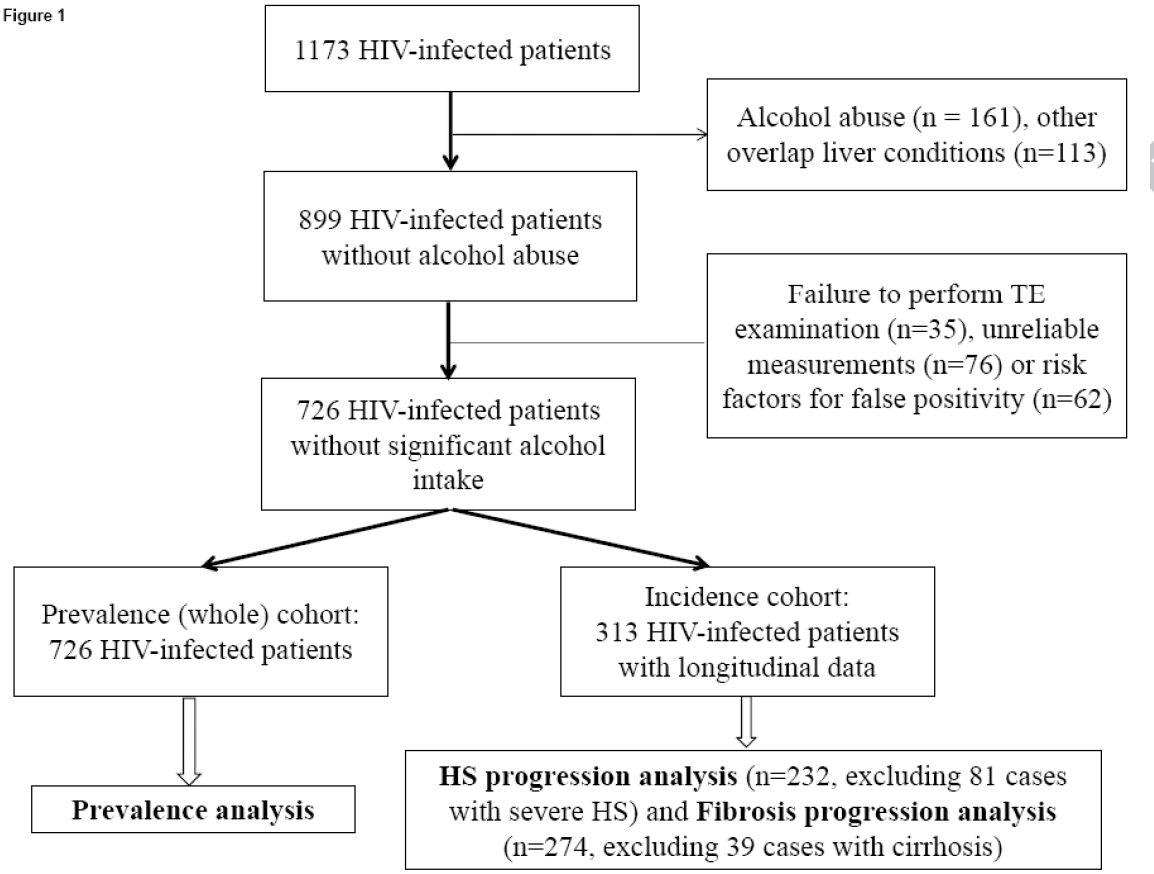
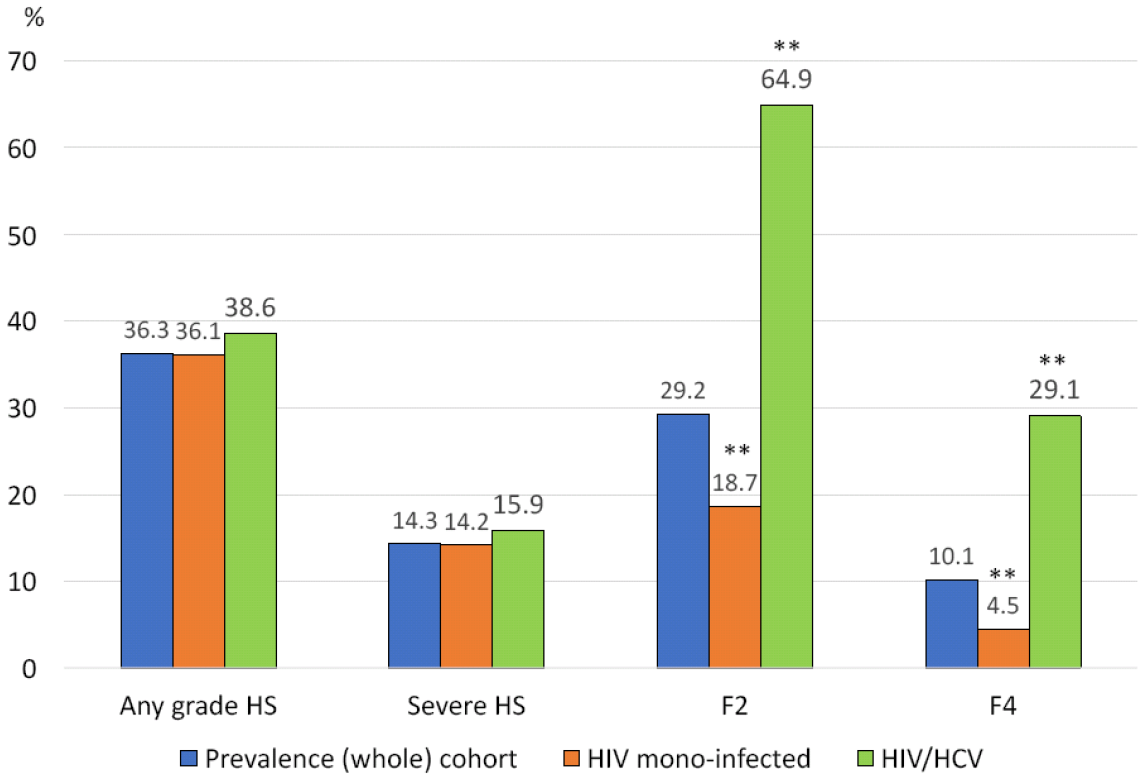
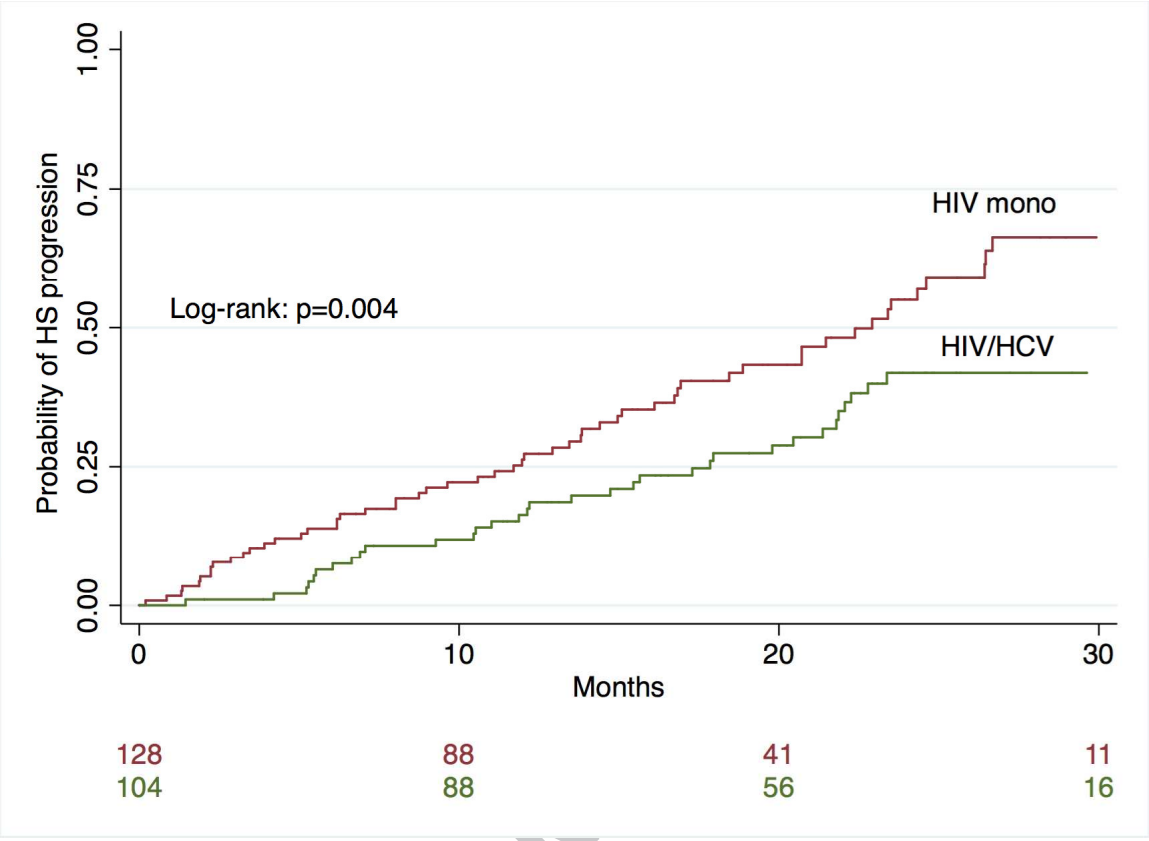
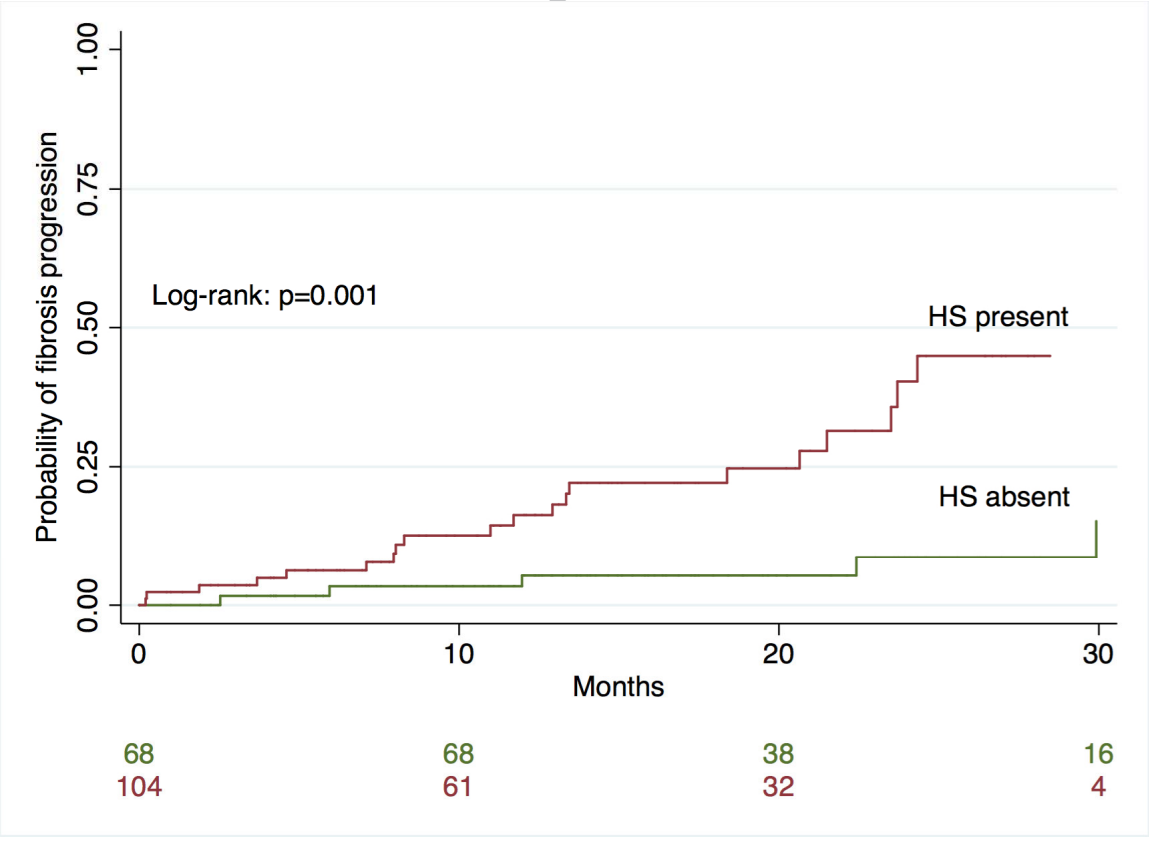
Figure 1






Probability of HS progression
0.00
0.25
0.50
0.75
1.00
Log-rank: p=0.004
HIV mono
HIV/HCV
0
10
20
30
Months
128 88 41 11
104 88 56 16


Probability of fibrosis progression
0.00
0.25
0.50
0.75
1.00
Log-rank: p=0.001
HS present
HS absent
0
10
20
30
Months
68 68 38 16
104 61 32 4

Highlights

- We investigated epidemiology of hepatic steatosis and fibrosis in HIV infected people
- Hepatic steatosis is common in both HIV mono-infection and HIV/HCV co-infection
- Hepatic steatosis progresses faster in HIV mono-infection than HIV/HCV co-infection
- In HIV mono-infection, hepatic steatosis drives fibrosis progression
- In HIV/HCV co-infection, HCV drives fibrosis progression