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Liver-related events in HIV-infected persons with occult cirrhosis

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Abstract:	Background Human immunodeficiency virus (HIV)-infected patients are at increased risk of liver-related mortality. The effect of occult cirrhosis (OcC), defined as preclinical compensated cirrhosis without any clinical findings, on liver-related events is unknown. Methods HIV-infected patients from two Canadian cohorts underwent transient elastography (TE) examination and were classified as: 1) OcC (TE ≥13 kPa with no sign of cirrhosis, including absence of thrombocytopenia and signs of advanced liver disease on ultrasound or gastroscopy); 2) overt cirrhosis (OvC) (TE ≥13 kPa with signs of cirrhosis); 3) non-cirrhotic patients (TE <13 kPa). Incidence and risk factors of liver-related events were investigated through Kaplan-Meier and Cox regression analyses, respectively. We estimated monitoring rates according to screening guidelines for hepatocellular carcinoma (HCC) by OcC and OvC status. Results 1092 HIV-infected patients (51% coinfected with hepatitis C virus) were included. Prevalence of OcC and OvC at baseline was 2.7% and 10.7%, respectively. During a median follow-up of 1.8 (interquartile range: 1.5– 2.8) years, the incidence of liver-related events in non cirrhotics, OcC, and OvC was 3.4 (95% confidence interval [CI]: 1.2-7.3), 34 (95% CI: 6-104), and 37 (95% CI: 16.95-69.05) per 1000 person-years, respectively. Baseline OcC (adjusted hazard ratio [aHR]: 7.1, 95% CI: 1.3-38) and OvC (aHR: 8.5, 95% CI: 2.8-26) were independently associated with liver-related events.

	Monitoring rates for HCC were lower in patients with OcC (24%) compared to those with OvC (40%). Conclusions HIV-infected patients with OcC have a high incidence of liver-related events. Greater surveillance and earlier recognition with appropriate screening strategies is necessary for improved outcomes.
Response to Reviewers:	A point-by-point reply to the editor's and reviewers' comments is provided in the attached cover letter.

Liver-related events in HIV-infected persons with occult cirrhosis

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Short title: Occult Cirrhosis in HIV

Summary: Occult cirrhosis affects 2.7% of HIV-infected patients, representing 20% of all cirrhosis cases. HIV-infected patients with occult cirrhosis have the same risk of liver-related events as those with clinically overt cirrhosis. HIV-infected patients with occult cirrhosis should receive greater surveillance for hepatocellular carcinoma.

Abstract

Background

Human immunodeficiency virus (HIV)-infected patients are at increased risk of liver-related mortality. The effect of occult cirrhosis (OcC), defined as preclinical compensated cirrhosis without any clinical findings, on liver-related events is unknown.

Methods

HIV-infected patients from two Canadian cohorts underwent transient elastography (TE) examination and were classified as: 1) OcC (TE ≥13 kPa with no sign of cirrhosis, including absence of thrombocytopenia and signs of advanced liver disease on ultrasound or gastroscopy); 2) overt cirrhosis (OvC) (TE ≥13 kPa with signs of cirrhosis); 3) non-cirrhotic patients (TE <13 kPa). Incidence and risk factors of liver-related events were investigated through Kaplan-Meier and Cox regression analyses, respectively. We estimated monitoring rates according to screening guidelines for hepatocellular carcinoma (HCC) by OcC and OvC status.

Results

1092 HIV-infected patients (51% coinfected with hepatitis C virus) were included. Prevalence of OcC and OvC at baseline was 2.7% and 10.7%, respectively. During a median follow-up of 1.8 (interquartile range: 1.5– 2.8) years, the incidence of liver-related events in non cirrhotics, OcC, and OvC was 3.4 (95% confidence interval [CI]: 1.2-7.3), 34.0 (95% CI: 6.0-104.0), and 37.0 (95% CI: 17.0-69.1) per 1000 person-years, respectively. Baseline OcC (adjusted hazard ratio [aHR]: 7.1, 95% CI: 1.3-38.0) and OvC (aHR: 8.5, 95% CI: 2.8-26.0) were independently associated with liver-related events. Monitoring rates for HCC were lower in patients with OcC (24%) compared to those with OvC (40%).

Conclusions

HIV-infected patients with OcC have a high incidence of liver-related events. Greater surveillance and earlier recognition with appropriate screening strategies is necessary for improved outcomes.

Keywords: HIV, occult cirrhosis, transient elastography, liver-related events, HCC surveillance.

Introduction

Liver disease is the leading cause of non-AIDS related deaths in people living with the human immunodeficiency virus (HIV)[1]. HIV-infected individuals have multiple risk factors for liver injury, including coinfections with hepatitis C (HCV) and B (HBV) viruses, metabolic conditions triggering non-alcoholic fatty liver disease (NAFLD), excessive alcohol intake, and antiretroviral therapy (ART) inducing hepatotoxicity[2, 3]. This hypothetical multi-hit process can then lead to cirrhosis, hepatocellular carcinoma (HCC), and complications associated with end-stage liver disease (ESLD) such as ascites, hepatic encephalopathy, and variceal bleeding[4]. Up to 63% of patients with liver disease are diagnosed with liver cirrhosis only at the first episode of hepatic decompensation[5]. Therefore, identifying patients with underlying liver cirrhosis is critical as surveillance for HCC and esophageal varices can be promptly initiated[6].

A major obstacle to the diagnosis of cirrhosis at the preclinical stage, also known as occult cirrhosis (OcC), is the lack of any clinical, laboratory and imaging findings. Patients with OcC do not have thrombocytopenia and have no features consistent with cirrhosis on imaging. Nonetheless, OcC is identified in up to 12% of patients referred for transient elastography (TE) examination and it accounts for up to 37% of all cirrhosis cases[7, 8]. HIV-negative patients with OcC are at risk of developing ESLD events, but they receive suboptimal surveillance for HCC when compared to patients with clinically overt cirrhosis (OvC)[7-9].

Liver biopsy is the gold standard for the diagnosis of liver cirrhosis but it is invasive and prone to sampling errors leading to the misdiagnosis of cirrhosis[10-12]. As such, it is unpractical as a screening tool or for the follow-up of HIV-infected patients, where the prevalence of liver

disease is high[13]. The measurement of liver stiffness (LSM) by TE is a validated non-invasive method to diagnose liver cirrhosis, with a reported area under the curve of 0.94[14]. TE is superior to simple fibrosis biomarkers, including the aspartate to platelet ratio index (APRI) and the fibrosis-4 score (FIB-4), in HIV-infected patients infected[15-17].

Thus far, the prevalence of OcC in HIV-infected patients and its impact on incident liver-related events has not been reported. We used data from two large clinical Canadian cohorts to fulfill the following aims: (i) determine the prevalence and associated factors of OcC diagnosed by TE; (ii) evaluate the incidence of liver-related events in patients with OcC; and (iii) investigate monitoring rates, according to guidelines, for screening of HCC in patients with OcC.

Patients and methods

Study design and population

We conducted a retrospective analysis of the Canadian Coinfection Cohort (CCC) and the LIVEr in HIV (LIVEHIV) studies[18, 19]. The CCC is a prospective cohort of patients co-infected with HIV and HCV enrolled at 18 centres across Canada where they are followed-up every 6 months since 2003. Centres participating in the FibroScan sub-study assessed LSM by TE examination every 6 months. The LIVEHIV Cohort is a prospective screening program for NAFLD and liver fibrosis established in 2013 at McGill University Health Centre (MUHC), Montreal, Canada. All patients underwent screening for liver disease with yearly TE examination.

Ethics

All participants provided informed written consent. The Research Ethics Board of the Research Institute of MUHC approved the study (code 14-182-BMD and 2006-1875), which was conducted according to the Declaration of Helsinki.

Eligibility

All consecutive HIV-infected adults aged ≥18 years were eligible. Patients in the CCC who were enrolled in centres not participating in the FibroScan sub-study were excluded. Patients with failure of TE examination or unreliable LSM were also excluded.

Clinical and biological parameters

Data collected included demographic information, HIV and medications history, body mass index (BMI), history of type 2 diabetes mellitus[20], liver biochemistries, hematological and

virological parameters. Alcohol intake was measured by the Alcohol Use Disorders Identification Test (AUDIT-C) questionnaire, with a score ≥4 for men and ≥3 for women considered as hazardous alcohol intake[21]. The following fibrosis biomarkers were computed: APRI (with a cut-off value ≥2 suggesting liver cirrhosis); FIB-4 (with a cut-off value ≥3.25 suggesting advanced liver fibrosis)[17, 22]. Results of abdominal imaging and gastroscopies were recorded.

TE examination

The TE examination was performed in patients fasting for at least 3 hours. The standard M probe was used in all patients. The XL probe was used in cases of failure of TE with the M probe or if the BMI was greater than 30 kg/m^2. The following criteria were applied to define the result of TE as reliable: at least 10 validated LSM, and an interquartile range (IQR) <30% of the median LSM[23]. Hepatic steatosis measurement by controlled attenuation parameter (CAP) was available in the LIVEHIV Cohort. Any grade hepatic steatosis (>5% of hepatocytes) was defined as CAP ≥288 decibels per meter (dB/m)[24].

Definition of study groups

Patients were divided into four mutually exclusive subgroups. Patients with OcC had LSM ≥13 kPa (10.1 kPa with the XL probe[25]) and no evidence of advanced liver disease or portal hypertension, namely absence of: thrombocytopenia (<140 x 10^9/L), cirrhosis on abdominal imaging (liver nodularity, enlarged caudate lobe, splenomegaly ≥14 cm), esophageal varices or hypertensive portal gastropathy on gastroscopy, and ascites. Patients with OvC had LSM ≥13 kPa with evidence of advanced liver disease or portal hypertension, as listed above. Patients

classified as non-cirrhotic had LSM <13 kPa and no evidence of advanced liver disease or portal hypertension. Finally, patients classified as non-cirrhotic portal hypertension had LSM <13 kPa and evidence of advanced liver disease or portal hypertension. The 13 kPa cut-off has been chosen based on a meta-analysis[14].

Outcome measures

Liver-related events were prospectively collected by means of a dedicated outcome measures form. Liver-related events included occurrence of *de novo* ascites, variceal bleeding or banding, spontaneous bacterial peritonitis, hepatorenal syndrome, hepatic encephalopathy, HCC, liver transplantation, and death from liver-related causes. Screening interval for HCC was defined as receiving abdominal imaging at least every 12 months during the study period[26, 27].

Follow-up

Patients were followed from their first TE examination (baseline, or time zero) until they had a liver-related event, died, withdrew consent, were lost to follow-up (no visits for more than 1.5 years), or until administrative censoring (March 31, 2017 for the CCC and on January 14, 2017 for the LIVEHIV cohort). Non liver-related deaths were censored. The decision to initiate surveillance for HCC was left to the treating physician.

Statistical analysis

Cross-sectional component

The period prevalence was reported as the ratio of the total number of prevalent and incident cases to the total number of patients included in the study. The association between various risk

factors at inclusion and prevalent or incident OcC – among patients at risk for OcC - were assessed using a cross-sectional approach with unadjusted and adjusted logistic regression models. We reported results as adjusted odds ratios (aOR). Due to the cross-sectional nature of any such measured associations, we made no causal claims from these analyses.

Longitudinal component

Kaplan-Meier plots were used to show the cumulative incidences over time, as stratified by study group and coinfection status, using the log-rank test to test for differences between groups. The association between various risk factors and the incidence of *de novo* liver-related events were assessed with unadjusted and adjusted Cox proportional hazards models. Results were reported as adjusted hazard ratios (aHR) with 95% confidence intervals (CI). Finally, as an exploratory analysis, the proportion of patients – among those at risk for HCC – with adequate cirrhosis surveillance were reported descriptively and stratified by study group. The same analysis was stratified by source cohort and by HCV coinfection status. A two-sided level of significance of 5% was used for all statistical inferences.

Covariates

All adjusted regression models included covariates that were determined a priori to be clinically important; this list was further restricted due to limited event counts. The following baseline covariates were chosen: age, sex, aboriginal ethnicity, hazardous alcohol intake in past year, BMI, diabetes in past year, lipid lowering therapy in past year, nadir CD4 count, detectable HIV RNA in past year, HCV RNA positive, HIV duration and ART duration. Where multiple models were estimated for the same outcome, the model with the best goodness-to-fit measure, based on the Akaike Information Criteria (AIC), was chosen.

Results

After applying the inclusion and exclusion criteria, 1092 HIV-infected individuals were included, of whom 499 were HIV monoinfected, 556 were HIV/HCV coinfected and 37 were HIV/HBV coinfected (Figure 1). Failed or unreliable LSM comprised 7.0% of patients from the CCC and 5.8% of patients from the LIVEHIV cohort.

Prevalence, incidence and factors associated with occult cirrhosis

OcC and OvC represented 2.7% and 10.7% of our study population, respectively. OcC patients represented 19.9% of all patients with cirrhosis. The main characteristics by study group status at baseline are presented in Table 1. Figure 2 and Supplemental Table S1 report the distribution of study groups and the main characteristics by HCV and HBV coinfection status, respectively. The prevalence of OcC increased during the study period with 14 new cases, for an overall pooled period prevalence of 3.9%. Furthermore, over a median follow-up time of 1.8 (IQR: 1.5–2.8) years, the incidence rate of OcC was 10.0 (95% CI: 5.7–16.3) per 1000 person-years (PY). HIV monoinfected patients showed similar incidence of OcC compared to HCV coinfected patients. Conversely, those coinfected with HCV were more likely to develop OvC during follow-up compared to monoinfected patients (Figure 3a and 3b). Logistic regression identified HIV duration as an independent factor associated with the presence of OcC as compared to non-cirrhotic patients (aOR 1.44, 95% CI: 1.18-1.77) (Table 2). We also observed a tendency for higher BMI to be a factor associated with OcC.

Incidence and risk factors of liver-related events

The overall incidence of liver-related events was 8.6 (95% CI: 4.9–14.0) per 1000 PY, mainly driven by the occurrence of *de novo* ascites and HCC (Table 3). The incidence rate of liver-related events was similar between patients with OcC and OvC (Table 3; Figure 3c). Conversely, non-cirrhotic patients had a very low incidence of liver-related events, while patients with non-cirrhotic portal hypertension had an intermediate incidence. HCV coinfection showed a tendency to be associated with an increased incidence of liver-related events (Figure 3d). The presence of OcC and OvC at baseline, as well as longer HIV duration, were independent risk factors for liver-related events, with aHR of 7.12 (95% CI: 1.33-37.99), 8.5 (95% CI: 2.83-25.53), and 1.37 (95% CI: 1.09-1.73) respectively (Table 4).

Surveillance for HCC

Patients with OcC received 0.70 (95% CI: 0.51-0.92) abdominal imaging visits per PY, compared to 0.87 (95% CI: 0.76-0.98) for those with OvC. Furthermore, the monitoring rate of HCC according to screening guidelines[26, 27] was 24% (95%: CI 10-44) and 40% (95%: CI 30-49) in those with OcC and OvC, respectively (p=0.06, Supplemental Table S2). In patients with at least one HCC screening imaging, the annual rate of imaging was 0.97 (95% CI: 0.72-1.28) and 1.33 (95% CI: 1.16-1.51) per patient in those with OcC and OvC, respectively. One patient (HIV/HBV coinfected) with OcC developed HCC during the follow-up, accounting for an incidence of 15 per 1000 PY. At diagnosis, there were two lesions consistent with HCC, with the largest one measuring 6 cm and the smaller one 3 cm. This tumor was beyond any transplant criteria, including Milan Criteria, total tumor volume, Up-to-Seven, and UCSF criteria[28]. The patient was offered TACE and Sorafenib but declined. He died 7.8 months after the diagnosis. In

the OvC group, the 3 patients who developed HCC were HIV/HCV coinfected and were diagnosed at an earlier stage (single lesion ranging from 1.7 to 3.2 cm). They were offered transarterial chemoembolization (n=1) or liver transplant (n=2) and are still alive.

Discussion

In this well-characterized clinical cohort, we showed that OcC is a frequent occurrence, representing nearly 20% of all patients with liver cirrhosis in HIV-infected individuals. We also showed that liver-related events had similar incidence rates in HIV-infected patients with OcC and OvC, rendering essential for the HIV clinician to be aware of this clinical entity. Finally, patients with OcC do not receive screening at recommended intervals for detection of important ESLD complications, specifically HCC, which may result in a late diagnosis.

Until recently, the description of a liver as "cirrhotic" was sufficient to define patients' prognosis. Garcia-Tsao *et al* suggested that cirrhosis is rather a dynamic condition encompassing a more complex clinicopathological spectrum[29]. Given the lack of any clinical sign, patients at the preclinical stage of compensated cirrhosis represent a diagnostic challenge for clinicians, and often remain undiagnosed. The diagnosis of OcC based on LSM and the absence of clinical signs has previously been shown, in different patient populations, to be an indicator of poor prognosis[7, 9]. Individuals living with HIV are known to be at increased risk of liver cirrhosis and ESLD[1]. Our study is the first to report on the prevalence of OcC and its impact on liver-related events in HIV-infected patients.

In our large combined cohort of 1092 HIV-infected patients, OcC was found in 2.7% of cases, prevalence similar to that reported in other populations[7, 9]. Although seemingly comprising only a small proportion of patients at baseline TE, the prevalence of OcC increased to 3.9% during the follow-up period, with an annual incidence rate of 10 per 1000 PY. These changes in LSM may herald a poor prognosis, as reported in other patient populations[30-32].

The only independent factor associated with OcC at baseline vs. non-cirrhotic subgroup was longer duration of HIV infection, which is a proxy for exposure to multiple hepatotoxic hits[18]. Interestingly, HCV coinfection was not associated with an increased prevalence or incidence of OcC, but rather with the development of OvC. This could be explained by either a faster progression of HCV coinfected patients from earlier stage of liver disease to OvC[33] or because they are more frequently monitored with TE, and thus diagnosed more often. Higher BMI had a trend in being an independent risk factor for OcC, thus confirming the emerging concern around NAFLD in HIV-infected patients[18, 34]. Accordingly, hepatic steatosis diagnosed by CAP had the highest frequency in the OcC group (27%). Taken together, our findings suggest that clinicians should suspect OcC in patients with longer HIV infection and higher BMI even in absence of any sign of liver cirrhosis. Moreover, screening for liver cirrhosis should not be limited to HIV patients coinfected with HCV, as multiple risk factors may still be driving progressive liver fibrosis and we would miss important opportunities to prevent liver decompensation.

Patients with OcC were more likely to develop a liver-related event when compared to patients without cirrhosis, with a 10 times higher incidence rate. On the other hand, the incidence of a liver-related event was similar between those with OcC and OvC. Our findings are similar to a previous study by Merchante and colleagues where patients with cirrhosis had an incidence of hepatic decompensation of 46 per 1000 person-years[32]. Similarly, Macias *et al* reported that patients with LSM below 14.6 kPa have a lower risk of decompensation[35]. However, these studies did not differentiate between patients with and without clinical evidence of liver

cirrhosis. Furthermore, they only included HIV/HCV coinfected cases, so information about dynamics and evolution of OcC in HIV monoinfected patients was missing. In our study, the diagnosis of OcC at baseline was independently associated with the development of liver-related events. These findings underline that HIV-infected patients with OcC, whether or not HCV coinfected, constitute a group of patients beyond the traditional subset of patients with OvC, who are at high-risk of liver-related events.

Despite a high incidence of liver-related events, our cohort study shows that HIV-infected patients with OcC appear to be less frequently monitored with abdominal ultrasounds when compared to those with OvC. Guidelines advocate regular screening ultrasounds for HCC in patients with a known diagnosis of cirrhosis and in HBV/HIV coinfected patients. Adherence to HCC screening guidelines remains low in HIV-infected patients, with reported rates between 20% and 35%[36, 37]. Under recognition of cirrhosis at its preclinical stage, lack of awareness of liver-related complications, and potential patient-related factors may explain this low adherence[36]. Importantly, HIV-infected patients with HCC have a shorter expected survival when compared to HIV negative[38, 39]. Our findings suggest that HIV-infected patients should be screened for OcC with non-invasive diagnostic tools, such as TE, and that those with OcC should be considered for HCC surveillance.

Our study has several strengths. To our knowledge, it is the first study characterizing risk factors and dynamics of liver cirrhosis in its preclinical stage in HIV-infected patients. It relies on two prospectively maintained large cohorts of consecutive individuals living with HIV. We employed an accurate and validated non-invasive tool to diagnose liver cirrhosis[13, 40]. We wish to

acknowledge several limitations of our study. First, although we included a large number of patients, the follow-up period was relatively short. We observed a limited number of clinical outcomes and thus our estimates of incidence rates are imprecise. However, our findings showed that OcC patients behave as those with OvC in case of HIV infection. Second, because a cross-sectional approach was used to determine factors associated with OcC, no inferential conclusions can be derived. However, these associated factors could help identify who might be prioritized for screening. Third, we did not have data about the indication for ultrasound, which could have been performed for reasons other than HCC screening. Fourth, there is a potential for competing risk from death from other causes. Fifth, liver biopsy was not available in our study. However, we validated our findings longitudinally by demonstrating that OcC group had worse clinical outcomes than the non-cirrhotic group. Using liver biopsy in our cohort of more than 1,000 patients would not have been feasible.

In conclusion, OcC accounts for 1 in 5 cases of cirrhosis in HIV-infected patients. These patients, whether HCV coinfected or not, constitute a high-risk group prone to liver-related events. We advocate that HIV-infected patients with OcC should receive surveillance for HCC to the same degree as patients with OvC. Screening for cirrhosis with point of care non-invasive diagnostic tools, such as TE, should be considered in HIV-infected patients, especially in case of long duration of HIV infection and higher BMI.

Authors contributions

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

Disclaimer

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Conflict of interest

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 Réseau sida et maladies infectieuses du FRQ-S, National Institutes of Health, Merck, Gilead, and ViiV Healthcare, outside the submitted work. MD has served as an advisory board member for Merck, Janssen,

and Gilead. PW has acted as consultant for BMS, Gilead, Merck, Novartis. GS has received speaker fees from Merck, BMS, Gilead, Abbvie, and ViiV; served as an advisory board member for Merck, BMS, and Novartis; and has received research funding from Merck, ViiV, and Echosens. AB, TP, AH have nothing to disclose.

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Table 1. Patient characteristics at baseline by study group status (n=1092).

	Non-cirrhotic (n=795)	**Occult cirrhosis** (n=29)	**Overt cirrhosis** (n=117)	**Non-cirrhotic portal hypertension** (n=151)	**p**
Follow-up time (years)	1.53 (1.44-2.60)	2.62 (1.50-2.96)	2.48 (1.55-3.09)	2.36 (1.50-2.96)	<0.001
Age (years)	48.7 (40.7-54.8)	50.5 (45.2-54.8)	52.6 (48.1-57.5)	51.5 (45.6-56.6)	<0.001
Female (%)	206 (26)	8 (28)	25 (21)	37 (25)	0.742
MSM (%)	258 (32)	14 (48)	51 (44)	54 (36)	0.04
Ethnicity (%)					
Caucasian	339 (43)	15 (52)	88 (75)	97 (64)	<0.001
Black	166 (21)	3 (10)	9 (8)	15 (10)	<0.001
Latino	58 (7)	1 (3)	0	6 (4)	0.01
Asian	20 (3)	3 (10)	3 (3)	3 (2)	0.073
Indigenous	125 (16)	5 (17)	12 (10)	17 (11)	0.251
Unknown	93 (12)	3 (10)	5 (4)	15 (10)	0.111
BMI (Kg/m^2)	25.1 (22.7-28.4)	26.8 (24.1-30.7)	25.2 (22.1-27.5)	24.3 (21.0-26.8)	0.005
Obesity (BMI>30) (%)	106 (13)	6 (21)	15 (13)	12 (8)	0.17

Hazardous alcohol intake (%)	104 (13)	4 (14)	23 (20)	33 (22)	0.02
Active tobacco smoker (%)	266 (33)	11 (38)	62 (53)	80 (53)	<0.001
Active IDU (%)	197 (25)	5 (17)	44 (38)	64 (42)	<0.001
HIV duration (years)	11 (6-19)	19 (14-26)	19 (12-24)	16 (9-22)	<0.001
CD4 nadir (cells/μL)	209 (99-350)	121 (28-290)	153 (89-277)	180 (105-302)	0.039
CD4 cell count (cells/μL)	514 (340-720)	526 (416-673)	406 (272-606)	536 (367-719)	0.004
HIV viral load in $\log_{10}$ (units)	1.59 (1.59-1.63)	1.59 (1.59-1.60)	1.59 (1.59-1.59)	1.59 (1.59-1.59)	0.434
Undetectable HIV viral load (≤ 50 copies) (%)	590 (74)	22 (76)	90 (77)	118 (78)	0.949
Duration of ART (years)	7.2 (3.2-12.9)	11.4 (4.6-15.8)	11.1 (5.9-17.2)	9.0 (4.8-16.2)	<0.001
Current ART used (%)	655 (82)	20 (69)	103 (88)	134 (89)	0.019
NRTI	617 (78)	19 (66)	97 (83)	123 (81)	0.147
NNRTI	212 (27)	6 (21)	30 (26)	31 (21)	0.410

PI	329 (41)	10 (34)	49 (42)	71 (47)	0.501
Integrase inhibitors	237 (30)	8 (28)	44 (38)	59 (39)	0.066
Other	59 (7)	1 (3)	7 (6)	11 (7)	0.818
Exposure to Didanosine (mean years±SD)	0.26 ± 1.58	0.32 ± 1.17	0.26 ± 1.55	0.37 ±1.49	0.648
Exposure to Stavudine (mean years±SD)	0.56 ± 1.95	0.29 ± 0.95	0.23 ± 1.09	0.69 ± 2.26	0.266
HCV coinfection (%)	337 (42)	18 (62)	99 (85)	102 (68)	<0.001
HBsAg pos (%)	16 (2)	1 (3)	6 (5)	14 (9)	<0.001
Hypertension (%)	125 (16)	9 (31)	25 (21)	24 (16)	0.082
Diabetes (%)	145 (18)	7 (24)	27 (23)	31 (21)	0.526
INR	1.00 (0.93-1.03)	1.02 (1.00-1.13)	1.09 (1.00-1.15)	1.00 (0.98-1.07)	<0.001
Platelets (10^9/L)	212 (182-259)	208 (171-241)	130 (98.8-189)	133 (113-180)	<0.001
Total cholesterol (mmol/L)	4.5 (3.8-5.2)	3.8 (3.5-4.5)	3.9 (3.1-4.4)	4.1 (3.6-4.9)	<0.001
LDL cholesterol (mmol/L)	2.6 (2.0-3.2)	1.7 (1.2-2.7)	2.0 (1.5-2.5)	2.3 (1.8-2.8)	<0.001

HDL cholesterol (mmol/L)	1.2 (1.0-1.4)	0.9 (0.7-1.2)	1.1 (0.9-1.3)	1.1 (0.9-1.3)	<0.001
Triglycerides (mmol/L)	1.3 (0.9-2.0)	1.7 (1.1-2.5)	1.3 (0.9-1.7)	1.3 (0.9-2.1)	0.300
Creatinine (µmol/L)	80 (68-93)	78.0 (66.0-104)	82.5 (68.8-94.8)	77 (68-89)	0.794
Insulin (pmol/L)	75 (47-137)	148 (112-262)	92 (60-190)	66 (42-145)	<0.001
ALT (IU/L)	29 (20-47)	41 (29-84)	45 (29-79)	33 (20-52)	<0.001
AST (IU/L)	28 (21-39)	46 (29-55.2)	51 (32-80)	32 (23-48)	<0.001
Total bilirubin (µmol/L)	10 (7-15)	12 (9.35-18.5)	14 (9-20.1)	11 (8-17)	<0.001
Albumin (g/L)	41 (39-44)	41 (37-44)	40.5 (36.2-43)	42 (39-45)	0.007
APRI ≥2 (%)	13 (2)	4 (14)	33 (28)	10 (7)	<0.001
FIB-4 ≥3.25 (%)	16 (2)	4 (14)	47 (40)	27 (18)	<0.001
CAP (dB/m)	228 (192-259)	248 (212-292)	208 (172-237)	218 (174-259)	0.006
CAP ≥288 (%)	82/558 (15)	6/22 (27)	5/56 (9)	16/97 (16)	0.217

Legend: Continuous variables are expressed as median (IQR) and categorical variables are expressed as frequencies (%), unless otherwise specified. For the three-way comparison of patients with no cirrhosis, occult cirrhosis, or overt cirrhosis, *p*-values were computed using a Fisher's exact test for dichotomous variables, a chi-squared test for categorical variables, and a Kruskal-Wallis test for continuous variables, and are considered significant when below 0.05. CAP was available in 733 out of 1092 patients. Abbreviations; ALT, alanine aminotransferase;

APRI, AST-to-Platelet Ratio Index; ART, antiretroviral therapy; AST, aspartate aminotransferase; BMI, body mass index; HIV, human immunodeficiency virus; HDL, high-density lipoprotein cholesterol; IDU, injection drug use; IU, international units; LDL, low-density lipoprotein cholesterol; MSM, men who have sex with men; NNRTI, non-nucleoside reverse transcriptase inhibitors; NRTI, nucleoside reverse transcriptase inhibitors; PI, Protease Inhibitors; SD, standard deviation.

Table 2. Factors associated with occult cirrhosis by logistic regression analysis.

Variable	**OR (95% CI)**	**Model 1 aOR (95% CI)**	**Model 2 aOR (95% CI)**
Age (per 10 years)	1.36 (0.99-1.88)	1.45 (1.03-2.06)	-
Female sex (yes vs no)	0.97 (0.42-2.03)	1.07 (0.46-2.28)	1.19 (0.51-2.57)
Indigenous ethnicity (yes vs no)	0.51 (0.12-1.46)	-	-
Hazardous alcohol intake in past year (yes vs no)	1.04 (0.35-2.51)	-	-
BMI (per 5 units)	1.19 (0.9-1.5)	1.20 (0.92-1.52)	1.25 (0.95-1.58)
Diabetes in past year (yes vs no)	1.67 (0.73-3.52)	-	-
Lipid lowering therapy in past year (yes vs no)	1.12 (0.41-2.57)	-	-
Nadir CD4 count (per 100 cells)	0.94 (0.77-1.12)	-	-
Detectable HIVRNA in past year (yes vs no)	0.69 (0.2-1.79)	-	-
HCV coinfection (yes vs no)	1.21 (0.61-2.36)	1.46 (0.72-2.94)	1.30 (0.65-2.56)
HIV duration (per 5 years)	1.39 (1.15-1.69)	-	1.44 (1.18-1.77)
ART duration (per 5 years)	1.14 (0.88-1.47)	-	-
AIC		296.55	288.33

Legend: Occult cirrhosis patients (n=29) are compared to non-cirrhotic patients (n=795). Odds ratios (OR) and 95% confidence interval (CI) are presented for each variable in the unadjusted and adjusted analysis. AIC, Akaike information criterion; aOR, adjusted odds ratio; ART,

antiretroviral therapy; BMI, body mass index; HCV, hepatitis C virus; HIV, human immunodeficiency virus.

Table 3. Incidence rate of liver-related events during follow-up.

	Non-cirrhotic (n=795)		**Occult cirrhosis** (n=29)		**Overt cirrhosis** (n=117)		**Non-cirrhotic portal hypertension** (n=151)	
	Cases	**Incidence rate (95% CI)**	**Cases**	**Incidence rate (95% CI)**	**Cases**	**Incidence rate (95% CI)**	**Cases**	**Incidence rate (95% CI)**
Any liver event	5	3.4 (1.2-7.3)	2	34.0 (6.0-104.0)	8	37.0 (17.0-69.1)	4	12.7 (3.94-29.5)
Ascites	1	0.68 (0.04-2.97)	2	33.34 (5.54-102.89)	5	21.48 (7.7-46.16)	3	9.51 (2.37-24.66)
Varices with bleeding or banding	2	1.35 (0.22-4.16)	0	-	0	-	1	3.08 (0.18-13.55)
Spontaneous bacterial peritonitis	1	0.67 (0.04-2.96)	0	-	1	3.83 (0.22-16.85)	0	-
Hepatic encephalopathy	0	-	0	-	3	11.56 (2.87-29.97)	0	-
Hepatorenal syndrome	0	-	0	-	1	3.71 (0.21-16.32)	0	-
HCC	1	0.67 (0.04-2.96)	1	15.49 (0.88-68.13)	3	11.61 (2.89-30.08)	1	3.08 (0.18-13.55)
ESLD-related death	0	-	1	15.33 (0.87-67.44)	1	3.71 (0.21-16.31)	0	-

Legend: Incidence rates are presented as 1000 person-years (PY) with 95% confidence interval (CI). ESLD, end stage liver disease; HCC, hepatocellular carcinoma.

Table 4. Risk factors associated with any liver event by Cox proportional hazards regression analysis.

Variable	**HR (95% CI)**	**aHR (95% CI)**
Occult cirrhosis at baseline (yes vs no)	4.45 (0.96-20.62)	7.12 (1.33-37.99)
Overt cirrhosis at baseline (yes vs no)	8.49 (3.03-23.75)	8.5 (2.83-25.53)
Age (per year)	1.04 (1.01-1.07)	-
Female sex (yes vs no)	0.79 (0.22-2.78)	-
Hazardous alcohol intake in the past year (yes vs no)	2.97 (1.05-8.39)	-
BMI ≥ 30 in past year (yes vs no)	0.95 (0.22-4.17)	-
Diabetes in past year (yes vs no)	1.92 (0.61-5.98)	-
Lipid lowering therapy in past year (yes vs no)	0.46 (0.06-3.47)	-
Nadir CD4 count (per 100 cells)	0.79 (0.59-1.06)	-
Detectable HIVRNA in past year (yes vs no)	1.71 (0.54-5.38)	1.55 (0.51-4.67)
HCV coinfection (yes vs no)	1.83 (0.65-5.18)	-
HIV duration (per 5 years)	1.55 (1.23-1.96)	1.37 (1.09-1.73)
ART duration (per 5 years)	1.63 (1.14-2.32)	-

Legend: Hazard ratios (HR) and 95% confidence interval (CI) are presented for each variable in the unadjusted and adjusted analysis. aHR, adjusted hazard ratio; ART, antiretroviral therapy; BMI, body mass index; HCV, hepatitis C virus; HIV, human immunodeficiency virus.

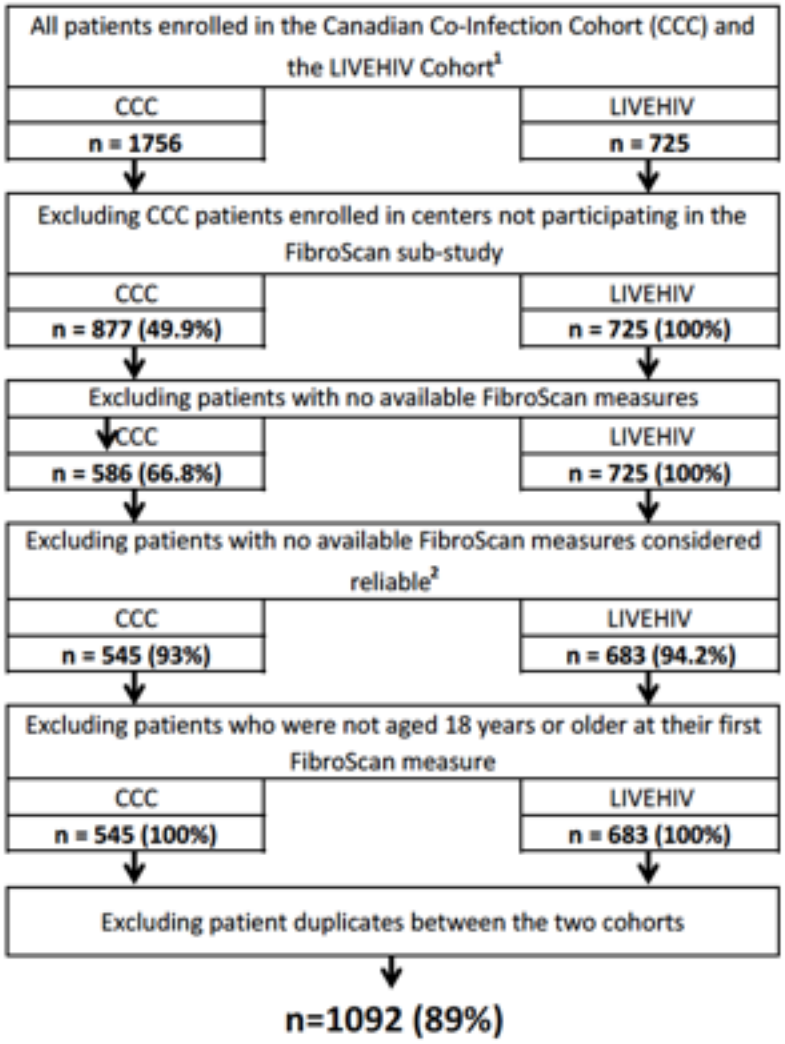
Figure legends

Figure 1. Flow chart displaying the selection of study participants, stratified by study cohort. **[1]** Administrative censoring was applied on March 31, 2017 for the CCC and on January 14, 2017 for the LIVEHIV cohort. **[2]** Liver stiffness measures by TE were considered reliable if the ratio of the IQR over the median of the 10 measures was no more than 30%.

Figure 2. Distribution of study groups (OvC, OcC, non-cirrhotic, non-cirrhotic portal hypertension) according to HCV and HBV coinfection status.

Figure 3. Survival curves of: (a) incidence of OcC by HCV coinfection status; (b) incidence of OvC by HCV coinfection status; (c) probability of liver-related events by study group category; (d) probability of liver-related events by HCV coinfection category. The p-values refer to log-rank test.

Figure 1: Sample Selection Flow Chart



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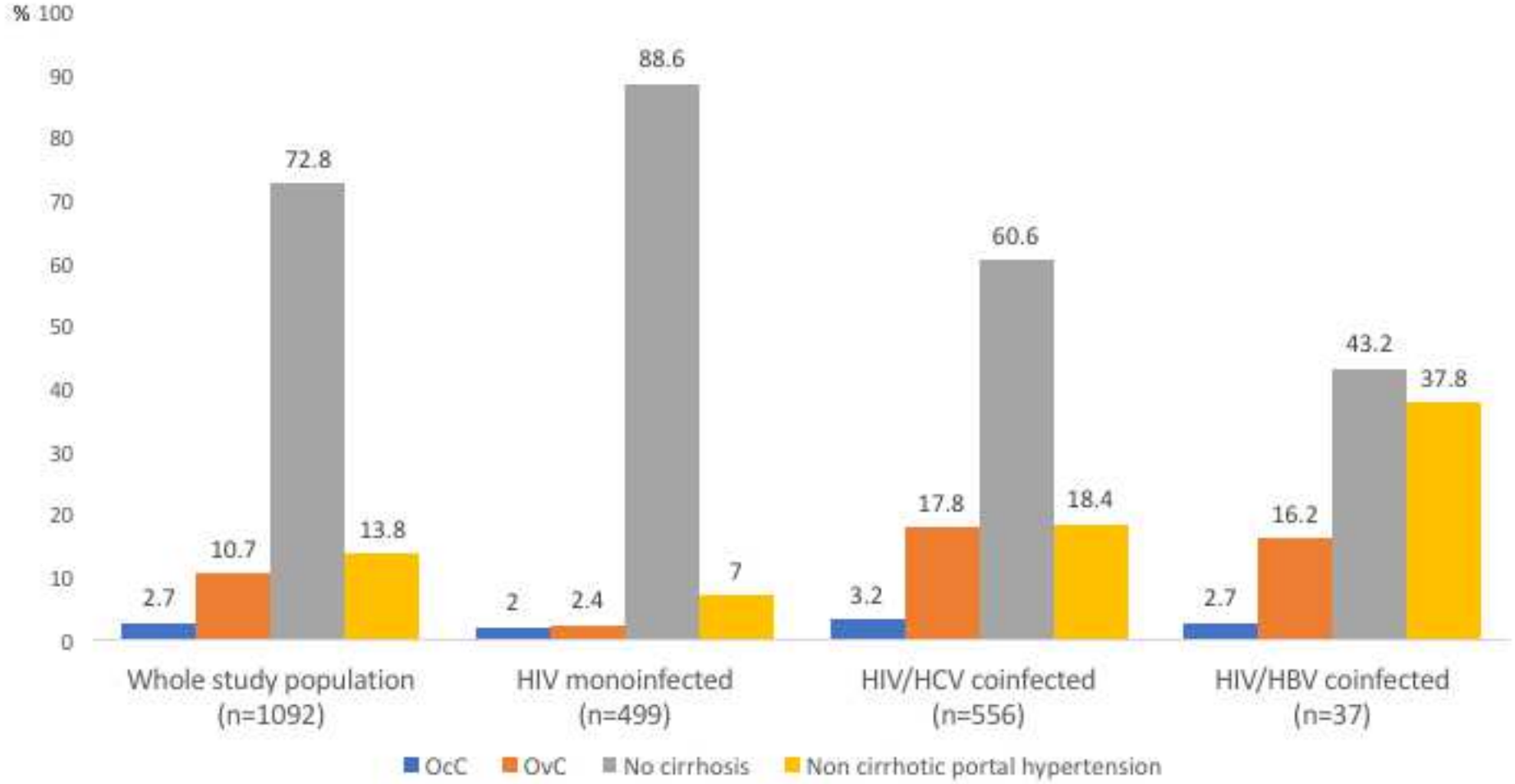

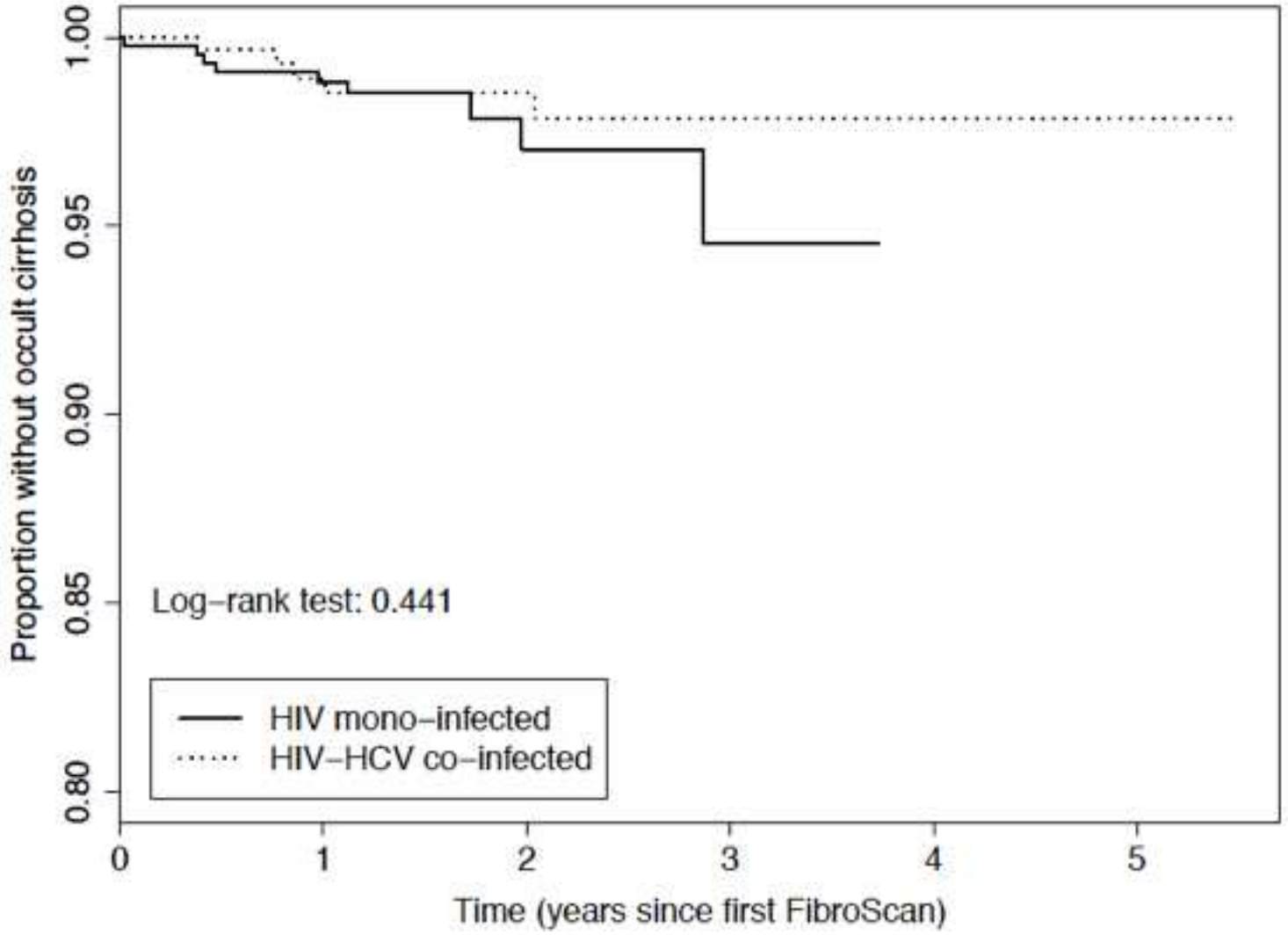

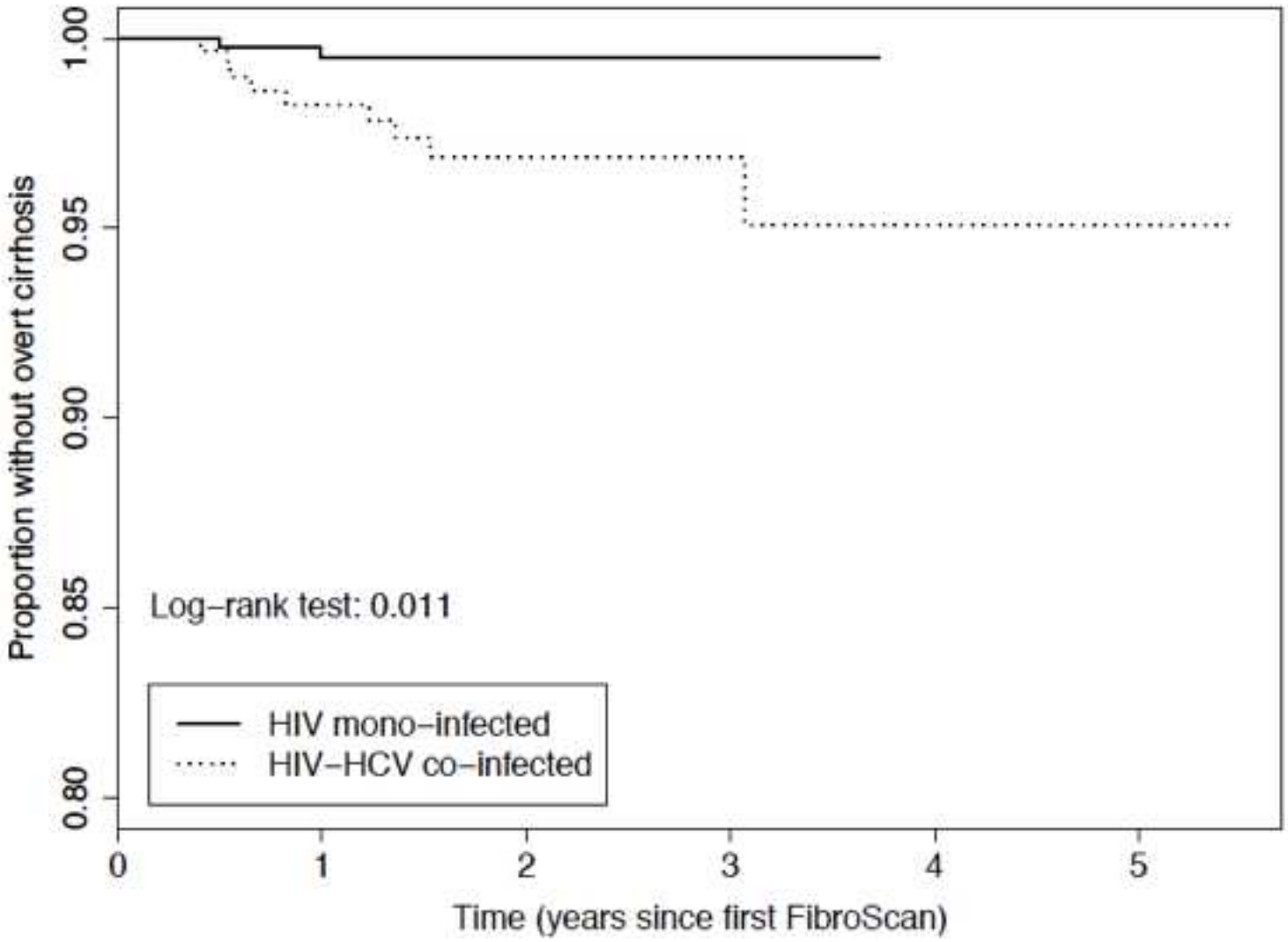

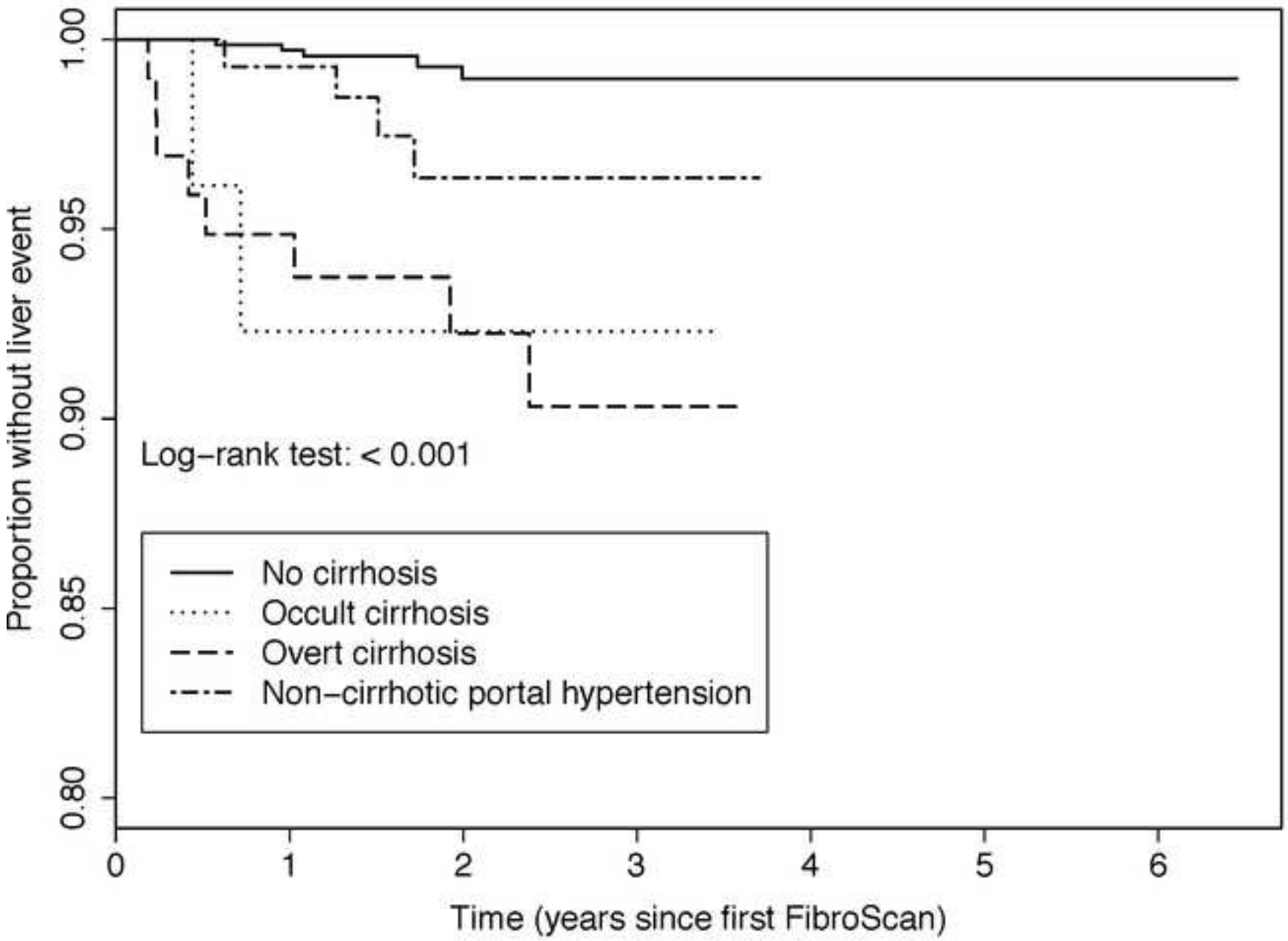

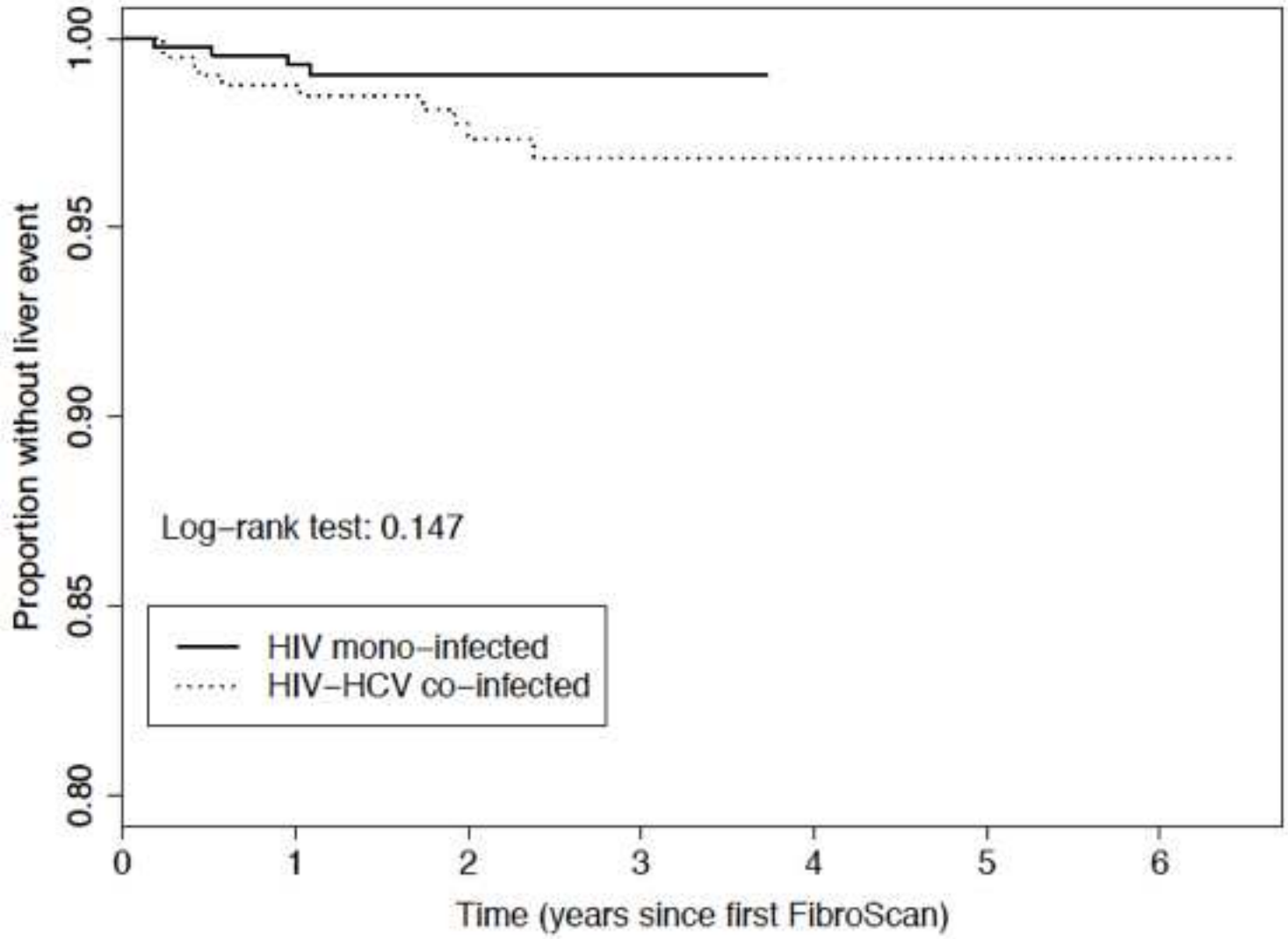

Supplemental Table S1. Patient characteristics at baseline by HCV and HBV coinfection status (n=1092).

	HIV monoinfected (n=499)	**HIV/HCV coinfected** (n=556)	**HIV/HBV coinfected** (n=37)	**p**
Total follow-up time (years)	1.50 (1.43-2.17)	2.36 (1.50-3.02)	2.14 (1.45-3.07)	<0.001
Age (years)	50.8 (42.9-57.5)	48.7 (41.6-54.2)	54.1 (49.0-61.0)	<0.001
Female (%)	119 (24)	152 (27)	3 (8.1)	0.204
MSM (%)	175 (35)	184 (33)	26 (70)	0.516
Ethnicity (%)				
Caucasian	166 (33)	350 (63)	20 (54)	<0.001
Black	158 (32)	29 (5)	(36)	<0.001
Latino	53 (11)	11 (2)	0	<0.001
Asian	16 (3)	12 (2)	2 (6)	0.339
Indigenous	1 (0)	156 (28)	0	<0.001
Unknown	105 (21)	7 (1)	1 (3)	<0.001
BMI (Kg/m^2)	25.6 (23.3-29.0)	24.6 (21.8-27.8)	25.8 (21.6-28.9)	<0.001
Obesity (BMI>30) (%)	81 (16)	55 (10)	2 (6)	0.002
Hazardous alcohol intake (%)	39 (8)	119 (21)	3 (8)	<0.001
Active tobacco smoker (%)	29 (6)	371 (67)	2 (6)	<0.001

Active IDU (%)	11 (2)	287 (52)	4 (10)	<0.001
HIV duration (years)	12.0 (7.0-20.0)	12.0 (6.0-20.0)	19.0 (15.0-23.0)	0.979
CD4 nadir (cells/μL)	209 (95-342)	200 (100-338)	73 (49-140)	0.938
CD4 cell count (cells/μL)	529 (369-732)	480 (312-691)	366 (262-596)	0.011
HIV viral load in log_{10} (units)	1.59 (1.59-1.62)	1.59 (1.59-1.60)	1.59 (1.59-1.62)	0.003
Undetectable HIV viral load (≤ 50 copies) (%)	376 (75)	416 (75)	31 (84)	0.808
Duration of ART (years)	7.94 (3.72-14.6)	7.44 (3.44-14.0)	8.02 (4.10-15.8)	0.455
Current ART use (%)	426 (85)	453 (81)	32 (87)	0.098
NRTI	404 (81)	421 (76)	30 (80)	0.044
NNRTI	172 (34)	101 (18)	17 (46)	<0.001
PI	197 (39)	245 (44)	17 (46)	0.134
Integrase Inhibitors	154 (31)	177 (32)	15 (40)	0.74
Other	31 (6)	47 (8)	1 (3)	0.195
Exposure to Didanosine (mean years ± SD)	0.44±1.98	0.13±1.04	0.50±1.70	<0.001
Exposure to Stavudine (mean years ± SD)	0.90±2.27	0.19±1.41	1.10±2.52	<0.001

HCV RNA pos (%)	-	328 (59)	-	-
Previously treated for HCV (%)	-	173 (31)	-	-
HCV genotype (%)				
1	-	351 (63)	-	-
2	-	26 (5)	-	-
3	-	80 (14)	-	-
4	-	19 (3)	-	-
Unknown	-	80 (14)	-	-
Hypertension (%)	99 (20)	78 (14)	3 (8)	0.013
Diabetes (%)	132 (26)	73 (13)	2 (6)	<0.001
International normalized ratio	1.01 (0.97-1.07)	1.00 (0.94-1.05)	1.07 (1.01-1.14)	0.037
Platelets (10^9/L)	205 (168-246)	200 (156-241)	156 (125-205)	0.071
Total cholesterol (mmol/L)	4.61 (3.95-5.37)	4.06 (3.47-4.64)	3.97 (3.61-4.61)	<0.001
LDL cholesterol (mmol/L)	2.70 (2.19-3.35)	2.23 (1.65-2.73)	2.01 (1.33-2.83)	<0.001
HDL cholesterol (mmol/L)	1.14 (0.95-1.40)	1.15 (0.95-1.39)	0.96 (0.93-1.34)	0.889
Triglycerides (mmol/L)	1.33 (0.92-2.21)	1.25 (0.90-1.77)	1.66 (1.16-2.08)	0.103
Creatinine (µmol/L)	83.0 (71.0-97.0)	77.0 (66.0-89.0)	83.0 (74.0-113.0)	<0.001
Insulin (pmol/L)	65.2 (43.2-112)	87.2 (54.5-162)	46.6 (41.2-90.4)	0.001

ALT (IU/L)	25.0 (19.0-36.0)	39.0 (23.0-67.0)	30.0 (21.0-42.5)	<0.001
AST (IU/L)	24.0 (20.0-30.0)	38.0 (26.0-60.0)	31.0 (24.0-47.0)	<0.001
Total bilirubin (µmol/L)	11.0 (7.4-15.0)	10.0 (7.0-18.0)	12.0 (9.0-14.4)	0.538
Albumin (g/L)	42.0 (40.0-44.0)	41.0 (37.0-43.0)	42.0 (39.3-43.8)	<0.001

Legend: Continuous variables are expressed as median (IQR) and categorical variables are expressed as frequencies (%), unless otherwise specified. For the two-way comparison of HIV/HCV coinfected vs. HIV monoinfected and HIV/HBV coinfected patients, p-values were computed using a Fisher's exact test for dichotomous variables, a chi-squared test for categorical variables, and a Wilcoxon rank-sum test for continuous variables, and are considered significant when below 0.05. Abbreviations; ALT, alanine aminotransferase; ART, antiretroviral therapy; AST, aspartate aminotransferase; BMI, body mass index; HBV, hepatitis B virus; HCV, hepatitis C virus; HDL, high-density lipoprotein cholesterol; HIV, human immunodeficiency virus; IDU, injection drug use; IU, international units; LDL, low-density lipoprotein cholesterol; MSM, men who have sex with men; NNRTI, non-nucleoside reverse transcriptase inhibitors; NRTI, nucleoside reverse transcriptase inhibitors; PI, Protease Inhibitors; SD, standard deviation.

Supplemental Table S2. Hepatocellular carcinoma screening rates in patients with at least one screening visit.

Population	Number of screening visits	Patients with at least one screening	Screening rate
Whole study population	698	350	0.80 (0.74-0.86)
Non-cirrhotic	317	205	0.62 (0.56-0.70)
Occult cirrhosis	45	18	0.97 (0.72-1.28)
Overt cirrhosis	224	68	1.33 (1.16-1.51)
Non-cirrhotic portal hypertension	112	59	0.73 (0.60-0.87)
HIV monoinfected	210	149	0.62 (0.54-0.71)
Non-cirrhotic	157	121	0.57 (0.49-0.67)
Occult cirrhosis	18	7	1.08 (0.66-1.66)
Overt cirrhosis	15	8	0.87 (0.5-1.38)
Non-cirrhotic portal hypertension	20	13	0.69 (0.43-1.04)
HIV/HCV coinfected	441	178	0.91 (0.83-1.00)
Non-cirrhotic	148	76	0.69 (0.58-0.81)
Occult cirrhosis	25	10	0.86 (0.57-1.25)
Overt cirrhosis	199	57	1.38 (1.2-1.58)
Non-cirrhotic portal hypertension	69	35	0.71 (0.56-0.90)

Legend: Screening rates are expressed per 1 person-year with 95% confidence interval (CI). HCV, hepatitis C virus; HIV, human immunodeficiency virus.