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Poorly Controlled HIV Infection: An Independent Risk Factor for Liver Fibrosis

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Abstract

Background—Liver disease is a major cause of mortality among HIV-infected persons. There is limited information about the extent to which HIV disease severity impacts liver disease progression.

Methods—We determined the incidence and predictors of advanced hepatic fibrosis measured by the FIB-4 index (≥3.25) in a large diverse population of HIV-infected patients without significant liver disease at baseline (FIB-4<1.45) in care between January 2000 and March 2014. We used Cox proportional hazards analysis to examine factors associated with progression to FIB-4 ≥3.25.

Results—Among 14,198 HIV-infected patients, HCV coinfection (adjusted hazard ratio [aHR] 1.9, 95% CI 1.6–2.1), HBV coinfection (aHR 1.5, 95% CI 1.2–1.8), alcohol use disorder (aHR 1.4, 95% CI 1.2–1.6) and diabetes (aHR 1.9, 95% CI 1.6–2.3) were associated with progression to advanced fibrosis in multivariable analysis. In addition, patients at each lower level of time-varying CD4 count had a significantly greater risk of progression, with a nearly 7-fold higher risk in those with CD4 <100 cells/mm^3 (aHR 6.9, 95% CI 5.8–8.3) compared with CD4 ≥500 cells/mm^3. An increasing gradient of risk was also observed among patients with higher time-varying

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HIV viral load (VL), with the greatest risk noted with VL ≥100,000 copies/ml (aHR 2.6, 95% CI 2.2–3.1) compared with VL <500 copies/ml.

Conclusion—Lower CD4 count and higher HIV VL were significantly associated with progression to advanced hepatic fibrosis in a dose-dependent manner, independent of the risk associated with traditional factors: HCV or HBV coinfection, alcohol, and diabetes. Our findings suggest that early treatment of HIV infection could mitigate liver disease.

Keywords

Liver disease progression; FIB-4; HIV; fibrosis; hepatitis

Introduction

Liver disease has emerged as a major cause of morbidity and mortality among HIV-infected individuals with the improvement in overall survival since the introduction of effective combination antiretroviral therapy (ART)[1]. While chronic hepatitis C virus (HCV) may account for much of this mortality[2], an excess burden of liver disease has been reported in HIV monoinfected patients.[3–5] Multiple studies have demonstrated accelerated progression to cirrhosis in HIV-HCV coinfected patients compared with HCV-monoinfected patients, and that ART mitigates the progression of liver disease in coinfected patients.[6–8] However, our current understanding of the clinical course of hepatic fibrosis is derived primarily from single-center studies of HIV-HCV coinfected patients with limited size and follow-up. Progression of liver disease in HIV monoinfected patients has not been well characterized and little is known about the extent to which HIV disease severity influences liver disease progression, particularly early in the disease course when interventions may have the greatest impact.

We conducted this study to define the incidence and predictors of progression to advanced hepatic fibrosis measured by the Fibrosis-4 (FIB-4) index in a well-characterized multicenter cohort of HIV-infected patients with minimal or no fibrosis at baseline. The FIB-4 index, which has been validated in a variety of settings, correlates with histologic stages of fibrosis[9] and unlike liver biopsy, is routinely measured at multiple time points. FIB-4 ≥3.25 is a well-validated threshold shown to be predictive not only of advanced fibrosis, but also of liver-related clinical outcomes and overall mortality.[9] Accounting for multiple risk factors for fibrosis, we sought to determine the role of HIV disease severity in the progression of liver disease among those with and without viral hepatitis.

Methods

Data Source & Study Population

The Center for AIDS Research Network of Integrated Clinical Systems (CNICS) cohort is a dynamic prospective clinical cohort of HIV-infected adults receiving care at eight participating academic sites across the US. Comprehensive clinical data including diagnoses, medications, laboratory, and demographic information collected through electronic medical records and other institutional data systems at each site are harmonized in the CNICS data repository. Data from each site are updated, undergo extensive quality assurance procedures,

and integrated in the repository quarterly (http://www.uab.edu/cnics). Institutional review boards at each site approved the study protocol.

All patients who entered the cohort on or after January 1, 2000, had a minimum of two FIB-4 scores and six months of follow-up, and a baseline FIB-4 score <1.45 which is below the threshold of significant fibrosis (comparable to METAVIR stage 0–1 fibrosis)[9] were included in this study.

Independent Variables

Patients were categorized according to their age at study entry, race/ethnicity classified as white (non-Hispanic), black (non-Hispanic), Hispanic and other/unknown, and history of injection drug use reported as a risk factor for HIV transmission. Additional baseline characteristics documented within six months of entry into the cohort included FIB-4; HCV coinfection defined as a detectable HCV RNA level, HCV genotype or HCV antibody; hepatitis B (HBV) coinfection defined as a positive hepatitis B surface antigen or detectable HBV DNA level; and body mass index (BMI) defined as underweight (<18.5 kg/m^2), overweight (25–29 kg/m^2) and obese (≥30 kg/m^2) using the normal range (18.5 to <25 kg/m^2) as the referent category. Alcohol use disorder was defined as a diagnosis of alcohol abuse or dependence recorded by the treating clinician based on a modified list of International Classification of Diseases, Ninth Revision [ICD-9] diagnostic codes (291.x, 303.x and 305.0) shown to be highly specific and moderately sensitive for alcohol use disorder in other settings.[9] Diabetes mellitus was defined as an ICD-9 diagnosis of diabetes mellitus and use of diabetes-related medication, use of diabetes-specific medication, or a hemoglobin A1C ≥ 6.5%; CD4 cell count was categorized as ≥500, 350–500, 200–349, 100–199, <100 cells/mm^3, and HIV viral load (VL) was classified as <500, 500–999, 10,000–99,999 and ≥100,000 copies/ml.

Outcome Measure

The primary endpoint was progression of liver disease to FIB-4 greater than or equal to 3.25. We computed the FIB-4 index using the formula: FIB-4 = (age [years]×AST [U/L]) / (platelet count [10^9/L]×(ALT [U/L])$^{1/2}$) and the closest platelet count to within a year of the date of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) testing, which occurred on the same day in over 92% of patients. In secondary analysis, we also examined the AST-platelet ratio index (APRI) as another noninvasive endpoint measuring hepatic fibrosis, using the formula: APRI = (AST [U/L] / upper limit of normal for AST (or 40 U/L))×100 / platelet count [10^9/L]. Advanced fibrosis was defined as APRI greater than 1.5.

Statistical Analysis

We calculated incidence rates and 95% confidence intervals for progression to FIB-4 ≥3.25. Follow-up began at the first FIB-4 measurement more than six months after a patient's first visit to allow for full ascertainment of baseline characteristics, and continued until the study endpoint, last available FIB-4 measurement, or administrative censoring on March 30, 2014, whichever occurred first.

We used a Cox proportional hazards model to estimate the relative hazards of FIB-4 progression. In addition to CD4 cell count and HIV VL, we included variables reported to be risk factors for liver-related outcomes in HIV-infected or HIV-HCV coinfected patients[9]: sex, race, HCV coinfection, HBV coinfection, and alcohol use disorder, and diabetes mellitus. CD4 cell count, HIV VL and diabetes were modeled as time-varying covariates. In the multivariable analysis, we adjusted for baseline FIB-4 modeled as a continuous variable and stratified by HCV status. We did not include age in our multivariable model since it is a component of the FIB-4 index, or HIV transmission risk factor due to collinearity between injection drug use and HCV infection. We repeated these models using APRI >1.5 as the outcome and included age as a separate covariate.

In secondary analyses, we assessed the interactions between CD4 count (CD4<200 cells/mm^3 / CD4≥200 cells/mm^3) and HIV VL (<500 copies/ml / ≥500 copies/ml), and between alcohol use disorder and HCV as dichotomous variables in the FIB-4 model. We included baseline BMI as a covariate in the full model to evaluate whether the effect of diabetes on FIB-4 progression was changed by the addition of BMI. We evaluated the impact of ART-mediated HIV viral suppression (<500 copies/ml) as a time-varying factor in a separate analysis. We stratified our model by platelet count level based on the distribution in our cohort (<220×10^9 cells/L, 220–269×10^9 cells/L and ≥270×10^9 cells/L) to examine whether HIV-associated thrombocytopenia influenced our findings. All analyses were performed using Stata 13 (College Station, TX).

Results

Between January 1, 2000 and March 31, 2014, 20,185 HIV-infected individuals initiated care in CNICS and had at least two FIB-4 measurements. Among these patients, 5,987 (29%) had a baseline FIB-4 ≥1.45 and were excluded from the analysis, resulting in a total of 14,198 patients in the study cohort. As shown in Table 1, the majority of the cohort was male (82%) with sex with men as a risk factor for HIV transmission (58%) and a median age of 38 years. The cohort was racially/ethnically diverse with 46% white/non-Hispanic, 34% black/non-Hispanic and 14% Hispanic. The prevalence of hepatitis C coinfection was 12%, and alcohol use disorder was identified in 9%. The median baseline FIB-4 score was 0.8 (interquartile range [IQR], 0.6–1.0).

Progression to Advanced Fibrosis

Progression to advanced fibrosis occurred in 1,386 patients (9.7%) in a median of 3 years (interquartile range [IQR] 1.2–5) during a total of 61,904 person-years of follow-up (PYFU) for an overall incidence of 2.2 per 100 PYFU (95% confidence interval [CI] 2.1–2.4). The incidence of advanced fibrosis was 4.7 per 100 PYFU (95% CI 4.2–5.3) among HIV-HCV coinfected patients compared with 1.9 per 100 PYFU (95% CI 1.8–2.0) among HIV monoinfected patients.

The median FIB-4 at the end of follow-up among patients who progressed to advanced fibrosis was 4.2 (IQR 3.6–5.7). Compared to patients who had not progressed to advanced fibrosis, those who progressed were more likely to be black (41% vs. 34%), have a history of injection drug use (20% vs. 11%), HCV coinfection (24% vs. 10%), HBV coinfection (6%

vs. 3%), diabetes (5% vs. 4%), and a history of alcohol use disorder (14% vs. 9%), $P<0.01$ for all comparisons (Table 1). Patients who progressed to advanced fibrosis were also more likely to have a CD4 count less than 200 cells/mm^3 (31% vs. 16%, $P<0.001$) and detectable HIV VL ≥500 copies/ml (53% vs. 38%, $P<0.001$) at baseline as well as at the end of follow-up, at which time only 52% of patients who progressed were virally suppressed compared with 79% of non-progressors, $P<0.001$.

Risk Factors for Liver Disease Progression

In multivariable analysis, HCV coinfection (adjusted hazard ratio [aHR] 1.9, 95% CI 1.6–2.1), HBV coinfection (aHR 1.5, 95% CI 1.2–1.8), alcohol use disorder (aHR 1.4, 95% CI 1.2–1.6) and diabetes (aHR 1.9, 95% CI 1.6–2.3) were significantly associated with progression to advanced fibrosis, while race and sex were not (Table 2). In addition, each lower level of CD4 count was independently associated with progression to advanced fibrosis, with the greatest risk of progression observed in patients with the lowest CD4 count. An increasing gradient of risk was also observed among patients with higher time-varying HIV VL, with HIV VL ≥100,000 copies/ml carrying the greatest risk of progression. Patients with CD4 count <100 cells/mm^3 had a nearly 7-fold higher risk of progression (aHR 6.9, 95% CI 5.8–8.3) compared with patients with CD4 count ≥500 cells/mm^3. Similarly, patients with HIV VL ≥100,000 copies/ml had an aHR of 2.6 compared with those who were virally suppressed (95% CI 2.2–3.1). After controlling for other factors, time-updated viral suppression had an independent protective effect against progression to advanced fibrosis (aHR 0.6, 95% CI 0.6–0.7).

We observed comparable findings for both HIV monoinfected patients and HIV-HCV coinfected patients in stratified analyses as shown in Table 2. Alcohol use disorder, lower CD4 count and higher HIV VL were independent predictors of advanced fibrosis in both monoinfected and coinfected patients. The association between chronic HBV infection, diabetes and the less severe categories of CD4 count (350–500 cells/mm^3) and HIV VL (500–9999 copies/ml) were no longer statistically significant in HIV/HCV coinfected patients, potentially due to the smaller number of patients within these categories.

When we stratified our model by baseline FIB-4 using a cutoff (median) value of 0.8, the risk estimates remained unchanged and statistically significant. The incidence of advanced fibrosis was 3.1 per 100 PYFU (95% CI 2.9–3.3) among patients with baseline FIB-4 ≥0.8 and <1.45 compared with 1.4 per 100 PYFU (95% CI 1.3–1.6) among those with baseline FIB-4 <0.8.

We found comparable results when we examined advanced fibrosis measured by APRI >1.5 (Table 3). HCV coinfection (aHR 1.9, 95% CI 1.7–2.1), HBV coinfection (aHR 1.6, 95% CI 1.3–1.9), alcohol use disorder (aHR 1.3, 95% CI 1.1–1.4), diabetes (aHR 1.5, 95% CI 1.3–1.8), CD4 count (for CD4 <100 cells/mm^3, aHR 5.8, 95% CI 5.0–6.8) and HIV VL (for VL ≥100,000 copies/ml, aHR 2.2, 95% CI 1.9–2.6) remained independent risk factors for fibrosis. Age was not associated with APRI in these models.

Interaction between CD4 count and HIV VL

We found a statistically significant interaction between CD4 count and HIV VL on the risk of progression to advanced liver fibrosis (aHR 1.31, 95% 1.03–1.67, P=0.03). Patients with a CD4 count <200 cells/mm^3 had over three times the risk of progression to advanced fibrosis (aHR 3.3, 95% CI 2.7–4.0) compared to patients with a CD4 count ≥200 cells/mm^3, and patients with detectable HIV VL (>500 copies/ml) were also at significantly higher risk of progression (aHR 1.7, 95% CI 1.5–2.0) than patients with undetectable HIV VL. Having both low CD4 count (<200 cells/mm^3) and detectable HIV VL (≥500 copies/ml) resulted in having over seven-fold greater risk of liver disease progression (aHR 7.3, 95% CI 6.4–8.3).

Secondary Analyses with Alcohol, BMI & Platelets

We found no effect modification of HCV or other factors by alcohol use disorder. BMI was not associated with fibrosis progression, and did not change the risk estimate associated with diabetes. The association between FIB-4 progression and HCV, HBV, diabetes, CD4 count and HIV VL remained significant when we repeated the analysis at different levels of baseline platelet count (data not shown).

Discussion

In this study of over 14,000 HIV-infected individuals in care across the US with no more than minimal liver fibrosis at baseline, we found that nearly 10% progressed to advanced fibrosis during a median of 3 years of follow-up. The highest incidence of progression was seen in HIV-HCV coinfected patients who comprised 24% of those who progressed, consistent with previous studies of HIV-HCV coinfected patients that found progression to advanced fibrosis occurring in as few as 3–5 years[–].

The large size and diversity of our study cohort, with over 61,000 person years of follow up, enabled us to determine the independent contribution of multiple factors to the progression of liver fibrosis from minimal to advanced disease among those with and without viral hepatitis. We found that HCV coinfection, HBV coinfection, alcohol use disorder and diabetes were independently associated with progression to advanced fibrosis even among patients with the lowest baseline FIB-4 scores. In addition, after controlling for known risk factors, patients with suboptimal control of HIV infection were at particular risk of progression to advanced fibrosis whether or not they had viral hepatitis. Our findings were similar whether advanced fibrosis was measured by FIB-4 or APRI.

The significant impact of HIV infection on the progression of liver disease, apart from viral hepatitis, is evidenced by the increasing risk of advanced fibrosis with greater exposure to each lower CD4 level of count and higher level of HIV viremia in both HIV monoinfected and HIV-HCV coinfected patients after controlling for other factors. Moreover, our study is the first to demonstrate a significant interaction between CD4 count and HIV VL beyond the impact of each factor alone such that having both a low CD4 count and detectable HIV VL resulted in more than seven-fold increase in the risk of liver disease progression.

Our findings concur with previous observations that HIV-infected patients with hepatitis B or C and lower CD4 counts appear to be at greater risk of decompensated liver disease, and

liver-related deaths.[3] However, an association between lower CD4 count and liver fibrosis has been noted primarily in HIV-HCV coinfected cohorts[3–5] and has not been examined as extensively across all CD4 levels over time, in conjunction with HIV VL or in HIV monoinfected patients.

A deleterious effect of HIV VL on liver disease has been suggested by data evaluating the impact of ART on liver outcomes. Discontinuation of ART has been shown to be associated with clinical decompensation in patients with early cirrhosis and maintenance of ART with a reduced risk of significant fibrosis and liver-related events[6]. In our study, ART-mediated viral suppression significantly reduced the risk of fibrosis progression in a cohort of patients with minimal fibrosis at baseline. Moreover we found direct evidence that exposure to HIV viremia over time is a major risk factor for fibrosis progression, even after adjusting for CD4 count. These findings underscore the potential role of virus-mediated liver injury independent of immune depletion and exhaustion, which may explain why the combination of low CD4 and high HIV VL was particularly detrimental. There may be multiple mechanisms for this pathophysiology: HIV has been shown to infect and activate hepatic stellate cells, which play a key role in hepatic fibrogenesis.[7] The virus can also induce hepatocyte death via the CXCR4 chemokine coreceptor and promote a pro-fibrotic state within the liver through the expression of proinflammatory cytokines and monocyte activation. Markers of hepatic fibrogenesis have been shown to be elevated in HIV-infected patients compared to uninfected patients, and correlated with HIV viral level.

Consistent with the literature[8–11], diabetes was a major predictor of progression to advanced fibrosis in our cohort. Notably diabetes remained a risk factor even after adjusting for HCV coinfection and BMI. The mechanism for this association remains unclear. Insulin resistance can promote non-alcoholic fatty liver disease, which has been implicated as a major cause of unexplained liver aminotransferase elevation and advanced fibrosis in HIV-infected patients[12], and in contrast to some studies of HCV monoinfected patients, may do so in the absence of an elevated BMI.

Excessive alcohol use has been known to exacerbate liver disease in patients with chronic HCV monoinfection, however we as well as others[13] did not detect effect modification of HCV coinfection by alcohol use disorder. Black race, present in 41% of those who progressed, was not associated with advanced fibrosis when controlling for HIV disease markers and other factors. In contrast to other studies, we did not find a protective effect of black race on the development of fibrosis.

This study has a number of limitations that should be acknowledged. While FIB-4 has been well validated in HIV-HCV coinfected populations, it has not been evaluated as extensively in HIV monoinfected patients. In addition, as a non-invasive marker for fibrosis, FIB-4 has only moderate discriminatory power for the different stages of fibrosis and modest positive predictive value for advanced liver disease. FIB-4 values may also fluctuate due to comorbid conditions, both intrahepatic (e.g. hepatic injury from alcohol, medications, opportunistic infections) and extrahepatic (e.g. sepsis), that may not represent fibrosis per se. We restricted our laboratory results to those obtained in the outpatient setting to mitigate these effects and the large sample size of our cohort likely offset this variability. Despite these limitations,

FIB-4 has been shown to predict liver-related outcomes such as hepatic decompensation and death, and to out-perform liver biopsy in this regard. It is possible that thrombocytopenia due to immune dysregulation or marrow suppression from advanced HIV disease rather than from liver disease resulted in FIB-4 elevation in some cases. Our results were unchanged when we stratified by platelet count suggesting that thrombocytopenia independent of liver disease was unlikely to account for our findings. In addition, among patients who had FIB-4 progression, those with low CD4 count (<200 cells/mm^3) were just as likely to have an elevated AST as those with CD4 count ≥200 cells/mm^3 with median AST values at the end of follow-up (107 vs. 139 U/L respectively) that were not appreciably different. The same was true when examining AST by HIV VL (detectable or not), suggesting that HIV-associated thrombocytopenia was not the sole contributor of elevated FIB-4.

In this large and diverse multicenter cohort of HIV-infected patients, we found that lower CD4 count and higher HIV viremia were significantly associated with progression to advanced hepatic fibrosis in a dose-dependent manner, independent of the risk associated with traditional factors including HCV and HBV coinfection, alcohol, and diabetes. In addition, individuals with both a low CD4 count and detectable HIV VL had an even greater risk of liver disease progression beyond the effect of each factor alone. Our findings provide additional support for the early diagnosis of HIV and suggest that early and effective treatment of HIV infection could mitigate liver disease progression. Further research is needed to better understand the mechanism and scope of HIV-mediated liver disease and to define optimal strategies to reduce liver disease progression among HIV-infected individuals.

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Table 1

Baseline[a] Demographic and Clinical Characteristics of the Study Population by Progression to Advanced Liver Fibrosis (FIB-4 ≥3.25)

	Overall (N=14,198)	Non-Progressors[b] (n=12,812)	Progressors[b] (n=1,386)
Age, median years (IQR)	38 (31–45)	38 (31–44)	40 (34–46)
Sex, male	11,627 (82)	10,508 (82)	1119 (81)
Race			
White	6548 (46)	5927 (46)	621 (45)
Black	4879 (34)	4315 (34)	564 (41)
Hispanic	1988 (14)	1830 (14)	158 (11)
Other	783 (6)	740 (6)	43 (3)
HIV Risk factor			
MSM	8227 (58)	7582 (59)	645 (47)
Heterosexual	3635 (26)	3271 (26)	364 (26)
IDU	1628 (11)	1348 (11)	280 (20)
Other	708 (5)	611 (5)	97 (7)
Chronic hepatitis C	1666 (12)	1339 (10)	327 (24)
Chronic hepatitis B	521 (4)	434 (3)	87 (6)
Alcohol use disorder	1319 (9)	1119 (9)	200 (14)
Diabetes mellitus	530 (4)	456 (4)	74(5)
CD4, cells/mm^3			
≥500	5497 (39)	5129 (40)	368 (27)
350–500	3237 (23)	2958 (23)	279 (20)
200–349	3010 (21)	2703 (21)	307 (22)
100–199	1420 (10)	1221 (10)	199 (14)
<100	1034 (7)	801 (6)	233 (17)
HIV RNA level, copies/ml			
<500	8594 (61)	7940 (62)	654 (47)
500–9999	2155 (15)	1924 (15)	231 (17)
10,000–99,999	2511 (18)	2196 (17)	315 (23)
≥100,000	938 (7)	752 (6)	186 (13)
FIB-4, median (IQR)	0.8 (0.6–1.0)	0.8 (0.6–1.0)	1.0 (0.7–1.2)

[a] Chronic hepatitis C, hepatitis B, alcohol use disorder, diabetes, CD4 count, HIV RNA level and FIB-4 represented baseline measurement within six months of study entry.

[b] All comparisons between patients who progressed and those who did not were statistically significant to $P<0.01$ with exception of sex ($P=0.2$).

IQR, interquartile range; MSM, men who have sex with men; IDU, injection drug use.

Table 2

Factors Associated with Progression to Advanced Liver Fibrosis Among Patients with Baseline FIB<1.45

	Overall (n=14,198)			HIV-monoinfected (n=12,532)			HCV-coinfected (n=1,666)		
Factor	**aHR**	**95% CI**	***P* Value**	**aHR**	**95% CI**	***P* Value**	**aHR**	**95% CI**	***P* Value**
Male sex	1.0	0.9–1.2	0.82	1.0	0.9–1.2	0.97	1.1	0.8–1.4	0.53
Race (reference: White)									
Black	0.9	0.8–1.1	0.26	0.9	0.8–1.0	0.18	1.0	0.8–1.3	1.00
Hispanic	1.0	0.8–1.1	0.59	1.0	0.8–1.2	0.68	0.8	0.5–1.3	0.39
Other	0.8	0.6–1.0	0.09	0.7	0.5–1.1	0.09	0.9	0.5–1.6	0.69
Chronic hepatitis C	1.9	1.6–2.1	<0.001	--	--	--	--	--	--
Chronic hepatitis B	1.5	1.2–1.8	0.001	1.5	1.2–2.0	<0.001	1.1	0.6–1.8	0.77
Alcohol use disorder	1.4	1.2–1.6	<0.001	1.4	1.2–1.7	<0.001	1.3	1.0–1.7	0.04
Diabetes mellitus *	1.9	1.6–2.3	<0.001	2.0	1.6–2.5	<0.001	1.3	0.8–2.0	0.26
CD4 count *, cells/mm^3									
≥500	--	--	--	--	--	--	--	--	--
350–500	1.3	1.1–1.5	0.002	1.3	1.1–1.6	0.007	1.2	0.9–1.7	0.22
200–349	1.9	1.6–2.2	<0.001	1.9	1.6–2.3	<0.001	1.8	1.3–2.5	<0.001
100–199	2.9	2.4–3.5	<0.001	3.3	2.7–4.0	<0.001	1.8	1.3–2.8	0.001
<100	6.9	5.8–8.3	<0.001	7.9	6.5–9.7	<0.001	4.0	2.7–5.8	<0.001
HIV viral level *, copies/ml									
<500	--	--	--	--	--	--	--	--	--
500–9999	1.3	1.1–1.5	0.007	1.4	1.2–1.7	<0.001	0.8	0.6–1.2	0.36
10,000–99,999	1.4	1.2–1.7	<0.001	1.4	1.2–1.7	<0.001	1.5	1.1–1.9	0.01
≥100,000	2.6	2.2–3.1	<0.001	2.8	2.3–3.3	<0.001	2.0	1.4–2.9	<0.001
Baseline FIB-4 per unit	3.9	3.2–4.7	<0.001	4.3	3.4–5.3	<0.001	2.7	1.8–3.9	<0.001

* Time-varying

Table 3

Factors Associated with Progression to Advanced Liver Fibrosis Among Patients with Baseline APRI<0.5

	Overall (n=15,288)			HIV-monoinfected (n=13,639)			HCV-coinfected (n=1,649)		
Factor	**aHR**	**95% CI**	***P* Value**	**aHR**	**95% CI**	***P* Value**	**aHR**	**95% CI**	***P* Value**
Male sex	1.0	0.9–1.2	0.46	1.0	0.9–1.2	0.86	1.1	0.9–1.4	0.36
Age (per 10 years)	1.0	0.9–1.1	1.00	1.0	0.9–1.1	0.95	1.0	0.8–1.1	0.56
Race (reference: White)									
Black	0.9	0.8–1.1	0.32	0.9	0.8–1.0	0.12	1.1	0.9–1.4	0.49
Hispanic	1.1	0.9–1.2	0.42	1.1	0.9–1.3	0.28	0.8	0.5–1.3	0.33
Other	0.8	0.7–1.1	0.18	0.8	0.6–1.1	0.18	1.0	0.6–1.6	0.89
Chronic hepatitis C	1.9	1.7–2.1	<0.001	--	--	--	--	--	--
Chronic hepatitis B	1.6	1.3–1.9	<0.001	1.6	1.3–2.0	<0.001	1.4	0.8–2.4	0.19
Alcohol use disorder	1.3	1.1–1.4	0.001	1.3	1.1–1.6	<0.001	1.1	0.8–1.4	0.48
Diabetes mellitus *	1.5	1.3–1.8	<0.001	1.7	1.4–2.0	<0.001	1.0	0.6–1.5	0.89
CD4 count *, cells/mm^3									
≥500	--	--	--	--	--	--	--	--	--
350–500	1.3	1.1–1.5	<0.001	1.3	1.1–1.5	0.002	1.5	1.1–2.1	0.02
200–349	1.8	1.6–2.1	<0.001	1.7	1.5–2.0	<0.001	2.2	1.6–3.0	<0.001
100–199	2.7	2.3–3.2	<0.001	2.8	2.3–3.3	<0.001	2.6	1.8–3.7	<0.001
<100	5.8	5.0–6.8	<0.001	6.2	5.2–7.4	<0.001	4.4	3.0–6.3	<0.001
HIV viral level *, copies/ml									
<500	--	--	--	--	--	--	--	--	--
500–9999	1.2	1.1–1.4	0.003	1.3	1.1–1.6	<0.001	1.0	0.7–1.4	0.97
10,000–99,999	1.2	1.0–1.4	0.010	1.1	1.0–1.3	0.10	1.3	1.0–1.7	0.05
≥100,000	2.2	1.9–2.6	<0.001	2.3	1.9–2.7	<0.001	1.8	1.3–2.6	<0.001
Baseline APRI per unit	7.8	4.9–12.4	<0.001	9.2	5.5–15.6	<0.001	4.2	1.6–11.1	0.004

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* Time-varying