Relationship of Liver Disease Stage and Antiviral Therapy With Liver-Related Events and Death in Adults Coinfected With HIV/HCV

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Context Human immunodeficiency virus (HIV) accelerates hepatitis C virus (HCV) disease progression; however, the effect of liver disease stage and antiviral therapy on the risk of clinical outcomes is incompletely understood.

Objective To determine the incidence of end-stage liver disease (ESLD), hepatocellular carcinoma (HCC), or death according to baseline hepatic fibrosis and antiviral treatment for HIV/HCV coinfected individuals.

Design, Setting, and Participants Prospective cohort of 638 coinfected adults (80% black, 66% men) receiving care at the Johns Hopkins HIV clinic and receiving a liver biopsy and who were prospectively monitored for clinical events between July 1993 and August 2011 (median follow-up, 5.82 years; interquartile range, 3.42-8.85 years). Histological specimens were scored for hepatic fibrosis stage according to the METAVIR scoring system.

Main Outcome Measure Incidence of composite outcome of ESLD, HCC, or death.

Results Patients experienced a graded increased risk in incidence of clinical outcomes based on baseline hepatic fibrosis stage (classification range, F0-F4): F0, 23.63 (95% CI, 16.80-33.24); F1, 36.33 (95% CI, 28.03-47.10); F2, 53.40 (95% CI, 33.65-84.76); F3, 56.14 (95% CI, 31.09-101.38); and F4, 79.43 (95% CI, 55.86-112.95) per 1000 person-years ($P<.001$). In multivariable negative binomial regression, fibrosis stages F2 through F4 and antiretroviral therapy were independently associated with composite ESLD, HCC, or all-cause mortality after adjustment for demographic characteristics, injection drug use, and CD4 cell count. Compared with F0, the incidence rate ratio (RR) for F2 was 2.31 (95% CI, 1.23-4.34; $P=.009$); F3, 3.18 (95% CI, 1.47-6.88; $P=.003$); and F4, 3.57 (95% CI, 2.06-6.19; $P<.001$). Human immunodeficiency virus treatment was associated with fewer clinical events (incidence RR, 0.27; 95% CI, 0.19-0.38; $P<.001$). For the 226 patients who underwent HCV treatment, the incidence of clinical events did not significantly differ between treatment nonresponders and untreated patients (incidence RR, 1.27; 95% CI, 0.86-1.86; $P=.23$). In contrast, no events were observed in the 51 patients with sustained virologic response (n = 36) and relapse (n = 15), including 19 with significant fibrosis.

Conclusion In this cohort of patients with HIV/HCV coinfection, hepatic fibrosis stage was independently associated with a composite outcome of ESLD, HCC, or death.

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Hepatitis C virus (HCV) coinfection occurs frequently in persons infected with the human immunodeficiency virus (HIV) because of shared routes of acquisition.[1,2] In the setting of effective HIV antiretroviral therapy (ART), the presence of HCV infection has been associated with an increased risk of death compared with those with HIV monoinfection. For example, in the North American AIDS Cohort Collaboration on Research and Design, HCV coinfected persons had an 85% greater risk of death.[3] Furthermore, in other cohort studies, HCV-related liver disease has emerged as a leading cause of morbidity and mortality in coinfected persons due, in part, to more rapid progression of liver disease with concurrent HIV infection; however, whether the risk of clinical outcomes differs by the liver fibrosis stage is unknown.[4-8]

Little is known about the effect of antiviral treatment for both HIV and HCV on clinical outcomes. Although some studies have suggested that ART for HIV may slow HCV disease progression, this effect has not been consistent across all studies and most have been retrospective in nature.[9,10] Similarly, HCV treatment guidelines recommend that it be administered to coinfected persons with the greatest risk of liver disease pro-

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gression as determined by histological liver disease staging.[11,12] Nevertheless, based on data suggesting rapid progression of HCV disease in patients infected with HIV, there is uncertainty about the relationship of histological disease stage and subsequent clinical events; furthermore, the effect of treatment for HCV, HIV, or both on the risk of these outcomes is incompletely defined.[13]

Accordingly, the objective of this study was to determine the incidence rates of end-stage liver disease (ESLD), hepatocellular carcinoma (HCC), or death (all-cause and liver-related mortality) among carefully characterized HIV/HCV coinfected adults according to their baseline histological disease stage and their exposure to effective treatment for HIV and HCV infections.

METHODS

Study Population

The study population consisted of 638 adults coinfected with HIV/HCV who received medical care at the Johns Hopkins University HIV and HIV/HCV Coinfection Clinics and who had a liver biopsy between July 1993 and August 2011. Liver biopsy is the standard of care in the clinic and was routinely offered to patients with chronic HCV and no evidence of ESLD. The patients in this biopsy cohort were representative of the overall clinic population with respect to age, race, injection drug use, and alcohol use.

Patients were prospectively followed up before and after liver biopsy with clinical and laboratory evaluations at approximately 3-month intervals in accordance with the protocol for routine medical care. Data on patient demographics, health-related behaviors (eg, drug and alcohol use), clinical diagnosis, prescribed medications, and laboratory tests were abstracted from medical records from the time of enrollment. Alcohol abuse (past or active) was defined by clinician diagnosis. Information on self-reported race is routinely collected by the institution at the time of registration. Data on the treatment of HIV and HCV infections were captured, including types of medications, duration of exposure, and treatment outcomes. Antiretroviral therapy was defined as regimens that included multiple agents with at least 1 HIV-1 protease inhibitor, nonnucleoside reverse transcriptase inhibitor, or integrase inhibitor. Treatment for HCV infection included interferon alfa or pegylated interferon with ribavirin. Laboratory assessments, conducted by licensed clinical laboratories, included complete blood cell count, serum chemistry panel, aspartate aminotransferase and alanine aminotransferase levels, CD4 cell count, HCV serology, HCV genotype, and plasma HIV-1 RNA and HCV RNA levels (the latter assessed by reverse-transcriptase polymerase chain reaction).

Liver Histology

Transcutaneous liver biopsy was performed using an 18-gauge needle. Liver tissue was fixed in 10% formalin, and paraffin-embedded sections were stained with hematoxylin and eosin and trichrome. Specimens deemed to be adequate based on specimen size and number of portal tracts were evaluated by a single pathologist (M.S.T.). The median length of biopsy specimens was 12.0 mm (interquartile range [IQR], 10.0-14.0 mm); 66% of 638 specimens included 10 or more portal tracts. Biopsies were scored for activity grade and fibrosis stage according to the METAVIR system, which classifies fibrosis according to a 5-point scale: F0, no fibrosis; F1, portal fibrosis without septa; F2, portal fibrosis with few septa; F3, numerous septa without cirrhosis; F4, cirrhosis.[14,15]

Clinical Outcomes

Liver-related and other clinical events were ascertained from medical records by trained clinicians using standardized forms to capture the date and characteristics of the event. *End-stage liver disease* was defined as evidence of hepatic decompensation (eg, variceal hemorrhage, hepatic encephalopathy, and ascites). The HCC diagnosis was based on radiologic characterization, serum α-fetoprotein level, pathological evaluation, or both. Death information was obtained using a combination of medical records and the National Death Index (NDI). All deaths were reviewed by a 3-physician member liver outcomes committee; members were blinded to the patient's liver disease stage and treatment status. Cause of death was classified as definitely liver related, probably liver related, possibly liver related, probably not liver related, or unknown. Deaths ascertained from NDI data included primary and underlying causes; deaths for which liver disease was mentioned as either a primary or underlying cause were considered to be liver related.

Statistical Methods

Descriptive statistics were used to characterize the population. Two main composite outcomes were analyzed: (1) *Any clinical outcome* defined as ESLD, HCC, or death (all-cause); and (2) *liver-related clinical outcomes* defined as ESLD, HCC, or liver-related death (classified as liver related by the NDI or definitely or probably liver related by the liver outcomes committee). Survival analysis was conducted to ascertain the association between baseline fibrosis stage and antiviral therapy with the 2 outcomes. The time origin of the analysis was the date of the liver biopsy. Individuals were censored if they had the outcome of interest, 1 year after their last clinic visit or August 1, 2011, whichever came first. If an individual experienced multiple events (eg, HCC and death), the date of the first event was used in the analysis. Kaplan-Meier survival curves were constructed and compared across covariates of interest using the log-rank test.

Incidence rates per 1000 person-years for each composite outcome were calculated by fibrosis stage and other covariates of interest. To estimate the crude and independent associations between fibrosis stage and antiviral therapy and the 2 outcomes of interest, we used univariate and multivariable negative binomial regression to es-

timate incidence rate ratios (RRs). Negative binomial regression was used instead of Poisson regression because of overdispersion of the variance relative to the mean. The primary analysis, which was designated a priori, was to compare the incidence of any clinical outcome and of any liver-related outcome among individuals with stages F1, F2, F3, and F4 to a reference group of F0. A test for trend was calculated by including fibrosis stage in the negative binomial regression model as an ordinal variable. The *P* value from this ordinal variable was considered as a test for trend. Multivariate models included both time-fixed (ie, race, sex, age at biopsy, history of injection drug use) and time-varying (ie, CD4 cell count, percentage of HIV-1 RNA measures <400 copies/mL, current exposure to ART) covariates. Variables were included in multivariable models if they were significantly associated with the outcome of interest at the level $P<.10$ or if they were deemed a priori to be biologically important (eg, age, sex, and race). Due to collinearity, HIV-1 RNA suppression and current ART exposure were not included in the same multivariable model; current ART was retained in the final model over viral suppression because it demonstrated a stronger statistical association with the outcomes. In the final multivariable model, covariates with $P<.05$ were considered statistically significant.

Because this was a clinical cohort, time-varying covariates were updated for the regression models every time an individual had a visit to the clinic and a CD4 cell count was available. The 29 individuals with missing CD4 cell count, HIV-1 RNA measures, or both at the time of biopsy entered the analysis and accumulated person-time from the date of the first available CD4 cell count rather than the date of the first biopsy (median, 2.78 years after biopsy). Additionally, 25% of 12 300 visits with a CD4 cell count available were missing corresponding HIV-1 RNA measurements. For visits in which HIV-1 RNA measures were missing, the value from the previous visit was carried forward. The data set including all time-fixed and time-varying covariates was used for all crude and multivariable models.

Hepatitis C virus treatment outcomes were defined as nonresponse, relapse, or sustained virologic response (SVR) according to standard definitions.[11,12] Individuals could have multiple courses of treatment and could contribute to multiple groups depending on the outcome of each individual course of treatment. The effect of treatment was evaluated using a time-varying covariate and was characterized by comparing incidence rates according to treatment and outcome (no HCV treatment, virologic nonresponse, relapse, and SVR). Hepatitis C virus treatment was not included in multivariable models because no outcomes were observed in patients with SVR and relapse. For this analysis, fibrosis stages F0 and F1 were combined as were F2, F3, and F4 due to small cell sizes after stratification by biopsy stage, HCV treatment, and HCV treatment outcome. The groupings of F0 and F1, and F2, F3, and F4 were designated a priori based on biological plausibility.

Three sensitivity analyses were performed. The first considered the definition of liver-related death; 2 different scenarios were considered: (1) only liver-related deaths confirmed by NDI were considered as liver-related deaths; and (2) excluding NDI liver-related deaths classified by the liver outcomes committee as possible or probably not related (eTable 1 available at http://www.jama.com). The results were not significantly different. The second sensitivity analysis considered the missing HIV-1 RNA measures in 2 ways: (1) multiple imputation of missing data; and (2) listwise deletion, which included only visits at which both CD4 cell count and HIV-1 RNA measurements were available; this involved 9209 visits (from 12 300) and 632 individuals (6 did not have any concurrent CD4 cell count and HIV-1 RNA measurements during follow-up; eTable 2). The results were not significantly different. The final sensitivity analysis used Cox proportional hazards models, including both time-fixed and time-varying covariates, to repeat all prior analyses (eTable 3). The assumption of proportionality was tested graphically by comparing the cumulative hazard function across different exposure categories for all variables included in the model. The assumption was met for all variables. The results were also unchanged. All statistical analyses were performed using Stata version 9 (StataCorp LP) and SAS for Windows version 9.2 (SAS Institute Inc).

All procedures and protocols for this study were reviewed and approved by the Johns Hopkins Institutional Review Board. Written informed consent was obtained from all patients.

RESULTS

Study Population

Demographic and clinical characteristics of the study population at the time of initial fibrosis staging are shown in TABLE 1. The median age was 45.6 years (IQR, 40.8-49.6 years). Of the 638 patients, 80% were black; 66%, men; 76%, past or active injection drug users; and 47%, alcohol abusers. At the time of initial biopsy, most patients (69%) were taking ART. The median cumulative exposure to ART prior to biopsy was 1.66 years (IQR, 0-4.21 years). The median CD4 cell count was 381 cells/μL (IQR, 238-550 cells/μL); 18% of individuals had a CD4 cell count of less than 200 cells/μL. The HIV-RNA level was undetectable (<400 copies/mL) in 56% of patients and greater than 10 000 copies/mL in 27%. The baseline median aspartate aminotransferase and alanine aminotransferase levels were 50 U/L (IQR, 35-79 U/L) and 48 U/L (IQR, 31-82 U/L). On initial staging, 467 patients (73%) had a METAVIR fibrosis stage consistent with no fibrosis (F0, n=208) or minimal portal fibrosis (F1, n=259). Sixty patients with portal fibrosis with few septa were staged at F3 and 41 patients with portal fibrosis with many septa were staged at F3. The remaining 70 patients with cirrhosis were staged at F4.

Incidence Rates of ESLD, HCC, and Death

The median follow-up time after biopsy was 5.82 years (IQR, 3.42-8.85 years). Overall, 150 clinical events (HCC, 5 cases; ESLD, 14 cases; all-cause death, 131) were observed during 3888.3 person-years (incidence rate per 1000 person-years, 38.58; 95% CI, 32.87-45.27). The incidence rates among patients with METAVIR stage F0 was 23.63 (95% CI, 16.80-33.24) and for stage F1 was 36.33 (95% CI, 28.03-47.10) per 1000 person-years (TABLE 2). The incidence rates for patients with fibrosis stages F0 and F1 were not significantly different (P=.07). Compared with patients with stage F0, those with F2 or greater had significantly higher incidence rates of clinical events; for F2, the incidence rates were 53.40 (95% CI, 33.65-84.76); F3, 56.14 (95% CI, 31.09-101.38); and F4, 79.43 (95% CI, 55.86-112.95) per 1000 person-years (P for trend <.001). FIGURE 1A shows the Kaplan-Meier curves for developing ESLD, HCC, or death (all-cause) after stratification by baseline fibrosis stage (log-rank test, P<.001).

Of the 150 events, 51 were designated as liver-related. The relationship between baseline fibrosis stage and the composite outcome of ESLD, HCC, or liver-related death was similar to that observed for all-cause mortality (Figure 1B; log-rank test, P<.001; P for trend <.001). Patients with cirrhosis had the highest incidence rate of liver events (RR, 43.56; 95% CI, 27.08-70.07) per 1000 person-years, whereas the lowest incidence rate was observed in patients with no fibrosis (RR, 2.86; 95% CI, 1.08-7.63) and with minimal fibrosis (RR, 10.20; 95% CI, 6.25-16.65) per 1000 person-years. No patient underwent a liver transplant.

After adjustment for confounders by multivariable negative binomial regression, liver fibrosis greater than METAVIR stage F1 remained independently associated with ESLD, HCC, or all-cause mortality as well as liver-related mortality (TABLE 3). The adjusted incidence RRs for cirrhosis (stage F4) were 3.57 (95% CI, 2.06-6.19) for all cause events and 16.82 (95% CI, 5.13-55.16) for liver-related events. Current ART exposure was independently associated with a decreased incidence of both all-cause events (adjusted incidence RR, 0.27; 95% CI, 0.19-0.38) and liver-related (adjusted incidence RR, 0.34; 95% CI, 0.18-0.66) events. In an alternative model that did not include ART exposure, HIV-1 RNA suppression was also independently associated with fewer all-cause events (0%-25% of HIV RNA measures <400 copies/mL compared with >75%: adjusted incidence RR, 2.38; 95% CI, 1.53-3.71) and liver-specific outcomes (adjusted incidence RR, 2.27; 95% CI, 1.08-4.80). Other characteristics independently associated with an increased risk of ESLD, HCC, or all-cause death included older age (>50 years), a history of injection drug use, and CD4 cell count lower than 200/µL. The adjusted incidence RRs for those older than 50 years was 1.71 (95% CI, 1.13-2.60) and for those with a history of injection drug use was 2.41 (95% CI, 1.41-4.12). Compared with a CD4 cell count of less than 200/µL, the adjusted incidence RRs for CD4 cell count from 200/µL to 350/µL was 0.27 (95% CI, 0.16-0.44) and for a CD4 cell count higher than 350/µL, 0.21 (95% CI, 0.14-0.31). Only older age (>50

Table 1. Characteristics of the Study Population at Baseline Liver Biopsy of Patients Coinfected With Human Immunodeficiency Virus and Hepatitis C Virus

Characteristics	No. (%) of Patients (n = 638)[a]
Age, median (IQR), y	45.6 (40.8-49.6)
Men	424 (66)
Black	512 (80)
History of alcohol abuse	300 (47)
History of injection drug use, n = 637	483 (76)
BMI, median (IQR), n = 461	25.3 (22.6-29.0)
Combination antiretroviral therapy	440 (69)
CD4 cell count/µL, n = 615	
<200	111 (18)
200-349	152 (25)
350-499	148 (24)
≥500	202 (33)
HIV RNA, copies/mL, n = 601	
<400	338 (56)
400-10 000	102 (17)
>10 000	161 (27)
ALT, median (IQR), U/L, n = 624	48 (31-82)
AST, median (IQR), n = 621	50 (35-79)
METAVIR hepatic fibrosis stage[b]	
F0	208 (33)
F1	259 (40)
F2	60 (9)
F3	41 (6)
F4	70 (11)
HCV genotype, n = 586	
1a	404 (69)
1b	127 (22)
Other	55 (9)
HCV viral load, median (IQR), n = 626	766 000 (500 000-2 330 000)

Abbreviations: ALT, alanine aminotransferase level; AST, aspartate aminotransferase level; BMI, body mass index, calculated as weight in kilograms divided by height in meters squared; HCV, hepatitis C virus; HIV human immunodeficiency virus; IQR, interquartile range.
[a] Unless otherwise specified in the Table.
[b] METAVIR hepatic fibrosis stages: F0, no fibrosis; F1, portal fibrosis without septa; F2, portal fibrosis with few septa; F3, numerous septa without cirrhosis; F4, cirrhosis.

Table 2. Incidence Rates by METAVIR Stage

METAVIR Fibrosis Stage[a]	No. of Events	Person-Years[b]	Incidence Rate per 1000 Person-Years (95% CI)[c]
All outcomes: ESLD, HCC, or death			
F0	33	1396.3	23.63 (16.80-33.24)
F1	57	1568.8	36.33 (28.03-47.10)
F2	18	337.1	53.40 (33.65-84.76)
F3	11	195.9	56.14 (31.09-101.38)
F4	31	390.3	79.43 (55.86-112.95)
Total	**150**	**3888.3**	38.58 (32.87-45.27)
Liver-related outcomes: ESLD, HCC, or liver-related death			
F0	4	1396.3	2.86 (1.08-7.63)
F1	16	1568.8	10.20 (6.25-16.65)
F2	9	337.1	26.70 (13.89-51.32)
F3	5	195.9	25.52 (10.62-61.31)
F4	17	390.3	43.56 (27.08-70.07)
Total	**51**	**3888.3**	13.12 (9.97-17.26)

Abbreviations: ESLD, end-stage liver disease; HCC, hepatocellular carcinoma.
[a] METAVIR fibrosis stages: F0, no fibrosis; F1, portal fibrosis without septa; F2, portal fibrosis with few septa; F3, numerous septa without cirrhosis; F4, cirrhosis.
[b] Person-years were calculated from the time of biopsy to the time of event or last follow-up.
[c] Tests for trend were significant for all-cause outcomes ($P<.001$) and liver-related outcomes ($P<.001$).

years) was independently associated with an increased risk of ESLD, HCC, or liver-related death (adjusted incidence RR, 2.05; 95% CI, 1.02-4.10).

HCV Treatment and Incidence of ESLD, HCC, and Death

Of the 638 enrolled patients, 226 (35%) underwent HCV treatment (TABLE 4). Treatment rates were lower among those with no or minimal fibrosis (F0 or F1; 28.7%, 134 of 467) than among those with advanced fibrosis (≥F2; 53.8%, 92 of 171; $P<.001$); however, the observed SVR rates were similar in both patient groups (17.1%, 21 of 123 with F0 or F1 and 16.9%, 15 of 89 with ≥F2; $P=.45$) . Similarity in rates of SVR or relapse in patient groups is shown in eTable 4 (available at http://www.jama.com). As shown in Table 4, stratified by severity of fibrosis, there were no significant differences in the incidence rates of ESLD, HCC, or all-cause mortality between HCV treatment nonresponders (defined as lack of HCV RNA suppression below the limit of detection during therapy) and untreated patients. For the 226 patients who underwent HCV treatment, the incidence of clinical events did not significantly differ between treatment nonresponders and untreated patients (incidence RR, 1.27; 95% CI, 0.86-1.86; $P=.23$). In contrast, no clinical events were observed in the 36 patients who experienced SVR or in the 15 patients who had HCV virologic response followed by virologic relapse while receiving HCV treatment, including 19 patients with significant fibrosis. FIGURE 2 shows the Kaplan-Meier curves for developing ESLD, HCC, or all-cause mortality after stratification by receipt of HCV treatment and, among those treated, virologic response pattern observed (log-rank test, $P=.005$).

COMMENT

In the era of effective ART, patients coinfected with HIV/HCV are at increased risk of morbidity and mortality compared with patients with HIV infection alone.[3] The underlying basis for this observation has been incompletely understood. In this context, we observed a graded risk in the increase in association between baseline liver fibrosis stage and incidence of clinical events in 638 coinfected adults who were followed up prospectively. The difference in incidence rates for patients with cirrhosis and no fibrosis was greater than 50 events per 1000 person-years. Importantly, we found that HIV treatment with ART, higher CD4 cell count, and effective HCV treatment were associated with significantly lower risk of clinical outcomes including those related to liver disease in some cases. As such, our findings have potential implications with respect to liver disease staging and initiation of antiviral therapy for coinfected persons.

Although patients coinfected with HIV/HCV are at greater risk for death than those with HIV alone, the contributions of HCV-related liver disease and other factors closely associated with HCV infection, namely injection drug use, have been difficult to delineate, often because of incomplete assessment of liver disease stage.[1,3,16] Our data demonstrating that hepatic fibrosis stage is independently associated with liver-related events or death suggest that the degree of liver disease itself contributes to the excess morbidity and mortality observed in coinfected patients. Furthermore, these findings are consistent with the current clinical practice of using fibrosis staging of patients coinfected with HIV/HCV for prognostication and guiding HCV treatment decisions.[11,12,17] Although screening for infection with HCV antibody testing is frequently performed in patients infected with HIV, fibrosis staging with liver biopsy has been limited in many clinical care settings due to the lack of availability, the risk of complications (including pain, bleeding, and death), and the relatively high cost of the procedure.[1,18] Alternatives for fibrosis staging such as noninvasive serum markers, liver stiffness measurement by elastography, or both warrant further investigation in this patient population.[19-25] However, the prospective utility of these methodologies to monitor HCV disease has not been established.

Based largely on expert opinion, guidelines for the management of HCV for patients infected with HIV recommend HCV disease staging with liver biopsy and the provision of HCV treatment to patients found to be at the

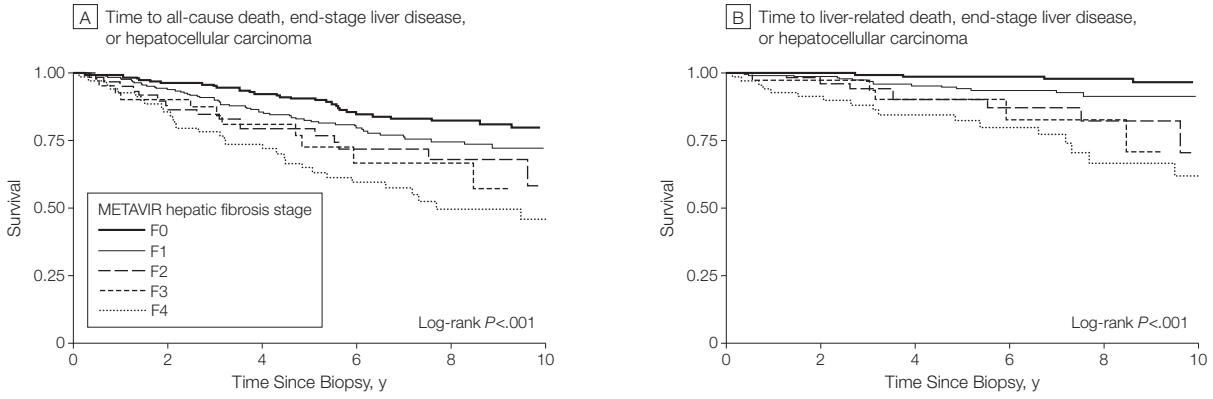
greatest risk of clinical outcomes.[11,12,17] Our finding that patients with no fibrosis had a relatively low incidence of liver-related events over approximately 6 years provides support for the expert recommendation for the deferral in such persons of current HCV therapies, which are associated with adverse effects, potential drug-drug interactions with ART, and reduced response rates in the coinfected population. On the other hand, our data demonstrating increased risk of liver-related events in patients with more advanced hepatic fibrosis suggest that avoiding HCV treatment may be associated with greater medical risk. Although our findings are informative, prospective confirmation of this observed graded risk relationship of fibrosis and incident clinical events is needed in other clinical settings.

Interestingly, in our cohort, patients who underwent HCV treatment and achieved transient (viral response followed by relapse) or sustained (SVR) suppression of HCV RNA did not experience any serious clinical outcomes during the observation period, including 19 patients with bridging fibrosis or cirrhosis. Although this observation might reflect selection bias in the types of treated and untreated patients, the incidence of clinical outcomes for untreated patients in our cohort was similar to that for treated patients with HCV virologic non-response. Furthermore, our findings are consistent with the observation in the Hepatitis C Antiviral Long-term Treatment Against Cirrhosis (HALT-C) study that ESLD, HCC, and death were less common in HCV monoinfected patients who achieved SVR or had relapse following HCV treatment.[26]

The relationship of effective HCV treatment and clinical outcomes in our cohort is encouraging; however, the overall effect of interferon alfa– and ribavirin-based HCV treatment on clinical outcomes was limited due to relatively low therapy uptake and infrequent viral response. For example, despite the presence of an on-site, dedicated HIV/HCV coinfection clinic, HCV treatment was administered to only about half of the patients with significant fibrosis established by liver biopsy. Although the reasons for the lack of HCV treatment were not measured in this study, low uptake of treatment has been previously associated in this population with comorbid conditions, uncontrolled HIV disease, and active substance abuse.[27,28]

Although efforts are needed to increase treatment uptake, the second limitation of HCV treatment with interferon alfa plus ribavirin in our cohort was low efficacy; more than 80% of 212 treated patients did not achieve HCV RNA suppression. The low SVR rates observed may reflect a largely African American, HCV genotype 1–infected patient population in our clinic; however, the SVR rate achieved was similar to that observed in clinical trials, including the multicenter, North American study of pegylated interferon plus ribavirin, the PARADIGM study.[29] This consistency across clinical trial and practice settings suggests that low SVR rates observed in HIV-infected patients may reflect intrinsic limitations of the treatment regimen. Hepatitis C virus N3/4A protease inhibitors used in combination with pegylated interferon plus ribavirin may offer higher SVR rates; however, the safety, tolerability, and efficacy have not been established in patients coinfected with HIV/HCV and such regimens have the potential for significant drug-drug interactions with ART.[30,31] Thus, our data underscore the need for accelerated research to test novel combinations of direct-acting antivirals for HCV in coinfected patients.[32]

Figure 1. Cumulative Survival Free of End-Stage Liver Disease, Hepatocellular Carcinoma, or Death From Baseline



No. at risk

METAVIR fibrosis stage												
F0	208	186	155	112	84	36	208	186	155	112	84	36
F1	259	222	181	127	75	34	259	222	181	127	75	34
F2	60	50	42	25	12	5	60	50	42	25	12	5
F3	41	32	22	11	9	3	41	32	22	11	9	3
F4	70	58	45	31	17	7	70	58	45	31	17	7

METAVIR hepatic fibrosis stages: F0, no fibrosis; F1, portal fibrosis without septa; F2, portal fibrosis with few septa; F3, numerous septa without cirrhosis; F4, cirrhosis.

We also observed that effective treatment of HIV infection was independently associated with a decreased risk of liver-related outcomes. After adjusting for potential confounders, coinfected patients receiving ART were approximately 66% less likely to experience ESLD, HCC, or liver-related death. Until recently, the decision to initiate ART has been based largely on the level of immunosuppression (ie, CD4 cell counts) or the development of AIDS-defining illnesses and the potential effect of earlier initiation of ART on HCV-related liver disease has been less clear. Largely based on retrospective and cross-sectional studies demonstrating the decreased likelihood of liver disease in coinfected patients taking ART, some expert guidelines recommend the initiation of ART in HIV/HCV coinfected patients independent of CD4 cell count.[12] Although our prospective data are not sufficient to answer the question of early initiation of ART (CD4 cell count >500 cells/μL), the observation that ART was independently associated with a lower risk of liver-related outcomes provides supportive evidence for the provision of ART to all coinfected patients who are willing and able to commit to therapy, as recently recommended by the Department of Health and Human Services Panel on Antiretroviral Guidelines for Adults and Adolescents.[33] However, an important exception to this recommendation may be coinfected patients with high CD4 cell counts who are considering HCV treatment because the potential for drug interactions between medications used to treat both infections may be complex.[33] As such, some cli-

Table 3. Crude and Adjusted Incidence Rate Ratios[a]

	ESLD, HCC, or All-Cause Mortality, Incidence RR (95% CI)				ESLD, HCC, or Liver-Related Mortality, Incidence RR (95% CI)			
	No. of Events[b]	Person-Years[b]	Crude	Adjusted[c]	No. of Events[b]	Person-Years[b]	Crude	Adjusted[c]
METAVIR fibrosis stage[d]								
F0	33	1363	1 [Reference]	1 [Reference]	4	1363	1 [Reference]	1 [Reference]
F1	57	1511	1.53 (0.97-2.41)	1.59 (0.99-2.55)	16	1511	3.86 (1.21-12.24)	3.53 (1.08-11.48)
F2	18	330	2.25 (1.22-4.16)	2.31 (1.23-4.34)	9	330	9.60 (2.72-33.90)	9.34 (2.60-33.58)
F3	11	194	2.50 (1.21-5.19)	3.18 (1.47-6.88)	5	194	10.03 (2.46-40.84)	11.15 (2.63-47.35)
F4	31	388	3.19 (1.88-5.40)	3.57 (2.06-6.19)	17	388	16.02 (5.01-51.25)	16.82 (5.13-55.16)
Race								
Black	124	3098	1 [Reference]	1 [Reference]	39	3098	1 [Reference]	1 [Reference]
White	26	687	1.01 (0.64-1.58)	1.01 (0.62-1.65)	12	687	1.51 (0.74-3.06)	1.38 (0.62-3.06)
Sex								
Men	100	2531	1 [Reference]	1 [Reference]	34	2531	1 [Reference]	1 [Reference]
Women	50	1254	0.99 (0.69-1.43)	0.86 (0.59-1.27)	17	1254	1.00 (0.53-1.87)	0.75 (0.38-1.46)
Age, y								
≤50	112	3064	1 [Reference]	1 [Reference]	35	3064	1 [Reference]	1 [Reference]
>50	38	721	1.46 (0.98-2.17)	1.71 (1.13-2.60)	16	721	1.95 (1.02-3.75)	2.05 (1.02-4.10)
Injection drug use								
No	18	956	1 [Reference]	1 [Reference]	10	956	1 [Reference]	1 [Reference]
Yes	131	2829	2.54 (1.52-4.24)	2.41 (1.41-4.12)	40	2829	1.46 (0.69-3.07)	1.66 (0.76-3.63)
CD4 cell count/μL[e]								
<200	67	594	1 [Reference]	1 [Reference]	14	594	1 [Reference]	1 [Reference]
200-350	28	824	0.29 (0.18-0.46)	0.27 (0.16-0.44)	11	824	0.57 (0.24-1.35)	0.54 (0.22-1.31)
>350	55	2364	0.22 (0.15-0.32)	0.21 (0.14-0.31)	26	2364	0.53 (0.26-1.08)	0.52 (0.25-1.09)
HIV-1 RNA measures <400 copies/mL, %[e,f]								
≥75	45	1891	1 [Reference]		20	1891	1 [Reference]	
26-75	43	981	1.87 (1.20-2.90)		12	981	1.16 (0.54-2.48)	
0-25	62	908	3.00 (1.98-4.54)		19	908	2.13 (1.07-4.25)	
ART exposure[e]								
No	74	929	1 [Reference]	1 [Reference]	22	929	1 [Reference]	1 [Reference]
Yes	76	2856	0.27 (0.19-0.39)	0.27 (0.19-0.38)	29	2856	0.36 (0.19-0.66)	0.34 (0.18-0.66)

Abbreviations: ART, antiretroviral therapy; ESLD, end-stage liver disease; HCC, hepatocellular carcinoma; RR, rate ratio.
[a] Incidence RRs were estimated using negative binomial regression.
[b] Events, person-years, and incidence rate ratios were calculated from the data set including time-varying covariates. Twenty-nine persons who had missing CD4 cell count, HIV-1 RNA measurements, or both at the time of biopsy entered the analysis and accumulated person-time from the date of the first available CD4 cell count rather than the date of the first biopsy (median, 2.78 years after biopsy).
[c] Adjusted for age, sex, race, injection drug use, time-varying CD4 cell count, and current ART exposure.
[d] METAVIR fibrosis stages: F0, no fibrosis; F1, portal fibrosis without septa; F2, portal fibrosis with few septa; F3, numerous septa without cirrhosis; F4, cirrhosis.
[e] Time-varying measures.
[f] Because of collinearity, HIV RNA suppression and receipt of ART were not included in the same multivariable model; current ART was retained in the final model over viral suppression because it demonstrated a stronger statistical association with the outcomes.

nicians and patients may choose to delay the initiation of ART until HCV treatment has been completed.[33]

This study had several limitations. First, the decisions to initiate or withhold HIV or HCV treatment were made by clinicians according to standard medical practice; the lack of randomization to these interventions introduces the potential for selection bias. For example, treatment may be greater in persons who are more focused on their health and less likely to engage in harmful behaviors. Interestingly, the incidence of clinical outcomes was similar in coinfected patients who received HCV treatment but did not respond and those who were not treated, suggesting that bias is unlikely to explain the observed treatment effect. Second, other factors that may affect liver disease, such as alcohol, may be incompletely measured. In our study, alcohol use was ascertained from clinical records, which may underestimate this exposure. Although questionnaires to estimate alcohol exposure exist, we have previously found these measures to not correlate well with liver disease in our population, underscoring the difficulty in quantifying alcohol exposure.[34,35] Third, we were unable to adjudicate the cause of death in all patients despite extensive efforts. Individuals with an unknown cause of death were excluded from analyses involving liver-related mortality; additional sensitivity analyses suggest that these missing data do not substantially affect our findings. Fourth, although our findings are likely generalizable to similar patient populations, replication in other clinical settings is needed before drawing definitive conclusions. Finally, the limited length of follow-up, number of person-years, and number of events reflected in wide confidence intervals for some results may represent potential limitations.

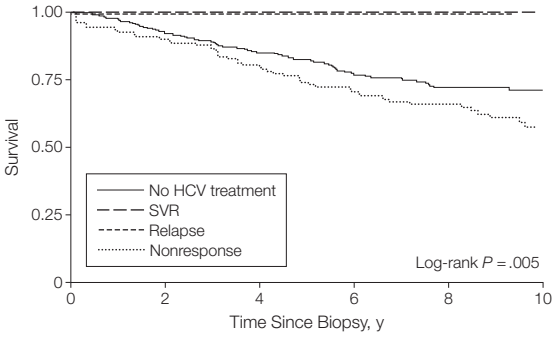
Among persons coinfected with HIV/HCV, baseline hepatic fibrosis stage was independently associated with the risk of liver-related complications and death, demonstrating a graded risk relationship with the lowest incidence observed among patients with no fibrosis. Independent of liver disease stage, effective antiviral therapy for both HIV and HCV infections was associated with a decreased risk of liver-related events and death. These data support recent guidelines that recommend HIV treatment for most coinfected persons who are willing and able to adhere to therapy, including those with high CD4 cell counts.[33] Furthermore, although SVR rates were modest, HCV treatment may benefit patients coinfected with HIV/HCV, particularly those with sig-

Table 4. Incidence Rates of End-Stage Liver Disease, Hepatocellular Carcinoma, and All-Cause Mortality by METAVIR Stage and Outcome of Hepatitis C Virus (HCV) Treatment[a]

	HCV Treatment			
		Yes (n = 226)[c]		
METAVIR Fibrosis Stage[b]	No (n = 412)	Nonresponse (n = 161)	Relapse (n = 15)	Sustained Virologic Response (n = 36)
F0-F1, n = 467				
No.	333	91	11	21
Events	69	20	0	0
Person-years	2242.3	503.3	54.2	91.6
Incidence rate (95% CI)[d]	30.77 (24.31-38.96)	39.74 (25.64-61.60)	0.0	0.0
F2-F4, n = 171				
No.	79	70	4	15
Events	36	23	0	0
Person-years	469.5	339.2	32.5	73.7
Incidence rate (95% CI)[d]	76.67 (55.31-106.29)	67.80 (45.05-102.03)	0.0	0.0

[a] For this analysis, fibrosis stages F0 and F1 were combined as were F2, F3, and F4 due to small cell sizes after stratification by biopsy stage, HCV treatment, and HCV treatment outcome. The groupings of F0 and F1, and F2, F3, and F4 were designated a priori based on biological plausibility.
[b] METAVIR fibrosis stages: F0, no fibrosis; F1, portal fibrosis without septa; F2, portal fibrosis with few septa; F3, numerous septa without cirrhosis; F4, cirrhosis.
[c] Sample sizes shown for response are defined at last HCV treatment; 14 people were still taking treatment at the end of follow-up or the outcome of their last treatment was unknown.
[d] Incidence rate is reported per 1000 person-years.

Figure 2. Cumulative Survival Free of End-Stage Liver Disease, Hepatocellular Carcinoma, or Death According to Response to Hepatitis C Virus (HCV) Treatment From Baseline



No. at risk						
No HCV treatment	610	397	302	196	118	45
SVR	0	19	24	15	9	7
Relapse	2	15	11	6	5	2
Nonresponse	17	109	100	81	59	26

Hepatitis C virus treatment was considered as a time-varying covariate because individuals could undergo multiple courses of treatment during follow-up with different outcomes. SVR indicates sustained virologic response.

nificant hepatic fibrosis. Nevertheless, these data highlight the need for more effective HCV treatment regimens for this population; clinical trials of novel combinations of direct-acting antivirals for HCV should be performed as soon as possible.

Author Contributions: Drs Limketkai and Sulkowski had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Mehta, Sutcliffe, Thomas, Sulkowski.
Acquisition of data: Limketkai, Higgins, Torbenson, Brinkley, Moore, Thomas, Sulkowski.
Analysis and interpretation of data: Limketkai, Mehta, Sutcliffe, Moore, Thomas, Sulkowski.
Drafting of the manuscript: Limketkai, Thomas, Sulkowski.
Critical revision of the manuscript for important intellectual content: Limketkai, Mehta, Sutcliffe, Higgins, Torbenson, Brinkley, Moore, Thomas, Sulkowski.
Statistical analysis: Mehta, Sutcliffe.
Obtained funding: Thomas, Sulkowski.
Administrative, technical, or material support: Higgins, Torbenson, Moore, Sulkowski.
Study supervision: Higgins, Thomas, Sulkowski.
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