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CD4 Recovery on Antiretroviral Therapy Is Associated With Decreased Progression to Liver Disease Among Hepatitis C Virus-Infected Injecting Drug Users

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Background. Human immunodeficiency virus (HIV) coinfection accelerates liver disease progression in individuals with chronic hepatitis C. We evaluated the associations of CD4, HIV RNA, and antiretroviral therapy (ART)-induced CD4 recovery with liver diagnoses in a prospective cohort of injecting drug users (IDUs).

Methods. We evaluated 383 coinfected IDUs in the Boston area, prospectively observed for a median of 1.8 years. Liver disease progression included the first occurrence of hepatocellular carcinoma, variceal bleeding, ascites, encephalopathy, or death due to hepatic failure. Multivariable-adjusted extended Cox models were specified to estimate hazard ratios (HRs) for comparisons of CD4, change in CD4 (from nadir), and HIV RNA with respect to liver disease progression events.

Results. Twenty-four persons experienced a liver disease progression event over 1155 person-years (2.1 per 100 person-years), including 20 deaths attributed to end-stage liver disease (1.7 per 100 person-years). CD4 at baseline and over follow-up strongly predicted liver disease progression (baseline CD4 <200 vs ≥200: HR = 5.23, 95% confidence interval [CI], 2.30–11.92; time-updated CD4 <200 vs ≥200: HR = 11.79, 95% CI, 4.47–31.07). Nadir CD4 was also a strong indicator (<100 vs ≥100: HR = 3.52, 95% CI, 1.54–8.06). A lack of CD4 recovery (failure to increase 100 cells over nadir) among ART initiators was associated with increased risk (HR = 7.69; 95% CI, 2.60–22.69). Human immunodeficiency virus RNA was not significantly associated with liver disease progression.

Conclusions. Impaired immune function was highly predictive of liver disease progression in this cohort of IDUs, and a lack of CD4 recovery on ART was associated with increased risk of progression to HCV-associated liver disease.

Keywords. CD4; CD4 lymphocyte count; drug users; hepatitis C; highly active antiretroviral therapy; HIV; immune reconstitution; liver/hepatitis; viral load.

Liver complications have emerged as a leading nonacquired immune deficiency syndrome-related cause of morbidity and mortality among human immunodeficiency virus (HIV)-infected populations receiving combination antiretroviral therapy (ART) [1–3]. Human immunodeficiency virus coinfection in the context of chronic hepatitis C virus (HCV) infection accelerates progression to clinical liver outcomes, at least among hemophiliacs [4–6], although the mechanisms have yet to be fully characterized. This is a significant issue in the United States, where 250 000–300 000 individuals (up to 30% of the HIV-infected population) are coinfected [7, 8]. The importance of this is magnified in populations of HIV-infected injecting drug users (IDUs), where the prevalence of HCV coinfection can reach 90% or more due to a shared mode of transmission [9–11].

Recovery and/or maintenance of an adequate CD4 count could facilitate the necessary immune response to control HCV and slow the progressive course of

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hepatic fibrosis. Some prior studies have suggested that CD4 count may be inversely associated with fibrosis, cirrhosis, hepatic decompensation, and/or death due to end-stage liver disease [12–19], although others have not [20–23]. There appears to be a complex interplay between the 2 viruses, host immunologic response, and treatment. Antiretroviral therapy has been shown to improve control of HIV and HCV [24–26], but the extent to which this effect is mediated by CD4 count and/or HIV viral load (VL) changes is unclear. In addition, previous studies have suggested that HIV- and HCV-coinfected individuals may have lesser recovery of CD4 count after being treated with ART compared with HIV-monoinfected persons [27–33]. Within coinfected populations, a greater CD4 rebound after ART could be an important protective factor with respect to liver outcomes.

Human immunodeficiency virus itself has been postulated to exacerbate chronic HCV by directly infecting hepatocytes or interacting with other cell types that affect liver function [34]. It follows then that HIV VL could affect progression of liver disease among coinfected populations to some degree [35, 36].

The goal of this prospective study was to estimate the predictive values of CD4, HIV VL, and ART-induced CD4 recovery with respect to clinical progression events related to chronic HCV liver disease in an urban cohort of HIV/HCV-coinfected IDUs.

METHODS

Study Population and Assessments

The study population was drawn from the Hepatitis C, HIV and Related Morbidity (CHARM) cohort study conducted at Boston University Medical Center and its affiliated healthcare centers. The CHARM study was initiated in August 2000 to prospectively evaluate the natural history of HCV infection and HIV/HCV coinfection in an inner city IDU population. Details on the CHARM cohort have been published elsewhere [37, 38]. Injecting drug users who were 18 years or older and had serologic evidence of HCV infection were eligible for the CHARM study. Of 444 HIV/HCV-coinfected individuals in CHARM, 10 enrolled after October 2007 (2%), 50 did not have available CD4 measures at baseline and for at least 1 follow-up visit (11%), and 1 was found to have had a liver disease progression event before enrollment (<1%). Thus, 383 (86%) IDUs met the inclusion criteria for this particular analysis. The CHARM study and the current analyses have been approved by the Boston University and Harvard University Institutional Review Boards, and informed consent was obtained from all participants.

Study visits and medical chart reviews for the CHARM cohort were conducted at enrollment and annually thereafter; as of 2005, follow-up visits and chart reviews were conducted semiannually. Patients were generally seen in the participating clinics as per usual HIV care at approximate 3-month intervals, at which time laboratory values, including $CD4^+$ T-cell counts and HIV plasma RNA VL, were collected. In addition, information on demographics, diagnoses, laboratory assays, substance use, and medication history was assessed by questionnaire and confirmed by chart review.

Liver Disease Progression Outcome

The primary outcome of interest, clinical liver disease progression, was defined as the first diagnosis of any of the following events: HCV-associated encephalopathy, variceal bleeding, ascites, spontaneous bacterial peritonitis, hepatocellular carcinoma, or death due to end-stage hepatic failure. Information on liver events was obtained from patients during study interviews, supplemented by chart review, and adjudicated and confirmed by a panel of clinical experts. Deaths were initially identified by chart review and confirmed via annual review of Massachusetts Death Registries and National Death Index searches.

Statistical Methods

Participants were considered to be at risk from study enrollment until the first occurrence of a liver disease progression event, death from any cause, loss to follow-up, or December 31, 2007. Longitudinal data were divided into 3-month intervals for the purposes of analysis. CD4 count (and change in CD4 from nadir), HIV RNA VL, ART initiation status, outcomes, and follow-up status were updated at each time point. If a value for CD4 or VL was missing for a given interval, previous values were carried forward for up to 1 year. Study participants who were lost to follow-up (did not return for a visit during the study period and had no data available for over 1 year) were censored at the time of their last known visit. Cox regression models were extended to include time-dependent variables and used to calculate unadjusted and multivariable-adjusted hazard ratios (HRs) and 95% confidence intervals (CIs). Adjusted models considered the covariates shown in Table 1. Reduced models were fit by removing covariates not associated with the outcome and which did not change the CD4 or VL effect estimate by 10% or more. All models were fit using SAS version 9.2 (SAS Institute Inc., Cary, NC).

RESULTS

Clinical liver disease progression events occurred in 24 of 383 study participants over 1155 person-years of follow-up (median 1.8, maximum 7.5 person-years). Of the 24 incident events, 12 (50%) were deaths due to end-stage liver disease; 10 (42%) were 1 or more diagnoses representative of hepatic decompensation (ascites, hepatic encephalopathy, spontaneous bacterial peritonitis, variceal bleeding); and 2 (8%) were hepatocellular carcinomas. Eighty-one individuals (21%) were lost to follow-up after contributing a median of 2.0 person-years. Distributions of demographic and clinical characteristics by CD4 count and HIV

Table 1. Distribution of Baseline Characteristics Overall and in Relation to CD4 Count (Cells/μL) and HIV Viral Load (Copies/mL)

		CD4 Count (Cells/mm^3)		HIV RNA Viral Load (Copies/mL)		
Variable[a]	Total N = 383 N (%)[b]	<200 N = 89 N (%)[b]	≥200 N = 288 N (%)[b]	≤75 N = 155 N (%)[b]	76–10 000 N = 119 N (%)[b]	>10 000 N = 92 N (%)[b]
Age >45 years	212 (55)	43 (48)	166 (58)	107 (69)	62 (52)	34 (37)
Male	276 (72)	66 (74)	205 (71)	118 (76)	78 (66)	66 (72)
Race						
Black non-Hispanic	171 (45)	36 (40)	132 (46)	76 (49)	48 (40)	38 (41)
White non-Hispanic	104 (27)	24 (27)	78 (27)	38 (25)	38 (32)	25 (27)
Hispanic	100 (26)	28 (31)	71 (25)	37 (24)	32 (27)	26 (28)
Other	8 (2)	1 (1)	7 (2)	4 (3)	1 (1)	3 (3)
History of diabetes	41 (11)	9 (10)	31 (11)	24 (15)	8 (7)	7 (8)
Markers of HBV	272 (78)	68 (83)	200 (76)	111 (77)	81 (76)	71 (80)
FIB-4						
<1.45 (mild fibrosis)	151 (41)	32 (38)	115 (41)	64 (42)	46 (39)	36 (40)
1.45–3.25 (moderate)	147 (40)	29 (34)	117 (42)	61 (40)	48 (41)	34 (38)
>3.25 (advanced)	72 (19)	24 (28)	48 (17)	29 (19)	24 (20)	19 (21)
HCV genotype 1	176 (80)	41 (85)	133 (79)	74 (77)	59 (83)	39 (80)
HCV viral load ≥10^6 IU/mL	106 (47)	31 (58)	74 (44)	39 (44)	36 (51)	28 (47)
HCV treatment	27 (7)	4 (5)	23 (8)	13 (9)	9 (8)	5 (6)
Duration of IDU >25 years	154 (48)	40 (51)	113 (47)	67 (51)	52 (53)	30 (38)
Current IDU	103 (27)	30 (34)	71 (25)	30 (20)	36 (31)	30 (33)
AUDIT						
<8	102 (56)	24 (51)	76 (58)	40 (63)	34 (57)	24 (46)
8–19 (hazardous)	54 (30)	14 (30)	37 (28)	13 (21)	18 (30)	20 (38)
≥20 (dependence)	27 (15)	9 (19)	18 (14)	10 (16)	8 (13)	8 (15)
Nadir CD4						
<50	61 (16)	46 (52)	15 (5)	22 (14)	19 (16)	18 (20)
50–199	114 (30)	42 (48)	71 (25)	48 (31)	31 (26)	32 (35)
≥200	203 (54)	0 (0)	202 (70)	85 (55)	69 (58)	41 (45)
CD4						
<200	89 (24)	89 (100)	0 (0)	19 (12)	26 (22)	40 (43)
200–499	161 (43)	0 (0)	161 (56)	72 (47)	54 (45)	32 (35)
≥500	127 (34)	0 (0)	127 (44)	63 (41)	39 (33)	20 (22)
HIV RNA						
≤75	155 (42)	19 (22)	135 (48)	155 (100)	0 (0)	0 (0)
76–10 000	119 (33)	26 (31)	93 (33)	0 (0)	119 (100)	0 (0)
>10 000	92 (25)	40 (47)	52 (19)	0 (0)	0 (0)	92 (100)
Initiated ART						
At baseline	281 (81)	65 (79)	212 (82)	130 (88)	83 (80)	62 (78)
In follow-up	37 (11)	12 (15)	25 (10)	13 (9)	10 (10)	9 (11)
Never	27 (8)	5 (6)	21 (8)	5 (3)	11 (11)	9 (11)

Abbreviations: ART, antiretroviral therapy; AUDIT, alcohol use disorders identification test; FIB-4, fibrosis-4; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IDU, injecting drug use.

[a] Missing observations for each variable (N, %): age, 0 (0); sex, 0 (0); race, 0 (0); diabetes, 0 (0); HBV, 33 (9); FIB-4, 13 (3); HCV genotype, 162 (42); HCV viral load, 157 (41); HCV treatment, 19 (5); years of IDU, 60 (16); current IDU, 3 (1); alcohol, 200 (52); nadir CD4, 5 (1); CD4, 6 (2); HIV viral load, 17 (4); ART initiation, 38 (10).

[b] Percentages are among the nonmissing.

VL status at baseline are displayed in Table 1. Age at enrollment ranged from 24 to 69 years (median 45), and there was a higher proportion of older patients among the high CD4 and HIV RNA <75 copies/mL categories. Nearly three-quarters were male, and black non-Hispanics (45%) were represented more than other ethnicities. Most were not diabetic, but 272 had markers of hepatitis B virus (HBV) infection: of these, 9 had evidence of active infection (positive DNA, surface antigen, or e antigen), whereas 263 had evidence of prior infection only (surface or core antibody). Where known, patients were largely

infected with HCV genotype 1, and HCV RNA was inversely associated with CD4 count. Few (7%) reported having been treated for HCV infection with interferon/ribavirin. Nineteen percent were characterized at enrollment as having advanced liver fibrosis evidenced by fibrosis-4 (FIB-4) above 3.25, a validated index score based on age and liver function biomarkers [39]. Advanced fibrosis as defined by FIB-4 was elevated among those with low baseline CD4 (28% vs 17%). Approximately half the population had been injecting drugs for more than 25 years, and 27% reported that they were currently injecting (within 6 months of enrollment). Forty-four percent reported hazardous alcohol intake as defined by an AUDIT score ≥8. Most had initiated ART, and 42% had suppressed HIV VL at enrollment.

Table 2 presents unadjusted HRs for liver disease progression for covariates other than CD4 and VL. We observed no association of any of these covariates with liver disease progression, although HRs were slightly elevated for male vs female gender (HR = 2.33; 95% CI, 0.80–6.84) and earlier year of enrollment (≤2001 vs >2001: HR = 2.37; 95% CI, 0.87–6.46).

Table 3 summarizes the HRs for the associations of CD4 measures with liver disease progression. Overall, CD4 variables were consistently strong and significant predictors of liver outcomes, with and without adjustment for covariates. In the adjusted model, those with a nadir <100 cells/μL had 3.5 times the risk of liver disease progression relative to those with nadirs of 100 or more (adjusted HR [aHR] = 3.52; 95% CI, 1.54–8.06). Baseline CD4 <200 cells/mm^3 compared with >200 cells/mm^3 was also associated with a significantly increased risk (aHR = 5.23; 95% CI, 2.30–11.92). Covariate adjustment generally increased the magnitude of the associations between CD4 and liver outcomes compared with unadjusted estimates (Table 3). Time-updated CD4 showed even more extreme estimates (aHR = 11.79; 95% CI, 4.47–31.07), whereas use of a 3-month or 6-month lag resulted in slightly attenuated HRs (Table 3).

In a subgroup analysis among 318 individuals who initiated ART, individuals who failed to attain at least a 100 cell increase from nadir in CD4 had a significantly higher risk of liver disease progression (HR = 7.69; 95% CI, 2.60–22.69; see Table 4). In models using a 3-month or 6-month lag for change in CD4, the magnitude was attenuated and no longer statistically significant (Table 4). These results suggest that more recent drops in CD4 are more strongly associated with liver events among HIV/HCV-coinfected IDUs.

Results for the associations between HIV VL measures and liver disease progression are shown in Table 5. None of the models investigating HIV RNA as a predictor suggested a significant association with liver disease progression. It should be noted that there was a nontrivial amount of missing data during follow-up, which may have impacted the time-updated analyses of HIV VL and liver events in this cohort (Table 5). In general, adjusted estimates were attenuated relative to unadjusted estimates, suggesting that HIV VL may at most be only a marginal predictor of liver outcomes when controlling for other factors (ie, CD4) in this population. Time-updated and 3-month or 6-month lagged analyses of HIV VL did not appreciably change results (Table 5), nor did analyses of HIV RNA as a log-transformed continuous variable (data not shown).

We observed 20 deaths due to end-stage liver disease in 1170 person-years of follow-up (1.7 liver-related deaths per 100 person-years) in this HIV/HCV-coinfected IDU population. An additional 34 individuals died for reasons that were not attributed to liver complications; 32 of these occurred while the patient remained at risk for primary liver outcomes. Causes given for nonliver deaths were as follows: non-HIV-related infection/sepsis (10); HIV-related (8); drug overdose (5); cardiac (3); accidental/injury (1); renal (1); respiratory (1); unknown (5). To address the issue of competing risks, we conducted a sensitivity analysis in which final models were weighted using inverse probability weights (IPW) for likelihood of nonliver death based on individual covariate histories. Results from IPW models accounting for death due to competing causes (data not shown) were not substantially different than those from the unweighted models reported here.

Table 2. Unadjusted Relative Hazards of Liver Disease Progression Events for Baseline Covariates

Variable	Unadjusted HR (95% CI)
Age >45 vs ≤45 years	1.57 (0.68, 3.59)
Male vs female	2.33 (0.80, 6.84)
Race/Ethnicity	
Black non-Hispanic	1.57 (0.51, 4.82)
Hispanic	1.62 (0.47, 5.54)
White non-Hispanic	Referent
History of diabetes	1.52 (0.52, 4.44)
Markers of HBV	0.65 (0.27, 1.59)
HCV Genotype G1	1.58 (0.36, 6.90)
HCV RNA (IU/mL): ≥10^6	0.72 (0.30, 1.75)
Interferon Treatment	1.78 (0.41, 7.67)
Audit Score ≥8	1.72 (0.48, 6.08)
Concurrent IDU	0.71 (0.27, 1.91)
Over 25 years as IDU	0.90 (0.38, 2.12)
Initiation of ART	1.92 (0.45, 8.33)
Enrollment during 2000–2001	2.37 (0.87, 6.46)

Abbreviations: ART, antiretroviral therapy; AUDIT, alcohol use disorders identification test; CI, confidence interval; HBV, hepatitis B virus; HCV, hepatitis C virus; HR, hazard ratio; IDU, injecting drug use.

DISCUSSION

In this prospective analysis of clinical liver disease progression in a cohort of HIV/HCV-coinfected IDUs, CD4 was a consistently

Table 3. Relative Hazards of Liver Disease Progression Events by CD4 Count (Cells/μL) Status

Variable	Person-Years	Events	Unadjusted HR (95% CI)	Adjusted[a] HR (95% CI)
Nadir CD4 at entry				
<100	248	11	2.86 (1.28, 6.38)	3.52 (1.54, 8.06)
≥100	882	13	Referent	Referent
Missing	26	0	–	–
CD4 Count at Entry				
<200	230	13	4.40 (1.97, 9.83)	5.23 (2.30, 11.92)
≥200	892	11	Referent	Referent
Missing	33	0	–	–
Time-updated CD4				
<200	223	16	8.59 (3.53, 20.89)	11.79 (4.47, 31.07)
≥200	844	7	Referent	Referent
Missing	89	1	1.56 (0.19, 13.10)	1.46 (0.17, 12.37)
Lagged CD4 (3-month)				
<200	218	13	4.63 (2.07, 10.35)	5.88 (2.43, 14.27)
≥200	848	11	Referent	Referent
Missing	90	0	–	–
Lagged CD4 (6-month)				
<200	216	14	5.45 (2.41, 12.28)	7.07 (2.90, 17.26)
≥200	851	10	Referent	Referent
Missing	89	0	–	–

Abbreviations: CI, confidence interval; HR, hazard ratio.

[a] Final adjusted models are reduced from fully adjusted models, having removed covariates that did not significantly predict liver disease progression and did not substantially change the estimate for the association of interest. Models for baseline nadir CD4 and baseline CD4 are adjusted for HCV viral load ($\geq 10^6$, $<10^6$) only. The model for current CD4 is adjusted for HIV viral load (≤75, 76–10 000, >10 000) and calendar year (continuous). The models for lagged CD4 are adjusted for HIV viral load (≤75, 76–10 000, >10 000) and HCV viral load ($\geq 10^6$, $<10^6$).

strong inverse predictor of progression across various modeling strategies. In addition, smaller increases in CD4 count from nadir among ART initiators were associated with substantially increased risk of progression. In contrast, there was no evidence of an effect of HIV VL on clinical progression of liver disease due to chronic HCV, particularly when CD4 and other covariates were accounted for. Two other groups have reported protective associations between CD4 and various endpoints related

Table 4. Relative Hazards of Liver Disease Progression Events by Time-Dependent Increase in CD4 Count (Cells/μL) From Nadir Among ART Initiators (*N* = 318)

Variable	Person-Years	Events	Unadjusted HR (95% CI)	Adjusted[a] HR (95% CI)
Time-updated change in CD4				
≤100	361	16	5.13 (1.88, 14.01)	7.69 (2.60, 22.69)
>100	556	5	Referent	Referent
Missing	81	1	1.55 (0.18, 13.73)	3.39 (0.37, 31.33)
Lagged change in CD4 (3-month)				
≤100	360	12	1.86 (0.80, 4.32)	1.86 (0.80, 4.32)
>100	557	10	Referent	Referent
Missing	81	0	0 (0, ∞)	0 (0, ∞)
Lagged change in CD4 (6-month)				
≤100	362	12	1.88 (0.81, 4.36)	1.88 (0.81, 4.36)
>100	557	10	Referent	Referent
Missing	80	0	0 (0, ∞)	0 (0, ∞)

Abbreviations: ART, antiretroviral therapy; CI, confidence interval; HR, hazard ratio.

[a] Final adjusted models are reduced from fully adjusted models, having removed covariates that did not significantly predict liver disease progression and did not substantially change the estimate for the association of interest. The model for current change in CD4 is adjusted for HIV viral load (≤75, 76–10 000, >10 000), nadir CD4 (continuous), and concurrent IDU. Models for lagged change in CD4 do not include any of the covariates under study.

Table 5. Relative Hazards of Liver Disease Progression Events by HIV Viral Load (Copies/mL)

Variable	Person-Years	Events	Unadjusted HR (95% CI)	Adjusted[a] HR (95% CI)
HIV RNA at entry				
≤75	469	10	Referent	Referent
76–10 000	342	5	0.66 (0.22, 1.92)	0.53 (0.18, 1.56)
>10 000	270	8	1.35 (0.53, 3.41)	0.75 (0.28, 2.03)
Missing	75	1	0.64 (0.08, 5.04)	0.57 (0.07, 4.57)
Time-updated HIV RNA				
≤75	347	10	Referent	Referent
76–10 000	237	2	0.27 (0.06, 1.23)	0.25 (0.05, 1.15)
>10 000	180	6	1.15 (0.42, 3.18)	0.87 (0.31, 2.43)
Missing	391	6	1.20 (0.38, 3.82)	1.28 (0.40, 4.08)
Lagged HIV RNA (3-month)				
≤75	365	9	Referent	Referent
76–10 000	250	4	0.60 (0.19, 1.97)	0.53 (0.16, 1.75)
>10 000	193	6	1.25 (0.44, 3.51)	0.93 (0.31, 2.76)
Missing	348	5	1.22 (0.36, 4.18)	1.70 (0.47, 6.12)
Lagged HIV RNA (6-month)				
≤75	381	9	Referent	Referent
76–10 000	263	4	0.62 (0.19, 2.01)	0.54 (0.16, 1.77)
>10 000	203	7	1.42 (0.53, 3.81)	1.06 (0.37, 3.05)
Missing	309	4	1.01 (0.27, 3.80)	1.31 (0.34, 5.12)

Abbreviations: CI, confidence interval; HIV, human immunodeficiency virus; HR, hazard ratio.

[a] Final adjusted models are reduced from fully adjusted models, having removed covariates that did not significantly predict liver disease progression and did not substantially change the estimate for the association of interest. The models for baseline and current HIV viral load are adjusted for baseline CD4 (<200, ≥200) only. The models for lagged HIV viral load are adjusted for baseline CD4 (<200, ≥200), HCV viral load ($\geq 10^6$, $<10^6$), and age (continuous).

to chronic hepatitis in IDUs, consistent with our findings [25, 26]. In our study, baseline CD4, nadir CD4, current CD4, and lagged CD4 were all strong and significant predictors of liver disease progression and were not strongly influenced by HIV VL or other factors in adjusted models. If HIV coinfection accelerates progression to liver outcomes in those with chronic HCV, then initiation and maintenance of ART would confer benefit in this context [24–26]. However, CD4 rebound in response to ART may be muted among HIV/HCV-coinfected persons, although results have been inconsistent [27–33]. Furthermore, virologic suppression in response to ART may be decreased among current IDUs [40]. Given that CD4 seems to be an important predictor of liver outcomes among HIV/HCV-coinfected, those who respond to ART (exhibited by greater increases in CD4 from nadir) should have a slower rate of progression, which is consistent with our results. It appears that ART should preferably be administered before immune impairment becomes severe, as evidenced by the strong inverse association we observed between nadir CD4 and clinical liver events.

Human immunodeficiency virus has been proposed to directly infect hepatocytes or indirectly interact with HCV [34]. Our results showed no discernible association between HIV VL and liver events, especially once CD4 and other factors were accounted for, which is consistent with some but not all previous reports [2, 12, 15, 16, 21, 35]. In particular, our findings contrast with those presented by Brau et al [35], who reported that HIV VL significantly predicted fibrosis progression rate while CD4 count did not in a population of coinfected individuals that had undergone liver biopsies.

It should be noted that a high proportion of patients in this study cohort also had evidence of infection with hepatitis B (78%), which is perhaps not surprising due to shared parenteral mode of transmission. This additional viral burden may potentially be an important factor in interpreting and generalizing these results. However, it should be noted that our analyses did not show a significant association between HBV positivity and progression of liver disease, and addition of this variable to adjusted models did not substantially alter estimates for the associations of interest.

This study has several limitations. First, there were relatively few observed outcomes, and longer follow-up might have yielded more outcomes. However, estimates from models of CD4 and change in CD4 were consistent and highly statistically significant, giving evidence of the strong influence of CD4 on liver outcomes and/or proof of concept that significant associations could be detected in this dataset. Second, there was a nontrivial amount of missing data, particularly among covariates such as HCV RNA, HCV genotype, and AUDIT score (alcohol intake). Missing HCV RNA may not be a major concern, because there

is little evidence to suggest that it predicts liver endpoints, thereby limiting its potential as a confounder for these analyses. Similarly, missing data on HCV genotype may not be overly troublesome given that genotype 1 appears to be the predominant virus among IDUs in this study population and elsewhere. On the other hand, alcohol abuse has been implicated in progression of liver disease, so missing AUDIT scores may have introduced some bias. A third limitation of this study is that these results may not be directly generalizable to other populations, in particular those without a history of injecting drugs. Finally, residual confounding by unknown or inadequately measured factors cannot be fully discounted. However, steps were taken throughout the analysis to assess and minimize confounding by known risk factors for HCV liver disease progression.

CONCLUSIONS

In summary, baseline and current CD4, nadir CD4, and change in CD4 from nadir among those on ART were strong predictors of clinical liver disease progression events in this prospective analysis of HIV/HCV-coinfected IDUs, whereas other factors including HIV VL were not. To our knowledge, this is the first time these findings have been reported in an IDU population. Additional prospective studies and experimental studies are warranted to elucidate the relevant immunologic mechanisms and synergistic pathogenesis of liver disease in HIV/HCV coinfection. Taken together, these results support prompt institution of ART for HIV/HCV-coinfected IDUs and careful attention to those who do not manifest a substantial increase in CD4 count. However, it remains to be determined whether a poor CD4 response is causally related to risk of liver disease progression or whether conditions leading to liver disease progression by other mechanisms also lead to impaired CD4 response.

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