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ORIGINAL RESEARCH

HIV virological rebounds but not blips predict liver fibrosis progression in antiretroviral-treated HIV/hepatitis C virus-coinfected patients

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Objectives

Antiretroviral interruption is associated with liver fibrosis progression in HIV/hepatitis C virus (HCV) coinfection. It is not known what level of HIV viraemia affects fibrosis progression.

Methods

We evaluated 288 HIV/HCV-coinfected cohort participants with undetectable HIV RNA (< 50 HIV-1 RNA copies/mL) on two consecutive visits while on combination antiretroviral therapy (cART) without fibrosis [aspartate aminotransferase to platelet ratio index (APRI) < 1.5], end-stage liver disease or HCV therapy. An HIV blip was defined as a viral load of ≥ 50 and < 1000 copies/mL, preceded and followed by undetectable values. HIV rebound was defined as: (i) HIV RNA ≥ 50 copies/mL on two consecutive visits, or (ii) a single HIV RNA measurement ≥ 1000 copies/mL. Multivariate discrete-time proportional hazards models were used to assess the effect of different viraemia levels on liver fibrosis progression (APRI ≥ 1.5).

Results

The mean age of the patients was 45 years, 74% were male, 81% reported a history of injecting drug use, 51% currently used alcohol and the median baseline CD4 count was 440 [interquartile range (IQR) 298, 609] cells/μL. Fifty-seven (20%) participants [12.4/100 person-years (PY); 95% confidence interval (CI) 9.2–15.7/100 PY] progressed to an APRI ≥ 1.5 over a mean 1.1 (IQR 0.6, 2.0) years of follow-up time at risk. Virological rebound [hazard ratio (HR) 2.3; 95% CI 1.1, 4.7] but not blips (HR 0.5; 95% CI 0.2, 1.1) predicted progression to APRI ≥ 1.5. Each additional 1 $\log_{10}$ copies/mL HIV RNA exposure (cumulative) was associated with a 20% increase in the risk of fibrosis progression (HR 1.2; 95% CI 1.0–1.3).

Conclusions

Liver fibrosis progression was associated with HIV rebound, but not blips, and with increasing cumulative exposure to HIV RNA, highlighting the importance of achieving and maintaining HIV suppression in the setting of HIV/HCV coinfection.

Keywords: fibrosis, hepatitis C virus, HIV, virological blips, virological rebound.

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Introduction

HIV combination antiretroviral therapy (cART) has led to a substantial decrease in AIDS-related morbidity and mortality in HIV-positive individuals [1]. However, among those coinfected with the hepatitis C virus (HCV), liver-related diseases including cirrhosis, hepatocellular carcinoma (HCC), and end-stage liver disease (ESLD) have emerged as leading causes of comorbidity and death [2,3]. It is well established that HIV infection negatively impacts the natural history of HCV by accelerating the progression of liver disease and reducing the likelihood of achieving a sustained virological response with HCV antiviral therapy [3,4]. Identifying factors that can be acted on to modify liver fibrosis progression rates among patients untreated for HCV remains highly relevant despite the prospect of very effective HCV treatments on the horizon. It may be some time before patients will be able to access such therapy and, in many parts of the world, their cost will be prohibitive.

Even during effective HIV treatment, routine testing may occasionally reveal episodes of detectable HIV viraemia (i.e. virological blips) punctuating periods of virological suppression [5–9]. Factors contributing to blips include: HIV replication bursts from stable reservoirs, ongoing cycles of replication, random biological fluctuation, and the consequence of increasingly sensitive detection methods [10–14]. HIV RNA blips do not appear to be associated with decreased antiretroviral adherence or dose-timing irregularities [5–9]. HIV RNA blips > 500 HIV-1 RNA copies/ml have been associated with subsequent virological rebound [15] and with a dampened CD4 cell count increase [16,17] and thus could affect outcomes in coinfection.

In contrast, virological rebounds have been identified as an independent predictor of loss to follow-up [18]. Virological rebounds have been defined as detectable RNA levels on two occasions after HIV suppression is achieved or as HIV RNA values ≥ 1000 copies/mL [15,18]. HIV RNA rebounds are generally interpreted as evidence of poor adherence. Other factors contributing to HIV viral rebounds include the presence of pre-existing resistance mutations that are expressed following the initiation of cART, poor gastrointestinal absorption, and drug–drug interactions leading to diminished antiretroviral drug levels [15,18].

While HIV viral blips and rebounds have been well evaluated in HIV monoinfection, their effects on the natural history of HCV-induced liver disease and HCV antiviral treatment outcomes have not been described in HIV/HCV coinfection. Treatment interruption has been associated with liver fibrosis progression in HIV/HCV coinfection [19], but it is not known if low levels of viraemia might also affect the natural history of liver disease. To this end, we evaluated HIV RNA blips and rebounds as predictors of liver fibrosis progression in HIV/HCV coinfection.

Methods

Study setting and population

The Canadian Co-infection Cohort Study (CCC; CTN222) is a prospective multicentre study recruiting HIV/HCV-coinfected patients from existing HIV clinic populations at 16 centres across Canada since 2003. As of July 2012, 1119 patients were enrolled. Details of the cohort design and protocol have been published previously [20]. Eligible patients were adults aged over 16 years with documented HIV infection [enzyme-linked immunosorbent assay (ELISA) with western blot confirmation] and with chronic HCV infection or evidence of HCV exposure [e.g. HCV seropositive by ELISA with recombinant immunoblot assay (RIBA) II or enzyme immunoassay (EIA) confirmation, and/or HCV RNA positive]. After providing written informed consent, participants underwent an initial evaluation followed by study visits every 6 months. Sociodemographic, behavioural and clinical care information was collected using standardized questionnaires. At each visit, laboratory assessments included complete blood count, creatinine measurement, liver profile, plasma HIV RNA measurement (COBAS TaqMan HIV-1 Test, Roche Diagnostics, Laval, Quebec, Canada; limit of detection 40 copies/mL), CD4 T cell count and plasma HCV RNA measurement (COBAS Amplicor HCV Test, v2.0, Roche Diagnostics, Laval, Quebec, Canada; limit of detection 60 IU/mL). The study was approved by the community advisory committee of the Canadian HIV Trials Network (CIHR)-Canadian HIV Trials Network and the research ethics boards of all participating institutions.

The analytic sample (n = 288) included participants 16 years of age or older who were chronically infected with HCV and who were currently on HIV antiretroviral treatment with at least two consecutive visits and two consecutive undetectable HIV RNA measurements in follow-up or undetectable HIV RNA at cohort entry with prior stable antiretroviral treatment defined as > 1 year on combination antiretroviral therapy (cART). The primary outcome of interest was the progression to liver fibrosis; thus, participants with significant fibrosis or ESLD at study entry were excluded (see definitions below). Patients were censored on their last clinic visit prior to July 2012, when an outcome occurred, at death or at initiation of HCV treatment.

Definitions

The aspartate aminotransferase (AST) to platelet ratio index (APRI) was used as a noninvasive surrogate for liver fibrosis

and defined as: 100 × (AST/upper limit of normal)/platelet count (10^9/L) [21,22]. An APRI score ≥ 1.5 has been validated as a marker of significant liver fibrosis in coinfected patients (corresponding to a biopsy score > F2) [21].

HIV RNA virological 'blips' were defined as an HIV RNA value ≥ 50 copies/mL and < 1000 copies/mL, preceded and followed by an undetectable value (< 50 copies/mL) [23,24]. HIV RNA virological 'rebounds' were determined as either: (i) an HIV RNA value ≥ 50 copies/mL during two consecutive serological measurements, or (ii) a single HIV RNA measurement ≥ 1000 copies/mL [15].

ESLD diagnoses included liver cirrhosis, ascites, hepatic encephalopathy, bleeding esophageal varices, spontaneous bacterial peritonitis and hepatocellular carcinoma [25]. Time since HIV diagnosis was determined using the date of HIV seroconversion, where known, or the date of the first positive HIV antibody test. The duration of HCV infection was determined using the date of HCV seroconversion, if known, or the year of first injecting drug use (IDU) or blood product exposure as a proxy of HCV infection.

Alcohol abuse was defined as self-reported alcohol intake of more than two drinks per day or binge drinking (greater than six drinks at any one time).

Statistical analysis

For all analyses, baseline (time zero) corresponded to cohort entry for those on stable cART with undetectable HIV RNA or the second of two consecutive visits at which HIV RNA was observed to be undetectable for those starting cART during follow-up.

Incidence rates of liver fibrosis were estimated among those without fibrosis at baseline by dividing the number of participants developing the outcome by the number of person-years (PY) at risk, and expressed in cases per 100 PY. Poisson count models were used to calculate confidence intervals (CIs) for incidence rates.

Multivariate proportional hazards models were built to assess the effect of different states of HIV viraemia on progression to significant liver fibrosis (APRI ≥ 1.5) using variables that were determined *a priori* to be clinically important. We used a discrete time version of the Cox model (with a complementary log log link function, an offset to allow for variation in the time between visits and robust standard errors) [26] because liver fibrosis could only be assessed at each cohort visit. Final models were adjusted for both time-independent covariates fixed at baseline [age, gender, ethnicity, alcohol abuse and ln(APRI)] and time-dependent exposures. The natural logarithm of the APRI [ln(APRI)], which nearly normalizes the distribution [22], was used in all analyses. Time-dependent exposures were: CD4 cell count, virological blip and virological rebound status. Once a blip or rebound had occurred, this status was kept 'on' for future risk intervals. In a secondary analysis, viral blip and rebound categories were replaced with cumulative log copies of HIV RNA.

In a sensitivity analysis, we estimated the association between significant fibrosis progression and cumulative log copies of HIV RNA where the latter was represented by a linear spline with two knots selected *a priori* at 50 and 1000 copies/mL [26]. The second knot corresponds to the threshold used to differentiate viral blips from rebounds.

All analyses were performed using STATA software version 11 (StatCorp LP, College Station, TX, USA).

Results

At the time of analysis, 1119 HIV/HCV-coinfected participants were enrolled in the CTN222 cohort (Fig. 1). Data were analysed for 288 participants who met study inclusion criteria. The mean age of the patients was 45 years, 26% were female, 14% were aboriginal, 82% reported a history of IDU, and 51% currently used alcohol. The median baseline CD4 T-lymphocyte count was 440 cells/μL [interquartile range (IQR) 298, 609 cells/μL]. Baseline characteristics comparing those who did and did not progress to advanced fibrosis, as determined by APRI > 1.5, are shown in Table 1. Most characteristics were similar. However, those progressing to fibrosis were more likely to be on protease inhibitor-based cART at baseline than those not progressing to fibrosis [n = 47 (82%) *vs.* 151 (65%), respectively].

Fifty-seven participants (20%) [12.4/100 PY; 95% CI 9.2–15.7/100 PY] progressed to an APRI ≥ 1.5 over a mean 1.1 (IQR 0.6, 2.0) years of follow-up time at risk (Table 2). Multivariate discrete proportional hazards models of factors associated with progression to significant fibrosis are shown in Table 3 (also represented in Fig. 2). Viral rebounds [adjusted hazard ratio (HR) 2.3; 95% CI 1.1–4.7] but not blips (adjusted HR 0.5; 95% CI 0.2–1.1) predicted progression to APRI ≥ 1.5. Each additional 1 $\log_{10}$ copies/mL HIV RNA exposure (cumulative) was associated with an 20% increase in risk of progression to significant fibrosis (adjusted HR 1.2; 95% CI 1.0–1.3). Only eight of 44 participants experiencing rebound were reported to be on a treatment interruption, suggesting nonadherence in the remainder. Other factors associated with progression to significant fibrosis were baseline ln(APRI), older age and alcohol abuse.

The sensitivity analysis using a linear spline was consistent with our main findings: adjusted HRs (95% CI) per 1 log copies/ml of: 0.7 (0.2–2.1) for HIV RNA < 50 copies/mL; 0.7 (0.1–6.0) for 50–1000 copies/mL and 1.4 (1.3–1.6) for > 1000 copies/mL. These findings suggest that the risk of fibrosis progression only clearly increased at HIV RNA levels > 1000 copies/mL.

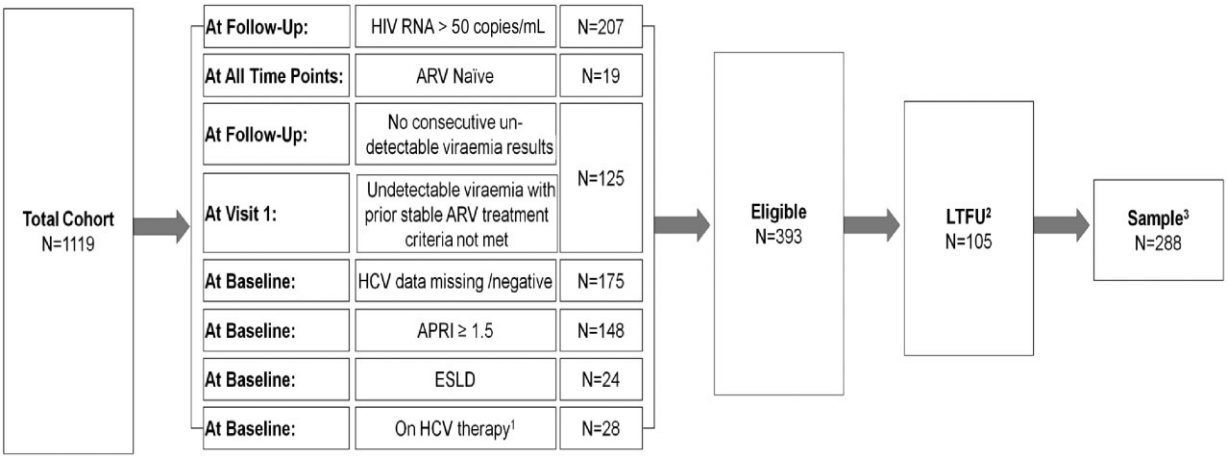

Fig. 1 Participant selection flow chart. [1]Hepatitis C virus (HCV) treatment censoring was carried out during the follow-up period. Antiretroviral (ARV) interruption was not censored. [2]Participants not attending visits beyond study enrolment. [3]The analysed data set is comprised of 'valid risk-sets'. If one or multiple visits were skipped then that risk-set was excluded from analysis. APRI, aspartate aminotransferase to platelet ratio index; ESLD, end-stage liver disease; LTFU, lost to follow-up.

Table 1 Sociodemographic and clinical characteristics of HIV/hepatitis C virus (HCV)-coinfected patients at baseline according to whether they progressed to significant liver fibrosis [aspartate aminotransferase to platelet ratio index (APRI) ≥ 1.5] in follow-up

	Total (n = 288)	Progressors (n = 57)	Nonprogressors (n = 231)
Follow-up time (years) [median (IQR)]	1.5 (0.7, 2.9)	1.0 (0.5, 1.9)	1.8 (0.9, 3.0)
Age (years) [median (IQR)]	45 (40, 50)	46 (42, 51)	45 (40, 50)
Female [n (%)]	75 (26)	15 (26)	60 (26)
Aboriginal [n (%)]	40 (14)	6 (11)	34 (15)
IDU ever [n (%)]	236 (82)	51 (89)	185 (80)
IDU in previous 6 months [n (%)]	90 (31)	16 (28)	74 (32)
Current alcohol use [n (%)]	148 (51)	32 (56)	116 (50)
Current alcohol abuse* [n (%)]	41 (28)	13 (42)	28 (24)
Time since HIV diagnosis (years) [median (IQR)]	12 (7, 17)	11 (7, 15)	12 (7.6, 18)
Duration of HCV infection (years) [median (IQR)]	19 (11, 27)	20 (12, 28)	19 (11, 26)
Nadir CD4 count (cells/μL) [median (IQR)]	150 (50, 249)	158 (84, 264)	150 (50, 240)
CD4 count (cells/μL) [median (IQR)]	440 (298, 609)	419 (249, 642)	440 (305, 602)
HIV RNA load (copies/mL) [median (IQR)]	49 (39, 49)	49 (39, 49)	49 (39, 49)
APRI [median (IQR)]	0.5 (0.4, 0.8)	0.8 (0.5, 1.1)	0.5 (0.4, 0.7)
On cART [n (%)]	277 (96)	55 (96)	222 (96)
cART regimen† [n (%)]			
PI	198 (69)	47 (82)	151 (65)
NNRTI	82 (28)	9 (16)	73 (32)
Others	16 (6)	1 (2)	15 (6)
HCV RNA ($\log_{10}$ copies/mL) [median (IQR)]‡	6.2 (5.4, 6.8)	6.5 (5.3, 6.8)	6.2 (5.4, 6.7)
HCV treatment naïve [n (%)]	253 (88)	48 (84)	205 (89)

cART, combination antiretroviral therapy; IDU, injecting drug use; PI, protease inhibitor; NNRTI, nonnucleoside reverse transcriptase inhibitor.
*Alcohol abuse was defined as self-reported alcohol intake of more than two drinks per day or binge drinking (greater than six drinks at any one time). †Sum of regimens >100% as some participants are on both PI, NNRTI and/or other cART. ‡For HCVRNA, only 114 [26/57 (46%) progressors and 88/231 (38%) non-progressors] had available quantitative HCV RNA values.

Given that baseline characteristics suggested that patients with liver fibrosis progression were more likely to use protease inhibitor-based cART, we performed a *post hoc* sensitivity analysis that included cumulative time on protease inhibitors from baseline and total duration of cART (to account for potentially longer duration of cART among those receiving protease inhibitors) as additional covariates in the main models above. Cumulative protease inhibitor use in follow-up was associated with progression to significant fibrosis (adjusted HR 2.4; 95% CI 1.2–4.9) and its inclusion in the model attenuated the estimates for viral rebound somewhat (adjusted HR 1.9; 95% CI 0.9–4.1). However, the effect of cumulative HIV RNA exposure was unchanged (adjusted HR 1.2; 95% CI 1.0–1.3 per 1 log copies/mL).

Table 2 Incidence of progression to significant fibrosis [defined as aspartate aminotransferase to platelet ratio index (APRI) ≥ 1.5] according to level of HIV RNA replication

	n (%)	Denominator	Person-years	Rate per 100/person-years (95% CI)
Overall	57 (20)	288	456.5	12.4 (9.2, 15.7)
No virological blip or rebound ever	42 (19)	216	303.8	13.8 (9.6, 18.0)
Virological blip only	3 (11)	28	45.8	6.6 (−0.9, 14.0)
Any virological rebound	12 (27)	44	69.4	17.3 (7.5, 27.1)
Number of follow-up visits with detectable HIV RNA				
0	38 (18)	209	304.2	12.5 (10.5, 14.4)
1	8 (19)	42	82.2	9.7 (3.0, 16.5)
2–3	5 (25)	20	36.2	13.8 (1.7, 25.9)
> 3	1 (17)	6	18.3	5.5 (−5.3, 16.2)
Cumulative log copies of HIV RNA up to last visit				
< 2	39 (17)	224	330.7	11.8 (8.1, 15.5)
2–4	4 (20)	20	43.3	9.2 (0.2, 18.3)
> 4	9 (27)	33	66.9	13.4 (4.7, 22.2)

CI, confidence interval.

Table 3 Multivariate discrete time proportional hazards models of factors associated with time to developing significant fibrosis (APRI ≥ 1.5) in follow-up

	Primary analyses		Secondary analyses	
	Adjusted HR	95% CI	Adjusted HR	95% CI
Time-updated exposures				
Virological blip	0.5	0.2,1.1	–	–
Virological rebound	2.3	1.1,4.7	–	–
Total log copies HIV RNA	–	–	1.2	1.0,1.3
CD4 count (per 100 cells/μL)	1.0	0.9,1.2	1.0	0.9,1.1
Time-independent baseline covariates				
Age (per 10 years)	1.3	0.9,1.8	1.3	0.9,1.8
Sex (female)	1.2	0.6,2.3	1.3	0.6,2.6
Ethnicity (Aboriginal)	1.0	0.4,2.7	0.8	0.3,2.4
Current alcohol abuse	1.2	0.7,2.1	1.2	0.7,2.3
ln (APRI)	6.3	3.1,12.6	5.9	2.9,12.1

APRI, aspartate aminotrasferase to platelet ratio; CI, confidence interval; HR, hazard ratio.

Discussion

Lack of continuous HIV suppression negatively influences clinical outcomes in HIV infection. The Strategies for Management of Antiretroviral Therapy (SMART) study demonstrated that episodic CD4 T-lymphocyte count-guided ART interruption is associated with accelerated immunodeficiency and increased HIV replication [27]. Moreover, interrupted ART increased the risk of morbidity and mortality by both opportunistic infection and nonopportunistic disease [28]. The HR for major hepatic, cardiovascular and renal diseases was 1.8 (95% CI 1.2–2.9). Hepatic disease outcomes were identified based on histological (liver biopsy and autopsy), clinical (ascites, hepatic encephalopathy and varices), laboratory (prothrombin time/international normalized ratio and albumin) and radiological criteria [28].

In HIV/HCV-coinfected individuals, the interruption of ART has been associated with an increased risk of

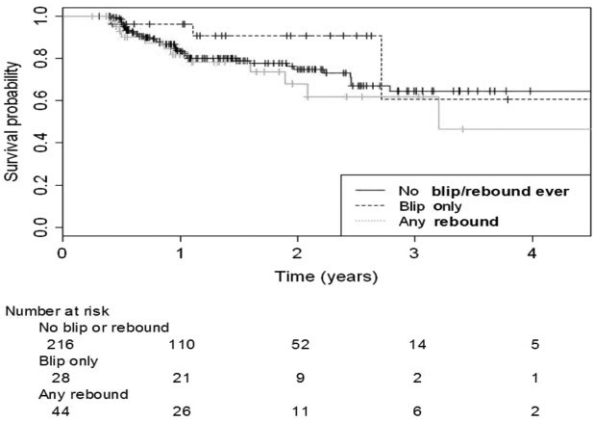

Fig. 2 Kaplan–Meier estimated time to significant fibrosis [aspartate aminotransferase to platelet ratio index (APRI) ≥ 1.5] stratified by HIV RNA blips and rebound.

opportunistic and nonopportunistic infection outcomes [19,29]. Liver biopsy studies have shown that detectable HIV RNA levels, as a consequence of inadequate HIV suppression, pose a risk for accelerated liver fibrosis [30,31]. As a consequence of the inherent inconsistency and limited availability of liver biopsies, serum biochemical indexes have been used to further investigate hepatic disease. APRI studies demonstrate that interrupted ART is associated with liver fibrosis progression and ESLD [19,32].

The published literature is inconsistent as to whether virological blips predict adverse clinical outcomes such as death and end-organ disease [16,17,33–39]. This is in part attributable to inconsistent definitions. Blips defined as transiently detectable viraemia within the 50–400 copies/mL range do not seem to increase the risk of virological failure [8,9]. However, greater magnitude blips (i.e. 500–999 copies/mL) are associated with subsequent treatment failure [15,16,35,36].

There are several proposed mechanisms by which nonsuppressed HIV viraemia may contribute to accelerated fibrosis [40]. These include impaired HCV-specific immune response [41] and cytokine deregulation leading to increased inflammatory milieu within the liver leading to activation of profibrotic processes [42] and the potential for greater drug-induced hepatotoxicity [43,44]. Increased microbial translocation from the gut during periods of viral rebound may contribute to increased concentrations of inflammatory markers (i.e. tumour necrosis factor alpha and interleukin-6) within the liver parenchyma contributing to increased fibrosis progression [45].

Our study has several strengths. It was nested in a large, prospective cohort study that is broadly representative of HIV/HCV-coinfected persons in care in Canada. In previous studies, patients were only selected based on having undergone liver biopsy, which potentially introduces selection bias. Additional methods to quantify fibrosis including biopsy, transient elastography and other calculated systems (e.g. FibroTest BioPredictive, Paris, France) would ideally have been valuable to corroborate our findings using APRI. However, there is ample literature demonstrating a strong correlation between APRI and other methods of evaluating liver fibrosis [46,47].

Limitations of our analyses are noted, including a relatively short period of follow-up. The fact that viral rebound was identified as a predictor of fibrosis progression despite this short period of follow-up highlights the critical role that achieving and maintaining HIV RNA suppression can play in protecting the liver from HCV-induced injury. Our relatively small sample size and short follow-up duration also limited inference about other variables traditionally associated with fibrosis progression such as age, sex and alcohol use, which were not significantly associated with fibrosis progression in our analyses. Interestingly, protease inhibitor use appeared to be an additional strong predictor of fibrosis progression in sensitivity analyses even after accounting for time on cART. Inclusion of protease inhibitor use in our models attenuated, but did not remove the association of viral rebound with fibrosis progression. It is possible that protease inhibitor use is simply a marker of more advanced HIV disease and more frequent episodes of viral rebound prior to cohort entry which may have affected risk of fibrosis progression in this cohort. Protease inhibitor use might also be a proxy for poor adherence if, because of their higher barrier to resistance, protease inhibitors were given preferentially to patients expected not to adhere to therapy. Alternatively, there is evidence that boosted protease inhibitors may contribute to long-term hepatoxicity both directly and indirectly through metabolic changes such as insulin resistance and hepatic steatosis [48]. We were unable to fully explore the association of protease inhibitor use and fibrosis progression in these analyses as data on total exposure to protease inhibitors prior to cohort entry were not available for all patients.

Liver fibrosis progression, as estimated by APRI score, was greater in patients experiencing HIV rebound, but not blips, and was associated with the degree of HIV RNA exposure over time. Optimizing antiretroviral adherence, which would reduce the frequency of virological rebound episodes, may protect the liver from HCV-induced liver fibrosis progression.

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Author contributions: As the corresponding author, MBK has had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. She supervised the study design, conduct and reporting and participated in revising the manuscript. CC conceived the study, revised results and drafted the manuscript. KR-K conducted the data analysis and prepared data reports for use in the manuscript. All of the other authors participated by recruiting and following patients in the cohort and critically reviewed the manuscript as part of the writing

group. All authors have seen and approved the final manuscript and have participated sufficiently in the work to take public responsibility for its content.

Appendix

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