

Tobacco Smoking Is Not Associated With Accelerated Liver Disease in Human Immunodeficiency Virus-Hepatitis C Coinfection: A Longitudinal Cohort Analysis

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Background. Tobacco smoking has been shown to be an independent risk factor for liver fibrosis in hepatitis C virus (HCV) infection in some cross-sectional studies. No longitudinal study has confirmed this relationship, and the effect of tobacco exposure on liver fibrosis in human immunodeficiency virus (HIV)-HCV coinfecting individuals is unknown.

Methods. The study population consisted of participants from the Canadian Co-infection Cohort study (CTN 222), a multicenter longitudinal study of HIV-HCV coinfecting individuals from 2003 to 2014. Data were analyzed for all participants who did not have significant fibrosis or end-stage liver disease (ESLD) at baseline. The association between time-updated tobacco exposure (ever vs nonsmokers and pack-years) and progression to significant liver fibrosis (defined as an aspartate-to-platelet ratio index [APRI] ≥ 1.5) or ESLD was assessed by pooled logistic regression.

Results. Of 1072 participants included in the study, 978 (91%) had ever smoked, 817 (76%) were current smokers, and 161 (15%) were previous smokers. Tobacco exposure was not associated with accelerated progression to significant liver fibrosis nor with ESLD when comparing ever vs never smokers (odds ratio [OR] = 1.06, 95% confidence interval [CI], 0.43–1.69 and OR = 1.20, 95% CI, 0.21–2.18, respectively) or increases in pack-years smoked (OR = 1.05, 95% CI, 0.97–1.14 and OR = 0.94, 95% CI, 0.83–1.05, respectively). Both time-updated alcohol use in the previous 6 months and presence of detectable HCV ribonucleic acid were associated with APRI score ≥ 1.5 .

Conclusions. Tobacco exposure does not appear to be associated with accelerated progression of liver disease in this prospective study of HIV-HCV coinfecting individuals.

Keywords. cohort study; HCV; HIV; liver disease; tobacco.

Human immunodeficiency virus (HIV)-hepatitis C virus (HCV) coinfection is associated with more rapid progression towards liver fibrosis [1–3] and ultimately leads to higher rates of liver failure and death, compared with HCV-monoinfected individuals [4,5]. In animal models, smoking results in the production of cytotoxic chemicals that induce oxidative stress, leading to lipid peroxidation, stellate cell activation, and ultimately liver fibrosis [6–9]. In a clinical setting, pack-years of tobacco smoking has been associated with a dose-dependent relationship with stage of fibrosis in individuals with nonalcoholic fatty liver disease

[10,11]. Tobacco smoking has been shown to be an independent risk factor for liver fibrosis in HCV monoinfection in some cross-sectional studies [12,13]. The effect of smoking on liver fibrosis in individuals with HIV-HCV coinfection has not been evaluated. Individuals infected with HIV are almost twice as likely to smoke as individuals who are not infected [14]; therefore, tobacco smoking may represent an important modifiable risk factor for liver disease progression in HIV-HCV coinfection. We performed a prospective evaluation of smoking in HIV-HCV coinfection to assess the impact of smoking on the development of significant fibrosis and end-stage liver disease (ESLD) in coinfecting Canadians.

METHODS

The Canadian Coinfection Cohort Study

The Canadian Co-infection Cohort study (CTN 222) is a longitudinal cohort recruiting HIV-HCV coinfecting persons from 18 HIV clinics across Canada. To be eligible, participants must be 16 years or older, have documented HIV infection (HIV positive by enzyme-linked immunosorbent assay [ELISA] with Western blot confirmation), and show evidence of HCV

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infection (HCV seropositive by ELISA with recombinant immunoblot assay II or enzyme immunoassay confirmation, or if serologically false negative, HCV ribonucleic acid [RNA] positive). Every 6 months, information on socio-demographic factors and drug exposures is gathered through a questionnaire and a blood sample is collected. Detailed information on the cohort design and protocol has been previously published elsewhere [15]. As of October 1, 2014, 1381 persons had been recruited. Approval has been obtained from the relevant ethics committee for each study site. Individual written informed consent and the Canadian Co-infection Cohort Study protocol conform to the ethical guidelines of the 1975 Declaration of Helsinki.

Tobacco Smoking Exposure

Tobacco smoking behaviors were assessed through participant self-report. At cohort entry, participants were asked to report their history of tobacco smoking (age at initiation if they have ever smoked, age at discontinuation if they are ex-smokers, and the number of cigarettes smoked per day). At each study visit, participants updated their cigarette use in the past 6 months, including their current smoking status and the number of cigarettes smoked per day if they smoked. Those who reported quitting since the last interview were also asked to report the number of months elapsed since they quit. A cumulative measure of lifetime smoking exposure (pack-years) was obtained by multiplying the number of packs of cigarettes smoked per day (assuming there are 20 cigarettes per pack) with number of years smoked.

Aspartate-to-Platelet Ratio Index Score and Liver-Related Morbidity and Mortality

At each visit, we calculated the aspartate (AST)-to-platelet ratio index (APRI) score as follows: $100 \text{ [AST (units/liter)/upper limit of normal]/platelet count (} 10^9\text{/liter)}$. An APRI score ≥ 1.5 indicates significant liver fibrosis (equivalent to a score ≥ 2 on the Metavir scale) [16, 17]. This validated biomarker was selected instead of liver biopsy (the gold standard) because the latter is expensive, prone to sampling error, and unethical to perform every 6 months for research purposes. Because transient elastography (FibroScan) was not performed by all study sites and the number of repeated measures was limited, it could not be used in this study.

End-stage liver disease was defined by a clinical diagnosis of liver cirrhosis, ascites, portal hypertension, spontaneous bacterial peritonitis, encephalopathy, esophageal varices, or hepatocellular carcinoma. Participants were categorized as having experienced a hepatic event if they had a diagnosis of ESLD or ESLD was identified as the cause of death. Dedicated case report forms were completed by study sites in the event of death or ESLD diagnosis. Two investigators independently classified causes of death using the Coding of Death in HIV (CoDe) system [18]. Participants in British Columbia, Alberta, and Quebec (74% of the cohort) were linked to provincial vital statistics to capture information on deaths among patients lost to follow-up.

Statistical Analyses

The analytical sample consisted of all participants without significant fibrosis (defined as $\text{APRI} \geq 1.5$) or ESLD events at cohort entry. Included participants were censored at initiation of HCV treatment, which can affect the APRI measure. Missing data were handled with multiple imputation implemented using chained equations, producing 10 imputed datasets.

We performed a survival analysis to assess the association of tobacco smoking with progression to significant fibrosis. We used pooled logistic regression fitted with generalized estimating equations (GEEs) to account for the longitudinal nature of the data. Time was modeled with a polynomial of the visit number up to the fourth order to incorporate flexibility in the impact of time on the hazard. Different correlation structures were tested to find the best fitting model using the quasi-likelihood under the independence model criterion. The exchangeable structure provided the best fit.

Tobacco smoking exposure was modeled with a time-updated indicator for ever smoking and time-updated pack-years, centered around the mean for ease of interpretation. We adjusted for baseline age, sex, estimated time since HCV infection, and a monthly income lower than Canadian dollar rate (CAD) \$1500. We further adjusted for time-updated reports of alcohol use, injection drug use (IDU), CD4 cell count, HIV viral load, presence of detectable HCV viral load, and impaired fasting glucose (glucose ≥ 6.1 and fasting) or glucose intolerance (glucose ≥ 7.8 and not fasting), depending on fasting status. Duration of HCV infection was based on the date of HCV seroconversion, if known, or year of first IDU or blood product exposure as a proxy of HCV infection [19].

Sensitivity Analyses

A sensitivity analysis was performed to assess the presence of an interaction between alcohol use and tobacco smoking by stratifying for alcohol use in the 6 months preceding cohort entry. In a second analysis, the occurrence of a hepatic event was used as the outcome. The analytical sample and models used were identical to those described above.

In order to include all patients irrespective of baseline APRI score, a new analytical sample including those with an APRI score ≥ 1.5 or ESLD at cohort entry was defined for another sensitivity analysis. We then estimated the average response in the natural log of the continuous APRI score associated with cigarette use. This analysis was performed by fitting a linear regression with GEE, adjusting for the same covariates as described above. Because changes in $\ln(\text{APRI})$ are difficult to interpret clinically, the coefficients obtained were back-transformed by exponentiation to represent multiplicative changes in APRI score.

In order to investigate the potential impact of various aspects of tobacco smoking, the analyses were repeated by decomposing tobacco exposure into multiple variables in a time-updated

manner. An indicator for ever smoking was included, as well as the number of cigarettes smoked per day, age at initiation, years since initiation, and years since cessation, when applicable. Continuous exposure variables were centered around the mean.

Finally, all analyses were repeated after excluding those without active HCV replication at baseline (who achieved sustained virologic response after HCV treatment or spontaneous clearers), to corroborate our results in a group strictly comprising actively coinfecting persons. Stata, version 13 (StataCorp, College Station, TX) was used to perform all analyses.

RESULTS

Of 1381 coinfecting individuals, 268 had APRI scores ≥ 1.5 and 41 were on HCV treatment at cohort entry, leaving 1072 individuals who met the inclusion criteria. The median (interquartile range [IQR]) follow-up period was 1.7 years (IQR, 0.5–4.5), for a total of 3197.25 person-years of follow-up. Demographic and clinical characteristics of the cohort are demonstrated in Table 1. Most patients were males with low income, and median age was 44 years (IQR, 38–49). More than half of participants had an undetectable HIV viral load, and median CD4 count was 418 (IQR, 270–590) at baseline. At baseline, 36% of participants had used injection drugs in the previous 6 months, whereas approximately half reported alcohol or marijuana use.

Table 1 also describes tobacco exposure in the cohort. The vast majority of participants were ever smokers (91%) and remained current smokers (76%). Of current smokers, the median time since smoking initiation was 30 years (IQR, 24–36), the median number of cigarettes smoked per day was 13 [10, 20], and 12% reported quitting during follow-up. Among ex-smokers, median time since smoking cessation was 4 years [1, 14] and 31% started smoking again during follow-up.

During follow-up, there were 197 incident cases of progression to an APRI ≥ 1.5 (incidence: 61.6 cases/1000 person-years) and 89 incident cases of ESLD (29.6 cases/1000 person-years). Results from regression analyses are presented in Table 2. No significant association between smoking exposure and progression to liver fibrosis or ESLD was observed. Progression to APRI score ≥ 1.5 or ESLD was not accelerated in ever versus never smokers. Likewise, progression to APRI score ≥ 1.5 or ESLD was not influenced by increased pack-years. Furthermore, tobacco smoking was not associated with a change in the median APRI score (Table 2).

Baseline characteristics such as sex, age, duration of HCV infection, and monthly income were not associated with progression to liver fibrosis or ESLD. There was no association with IDU in the past 6 months, CD4 count or viral load at last study visit, nor with glucose intolerance (Table 2). Factors which appeared to accelerate progression to liver disease (APRI ≥ 1.5) were currently having detectable HCV RNA and alcohol use in the past 6 months. Although neither was

Table 1. Demographic and Clinical Characteristics at Cohort Entry

Characteristics	N (%) or Median (IQR)
Participants, N	1072
Study visits, median (IQR)	3 (2–7)
Years of follow-up, median (IQR)	1.7 (0.5–4.5)
Age, median (IQR)	44 (38–49)
Male, n (%)	757 (71)
Risk factor for HCV acquisition	
Injection drug use	609 (57)
Sex	151 (14)
Blood transfusion	61 (6)
Other	65 (6)
Unknown/Missing	186 (17)
Risk factor for HIV acquisition	
Injection drug use	553 (52)
Sex	357 (33)
Blood transfusion	43 (4)
Other	48 (4)
Unknown/Missing	71 (7)
Monthly income less than CAD \$1500, n (%)	821 (77)
Homeless, n (%)	130 (12)
Alcohol use in the past 6 mo, n (%)	547 (51)
Injection drug use in the past 6 mo, n (%)	384 (36)
Marijuana smoking in the past 6 mo, n (%)	565 (53)
Years since HCV infection, median (IQR)	17.6 (9.9–25.3)
Active HCV replication, n (%)	843 (79)
Years since HIV diagnosis, median (IQR)	10.5 (5.6–16.0)
CD4 count, median (IQR)	418 (270–590)
Undetectable HIV viral load (<50 copies/mL), n (%)	615 (57)
HIV viral load if detectable, median (IQR)	2047 (130–22 711)
APRI score [17], median (IQR)	0.5 (0.3–0.8)
Ever smoked, n (%)	978 (91)
Current smoker, n (%)	817 (76)
Age at smoking initiation among current smokers, median (IQR)	13 (11–16)
Years since initiation among current smokers, median (IQR)	30 (24–36)
Number of cigarettes/day among current smokers, median (IQR)	13 (10–20)
Ex-smoker, n (%)	161 (15)
Age at smoking initiation among ex-smokers, median (IQR)	15 (12–18)
Age at smoking cessation among ex-smokers, median (IQR)	38 (28–45)
Years since cessation among ex-smokers, median (IQR)	4 (1–14)
Reinitiation during follow-up	49 (31)

Abbreviations: APRI, aspartate-to-platelet ratio index; CAD, Canadian dollar rate; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IQR, interquartile range.

associated with accelerated progression to ESLD, this could be attributable to the small number of outcomes, resulting in a loss of power.

When data were examined by strata of alcohol use, we still did not observe any association between tobacco smoking and acceleration of liver disease progression, although the point estimate for ever smoking was elevated among alcohol users, as presented in Table 3.

Table 2. Association Between Smoking Behaviors and Progression to Liver Fibrosis or End-Stage Liver Disease Assessed by Pooled Logistic Regression or Linear Regression With Generalized Estimating Equations

Characteristics	APRI ≥ 1.5 (197 Events) OR (95% CI)	ESLD (89 Events) OR (95% CI)	Continuous APRI Score Exp(β) ^a (95% CI)
Time updated smoking behavior			
Ever vs never smoker	1.06 (.43–1.69)	1.20 (.21–2.18)	0.88 (.75–1.01)
Pack-years ^b (per 10 pack-years)	1.05 (.97–1.14)	0.94 (.83–1.05)	0.98 (.97–1.00)
Baseline characteristics			
Female	1.30 (.88–1.73)	1.14 (.58–1.70)	0.91 (.81–1.00)
Age	0.97 (.88–1.06)	1.21 (1.06–1.36)	1.03 (1.00–1.06)
Years since HCV infection (per 5 y)	1.03 (.95–1.11)	1.06 (.95–1.16)	1.02 (.99–1.04)
Monthly income less than CAD \$1500	0.70 (.45–0.95)	0.79 (.39–1.20)	0.92 (.81–1.02)
Updated characteristics			
Alcohol use in the past 6 mo	1.56 (1.04–2.07)	0.90 (.51–1.30)	1.07 (1.03–1.12)
Injection drug use in the past 6 mo	0.84 (.55–1.12)	0.67 (.32–1.02)	1.01 (1.00–1.01)
CD4 cell count at the last study visit (per 100 cells)	0.94 (.87–1.01)	0.99 (.88–1.11)	0.98 (.97–0.99)
HIV viral load (log copies/mL) at the last study visit	1.10 (.94–1.27)	0.97 (.66–1.28)	1.01 (.99–1.03)
Detectable HCV RNA	3.53 (1.64–5.41)	1.56 (.54–2.58)	1.64 (1.48–1.81)
Glucose intolerance ^c	1.03 (.64–5.41)	1.47 (.72–2.23)	1.04 (.99–1.10)

Abbreviations: APRI, aspartate-to-platelet ratio index; CAD, Canadian dollar rate; CI, confidence interval; ESLD, end-stage liver disease; HCV, hepatitis C virus; HIV, human immunodeficiency virus; OR, odds ratio; RNA, ribonucleic acid.

^a Back-transformed results represent changes in APRI score per year on the multiplicative scale.

^b Centered at mean if current smoker, 0 if ex- or never smoker.

^c Impaired fasting glucose (glucose ≥ 6.1 and fasting) or impaired glucose tolerance (glucose ≥ 7.8 and not fasting).

Finally, the exposure was decomposed into several different smoking exposure variables: ie, indicator for ever smoking, as well as the number of cigarettes smoked per day, age at initiation, years since initiation, and years since cessation, when applicable. None of these aspects of tobacco smoking investigated was associated with development of liver fibrosis and ESLD or with increases in the median APRI score (data not shown). Restricting the analyses to those with active HCV replication at

baseline did not produce substantially different results to those presented here (data not shown).

DISCUSSION

To our knowledge, this is the first longitudinal study to examine tobacco exposure and risk of progression of liver disease among HIV-HCV coinfecting individuals without fibrosis at baseline. Tobacco smoking was extraordinarily high in cohort participants,

Table 3. Association Between Smoking Behaviors and Progression to Liver Fibrosis, Stratified by Baseline Alcohol use

	No Alcohol Use at Baseline (93 Events) OR (95% CI)	Alcohol Use at Baseline (104 Events) OR (95% CI)
Time updated smoking behavior		
Ever vs never smoker	0.78 (.06–1.50)	1.23 (.25–2.20)
Pack-years ^a (per 10 pack-years)	1.05 (.91–1.18)	1.07 (.94–1.19)
Baseline characteristics		
Female	1.47 (.81–2.14)	1.05 (.54–1.56)
Age (per 5 y)	0.99 (.86–1.12)	0.94 (.80–1.08)
Years since HCV infection (per 5 y)	1.00 (.88–1.13)	1.06 (.96–1.17)
Monthly income less than CAD \$1500	0.66 (.32–1.00)	0.72 (.35–1.05)
Updated characteristics		
Injection drug use in the past 6 mo	0.90 (.46–1.35)	0.80 (.40–1.18)
CD4 cell count at the last study visit (per 100 cells)	0.99 (.89–1.08)	0.88 (.79–0.98)
HIV viral load (log copies/mL) at the last study visit	1.19 (.94–1.43)	1.02 (.80–1.25)
Detectable HCV RNA	3.72 (.62–6.82)	3.20 (.86–5.54)
Glucose intolerance ^b	0.97 (.50–1.45)	1.00 (.40–1.59)

Abbreviations: CAD, Canadian dollar rate; CI, confidence interval; HCV, hepatitis C virus; HIV, human immunodeficiency virus; OR, odds ratio; RNA, ribonucleic acid.

^a Centered at mean if ever smoker, 0 if never smoker.

^b Impaired fasting glucose (glucose ≥ 6.1 and fasting) or impaired glucose tolerance (glucose ≥ 7.8 and not fasting).

with over 90% reporting smoking in their lifetime. The current smoking rates were almost 5 times the Canadian average (16%) [20]. This high prevalence of smoking can be explained, in part, by the high proportion of participants using alcohol, marijuana, or injection drugs and who acquired infection through IDU, because these behaviors are correlated with tobacco smoking. However, we did not find evidence that tobacco smoking was associated with a faster progression to significant liver fibrosis, as measured by APRI scores, or to ESLD when comparing ever versus never smokers. Moreover, progression to APRI score ≥ 1.5 or ESLD was not influenced by number of pack-years of smoking. Of the characteristics examined, the only factors associated with accelerated progression to liver fibrosis were detectable HCV RNA and alcohol use, both of which are well known risk factors for liver disease. Some studies have found that smokers are at increased risk of insulin resistance, which is a risk factor for steatosis, necroinflammation, and fibrosis in nonalcoholic fatty liver disease [10, 21–26]. A direct effect of tobacco smoking on insulin activity has also been documented in some studies [10, 25, 26]. However, in our analyses, the estimates associated with smoking were unaffected by the inclusion of impaired fasting glucose or impaired glucose tolerance and progression to liver fibrosis or ESLD as a covariate.

Four other groups have examined the cross-sectional relationship between smoking and liver fibrosis in HCV mono-infection [12, 13, 27, 28]. Among 310 HCV patients who had been hospitalized for diagnostic liver biopsies, Pessione et al [12] found that individuals having more than 15 pack-year smoking history had greater Knodell liver fibrosis scores compared with never or ex-smokers in multivariate analysis (odds ratio [OR] = 1.9; 95% confidence interval [CI], 1.1–3.6). In another study involving 176 HCV-infected patients who underwent liver biopsies before beginning HCV treatment, Tsochatzis et al [28] examined heavy smokers (≥ 20 pack-year lifetime) and smokers (current and former smokers) versus never smokers. Former smokers included individuals who had quit smoking within 5 years, and never smokers were individuals who reported smoking in the remote past. They reported an OR for severe fibrosis (staging score ≥ 4) of 3.92 (95% CI, 1.36–11.35) and an OR for steatosis of 2.86 (95% CI, 1.07–7.68) for heavy smokers in multivariate analyses [28]. Finally, in the general population, tobacco smoking has been found to be associated with hepatocellular carcinoma in a meta-analysis examining 38 cohort and 58 case-control studies [29].

In contrast, Hezode et al [13] did not find any significant relationship between histological fibrosis score (F2–F3–F4) and either daily or lifetime smoking history in multivariate analysis of 244 HCV-monoinfected patients. Likewise, in a cohort of 170 patients, Dev et al [27] did not find an association between smokers versus never smokers in METAVIR fibrosis score. In this latter study, smokers included individuals who reported any smoking activity at time of presentation or in the past [27].

Reasons for discrepant findings between these studies may relate, in part, to the different definitions of smoking exposure used. Dev et al [27] considered an individual to be a smoker if he/she reported any smoking in the past. This definition would have included individuals with relatively small quantities of tobacco exposure. No information on the quantity of cigarettes smoked in the past, nor duration of smoking history, was available [27]. In the study by Tsochatzis et al [28], for many participants the duration of infection or liver disease was unknown. Thus, total lifetime tobacco exposure was analyzed without adjustment for the duration of liver illness, which may have influenced study findings. Furthermore, Pessione et al [12] found that one third of drinkers ceased alcohol consumption while continuing to smoke after they were informed of their HCV status. The presence of a synergistic relationship between alcohol consumption and tobacco smoking is generally accepted, and failure to account for past heavy alcohol use may have confounded observed associations [30].

In the general population, tobacco smoking is the most significant cause of preventable cardiovascular disease [31] and is the most important etiology of lung cancer, accounting for greater than 80% of deaths attributable to lung cancer in some developed countries [32, 33]. In addition, smoking is a key risk factor for community-acquired pneumonia and invasive pneumococcal disease with bacteremia [34, 35]. Given the well described health risks of tobacco smoking, the strikingly high smoking rates among HIV-HCV coinfecting individuals, and the excess rate of comorbidities in HIV-HCV coinfection [36, 37], further study is merited to elucidate whether the excess rate of some of these comorbidities may indeed be linked in part to tobacco consumption.

The current study has several strengths worth highlighting. This was a large, prospective cohort study with broad representation of HIV-HCV infected individuals in Canada. In many of the aforementioned studies that examined the cross-sectional association between tobacco smoking and accelerated liver fibrosis in HCV monoinfected patients, temporality could not be assessed and progression of liver fibrosis was not studied. In addition, at each of our study visits, participants were asked to report their cigarette use in the past 6 months. This enabled changes in smoking habits to be captured and accounted for in the analyses, over the course of the study period. Likewise, possible confounders such as alcohol use, drug use, glucose intolerance, and HIV stage were analyzed concurrently at each visit. Furthermore, although we used a noninvasive surrogate marker for significant fibrosis, clinical outcomes were used to corroborate our findings. A sensitivity analysis was performed to assess the presence of an interaction between alcohol use and tobacco smoking by stratifying for alcohol use in the 6 months preceding cohort entry. In addition, our analyses were repeated by decomposing tobacco exposure into multiple variables to capture smoking exposures in a time-updated

manner. There is a risk that using pack-years alone agglomerates packs of cigarettes smoked per day and years of smoking, and thus these pieces of information may be lost in the process. However, with both methods of analyses, we did not find an effect of tobacco exposure on acceleration of liver disease, strengthening our conclusion that tobacco smoking was not associated with liver disease progression in HIV-HCV coinfection.

There are also limitations of the current study that should be acknowledged. Because data were collected at 6-month intervals, it was impossible to determine the exact timing of progression to significant liver fibrosis between study visits. However, detailed information on changes in smoking habits since the last study visit was collected, allowing for cumulative measures of smoking to be used, thus mitigating the issue of interval censoring described here. Our primary analysis was also limited by the exclusion of participants with significant liver fibrosis or ESLD at cohort entry. It is possible that fast progressors were eliminated from the study population, leaving a greater proportion of “survivors”. However, the absence of an association between smoking and liver fibrosis was confirmed in a sensitivity analysis including those with significant liver fibrosis or ESLD at cohort entry. In our study, 15% of deaths were due to cancer and 7% were due to cardiovascular disease, both of which may be smoking related and could have acted as competing risks for our study outcomes.

The APRI score was selected as a marker for liver fibrosis because liver biopsy is invasive and cannot be used in a longitudinal research setting, and repeated measures of transient elastography are currently limited in our cohort. As reviewed by Lin et al [16], the APRI score can be used for staging of liver fibrosis, although it has less diagnostic accuracy than the FibroTest and transient elastography (Fibroscan). The APRI score has been found in one study to be less accurate for identification of significant fibrosis, severe fibrosis, and cirrhosis in HIV-HCV coinfection than in HCV mono-infection [16]. Nonetheless, despite these limitations, the APRI has been validated in our study population for detecting significant liver fibrosis with an area under the curve of 0.85 ± 0.06 [38]. In addition, APRI cutoffs of 1.5 and 2 have also been shown to be associated with cirrhosis, other adverse liver and clinical outcomes, and death in our cohort [39] as well as in other studies [39–41]. Fibroscan data were not available in sufficient numbers of patients to permit longitudinal analyses, although in future studies it will be of interest to corroborate our results with such data.

CONCLUSIONS

After careful characterization of smoking exposure and its temporal relationship to liver fibrosis evaluation, we did not find that tobacco exposure was associated with accelerated liver fibrosis in individuals infected with HIV-HCV. Although we cannot exclude an effect of increasing pack-years smoked on liver fibrosis, it is likely to be minimal and far less than that

associated with detectable HCV RNA and alcohol use. The elevated point estimate for ever smoking among individuals using alcohol suggests that previous studies may have been confounded by alcohol use. These findings are informative for physicians in counseling patients about factors that accelerate risk of hepatic fibrosis. Nonetheless, smoking was exceptionally common among coinfecting patients, and, given the broad range of detrimental health effects observed with tobacco smoking, smoking cessation should still be encouraged.

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