Progression of liver fibrosis following acute hepatitis C virus infection in HIV-positive MSM

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Background: Whether continued, accelerated liver fibrosis progression occurs following acute hepatitis C virus infection (AHCVI) in HIV-positive MSM is unknown.

Design and methods: HIV-positive MSM from the AIDS Therapy Evaluation in the Netherlands and MSM Observational Study for Acute Infection with Hepatitis C-cohorts with primary AHCVI and at least one fibrosis-4 (FIB-4) measurement less than 2 years before and 1 year after estimated AHCVI were included. Mixed-effect linear models were used to evaluate (time-updated) determinants of FIB-4 levels over time. Determinants of transitioning to and from FIB-4 ≤ 1.45 and >1.45 were examined using multistate Markov models.

Results: Of 313 MSM, median FIB-4 measurements per individual was 12 (interquartile range $=8-18$) and median follow-up following AHCVI was 3.5 years (interquartile range $=1.9-5.6$). FIB-4 measurements averaged at 1.00 [95% confidence interval (CI) $=0.95-1.05$] before AHCVI, 1.31 (95% CI $=1.25-1.38$) during the first year of AHCVI and 1.10 (95% CI $=1.05-1.15$) more than 1 year after AHCVI. Mean FIB-4 more than 1 year after AHCVI was higher for chronically infected patients compared with those successfully treated ($P=0.007$). Overall FIB-4 scores were significantly higher with older age, lower $CD4^+$ cell count, longer duration from HIV-diagnosis or AHCVI, and nonresponse to HCV-treatment. At the end of follow-up, 60 (19.2%) and eight MSM (2.6%) had FIB-4 between 1.45–3.25 and ≥ 3.25, respectively. Older age, lower $CD4^+$ cell count and detectable HIV-RNA were significantly associated with higher rates of progression to FIB-4 >1.45, whereas older age, longer duration from HIV-diagnosis and nonresponse to HCV-treatment were significantly associated with lower rates of regression to FIB-4 ≤ 1.45.

Conclusion: In this population of HIV-positive MSM, FIB-4 scores were higher during the first year of AHCVI, but FIB-4 ≥ 3.25 was uncommon by the end of follow-up. Well controlled HIV-infection appears to attenuate FIB-4 progression.

AIDS 2019, **33**:833–844

Keywords: acute hepatitis C virus infection, fibrosis-4, HIV/hepatitis C virus coinfection, liver fibrosis, MSM

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Received: 16 October 2018; revised: 17 December 2018; accepted: 18 December 2018.

DOI:10.1097/QAD.0000000000002138

ISSN 0269-9370

Introduction

Hepatitis C virus (HCV) infection is common in HIV-positive individuals due to shared routes of transmission. Since 2000, sexual transmission of HCV has continued to occur among HIV-positive MSM [1–3]. HIV coinfection may accelerate liver fibrosis progression in patients with chronic HCV infection [4,5]. However, these findings are based on studies among individuals in whom HCV infection generally preceded HIV infection. In these coinfected patients, development of liver cirrhosis typically takes 20 years or more after HCV infection [4]. Little is known about the progression of liver fibrosis in patients acquiring acute HCV infection while already infected with HIV, as is the case in HIV-positive MSM who have sexually acquired HCV. In this specific group, one study reported high rates of fibrosis progression in 29 HIV-positive MSM with acute HCV [6,7], which was not observed in a similar study in 38 patients [8]. Nonetheless, four of the 29 acute HCV cases described in the first study rapidly developed decompensated cirrhosis and death within 2–8 years after their infection, suggesting accelerated fibrosis progression [9]. Recently, another study including 178 patients with 213 episodes of acute HCV infection also showed high rates of significant liver fibrosis and cirrhosis development, as evaluated by noninvasive markers [10]. However, these studies are limited by relatively small sample sizes or short follow-up periods and hence whether continued accelerated fibrosis progression occurs in this particular setting remains unknown.

Liver biopsy is considered the gold standard of establishing liver fibrosis stage, but is invasive and has several drawbacks, including interobserver variability, sampling error and risk of complications [11]. Therefore, several noninvasive methods have been created, including the fibrosis-4 (FIB-4) score, which was developed in a population of HIV–HCV coinfected individuals and is calculated using a formula including a patient's age, serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels, as well as platelet count. An advantage of the FIB-4 score over liver biopsy is that it can be easily calculated for a large number of patients at different time points. Using a FIB-4 cut-off of ≤ 1.45 and ≥ 3.25, respectively, to exclude and confirm presence of advanced liver fibrosis (METAVIR score $\geq$F3 using liver biopsy), advanced liver fibrosis can be accurately rejected or confirmed in 87% of patients [12]. Subsequent studies have confirmed the value of FIB-4 in predicting significant fibrosis among HIV–HCV coinfected patients using several cut-offs, the majority of which found an area under the receiver operator characteristic curve more than 0.80 [13–17]. The ability of FIB-4 to confirm or reject advanced liver fibrosis and cirrhosis is comparable with that of transient elastography [15,18].

The presence of advanced liver fibrosis or cirrhosis increases the risk of end-stage liver disease and hepatocellular carcinoma (HCC) [19], and even in the era of the availability of highly effective direct-acting antiviral agents (DAAs), negatively affects treatment response [20,21]. Given that HCV continues to spread among HIV-positive MSM [2] and diagnosis of HCV infection might be late depending on HCV testing frequency, it is relevant to study whether there is continued, accelerated fibrosis progression among HIV-positive MSM following acute HCV infection. The aim of the current study was to longitudinally assess the course of liver fibrosis progression, as measured by the FIB-4 score, following acute HCV infection in a nationwide cohort of HIV-positive MSM in The Netherlands, and to assess possible determinants of fibrosis progression and regression.

Methods

Study population and data collection

Data from HIV-positive patients enrolled in routine care in The Netherlands were used for this study. Data were collected by the Dutch HIV Monitoring Foundation [Stichting HIV Monitoring (SHM)], which manages the ongoing AIDS Therapy Evaluation in the Netherlands (ATHENA) observational cohort initiated in 1998, including 98% of all patients with HIV infection in care in The Netherlands [22]. Patients were included in the current study if they were identified as MSM; had their first HCV-positive test between 1 January 1999 and 1 January 2015; were at least 18 years old; and were defined as having primary acute HCV infection. Furthermore, included patients were required to have at least one routine FIB-4 measurement (see below under 'assessment of liver fibrosis') available within 2 years before and at least one at least 1 year after the estimated date of HCV infection. Patients diagnosed with HCC or liver cirrhosis prior to HCV infection or diagnosed with HCV prior to HIV infection were not included.

Information on demographics, HIV-disease history, laboratory results, comorbidities and treatment for HIV and HCV, was derived from the SHM database. Additional data on HCV infection, collected in the MSM Observational Study for Acute Infection with Hepatitis C (MOSAIC) [23], were used to supplement data in the ATHENA cohort. Stored sera from patients in the MOSAIC study were back-tested for HCV serology and/or HCV RNA to more precisely estimate the moment of acute HCV infection. This allowed a larger number of acute HCV cases to be identified.

At initiation, the ATHENA cohort was approved by the Institutional Review Board of all participating centers. HIV-positive people in care can opt-out after being informed by their treating physician of the purpose of data collection. Data are pseudonymized before being provided

to investigators and may be used for scientific purposes. The MOSAIC study was approved by the Institutional Review Boards of the Amsterdam UMC (University of Amsterdam, Amsterdam, The Netherlands) and boards of directors for all participating centers.

Definitions

Primary acute HCV infection was defined as the presence of at least one negative anti-HCV antibody and/or negative HCV RNA test result, without any known prior positive anti-HCV antibody and/or HCV RNA test, followed by a positive anti-HCV antibody or HCV RNA positive test result, within a maximum interval of 365 days between the last negative and first positive test. The estimated date of HCV infection was the midpoint between the last negative and first positive test. If the date of the last negative anti-HCV antibody test was later than or at same time as the first HCV RNA positive test, the estimated date of acute infection was determined as 28 days before the date of first HCV RNA-positive test [24]. Spontaneous clearance was defined as two undetectable/negative HCV RNA tests following HCV infection in HCV untreated patients, with untreated patients having only a single undetectable/negative HCV RNA test classified as having possible spontaneous clearance. Sustained virological response (SVR) was defined as having at least one undetectable/negative HCV RNA test at least 22 weeks after the end of anti-HCV treatment or 'SVR' indicated in the patient's medical file. Suspected reinfection was defined as having a detectable HCV RNA test after spontaneous clearance or SVR. HCV genotype was not considered in this definition. The date of suspected reinfection was estimated as the midpoint between the last negative and first positive HCV RNA test.

Assessment of liver fibrosis

FIB-4 was calculated with the following formula including age (years), AST (IU/l), ALT (IU/l) and platelet count (10^9/l) [12]:

$$\text{FIB-4} = \frac{\text{age} \times \text{AST}}{\left(\text{platelets} \times \sqrt{\text{ALT}}\right)}$$

ALT, AST and platelet count measurements were allowed to span at most 14 days within each other. Age was kept constant at the estimated date of HCV infection. Time-points at which $CD4^+$ cell count and/or HIV RNA load were measured likely represented routine outpatient clinic visits and thus only FIB-4 measurements with a concomitant $CD4^+$ cell count or HIV RNA load were included. To reduce bias due to nonfibrosis-related increases or decreases in laboratory measurements, time-points with excessive measurements on any given parameter ($\geq$2 measurements during a single day or $\geq$3 measurements within 7 days) were considered indicative of acute illness or hospitalization and excluded. As HCV treatments may lower platelet count, thereby biasing FIB-4 scores towards higher liver fibrosis levels, FIB-4 measurements during HCV treatment were also excluded.

Covariates

The following covariate measurements were selected closest to the estimated date of HCV infection: age, self-reported alcohol intake, diabetes mellitus [defined as having at least one of the following: hemoglobin (Hb)A1c (IFCC) $\geq$48 mmol/mol, blood glucose (nonfasting) $\geq$11.1 mmol/l, fasting blood glucose $\geq$7.0 mmol/l, or use of antidiabetic medication], cardiovascular disease or risk thereof (statin use or SBP $>$ 140 mmHg or DBP $>$ 90 mmHg), BMI, $CD4^+$ cell count, HIV RNA load, combined antiretroviral therapy (cART) use including use of potentially hepatotoxic agents [dideoxynucleoside analogues (zalcitabine, didanosine or stavudine) or nevirapine], use of cotrimoxazole, AIDS-defining illness (any recorded event classified as Centers for Disease Control and Prevention category C), and hepatitis B virus infection (detectable hepatitis B surface antigen using a commercially available immunoassay). HCV genotype was included as a covariate and $CD4^+$ cell count, HIV RNA load, AIDS-defining illness and cART use were included as time-updated covariates.

Statistical analyses

Patient characteristics were described using data from the time-point closest to estimated date of HCV infection. Patients began follow-up at the first available FIB-4 measurement less than 2 years prior to the estimated date of HCV infection and continued until suspected HCV reinfection or last available FIB-4 measurement, whichever occurred first. We defined three HCV infection periods during follow-up (with respect to date of HCV infection): preinfection (before), acute infection (in the first year after) and postacute infection ($\geq$1 year after).

To evaluate determinants of FIB-4 levels across study time-points, we used a mixed-effect linear modeling approach. FIB-4 levels were log-transformed to ensure approximately normal distribution. Univariable differences ($\triangle$) in average log-FIB-4 levels between levels of risk factors were estimated along with their 95% confidence intervals (CIs). A random intercept was included in the model to account for between-patient variability at start of follow-up. A multivariable model was constructed by placing covariates with an associated P value of 0.05 or less in forward-stepwise fashion, while removing any covariates with a P value greater than this threshold. All Δ and 95% CI estimates were presented as back-transformed values.

To evaluate the evolution of liver fibrosis severity during follow-up, we modeled fibrosis as a Markov process between states of no/minimal/moderate and advanced/severe fibrosis. As two FIB-4 thresholds are proposed for

the detection of at least F3 fibrosis (1.45 with 80% sensitivity, 64% specificity; and 3.25 with 37% sensitivity, 94% specificity) [25], the FIB-4 threshold optimized on sensitivity (1.45) was selected in our analysis. Transitions between FIB-4 levels ≤ 1.45 and > 1.45 were modeled using a multistate time-homogenous Markov model during continuous time, allowing instantaneous rates of transitioning (or transition intensities) from ≤ 1.45 to > 1.45 and from > 1.45 to ≤ 1.45 to be estimated. We also examined the effects of using a higher FIB-4 threshold of 3.25 and using a three-state model (≤ 1.45, to and from > 1.45 and < 3.25, to and from ≥ 3.25). We corrected for misclassification by assuming that the probability distribution of observed given the true liver fibrosis state was binomial and not dependent on covariates, while correcting transition counts using the Viterbi algorithm. Using maximum likelihood methods in the above framework, a proportional hazards model was fit to estimate hazards ratios between covariate levels and their 95% CI. Covariates whose 95% CIs did not cross 1 were selected in forward-stepwise fashion to create a multivariable model.

HCV infection period and successful HCV treatment response (time-updated) were separately added to the final multivariable models. Furthermore, multivariable models were repeated in a sensitivity analysis while excluding patients with spontaneous clearance or excluding all measurements in the acute phase of HCV infection.

Analyses were performed using Stata version 13.1 (StataCorp LP, College Station, Texas, USA) and the 'msm' package in R version 3.4.1 (R Core Team, Vienna, Austria). *P* values less than 0.05 were considered statistically significant.

Table 1. Characteristics of 313 HIV-positive MSM at the time of primary acute hepatitis C virus infection.

	Number (%) or median (IQR)
Age (years)	42.6 (35.9–47.7)
Dutch origin	257 (82.1%)
MOSAIC study participant	102 (32.6%)
Year of HCV infection	2010 (2007–2012)
Interval between last HCV negative and first HCV positive test (years)	0.4 (0.3–0.6)
HCV genotype	
1	205 (65.5%)
2	22 (7.0%)
3	4 (1.3%)
4	56 (17.9%)
Unknown	26 (8.3%)
Interval between first HIV-positive test and estimated date of HCV infection (years)	4.1 (1.3–9.0)
AIDS-defining illness before HCV infection	50 (16.0%)
Nadir $CD4^+$ cell count (cells/μl)	220 (140–320)
Nadir $CD4^+$ cell count <250 cells/μl	178 (56.9%)
$CD4^+$ cell count (cells/μl)	500 (380–670)
cART naive (1 missing value)	95 (30.4%)
HIV RNA (copies/ml)	50 (40–16 000)
Undetectable HIV RNA (<50 copies/ml)	157 (50.2%)
Ever use of dideoxynucleosides[a] (1 missing value)	48 (15.4%)
Ever use of nevirapine (1 missing value)	88 (28.1%)
Ever use of cotrimoxazole (1 missing value)	80 (25.6%)
Weekly alcohol consumption	
0–7 U	175 (55.9%)
≥8 U	56 (17.9%)
Unknown	82 (26.2%)
BMI (17 missing values)	22.8 (21.3–24.4)
Total cholesterol, mmol/l (4 missing values)	4.3 (3.6–5.1)
Use of statins	10 (3.2%)
Diabetes mellitus	8 (2.6%)
Hypertension (21 missing values)	38 (13.0%)
HBsAg positive (2 missing values)	9 (2.9%)

cART, combination antiretroviral therapy; HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus; IQR, interquartile range; MOSAIC, MSM Observational Study for Acute Infection with Hepatitis C.
[a]Dideoxynucleoside analogues; zalcitabine (DDC), didanosine (DDI) or stavudine (D4T).

Results

Study population

In total, 501 HIV-positive MSM with a first episode of acute HCV infection from 1999 to 2015 were identified. Of these, 188 were not included for the following reasons: follow-up shorter than 1 year or absence of FIB-4 measurements 1 year after estimated date of HCV infection ($n = 41$), absence of FIB-4 measurements within 2 years prior to estimated date of HCV infection ($n = 125$), no FIB-4 measurements during entire follow-up ($n = 20$) and HCC or liver cirrhosis diagnosed prior to the estimated date of HCV infection ($n = 2$). As a result, 313 individuals were included in analysis (Supplementary Fig. 1, http://links.lww.com/QAD/B427).

Characteristics of the study population at the time of acute HCV infection are described in Table 1. Median interval between last HCV negative and first positive test used to calculate the estimated date of infection was 0.4 years [interquartile range (IQR) 0.3–0.6]. Median follow-up was 3.5 years (IQR 1.9–5.6) following acute HCV infection. During the course of follow-up, 40 patients spontaneously cleared HCV (of whom 11 patients had only one negative HCV RNA test available). Of the 273 patients without spontaneous clearance, 45 were never treated and 228 were treated at least once (Supplementary Fig. 1, http://links.lww.com/QAD/B427). First-line treatments were as follows: pegylated-interferon ± ribavirin ($n = 205$), pegylated-interferon ± ribavirin with first-generation HCV protease-inhibitor ($n = 19$), DAA alone ($n = 4$). Median time from estimated date of HCV infection to first treatment initiation was 5.9 months (IQR 4.2–9.8). Reinfection occurred in 49 patients a median of 2.7 years (IQR 1.6–4.4) after initial HCV infection.

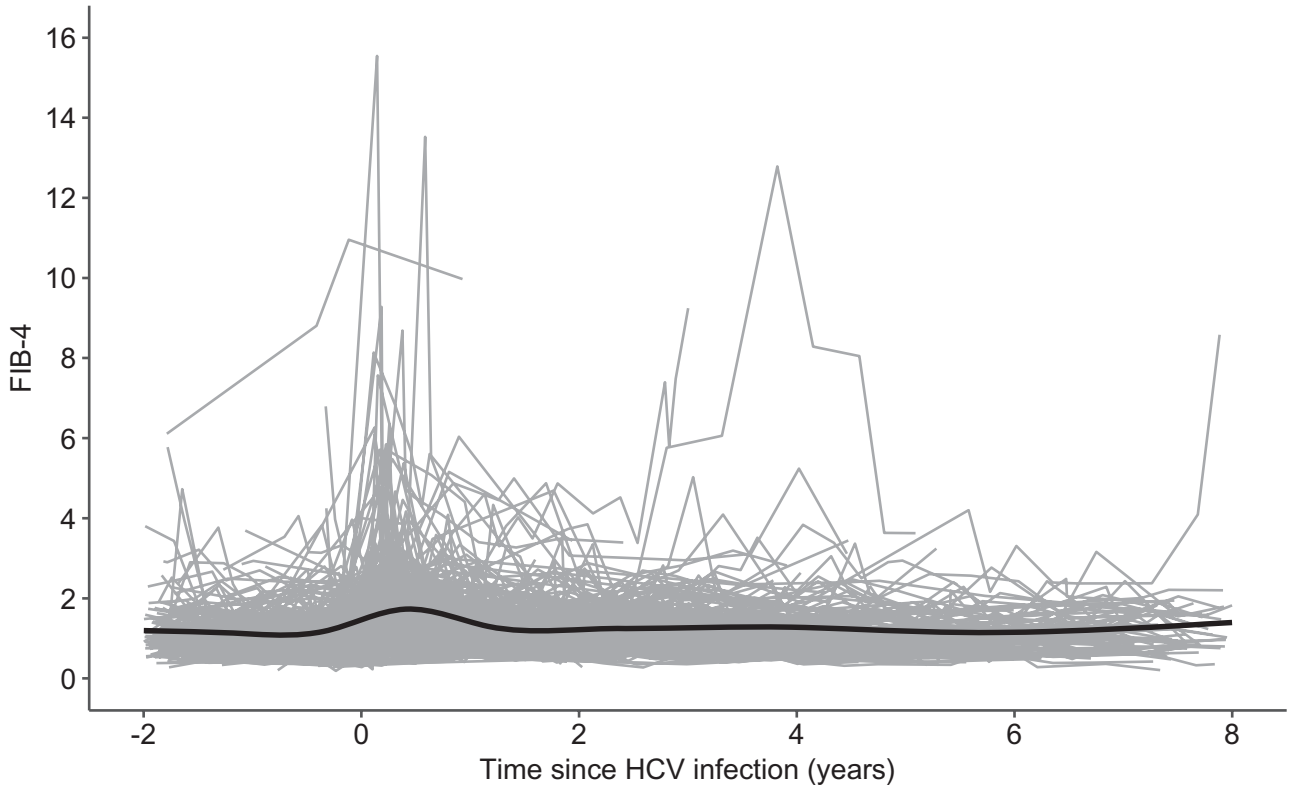

Fig. 1. Observed (gray lines) and modeled (black solid line) fibrosis-4 patterns over time before, around and after primary acute hepatitis C virus infection in 313 HIV-positive MSM. Modeled fibrosis-4 over time determined using generalized additive regression including splines with three knots.

Fibrosis-4 progression over time

Median number of FIB-4 measurements per patient was 12 (IQR 8–18). FIB-4 levels appeared mostly stable over time with peaks in some patients shortly after acute infection (Fig. 1). At the last FIB-4 measurement, 245 patients (78.3%) had FIB-4 ≤ 1.45, 60 (19.2%) had FIB-4 >1.45 and < 3.25, and 8 (2.6%) had FIB-4 ≥ 3.25. Of the eight patients with FIB-4 ≥ 3.25, five had FIB-4 between 1.45–3.25 and two had FIB-4 ≤ 1.45 before acute HCV infection. Compared with all other patients, median age at acute HCV infection in these eight patients was higher (50.8 versus 40.8 years, $P = 0.004$), a higher proportion had ever used dideoxynucleoside analogues (75.0 versus 13.8%, $P < 0.001$), and median time between first HIV-positive test and estimated date of HCV infection was longer (11.3 versus 3.9 years, $P < 0.001$).

Determinants of fibrosis-4 progression over time

In multivariable analysis (Table 2), factors that were significantly associated with higher FIB-4 scores during overall follow-up were HCV infection period ($P < 0.001$), older age at HCV infection ($P < 0.001$), increasing time since HIV diagnosis ($P = 0.004$), and lower $CD4^+$ cell count ($P < 0.001$). These associations remained statistically significant when excluding patients with spontaneous clearance or excluding all FIB-4 measurements during the acute phase of HCV infection. When incorporating HCV treatment outcomes (time-updated) in the multivariable model among patients without spontaneous clearance, those with an SVR had lower overall FIB-4 scores (−0.17, 95% CI −0.20, −0.14) compared with those without an SVR ($P < 0.001$). From the mixed model, FIB-4 measurements averaged at 1.00 (95% CI 0.95–1.05) preinfection, 1.31 (95% CI 1.25–1.38) during acute infection and 1.10 (95% CI 1.05–1.15) postacute infection, and differed significantly between HCV outcome category [spontaneous clearance, successfully treated or never treated/failed all treatments (chronic HCV infection), $P < 0.0001$, Fig. 2]. More specifically, FIB-4 in the acute phase of HCV infection was significantly higher compared with that in both the preinfection and postacute phase for all HCV outcome categories. Furthermore, mean FIB-4 in the postacute infection phase was significantly higher for chronically HCV-infected patients compared with those successfully treated ($P = 0.007$).

Evolution of fibrosis-4 scores over time

A total of 53 transitions from a FIB-4 score of ≤ 1.45 to >1.45 was observed, resulting in an intensity rate of 11.7/100 person-years (95% CI 9.3–14.6, cumulative probability 9.8% at end of follow-up). The majority of these transitions occurred during the acute phase

Table 2. Factors associated with fibrosis over time, as measured by the fibrosis-4 score, following acute hepatitis C virus infection in HIV-positive MSM.

	Univariable analysis			Multivariable analysis[a]		
	Coefficient	95% CI	*P* value	Coefficient	95% CI	*P* value
Age at HCV infection (years)			<0.001			<0.001
≤40 (ref)	–	–		–	–	
>40–≤50	0.38	0.27–0.49		0.33	0.23–0.44	
>50	0.88	0.68–1.11		0.77	0.58–0.98	
HCV-related variables						
HCV infection period			<0.001			<0.001
Preinfection (ref)	–	–		–	–	
Acute phase	0.32	0.28–0.36		0.30	0.26–0.34	
Postacute phase	0.10	0.07–0.12		0.12	0.09–0.15	
HCV genotype			0.84			
1 (ref)	–	–				
4	−0.07	−0.17–0.05				
Other	0.04	−0.11–0.21				
Spontaneous HCV clearance	−0.04	−0.16–0.10	0.58			
HIV-related variables at HCV infection						
Time since HIV diagnosis (per year)	0.02	0.01–0.02	<0.001	0.01	<0.01–0.02	0.004
cART naive	−0.08	−0.16–0.01	0.09			
Ever use of dideoxynucleosides[b]	0.23	0.09–0.39	0.001			
Ever use of nevirapine	0.16	0.05–0.28	0.002			
Ever use of cotrimoxazole	0.11	0.01–0.23	0.047			
Nadir $CD4^+$ cell count <250/μl	0.09	−0.01–0.19	0.07			
HIV-related variables (time-updated)						
AIDS-defining illness	0.03	−0.05–0.12	0.46			
$CD4^+$ cell count, cells/μl (log_{10} transformed)	−0.46	−0.50 to −0.41	<0.001			
$CD4^+$ cell count (cells/μl)			<0.001			<0.001
>500 (ref)	–	–		–	–	
350–499	0.10	0.07–0.13		0.09	0.06–0.12	
<350	0.32	0.27–0.37		0.29	0.25–0.34	
HIV RNA, copies/ml (log_{10} transformed)	0.03	0.02–0.04	<0.001			
Undetectable HIV RNA (<50 copies/ml)	−0.03	−0.05 to −0.01	0.03			
Alcohol use and comorbidities at HCV infection						
HBsAg positive	0.01	−0.23–0.32	0.94			
Weekly alcohol consumption			0.36			
0–7 U (ref)	–	–				
≥8 U	−0.08	−0.18–0.04				
Missing	0.07	−0.04–0.18				
Diabetes mellitus	0.01	−0.24–0.33	0.97			
CVD risk[c]	0.27	0.12–0.45	<0.001			
BMI	0.01	−0.01–0.03	0.13			

cART, combination antiretroviral therapy; CI, confidence interval; CVD, cardiovascular disease; HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus.
[a]In multivariable analysis, we preferred categorical variables for $CD4^+$ cell count and HIV RNA over continuous variables.
[b]Dideoxynucleoside analogues; zalcitabine (DDC), didanosine (DDI) or stavudine (D4T).
[c]Defined as statin use or SBP of more than 140 mmHg or DBP of more than 90 mmHg.

(cumulative probability 8.7%) compared with postacute phase of infection (cumulative probability 2.5%). A total of 116 transitions from a FIB-4 score of >1.45 to ≤ 1.45 was observed, resulting in an intensity rate of 24.0/100 person-years (95% CI 17.6–32.9, cumulative probability 20.2% at end of follow-up). These transitions occurred slightly more frequently in the acute versus postacute phase of infection (cumulative probability 28.8 and 16.8%, respectively).

In multivariable analysis (Table 3), older age, lower $CD4^+$ cell count, and detectable HIV RNA were significantly associated with higher rates of transitioning to FIB-4 >1.45. Older age and increasing time since HIV diagnosis were associated with lower rates of transitioning to FIB-4 ≤ 1.45. These observations were comparable when excluding patients with spontaneous clearance, except any exposure to dideoxynucleoside analogues significantly reduced the rate of transitioning to FIB-4 ≤ 1.45 and time since HIV diagnosis was no longer statistically significant (Table 3). The three-state Markov model demonstrated comparable findings (data not shown). We also examined the effect of using a higher FIB-4 threshold of 3.25; however, the few number of transitions ($n=12$ from <3.25 to ≥ 3.25, and $n=4$ from ≥ 3.25 to <3.25) precluded any further analysis. In a post-hoc analysis among those without spontaneous clearance, treatment-induced SVR was associated with increased rates of transitioning to FIB-4 ≤ 1.45 in the multivariable model (adjusted hazard ratio 3.55, 95% CI 1.18–10.72).

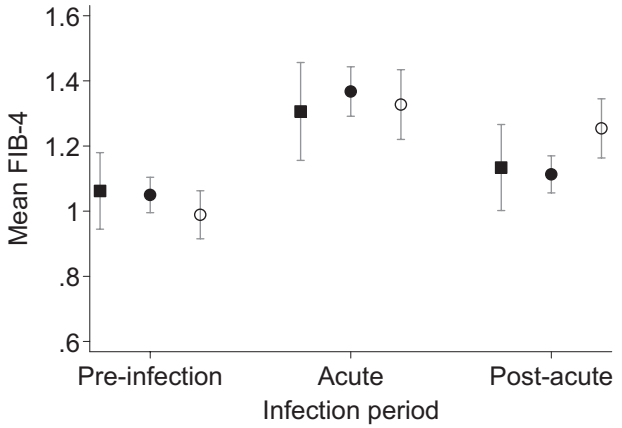

Fig. 2. Mean fibrosis-4 score and corresponding 95% confidence intervals in the preinfection, acute infection and postacute infection periods for different hepatitis C virus outcome groups. Hepatitis C virus outcome groups: spontaneous clearance (black square), successfully treated (black dot), no spontaneous clearance and never successfully treated (chronic hepatitis C virus infection, white dot). Mean fibrosis-4 scores were estimated using a multivariable mixed model including age category at hepatitis C virus infection, time since HIV diagnosis, $CD4^+$ cell count category, hepatitis C virus outcome group, infection period and the interaction between hepatitis C virus outcome group and infection period.

Discussion

In this study of 313 HIV-positive MSM, we longitudinally assessed changes in FIB-4 score following acute HCV infection. Overall, we found higher FIB-4 scores during the acute phase of infection, defined within the first year, which later decreased for the majority of patients. Compared with successfully treated patients, those with chronic HCV infection had significantly higher FIB-4 in the postacute infection period. By the end of the median 3.5 year follow-up period following acute HCV infection, only 2.6% of patients had FIB-4 ≥ 3.25 and the large majority (78.3%) had FIB-4 ≤ 1.45. Higher overall FIB-4 scores were associated with older age, lower $CD4^+$ cell count, increasing time since HIV diagnosis, and the acute and postacute phases of HCV infection when compared with the preinfection phase. Older age, lower $CD4^+$ cell count and detectable HIV RNA, were also associated with a higher rate of progression to FIB-4 more than 1.45, and both older age and increasing time since HIV diagnosis with a lower rate of regression to FIB-4 ≤ 1.45. We did not find an association between HCV genotype and progression of liver fibrosis, consistent with a recent report by Steininger *et al.* [10]. Not surprisingly, successful response to HCV treatment was associated with lower overall FIB-4 scores and an increased rate of regression to FIB-4 ≤ 1.45. Our data represent one of the largest sample sizes and longest follow-up for this population with acute HCV infection to date.

In contrast to some previous studies among HIV–HCV coinfected MSM [6,7,9,10], we did not find high rates of advanced liver fibrosis, nor evidence of continued, accelerated liver fibrosis progression. Our findings are in line with another study, showing that fibrosis progression rates, measured using transient elastography, were highest in the first 3 months after acute HCV infection and strongly decreased thereafter [8]. In addition, their study demonstrated that higher serum ALT levels at the time of transient elastography measurement were associated with faster rates of fibrosis progression. Both our findings suggest a temporary peak of high ALT levels during the acute phase of HCV infection, which wanes once chronic HCV infection is established. It remains controversial whether noninvasive measurements during the first few months after acute HCV infection are truly reflective of liver fibrosis or are simply indicative of inflammation during acute hepatitis. Importantly, the results from our multivariable models did not change when excluding measurements obtained during the acute phase of HCV infection.

The fact that much of our population was successfully treated within a short time after acute HCV infection may have contributed to the low rates of advanced liver fibrosis. In HIV–HCV coinfected patients, SVR is found to be significantly associated with improvements in liver fibrosis, both after treatment with pegylated-interferon-based regimens and DAAs [26–28]. Nevertheless, mean FIB-4 scores of patients with chronic HCV infection were below the 1.45 cut-off in the postacute phase of HCV infection, indicating that most of these patients did not have advanced liver fibrosis despite this mean being significantly higher compared with patients with treatment-induced SVR.

Similar to other studies [29–35], poorly controlled HIV infection and increasing time since HIV diagnosis were significantly associated with higher fibrosis levels, thereby providing further evidence that HIV infection may indeed aggravate liver fibrosis. The possible underlying mechanisms of this finding are the subject of ongoing research and include oxidative stress, immune-mediated injury, gut microbial translocation, and systemic inflammation [36]. Moreover, patients with FIB-4 ≥ 3.25 by the end of follow-up were older at the time of acute HCV infection, had a significantly longer duration of known HIV infection, and had more extensive use of dideoxynucleoside analogues, known to affect liver fibrosis progression [30,34,37–39]. This suggests that previous liver damage in these patients, due to age, HIV and/or use of hepatotoxic drugs, could evoke accelerated liver fibrosis after acute HCV infection.

Our study has several limitations. First, we used a noninvasive measure of liver fibrosis. For patients with a FIB-4 between 1.45 and 3.25 (19.2% of our study

Table 3. Determinants of transitioning between fibrosis-4 ≤ 1.45 and fibrosis-4 >1.45.

	Univariable		Multivariable[a]		Excluding patients with SC Multivariable[a]	
	FIB-4 ≤ 1.45 → >1.45	FIB-4 > 1.45 → ≤ 1.45	FIB-4 ≤ 1.45 → >1.45	FIB-4 > 1.45 → ≤ 1.45	FIB-4 ≤ 1.45 → > 1.45	FIB-4 > 1.45 → ≤ 1.45
Age at HCV infection						
≤40	1.00	1.00	1.00	1.00	1.00	1.00
>40–≤50	3.14 (1.77–5.57)	0.43 (0.23–0.82)	3.34 (1.68–6.63)	0.38 (0.16–0.88)	3.23 (1.69–6.18)	0.32 (0.14–0.76)
>50	9.18 (4.87–17.31)	0.27 (0.12–0.63)	13.28 (6.22–28.36)	0.30 (0.10–0.89)	9.95 (4.86–20.35)	0.23 (0.08–0.70)
HCV-related variables						
HCV infection period						
Preinfection	1.00	1.00				
Acute phase	0.45 (0.20–1.01)	7.33 (0.27–>100)				
Postacute phase	0.11 (0.06–0.23)	3.79 (0.14–>100)				
HCV genotype						
1	1.00	1.00				
4	0.56 (0.31–1.01)	0.32 (0.09–1.13)				
Other	2.24 (0.97–5.15)	3.40 (1.41–8.21)				
Spontaneous HCV clearance	0.87 (0.36–2.07)	2.76 (1.03–7.38)				
HIV-related variables at HCV infection						
Time since HIV diagnosis (per year)	1.03 (0.99–1.06)	0.92 (0.87–0.97)	1.02 (0.98–1.06)	0.91 (0.85–0.98)		
cART naïve	0.86 (0.54–1.39)	2.35 (1.29–4.27)				
Ever use of dideoxynucleosides[b]	1.43 (0.91–2.25)	0.29 (0.13–0.65)			1.46 (0.85–2.50)	0.27 (0.08–0.84)
Ever use of nevirapine	2.08 (1.36–3.18)	0.58 (0.32–1.08)				
Ever use of cotrimoxazole	1.41 (0.91–2.20)	0.67 (0.35–1.31)				
Nadir $CD4^+$ cell count <250/μl	1.18 (0.76–1.82)	0.86 (0.46–1.61)				
HIV-related variables (time-updated)						
AIDS-defining illness	0.99 (0.59–1.68)	0.40 (0.18–0.91)				
$CD4^+$ cell count, cells/μl (log_{10} transformed)	0.12 (0.04–0.34)	1.05 (0.25–4.42)				
$CD4^+$ cell count (cells/μl)						
>500	1.00	1.00	1.00	1.00	1.00	1.00
350–499	1.47 (0.86–2.51)	1.14 (0.51–2.57)	2.09 (1.18–3.70)	2.32 (0.99–5.42)	2.35 (1.31–4.23)	2.85 (1.13–7.17)
<350	2.38 (1.37–4.12)	0.87 (0.38–2.00)	3.63 (1.97–6.68)	1.93 (0.79–4.72)	4.08 (2.20–7.59)	2.22 (0.86–5.76)
HIV RNA, copies/ml (log_{10} transformed)	1.59 (1.35–1.88)	1.29 (1.00–1.67)				
Undetectable HIV RNA (<50 copies/ml)	0.45 (0.28–0.72)	0.55 (0.27–1.12)	0.41 (0.24–0.68)	1.22 (0.47–3.17)	0.47 (0.28–0.79)	1.59 (0.56–4.51)
Alcohol use and comorbidities at HCV infection						
HBsAg positive	1.53 (0.99–2.38)	0.56 (0.31–1.00)				
Weekly alcohol consumption						
0–7 U	1.00	1.00				
≥8 U	0.57 (0.30–1.10)	0.41 (0.12–1.42)				
Missing	1.38 (0.87–2.19)	1.52 (0.82–2.81)				
Diabetes mellitus	1.88 (0.51–6.87)	1.95 (0.28–13.38)				
CVD risk[c]	1.27 (0.74–2.18)	0.31 (0.11–0.83)				
BMI	1.00 (0.92–1.08)	0.95 (0.83–1.09)				

cART, combination antiretroviral therapy; CVD, cardiovascular disease; FIB-4, fibrosis-4; HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus; SC, spontaneous clearance.
[a]In multivariable analysis, we preferred categorical variables for $CD4^+$ cell count and HIV RNA over continuous variables.
[b]Dideoxynucleoside analogues; zalcitabine (DDC), didanosine (DDI) or stavudine (D4T).
[c]Defined as statin use or SBP of more than 140 mmHg or DBP of more than 90 mmHg.

population by the end of follow-up) it is uncertain whether advanced liver fibrosis is present or not. Our finding that only 2.6% of patients had FIB-4 at least 3.25 at the end of follow-up, equivalent to METAVIR at least F3 fibrosis, might underestimate the extent of liver fibrosis. Second, we used routine clinical data and hence data collected on FIB-4 scores were not standardized. Limited data were available on comorbidities and substance use. Third, not all patients classified as spontaneous clearers had two negative HCV RNA tests, thus some might have been misclassified. Reinfection was also difficult to distinguish from relapse for some patients, particularly those with the same genotype.

In conclusion, in this population of HIV-positive MSM with well defined acute HCV infection, only a minority had advanced liver fibrosis and/or cirrhosis, while we did not find evidence for continued accelerated liver fibrosis progression. Well controlled HIV infection appeared to attenuate FIB-4 progression.

Acknowledgements

The authors would like to thank all participants of the ATHENA cohort and the MOSAIC study.

Authors' contributions: A.M.N. performed data management, data analysis and drafted the article. K.W.K. and C.S. contributed to data management and analysis. A.B. contributed to data analysis and drafted parts of the article. A.M.N., K.W.K., F.W.N.M.W., J.T.M.v.d.M., M.P., P.R. and M.v.d.V. conceived the research question and study design. All authors critically revised the article.

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institution received remuneration. F.W.N.M.W. has received consultancy fees from Gilead and ViiV outside the submitted work. M.P.'s institution has received speakers fees and independent scientific support from Gilead Sciences, Roche, MSD and Abbvie, outside the submitted work. P.R. through his institution has received independent scientific grant support from Gilead Sciences, Janssen Pharmaceuticals Inc, Merck & Co and ViiV Healthcare; he has served on scientific advisory boards for Gilead Sciences, ViiV Healthcare, Merck & Co, Teva Pharmaceutical Industries, and on a data safety monitoring committee for Janssen Pharmaceuticals Inc; for which his institution has received remuneration; all outside the submitted work. M.v.d.V.'s institution has received speakers fees from Abbvie, Bristol-Myers-Squibb, Gilead, Johnson & Johnson, MSD and ViiV outside the submitted work and research grant from Abbvie, Gilead, Johnson&Johnson and Merck Sharp Dome. For the remaining authors none were declared.

A.M.N. was financially supported by the 'Aidsfonds' Netherlands (grant 2013.037). The ATHENA database is maintained by the Stichting HIV Monitoring and supported by a grant from the Dutch Ministry of Health, Welfare and Sport through the Centre for Infectious Disease Control of the National Institute for Public Health and the Environment.

Conflicts of interest

There are no conflicts of interest.

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