

Liver Fibrosis Regression in People Living With HIV After Successful Treatment for Hepatitis C

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Background: Successful treatment of hepatitis C virus (HCV) can lead to liver fibrosis regression. It is not known who will experience fibrosis regression or how quickly it will occur.

Methods: We modeled transient elastography (TE) measurements from 1470 HIV–HCV coinfecting participants followed in cohorts contributing data to InCHEHC, an international collaboration. Participants were eligible if they had at least 1 TE measurement in the year before starting a successful direct-acting antiviral treatment

for HCV. This measurement was used to classify participants into 1 of 3 fibrosis subgroups. We analyzed measurement sequences in each subgroup using a covariate-adjusted generalized additive mixed model, with an adaptive spline representing changes in the mean measurement before, during, and after treatment.

Results: Each fibrosis subgroup had a distinctly different response. Most participants with cirrhosis (F4, TE ≥ 14.6 KPa) before HCV treatment did not show meaningful fibrosis regression—approximately 70% were predicted to remain >12 KPa 3 years

Received for publication September 19, 2024; accepted December 27, 2024.

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The CEASE Study received investigator-initiated funding support from Gilead. The Co-EC Study received investigator-initiated funding support from Bristol Myers Squibb. The ATHENA database is 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. The Swiss HIV Cohort Study is supported by the Swiss National Science Foundation (Grant 201369) and by the SHCS research foundation. The CoRIS cohort is supported by CIBER—Consorcio Centro de Investigación Biomédica en Red—(CB21/13/00091), Instituto de Salud Carlos III, Ministerio de Ciencia e Innovación and Unión Europea—NextGenerationEU. The ANRS CO13 HepaviH cohort is supported by the ANRS Emerging Infectious Diseases. The Canadian Coinfection Cohort is supported by Fonds de recherche du Québec—Santé; the Canadian Institute for Health Research (CIHR; FDN-143270); and the CIHR Canadian HIV Trials Network (CTN222). This study was funded by the Australian Government National Health and Medical Research Council (Grant numbers GNT1132902 and GNT2020121). We gratefully acknowledge the contribution to this work of the Victorian Operational Infrastructure Support Program received by the Burnet Institute. None of these funding sources had any role in study design; in the collection, analysis, and interpretation of data; in the writing of the report; or in the decision to submit this article for publication.

Presented at the IAS 2023, Brisbane (Poster MOPEB06—IAS_2023_Abstracts.pdf).

M.B.K. reports grants for investigator-initiated studies from ViiV Healthcare, AbbVie, and Gilead; consulting fees from ViiV Healthcare, AbbVie, and Gilead, all outside the submitted work; and is supported by a Tier I Canada Research Chair. M.v.d.V. reports grants or contracts and consulting fees from Gilead, ViiV Healthcare, and MSD to his institution. J.S.D. reports investigator-initiated research funding to his institution from Gilead Sciences; investigator-initiated and company-sponsored research funding to his institution from AbbVie; and consulting fees unrelated to this work to his institution from AbbVie. G.M. reports grants or contracts from Gilead, AbbVie, ViiV Healthcare, and Janssen to her institution; payment or honoraria for lectures, presentations, speakers' bureaus, manuscript writing or educational events; and support for attending meetings or travel expenses from Gilead; and participation on a data safety monitoring board or advisory board for Gilead, ViiV Healthcare, and AstraZeneca. K.L. reports honoraria for advice or public speaking from Gilead, MSD, and ViiV Healthcare; support for attending meetings or travel expenses from Gilead and MSD; and a leadership or fiduciary role in other board, society, committee, or advocacy groups, paid or unpaid, from Spikmm. A.R. reports support to his institution for advisory boards or travel grants from MSD, Gilead Sciences, and Pfizer, and an investigator-initiated trial grant from Gilead Sciences; all remuneration to A.R. was paid to his home institution, and all remuneration was provided outside the submitted work. M.S. reports investigator-initiated research grants from Gilead Sciences and AbbVie. M.H. reports investigator-initiated research grants from Gilead Sciences and AbbVie. J.Y., S.W., R.S.-D., A.S., D.K.v.S., J.B., and L.W. declare no competing interests.

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's Web site (www.jaids.com).

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after treatment ended. Participants with significant fibrosis (F2–F3, TE ≥ 7.2 and <14.6 KPa) showed appreciable regression in the first 2 years after treatment, falling on average to levels <7.2 KPa. Those without fibrosis before treatment (F0–F1) did not progress.

Conclusions: Most coinfecting people with cirrhosis before HCV cure will remain cirrhotic. For those with significant fibrosis, regression can be expected within 2 years to levels not normally associated with an increased risk of end-stage liver disease. A TE measurement 2 years after cure should give a reliable estimate of residual fibrosis.

Key Words: cirrhosis, direct-acting antivirals, generalized additive mixed model, liver stiffness, sustained virologic response, transient elastography

(*J Acquir Immune Defic Syndr* 2025;99:166–174)

INTRODUCTION

Hepatitis C virus (HCV) coinfection accelerates the progression of liver disease¹ and increases the risk of liver-related and all-cause mortality among people living with HIV.^{2,3} Curing HCV is, therefore, particularly important for people living with HIV–HCV coinfection. Direct-acting antivirals (DAAs) for HCV have dramatically increased the rate of cure, are now widely available, and have the potential to greatly reduce liver disease and mortality.

Currently, it is recommended that all people with advanced liver fibrosis or cirrhosis before HCV treatment continue to be screened every 6 months for hepatocellular carcinoma (HCC) after cure.⁴ However, there is mounting evidence that fibrosis, and even cirrhosis, is reversible.⁵ HCV cure could result in regression of fibrosis to levels that would normally not be associated with an increased risk of end-stage liver disease. It is not known who will experience fibrosis regression, how quickly it will occur, and whether people with fibrosis regression require ongoing monitoring.⁶ To date, studies exploring fibrosis regression have had small samples and lacked long-term data, particularly in the DAA era.⁷

Noninvasive measures of fibrosis have replaced liver biopsy for disease staging because of their ease and safety.⁷ The most commonly used serologic markers [aminotransferase-to-platelet ratio index (APRI) and fibrosis index based on 4 factors (FIB-4)], while accurate at predicting liver disease stage and endstage liver disease before treatment, no longer reflect fibrosis after cure because components aspartate aminotransferase and alanine aminotransferase essentially measure HCV-associated inflammation.⁸ Forns Index and the Enhanced Liver Fibrosis Score also seem to have no value for monitoring fibrosis regression.^{9,10} In contrast, transient elastography (TE; FibroScan), a noninvasive technique to measure liver stiffness, can be used to track fibrosis in the postinflammatory period after cure.⁸ We have shown that among people with HIV–HCV coinfection staged as F2 to F4, liver fibrosis as measured by TE regresses after successful HCV treatment, once inflammation abates, at least in the short term (0.5–1.5 years after cure). It is not known whether fibrosis continues to regress to levels where risks of end-stage liver disease and HCC are reduced. In some, it is

likely that fibrosis or cirrhosis will persist and may even progress because of ongoing exposure to alcohol, fatty liver disease, or poorly controlled HIV.^{11,12}

Using a large collaborative study, we estimate the rate at which liver fibrosis, as measured by TE, regresses after successful HCV treatment with DAAs for those with HIV–HCV coinfection. We consider regression beyond 1.5 years after cure and specifically consider regression for those with pretreatment cirrhosis.

METHODS

Study Participants

The InCHEHC Collaboration is a consortium of 11 prospective cohorts of people living with HIV, with cohorts in Australia, Canada, France, the Netherlands, Spain, and Switzerland.¹³ Data sets are prepared based on the HIV Cohorts Data Exchange Protocol (HICDEP—<https://hicdep.org/>) and submitted to a coordinating center (the Burnet Institute). All cohorts received approval from their regulatory or national ethics committees. Ethical approval for InCHEHC was obtained from the Alfred Hospital Ethics Committee (Melbourne, Australia). The current analysis includes data from 8 cohorts where participants with HIV–HCV coinfection were assessed for fibrosis by TE, with routine measurement in 4 cohorts and at the clinician's discretion in 4 cohorts (see Appendix A, Supplemental Digital Content, <http://links.lww.com/QAI/C458>).

Our study population was all HIV–HCV coinfecting participants (without hepatitis B) who achieved a sustained virologic response when treated for a primary HCV infection with an all-oral DAA regimen at the first attempt. That is, we excluded participants successfully treated with any interferon-based regimen who were then reinfected or who were previously unsuccessfully treated with an all-oral DAA regimen. We also excluded those known to be chronically infected with hepatitis B (hepatitis B surface Ag positive) when starting this first successful DAA regimen.

Main Analysis

We analyzed measurement sequences from each participant with a generalized additive mixed model.¹⁴ This model was fit in R (version 4.1.2) using the mgcv package (version 1.8-38). We assumed measurements were gamma distributed, with the mean estimated from model parameters through a natural log link function. The model included fixed effects for prespecified covariates and 2 smoothing terms. The first smoothing term was equivalent to a random intercept, to allow for repeated measurements from the same participant. The second smoothing term was a spline function representing the change in the mean over time, both before, during, and after treatment. For the spline function, we used an adaptive p-spline with prespecified knot placement. Knots were placed at yearly intervals, but with more frequent knots through the period of HCV treatment where change is rapid. In a previous analysis of data from a single cohort, we found this strategy gave more

plausible response curves than a natural cubic spline, with a peak response closer to the start of treatment.⁸

Each participant needed only a single TE measurement in the year before treatment to be included in our analyses. Including participants with just a single measurement avoids bias if participants with certain characteristics are more likely to be lost to follow-up.¹⁵ Models for longitudinal data fit by maximum likelihood and with a participant random effect have the attractive property that inference from the model is not affected by drop-out, provided participant missingness depends only on the participant's random effect and covariate values and not on the values of the unobserved measurements. Appropriate adjustments are made to model parameters at times when data are incomplete, based on the within-participant correlation.¹⁶ This makes model estimates of change more reliable than calculations based on raw data because repeated measurements are more likely in those with higher levels of fibrosis before treatment.

The date treatment began was designated as time zero. All available TE measurements were used for those included; however, individual measurement sequences were left censored until 6 months after any earlier unsuccessful interferon-based treatment and right censored at any detectable HCV viremia (if reinfecting). The last TE measurement in the year before starting treatment was used to classify participants into 1 of 3 fibrosis subgroups: F0–F1, <7.2; F2–F3, ≥7.2 and <14.6; F4, ≥14.6 KPa. These cutoffs were taken from a diagnostic study in HIV–HCV coinfection, where liver fibrosis was assessed by TE with biopsy as the reference.¹⁷

A review of literature shows that sex, age at HCV infection, and duration of infection are associated with fibrosis progression;^{18–20} age and sex are associated with fibrosis regression after successful interferon treatment.²¹ We used age at HCV diagnosis as a covariate—it is difficult to identify when infection took place²²—and calculated an approximate duration of infection from diagnosis until the start of the first successful treatment. Injection drug use as the likely mode of infection was identified in the analysis plan as a suitable proxy for hazardous drinking, a variable not available from all cohorts, because a high percentage of people who inject drugs also report hazardous drinking.^{23–25} Coinfected people have a faster rate of fibrosis progression when HIV replication is not suppressed,²⁶ and after successful HCV treatment, continued progression is more likely with uncontrolled HIV replication.¹² Hence the prespecified covariates in the main model were cohort, sex, age at diagnosis, duration of infection, injection drug use as the likely mode of infection, and time-dependent detectable HIV viral load.

We then used the fitted model to predict the rate of change during 1 year periods of relatively constant change; 1 period before treatment started (1.5–0.5 years), and 3 periods after treatment ended (0.5–1.5, 1.5–2.5, and 2.5–3.5 years). By sampling model parameters from their posterior distribution,²⁷ we repeatedly estimated slopes within these 4 periods for the following reference participant: a man diagnosed with HCV at age 40 years, starting a first successful HCV treatment 10 years later (reflecting median values; Table 1), most likely not acquiring HCV through injection drug use and with an undetectable HIV viral load. We then calculated an

approximate 95% credible interval (95% CrI) for the slope from the 2.5 and 97.5 percentiles of a distribution of 10,000 slope estimates. Using a similar process, we estimated the proportion of participants with a predicted liver stiffness ≥12 KPa at 1, 2, and 3 years after treatment ended. A cutoff of 12 KPa has been tentatively recommended for postcure monitoring of advanced liver disease.⁷ However, when predicting proportions, we used the covariate values for each participant (including the participant's random intercept) rather than those of a reference participant (without a random intercept).

Sensitivity Analyses

Three covariates specified in the analysis plan were not available for all cohorts. In a set of unplanned sensitivity analyses, we added additional covariates to the main model but restricted data to just the cohorts providing these covariates (see Appendix B, Supplemental Digital Content, <http://links.lww.com/QAI/C458>). In an additional unplanned sensitivity analysis, prompted by a reviewer's suggestion, we added 2 indicators to the main model, representing past exposure to didanosine and to any protease inhibitor, respectively. We also carried out 3 planned sensitivity analyses (see Appendix C, Supplemental Digital Content, <http://links.lww.com/QAI/C458>): 1 with data restricted to participants treated after HCV treatment became available to anyone with a chronic infection; 1 with a lower cutoff for cirrhosis (F4 ≥12 KPa); and 1 with fibrosis subgroups defined using a pretreatment measure of APRI. In a final unplanned sensitivity analysis, we restricted data to participants certain to have been chronically infected when treated.

RESULTS

Study Participants

Among 4093 HIV–HCV coinfecting participants successfully treated for a primary HCV infection with a DAA regimen at the first attempt, 2375 had no TE measurement within the year before starting treatment and 248 were missing the covariate values needed for modeling (Fig. 1). The remaining 1470 participants (36%) were included in the main analysis. Of these, 250 (15%) were classified as cirrhotic (F4) before treatment and 595 (35%) were classified as having significant fibrosis (F2–F3).

Compared with those without significant fibrosis (F0–F1), cirrhotic participants had a longer duration of infection, were more likely to have genotype 3 HCV and a lower CD4 cell count when starting treatment, and were more likely to have been exposed to didanosine or protease inhibitors (Table 1). Cirrhotic participants were less likely to be men reporting sex with men, slightly more likely to report hazardous drinking and more likely to have acquired HCV through injection drug use; however, they were less likely to report recent injection drug use. Note the high proportion of missing data for participant-reported behaviors. There were no appreciable differences between fibrosis subgroups in the age at diagnosis, sex ratio, median body mass index (BMI), or

TABLE 1. Characteristics of Participants in the Main Analysis

Participant Characteristics	Fibrosis Stage when Starting Treatment		
	F0–F1 <7.2 KPa (n = 752)	F2–F3 ≥7.2–<14.6 KPa (n = 513)	F4 ≥14.6 KPa (n = 205)
Median or percent (percent missing*)			
Female, %	21 (0)	18 (0)	20 (0)
When starting treatment			
Age, yrs	49 (0)	52 (0)	51 (0)
BMI	23 (27)	24 (22)	24 (27)
APRI	0.5 (25)	0.7 (24)	1.3 (31)
FIB-4	1.2 (25)	1.6 (24)	2.8 (31)
Men reporting sex with men	40 (34)	29 (41)	26 (41)
Reporting recent hazardous drinking†	14 (51)	16 (49)	16 (54)
Reporting recent injection drug use‡	24 (47)	17 (50)	13 (54)
HCV infection when starting DAA treatment			
Age at diagnosis, yrs§	39 (0)	39 (0)	38 (0)
Duration of infection, yrs	8 (0)	11 (0)	13 (1)
Never previously treated	80 (0)	76 (0)	63 (0)
Genotype 3, %	16 (19)	17 (22)	23 (22)
Infected through injection drug use, %	37 (0)	48 (0)	62 (0)
HIV infection when starting DAA treatment			
Undetectable HIV viral load, %	93 (0)	92 (2)	92 (5)
CD4 cell count, cells/μL	600 (5)	550 (3)	480 (7)
Prior AIDS diagnosis, %	21 (12)	26 (8)	25 (7)
ART exposure when starting DAA treatment¶			
Didanosine, %	15 (0)	20 (0)	22 (0)
Any protease inhibitor, %	45 (0)	57 (0)	59 (0)
Liver stiffness when starting DAA treatment			
Last TE measure in the year before, KPa	5.3 (0)	9.3 (0)	22 (0)
Interquartile range, KPa	0.7 (21)	1.4 (22)	3.6 (19)
Successful measurement rate#	95 (43)	94 (41)	93 (44)

Participants in the study population with at least 1 TE measurement in the year before starting their first successful DAA regimen and with covariate values available (n = 1470).

*A high percentage of missing values (≥10%) indicates a variable that was not available from all cohorts. Appendixes B and C, Supplemental Digital Content, <http://links.lww.com/QAI/C458>, provide more information on missing data.

†Hazardous drinking was defined as an AUDIT-C score of ≥3 for women or ≥4 for men.²⁸ The definition of “recent” varied between cohorts: the question was asked about behavior in the past month (10%), past 6 mo (70%), past year (5%), since last follow-up (4%), or without a specific recall period (11%).

‡The definition of “recent” varied between cohorts: the question was asked about behavior in the past month (5%) or past 6 mo (95%).

§The date of HCV diagnosis was assumed to be the earliest date of a first positive HCV antibody test or first positive HCV RNA test.

||Approximate only—from the date of HCV diagnosis until the date the successful HCV treatment started.

¶Past or current exposure to the antiretroviral drug or drug class.

#The mean rate is shown, because the median was 100% in all fibrosis subgroups and, therefore, uninformative.

ART, antiretroviral therapy; FIB-4, fibrosis index based on 4 factors.

the proportion with undetectable HIV viral load when starting treatment.

Participants included in the main analysis were similar to those excluded (see Appendix A, Section 1, Supplemental Digital Content, <http://links.lww.com/QAI/C458>). However those included had a longer duration of infection than those excluded, were less likely to be men reporting sex with men, and more likely to have acquired HCV through injection drug use: differences consistent with an oversampling of participants with significant fibrosis.

Main Analysis

Before treatment, median TE measurements in each fibrosis subgroup were F0–F1, 5.3 KPa [interquartile range (IQR), 4.4 to 6.1, minimum 2.3]; F2–F3, 9.3 KPa (IQR 8.0 to 11.3); F4, 22 KPa (IQR 17 to 32, maximum 75). Mean response curves for each fibrosis subgroup show a high

density of TE measurements in the year before starting treatment (Fig. 2), reflecting the participant selection process. After treatment ended, 523 participants (36%) had at least 1 TE measurement, with a median time to their last measurement of 0.9 years. There were relatively few cirrhotic participants with postcure measurements (F0–F1, 227; F2–F3, 204; F4, 92) but with a slightly higher median time to their last measurement (F0–F1, 0.8; F2–F3, 1.1; F4 1.2 years). For cirrhotic participants (F4), there were few data beyond 3 years after treatment ended (Fig. 2), and these data were more variable than data available from participants without significant fibrosis (F0–F1).

Each fibrosis subgroup had a distinctly different response after treatment ended (Fig. 3). For those without significant fibrosis (F0–F1), the mean response curve dipped through the treatment period, but the slope of the curve did not differ materially before or after treatment (Table 2). For those with significant fibrosis (F2–F3), the mean response

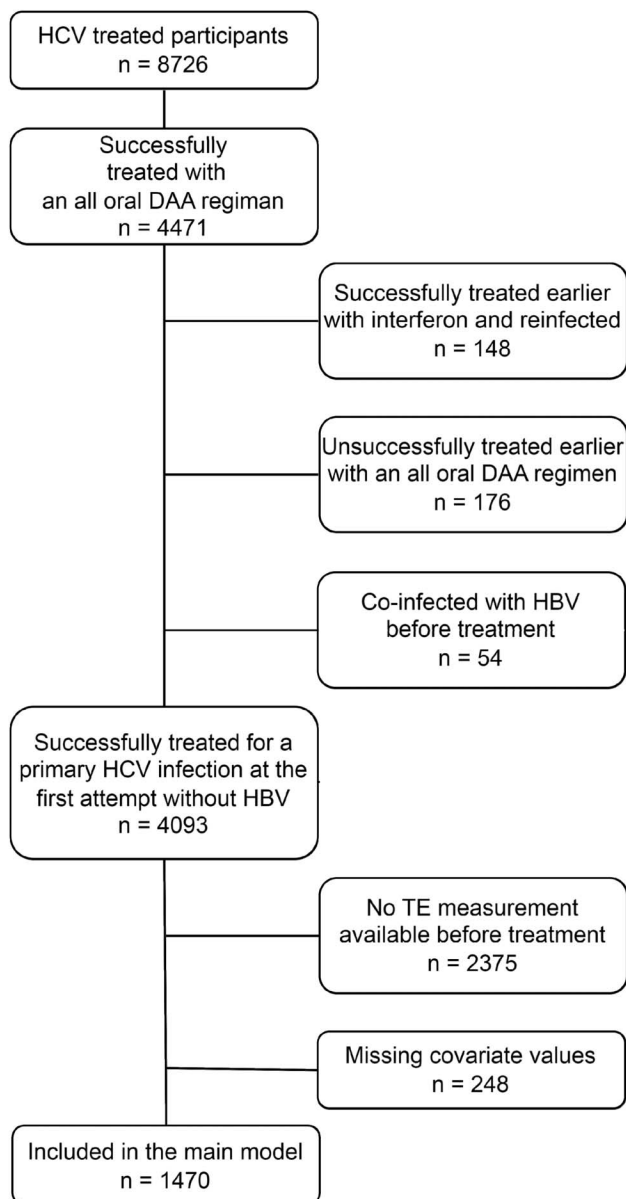


FIGURE 1. Study participant selection. The study population ($n = 4093$) was all coinfecting participants (without hepatitis B virus) who achieved a sustained virologic response when treated for a primary HCV infection with an all-oral DAA regimen at the first attempt. Those included in the main analysis ($n = 1470$) had to have at least 1 TE measurement in the year before starting this successful first DAA regimen and the covariate values needed for modeling.

curve dropped appreciably during treatment and declined further in the first year after treatment ended. Thereafter, the decline attenuated such that there was no additional decline in the third year after treatment. For those with cirrhosis (F4), the mean response curve dropped dramatically during treatment, but was relatively flat thereafter. Slope estimates do not rule out some decrease in absolute stiffness for F4 participants (Table 2), but the response curve shows that in a relative sense (Fig. 3 uses a log scale), any decrease was minimal and

the mean response curve never fell appreciably below the 14.6 KPa cutoff for cirrhosis. Consistent with this, a high proportion of participants >14.6 KPa when starting treatment were predicted to still be >12 KPa after treatment ended, and that proportion remained high over time (1 year: 0.76, 95% CrI 0.69 to 0.83; 2 years: 0.72, 95% CrI 0.63 to 0.80; 3 years: 0.69, 95% CrI 0.57 to 0.79). In contrast, for those starting treatment with significant fibrosis, the proportion predicted to be >12 KPa at 1 year after treatment ended was close to 0 (0.01, 95% CrI 0.00 to 0.02).

Sensitivity Analyses

Results from covariate sensitivity analyses (see Appendix B, Supplemental Digital Content, <http://links.lww.com/QAI/C458>) were consistent with the results of the main analysis. None of the covariates added in sensitivity analyses were strongly associated with liver stiffness (see Appendix B Section 1, Supplemental Digital Content, <http://links.lww.com/QAI/C458>).

The planned sensitivity analysis with data restricted to participants treated after treatment became available to anyone with a chronic infection had too few cirrhotic participants for reliable modeling of this subgroup (see Appendix C Section 2, Supplemental Digital Content, <http://links.lww.com/QAI/C458>). Most participants with cirrhosis (F4) or significant fibrosis (F2–F3) were treated earlier when fibrosis restrictions were in place; the data from these participants determined the shape of the response curve. With a lower cutoff for cirrhosis ($F4 \geq 12$ KPa), those classified as cirrhotic when starting treatment showed fibrosis regression for at least a year after treatment ended, similar to those with significant fibrosis (see Appendix C Section 3, Supplemental Digital Content, <http://links.lww.com/QAI/C458>). And with fibrosis subgroups defined by APRI, all fibrosis subgroups showed a similar pattern after treatment—fibrosis regression in the first year after treatment that attenuated with time (see Appendix C Section 4, Supplemental Digital Content, <http://links.lww.com/QAI/C458>).

Of the 1470 participants in the main analysis, 1385 (94%) were certain to have been treated while chronically infected, with treatment starting >6 months after the date of HCV diagnosis. A model fit to these participants gave results (not shown) that were almost identical to the main analysis.

DISCUSSION

We found different patterns of fibrosis regression—as measured by TE—according to the level of fibrosis before treatment in this large collaborative study of people with HIV–HCV coinfection successfully treated for HCV in the DAA era. Most participants with cirrhosis (F4, defined as ≥ 14.6 KPa) before HCV treatment did not show meaningful fibrosis regression—approximately 70% were predicted to remain >12 KPa 3 years after treatment. The largest reduction in liver stiffness occurred during treatment with relatively little improvement once inflammation abated, suggesting minimal reversibility of true fibrosis among cirrhotic participants. Adjustment for updated time-varying

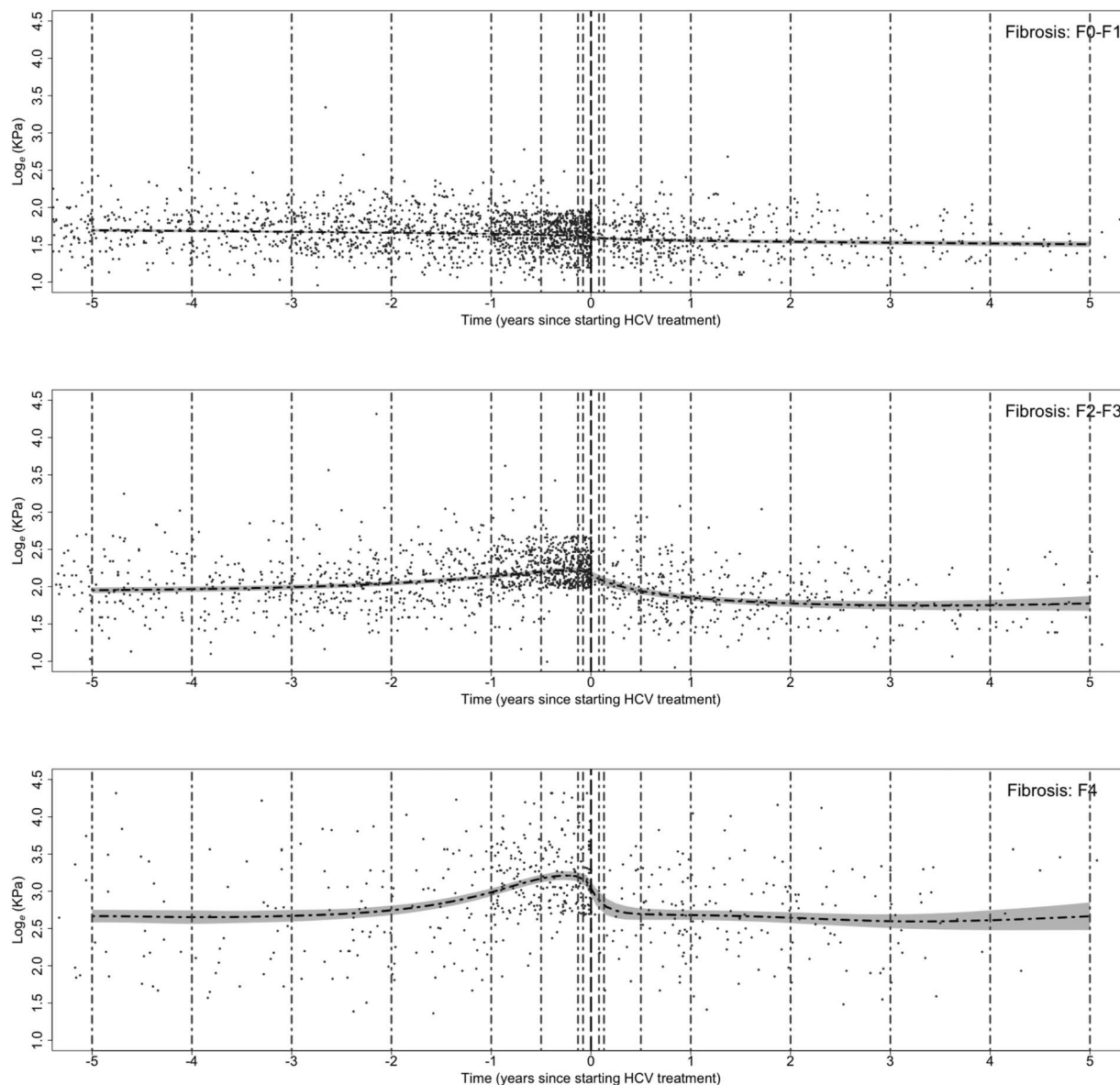


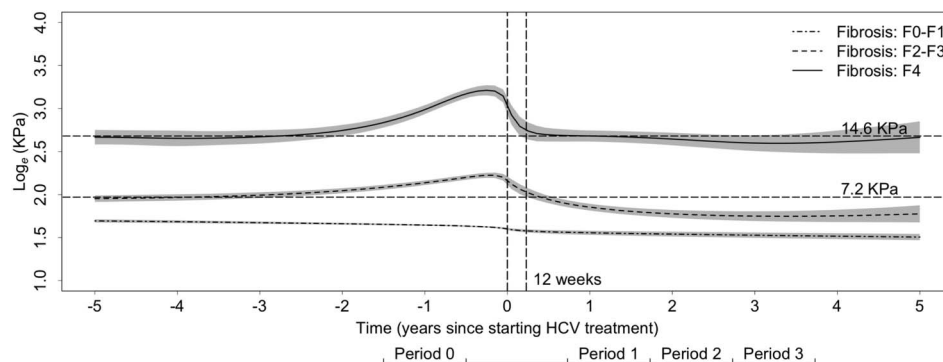
FIGURE 2. Mean response curves from the main analysis for each fibrosis subgroup. These 3 response curves are the results of the main analysis ($n = 1470$). Plots show all the TE measurements in that analysis and the prespecified knot placement within the range of the data for the adaptive p-spline. An adaptive p-spline with a cubic basis also requires a knot at both the minimum and maximum measurement and 3 arbitrary knots outside both the minimum and maximum measurements.²⁹

factors that might prevent fibrosis regression (detectable HIV RNA, BMI, or hazardous drinking), or for prior exposure to didanosine or protease inhibitors, made little difference to our estimates. The median TE measure among cirrhotic participants was high before treatment (22 KPa, IQR 17 to 32), thus many may have had severe liver architecture distortion and portal hypertension—factors associated with permanent liver damage.⁵ Given the failure to regress after HCV cure, alternative strategies such as antifibrotic therapies should be explored. A minority, however, did regress. Those in earlier stages of cirrhosis may have more potential for improvement because earlier stages of cirrhosis are characterized by regenerative nodules and active degradation of liver scarring

—identifying factors associated with regression will be important. Whether the risk of end-stage liver disease and HCC is reduced in those with postcure values <12 KPa remains to be determined.

In contrast to those with cirrhosis, participants with significant fibrosis (F2–F3, defined as ≥ 7.2 and <14.6 KPa) showed appreciable regression initially, falling on average to levels <7.2 KPa by 3 years after HCV cure, indicating an absence of fibrosis. Essentially none was predicted to have liver stiffness >12 KPa a year after cure, suggesting the risk for end-stage liver disease and hepatocellular carcinoma might be greatly reduced. However, the rate of regression attenuated thereafter. A measurement 2 years after treatment

FIGURE 3. A comparison of mean response curves for each fibrosis subgroup. These 3 response curves are the results of the main analysis ($n = 1470$), overlaid in 1 plot. The plot has reference lines for the cut-offs used to classify participants into 1 of 3 fibrosis subgroups, based on their last TE measurement in the year before starting their successful hepatitis C treatment. The periods for which slopes were estimated (Table 2) are shown below the horizontal axis.



should give a reasonable estimate of residual fibrosis—a routine fibroscan at this point could be helpful to establish a new baseline. Those without fibrosis before treatment (F0–F1) remained stable with no progression, consistent with clinical reasoning that early treatment remains the best way to prevent HCV-related fibrosis.

Little is known about fibrosis regression after successful treatment in the DAA era, or for those with HIV–HCV coinfection. Previous studies have been small (<100 participants), of short duration, have not assessed longitudinal changes, and have used heterogeneous inclusion criteria. Among people classified as cirrhotic before treatment, regression rates (defined as TE <12 KPa) varied widely from 38%–63%^{30–32}; higher than the rate estimated in this study. Likewise these studies show variable rates of regression among those classified as F3 before treatment (68%–95%).^{30,31} The only study in coinfecting participants combined F3 and F4 fibrosis groups ($n = 46$) and had a 74% rate of regression.¹² In some studies, a component of the estimated “regression” may have been early resolution of necroinflammation because TE values before and after treatment were compared without considering changes during treatment.^{31,32} As in our study, a biphasic decline in liver stiffness after DAA treatment has been shown in mono-infection, with the transition between phases at 4 weeks on treatment, consistent with an early reduction in necroinflammation followed by a slower resolution of fibrosis.³³ This was accompanied by a late reduction in spleen stiffness, at 24 weeks after treatment, implying that the second phase of improvement was related to the reversal of fibrosis. Improvement in this second phase may also

attenuate with time in mono-infection for the first 3 years after treatment.³²

HCV cure substantially reduces the risk of HCC. However, all guidelines recommend ongoing HCC surveillance of those with cirrhosis, as an appreciable risk of HCC remains after cure.³⁴ Our data support this: a high percentage of those with cirrhosis before treatment are predicted to remain >12 KPa with little further regression. Some guidelines extend HCC screening to those with F3 fibrosis.³⁵ The benefit of continued surveillance in those with significant fibrosis is unclear—the residual individual risk is not known and screening in this group may no longer be cost-effective.³⁶ Assuming a postcure fibrosis measure reflects current HCC risk, our study suggests that up to 30% of participants initially classified as cirrhotic and all of those classified as having significant fibrosis may no longer require HCC screening. This could save considerable resources.

However, it is not yet known how well noninvasive methods capture fibrosis regression and whether these methods can be used to stage fibrosis after cure in people treated for HCV. Fibrosis subgroups defined by APRI clearly do not identify those participants who fail to regress (see Appendix C Section 4, Supplemental Digital Content, <http://links.lww.com/QAI/C458>); TE is obviously superior.^{8,9} Guidelines currently do not recommend using TE to follow fibrosis regression after cure, nor have the cutoffs for staging fibrosis before treatment been validated after cure.⁷ Serial liver biopsies may fail to capture the full extent of morphologic improvement,^{31,37} and are not practical because of low acceptability, risk, and cost.^{38,39} A few small studies have correlated liver biopsy with TE measures postcure with mixed

TABLE 2. Estimated Change in Liver Stiffness Before and After Successful Treatment for Hepatitis C

Mean Change in KPa (95% Credible Interval)	Fibrosis Stage When Starting Treatment		
	F0–F1 <7.2 KPa	F2–F3 ≥ 7.2 – <14.6 KPa	F4 ≥ 14.6 KPa
Period (Fig. 3)			
0: 1.5 to 0.5 years before treatment starts	–0.1 (–0.1 to –0.1)	1.0 (0.7 to 1.3)	6.8 (5.1 to 8.5)
1: 0.5 to 1.5 years after treatment ends	–0.1 (–0.1 to –0.1)	–0.7 (–0.9 to –0.4)	–0.4 (–1.6 to 0.8)
2: 1.5 to 2.5 years after treatment ends	–0.1 (–0.1 to 0.0)	–0.2 (–0.4 to 0.0)	–0.7 (–1.7 to 0.2)
3: 2.5 to 3.5 years after treatment ends	–0.1 (–0.1 to 0.0)	0.0 (–0.3 to 0.2)	–0.1 (–1.2 to 1.1)

Estimates were made by simulation from the model fitted in the main analysis ($n = 1470$). This was a generalized additive mixed model with fixed effects for prespecified covariates and 2 smoothing terms: the first term equivalent to a random intercept to allow for repeated measurements from the same participant; the second term a spline function representing change in the mean measurement over time.

results.⁴⁰ In an informative study, fibrosis regression ($\leq F3$) was shown by biopsy in 61% of 33 cirrhotic participants surviving at least 4 years without HCC after successful interferon treatment.³⁰ The specificity for cirrhosis of a post-cure TE measure ≥ 12 KPa was high (95%) but sensitivity was low (61%); this cutoff missed an appreciable number of people who remained cirrhotic after cure.

The InCHEHC collaboration allowed us to include many more participants with significant fibrosis or cirrhosis than available from a single cohort and through modeling, estimate precise response curves for at least 3 years postcure. We used a statistical method that allowed us to model irregular repeated measurements that were not normally distributed, and where the mean response was expected to change differentially before, during and after HCV treatment. This method is robust to participant drop-out and does not require either ad hoc grouping of data (eg, binning), which potentially masks changes over time, or fitting a simple linear spline response, giving estimates sensitive to where knots are placed. These advantages make it the method of choice for studying fibrosis regression even with modest sample sizes.⁴¹

Our study has limitations. The participants with available measurements likely over-represent those with significant fibrosis. Routine measurement was more common for those with cirrhosis (see Appendix A, Supplemental Digital Content, <http://links.lww.com/QAI/C458>). This should ensure reliable data for this subgroup. For those without significant fibrosis, measurement would have been irregular but the data were far less variable (Fig. 2); response curves were precise for this subgroup. Not all prespecified covariates were available from all cohorts, although our covariate sensitivity analyses suggest that the covariates omitted from our main analysis were not essential for reliable results (see Appendix B, Supplemental Digital Content, <http://links.lww.com/QAI/C458>). We did not have a measure of steatosis, such as the controlled attenuation parameter (CAP), and so could not adjust for differences in steatosis between participants. However, in a sensitivity analysis, we found that adjustment for time-dependent BMI did not materially change our response curves for the different fibrosis subgroups. We anticipate that adjustment for CAP, were that possible, would likewise not change our results because there is a strong positive association between CAP and BMI—both steadily increase over time in coinfecting participants, unaffected by successful DAA treatment.⁴² Our results may not be generalizable to those with HCV monoinfection; however, a recent study showed similar regression in TE at 12 weeks postcure in both those with HIV–HCV coinfection on antiretroviral therapy and those with HCV monoinfection.⁴³ When fitting generalized additive models, decisions need to be made when fitting a smooth curve (the type of spline, the number, and placement of knots). We used a model shown to work well with data from a single cohort,⁸ but our modeling choices could hide or exaggerate elements of the mean response.

The extent to which fibrosis regresses after DAAs, the clinical and biologic factors that predict regression, and the resulting clinical impacts remain among the most important unanswered questions in the field. The method we use provides a template for studying fibrosis changes over the

long term. With this method we show that those with cirrhosis before starting DAAs largely remain cirrhotic. All those with significant fibrosis and up to 30% of those with cirrhosis show evidence of fibrosis regression after cure. It will be important to identify the characteristics of those with cirrhosis when starting treatment who do regress and whether those who regress have a lower risk of HCC to reduce the number of people who need to be monitored after cure for liver outcomes.

ACKNOWLEDGMENTS

The authors thank the study participants for their contribution to the research. The CEASE Study acknowledges all participants, participating sites, collaborating partners, and the Kirby Institute study team; and investigator-initiated funding support from Gilead. The Co-EC Study acknowledges all participants and site teams from The Alfred, Melbourne Sexual Health Centre, Prahran Market Clinic, Northside Clinic, Thorne Harbour Health, and Melbourne Health; people support from the Australian National Health and Medical Research Council; and investigator-initiated funding support from Bristol Myers Squibb. The ATHENA database is maintained by 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. The authors acknowledge the contribution of the Swiss HIV Cohort Study (SHCS) participants and team members. This study has been financed within the framework of the SHCS. Data from the SHCS are gathered by the 5 Swiss University Hospitals, 2 Cantonal Hospitals, 15 affiliated hospitals, and 36 private physicians. The authors would like to thank all clinicians and clinical research technicians participating in the SAIDCC database of the Infectious Diseases Unit of St Antoine Hospital (Paris, France). The authors acknowledge the contribution of the AQUITAINE scientific committee. The authors acknowledge the CoRIS Executive Committee and the centers and investigators involved in the CoRIS cohort. The CoRIS cohort is supported by CIBER—Consorcio Centro de Investigación Biomédica en Red—(CB21/13/00091), Instituto de Salud Carlos III, Ministerio de Ciencia e Innovación and Unión Europea—NextGenerationEU. The authors acknowledge the contribution of the Scientific Committee of the ANRS CO13 HEPAVIH including representatives of the sponsor (clinical research and pharmacovigilance department) and representatives of patient organizations including TRT5. The authors also acknowledge the ANRS CO13 HEPAVIH cohort participants, the study coordinators, the central coordinating team, and nurses for their assistance with study coordination, participant recruitment, and care. The ANRS CO13 Hepavir cohort is supported by the ANRS Emerging Infectious Diseases. The authors acknowledge the Canadian Coinfection Cohort (CCC) steering committee members, central coordinating staff, study participants, and community advisers. The authors also acknowledge Canadian Coinfection Cohort coinvestigators, study coordinators, and nurses for their assistance with study coordination, participant recruit-

ment, and care. The Canadian Coinfection Cohort is supported by Fonds de recherche du Québec-Santé, the Canadian Institute for Health Research (CIHR; FDN-143270), and the CIHR Canadian HIV Trials Network (CTN222). The authors gratefully acknowledge the contribution to this work by the Victorian Operational Infrastructure Support Program received by the Burnet Institute.

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