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Authors

Gardner, Annelys Roque

Ma, Yifei

Bacchetti, Peter

et al.

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Longitudinal Assessment of the Enhanced Liver Fibrosis Score in the Era of Contemporary HIV and Hepatitis C Virus Treatment

Annelys Roque Gardner,¹ Yifei Ma,² Peter Bacchetti,³ Jennifer C. Price,² Mark H. Kuniholm,⁴ Audrey L. French,⁵ Stephen Gange,^{6,7} Adaora A. Adimora,⁹ Howard Minkoff,⁸ Seble Kassaye,⁹ Igbo Oforokun,¹ William Rosenberg,¹⁰ Andrea A. Z. Kovacs,¹¹ and Phyllis C. Tien^{2,12}

¹Department of Medicine, Emory University, Atlanta, Georgia, USA; ²Department of Medicine, University of California San Francisco, San Francisco, California, USA; ³Department of Epidemiology and Biostatistics, University of California San Francisco, San Francisco, California, USA; ⁴Department of Epidemiology and Biostatistics, University at Albany, State University of New York, Rensselaer, New York, USA; ⁵Department of Medicine, Stroger Hospital, Cook County Health, Chicago, Illinois, USA; ⁶Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland, USA; ⁷Department of Medicine, University of North Carolina, Chapel Hill, North Carolina, USA; ⁸Department of Obstetrics and Gynecology, State University of New York Downstate Health Sciences University, Brooklyn, New York, USA; ⁹Department of Medicine, Georgetown University Medical Center, Washington, District of Columbia, USA; ¹⁰Institute for Liver and Digestive Health, Division of Medicine, University College London, London, United Kingdom; ¹¹Department of Pediatrics, University of Southern California, Los Angeles, California, USA; and ¹²Infectious Disease Section, Department of Veterans Affairs Medical Center, San Francisco, California, USA

Background. The trajectory of liver fibrosis is not well understood in the contemporary era of human immunodeficiency virus (HIV) and hepatitis C virus (HCV) therapy.

Methods. We assessed the Enhanced Liver Fibrosis (ELF) score, aspartate transaminase-to-platelet ratio index (APRI) and Fibrosis-4 (FIB-4) in 116 women with HIV/HCV coinfection over a 4-year period. Random-effects linear regression models examined the rate of fibrosis change 1–2 years before starting HCV treatment, within 1 year before starting (peri-HCV treatment), within 1 year after and 1–2 years post-HCV treatment in unadjusted and adjusted models including age, race, and changes from pretreatment of factors that might affect fibrosis (eg, alcohol, integrase strand inhibitor [INSTI] use, waist circumference, CD4 count).

Results. INSTI use nearly doubled from pre- to peri-HCV treatment. In unadjusted analysis, there was a 3.3% rate of rise in ELF pre-HCV treatment, 2.2% and 3.6% rate of decline during the peri- and 1-year post-HCV treatment period, respectively, followed by a 0.3% rise. Similar findings were observed for APRI and FIB-4. There was little effect on the estimated fibrosis trajectories after adjustment.

Conclusions. The apparent lack of decline in biomarkers of liver fibrosis beyond 1 year after HCV cure suggests that continued monitoring of liver fibrosis and interventions to mitigate progression in people with HIV after HCV cure remains essential.

Keywords. enhanced liver fibrosis score; ELF; hepatitis C; HIV; FIB-4; APRI; direct-acting antiviral therapy.

Chronic hepatitis C virus (HCV) coinfection is common in people with human immunodeficiency virus (PWH) [1], and is associated with faster progression of liver fibrosis and development of end-stage liver disease [2, 3]. Liver fibrosis progression in persons with HIV/HCV coinfection is due to a complex interplay of HIV and HCV effects, immune dysregulation, and metabolic alterations [4]. However, the trajectory of liver fibrosis in the time period leading up to HCV treatment and after HCV eradication is not well understood, especially in the contemporary era of HIV and HCV therapy.

We previously found that the presence of both HCV infection and greater visceral adiposity in PWH may be associated

with liver injury beyond what would be expected with HIV/HCV coinfection alone [5]. Visceral obesity increases with age and is a risk factor for fatty liver disease in PWH [6, 7] and, more recently, has been associated with use of integrase strand inhibitors (INSTIs) [8]. PWH who have HCV coinfection are often switched to INSTIs prior to initiating HCV treatment to reduce interactions between HIV and HCV direct-acting antiviral (DAA) therapy [9]. However, little is known about how these HIV and HCV treatments affect liver fibrosis trajectory.

Most HCV treatment studies prior to DAA therapy found significant decreases in liver fibrosis as well as in clinical end points such as hepatic decompensation and liver-related deaths after achievement of sustained virologic response (SVR) [10–12]. In the DAA era, most liver fibrosis studies in persons with HCV mono-infection [13–15] and HIV/HCV coinfection [16–18] have limited follow-up of less than 1 year after SVR. These studies assessed fibrosis change using noninvasive serum markers, aspartate transaminase-to-platelet ratio index (APRI) and Fibrosis-4 (FIB-4), as well as transient elastography (TE), but whether the short-term declines observed may be more a

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Correspondence: Phyllis Tien, MD, MSc, University of California, San Francisco, VAMC, Infectious Disease Section, 111W, 4150 Clement Street, San Francisco, CA 94121 (Phyllis.tien@ucsf.edu).

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result of decreases in liver inflammation than regression of liver fibrosis is unclear, because liver inflammation can affect APRI, FIB-4, and TE-measured liver stiffness values [19, 20]. We have shown an association of HIV/HCV coinfection with greater enhanced liver fibrosis (ELF) score, even after adjusting for TE-measured liver stiffness [21]. The ELF score, a marker of extracellular modeling, is derived from measurable serum markers of fibrosis: hyaluronic acid, amino-terminal propeptide of type III collagen (PIIINP), and tissue inhibitor of matrix metalloproteinase 1 (TIMP-1) [22]. Some have suggested that ELF may more accurately measure liver fibrosis than APRI and FIB-4, especially in PWH [21, 23]. In a study of people with HIV/HCV coinfection and HCV mono-infection, ELF also exhibited a linear relationship with histologic stage of fibrosis, suggesting that it can be used to accurately predict liver fibrosis and progression [23].

We investigate the trajectory of liver fibrosis biomarkers before and after DAA treatment over a 4-year period using ELF, APRI, and FIB-4 in women with HIV/HCV coinfection enrolled in the Women's Interagency HIV Study (WIHS) while controlling for changes in alcohol use, waist circumference (a marker of visceral obesity), INSTI use, and CD4 count. We hypothesized that in PWH and HCV coinfection, serum markers of liver fibrosis would decline post-HCV treatment, but the declines in ELF would be less than APRI and FIB-4.

METHODS

Study Population

The WIHS (now part of the Multicenter AIDS Cohort Study [MACS]-WIHS Combined Cohort Study [MWCCS]) is a multicenter prospective cohort study that was established in 1994 to investigate the progression of HIV in women with and without HIV infection [24]. Every 6 months, participants completed a physical examination, underwent laboratory tests, and completed a comprehensive interviewer-administered questionnaire, which collected information on sociodemographic characteristics, disease characteristics, and medication use. Participants provided signed informed consent at each visit and were compensated for participation in the study.

Of the 236 women that were known to have a history of HCV treatment, we excluded women with HCV mono-infection ($n = 26$), pretreatment but no posttreatment records ($n = 49$), and posttreatment but no pretreatment records ($n = 3$). Of the remaining 158 women, 42 were treated with pegylated interferon (PEG-IFN) plus ribavirin (RBV) and 116 were treated with DAAs. Our primary analysis consisted of the women with HIV/HCV coinfection who were treated with DAAs. These women had at least 1 visit within 2 years prior to first reporting HCV treatment, and at least 1 visit within 2 years after first reporting treatment. We also performed a secondary analysis

comparing the fibrosis biomarker trajectories of the DAA-treated versus the PEG-IFN plus RBV-treated women.

Outcomes

The ELF score was calculated from 3 biomarkers of extracellular matrix modelling measured in frozen sera that was stored at -70°C . An automated IMMUNO 1 immunoanalyzer (Siemens Medical Solutions Diagnostics) determined levels of TIMP-1, PIIINP, and hyaluronic acid via magnetic particle separation immunoassays as per the European Liver Fibrosis Study [22]. The TIMP-1 and PIIINP assays each used 2 monoclonal antibodies that bind to independent binding sites on their respective antigens. The hyaluronic acid assay uses hyaluronic acid binding protein, which is isolated from bovine nasal septum, in place of monoclonal antibodies. Tests were performed according to the manufacturer's instruction at iQur Limited (London, United Kingdom), and the levels of the individual markers and the ELF composite were provided. Based on previously published thresholds, an ELF score of <7.7 corresponds to no or mild fibrosis, $7.7-9.8$ to moderate fibrosis, $9.8- <11.3$ to severe fibrosis, and ≥ 11.3 to cirrhosis [23].

APRI was calculated using the equation $([\text{AST}/\text{ULN of AST}] \times 100)/\text{platelets } 10^9/\text{L}$, where AST is aspartate transaminase and ULN is upper limit of normal [25]. FIB-4 was calculated using the equation $(\text{age} \times \text{AST})/(\text{platelets } 10^9/\text{L} \times \text{ALT}^{1/2})$, where ALT is alanine transaminase [26]. Severe fibrosis was defined as an APRI ≥ 1.5 and FIB-4 ≥ 3.25 , moderate fibrosis as APRI $0.5-1.5$ and FIB-4 $1.45-3.25$, and minimal or no fibrosis APRI <0.5 and FIB-4 <1.45 [25, 26].

Covariates

Covariates included sociodemographic factors (age and race/ethnicity), history of drug use (current, ever), history of tobacco use (current, ever), history of marijuana use (current, ever), alcohol use defined as number of drinks/week (abstinence; mild, defined as consumption $>0-7$ drinks/week; moderate, $7-12$ drinks/week; heavy, >12 drinks/week), anthropometry (waist circumference, body mass index [BMI]), diabetes mellitus (defined by self-report of antidiabetes medications, fasting glucose ≥ 126 mg/dL, or self-report of a diagnosis of diabetes mellitus confirmed by an elevated fasting glucose), and insulin resistance estimated using the homeostasis model assessment (HOMA-IR). HIV-related factors included current CD4⁺ T-cell count, HIV RNA detectable versus undetectable, current use of antiretroviral therapy (ART), and use of INSTIs.

Statistical Analysis

Because fibrosis changes gradually over time, we modeled rates of change in fibrosis biomarkers per year (slopes or trajectories), rather than comparing average levels within time categories, with emphasis on changes in trajectories around the time of HCV treatment. We used models that allowed the slopes of

ELF, APRI, and FIB-4 to change between 4 periods: 2 years to 1 year prior to reporting HCV treatment (pre-HCV treatment), the year prior to when treatment was first reported (peri-HCV treatment), within 1 year after HCV treatment (1 year post-HCV treatment), and from 1 to 2 years after treatment was first reported (2 years post-HCV treatment). We describe the time period 1 year prior to reporting HCV treatment as the peri-HCV treatment period because patients are often advised to optimize their behaviors to ensure adherence to HCV DAAs, including decreasing alcohol and recreational drug use and demonstrating adherence to ART, as well as switching ART to avoid drug-drug interactions with DAAs in the year before starting HCV DAAs. We also compared trajectories of fibrosis biomarkers between those treated with HCV DAAs and those who reported being treated with PEG-IFN plus RBV. Change in fibrosis biomarkers over time was modeled with piecewise linear splines, with the splines having knots at 1 year before treatment, at treatment, and 1 year posttreatment, using all measurements together over the entire study time.

Sociodemographic and clinical characteristics of the study participants were described using mean (standard deviation [SD]) or median (interquartile range [IQR]) for continuous variables, and percentage for categorical variables in each of the time periods. We modeled all fibrosis biomarker measurements over the 4-year study period together in a linear regression model that included a random intercept term and a random slope term that applied across the entire study period. The random intercepts accounted for between-woman differences in fibrosis biomarkers at study entry, and random slopes allowed for between-woman differences in overall rates of fibrosis biomarker change over the study, beyond what could be explained by the potential explanatory factors that we evaluated. We used interactions of covariates with elapsed time within each period to estimate their effects on the slopes in each period. To evaluate possible explanations other than treatment for changes in slopes between periods, our models examined the effects of changes or percentage changes of mean level of continuous covariates between pre- and peri-, 1 year post-, and 2 years post-HCV treatment periods, except for age which was included as a time-varying covariate. INSTI use status in the peri-, 1 year post-, and 2 years post-HCV treatment period was classified into 4 groups when compared with the pre-HCV treatment period: stayed off (reference), switched-on, switched-off, stayed on. Other categorical variables were time independent and entered the models as they were. Our models focused on the effects of changes in waist circumference, number of drinks per week, CD4 count, and INSTI use while adjusting for patients' age and race. All 3 fibrosis biomarker measures were right skewed and therefore were normalized using log transformation. The resulting regression coefficients (95% confidence intervals [CIs]) were back transformed to reflect the

covariates' effects on the percentage rate of change per year. All the analyses were performed using STATA version 16 (StataCorp LP) and SAS version 9.4 (SAS Institute).

RESULTS

Population Characteristics

Table 1 shows the sociodemographic, lifestyle, metabolic, and clinical characteristics of the women included in our analysis at entry into the pre-HCV, peri-HCV, 1 year post-, and 2 years post-HCV treatment periods. Most were African American, and the median age at entry into the pre-HCV treatment period was 56 years. While more than half reported being abstinent from alcohol in all HCV treatment periods, the proportion of women reporting moderate to heavy drinking decreased from 12.2% in the pre-HCV treatment period to 4.4% and 3.6% in the peri-HCV and 1 year post-HCV treatment periods, respectively, but rose slightly to 4.9% in the 2 years post-HCV treatment period. Additionally, more than half reported a history of tobacco, marijuana, and injection drug use, but among current users only reports of current injection drug use showed substantial declines from the pre-HCV treatment to the 2 years post-HCV treatment period. The median BMI was in the overweight category (25 kg/m^2 to $< 30 \text{ kg/m}^2$) in all HCV treatment periods. Waist circumference appeared higher in the peri-HCV, 1 year post-, and 2 years post-HCV treatment periods compared to the pre-HCV treatment period, and the proportion with diabetes also increased, while HOMA-IR decreased until the 1 year post-HCV treatment period and subsequently increased again in the 2 years post-HCV treatment period.

Among the HIV characteristics, median CD4 count was above 500 cells/mm^3 in all treatment periods and was higher in the peri-HCV, 1 year post-, and 2 years post-HCV treatment periods compared to the pre-HCV treatment period. About three-quarters of women had an undetectable HIV viral load and the majority of women reported taking ART in all treatment periods, but only 26% reported INSTI use in the pre-HCV treatment period compared to 47%, 53%, and 57% in the peri-HCV, 1 year post-, and 2 years post-HCV treatment periods, respectively.

The mean number of data points contributed by each woman for evaluation of ELF was 1.02, 1.02, 1.04, and 1.18 in the pre-HCV treatment, peri-HCV treatment, and 1 year post-, and 2 years post-HCV treatment periods, respectively. For APRI, it was 1.77, 1.89, 1.81, and 1.88 in the pre-HCV treatment, peri-HCV treatment, 1 year post-, and 2 years post-HCV treatment period, respectively. For FIB-4, values were the same as APRI in all 4 treatment periods.

When compared to the pre-HCV treatment period, median values for ELF, APRI, and FIB-4 were lower in the peri-HCV, 1 year post-, and 2 years post-HCV DAA treatment periods (Figure 1). The median ELF value declined from a borderline

Table 1. Characteristics of the 116 Women With HIV/HCV Coinfection at Entry into the Pre-HCV Treatment, Peri-HCV Treatment, 1 Year Post-HCV Treatment, and 2 Years Post-HCV Treatment Periods

Characteristic	Pre-HCV Treatment (n = 103)	Peri-HCV Treatment (n = 116)	1 y Post-HCV Treatment (n = 115)	2 y Post-HCV Treatment (n = 107)
Demographics				
Race				
White	14	14	14	13
Black	68	69	69	68
Hispanic	15	14	14	15
Other	3.9	3.4	3.5	3.7
Age, median (IQR)	56 (51–59)	57 (52–60)	58 (53–61)	59 (54–62)
Lifestyle				
Drinks/week, mean (SD)				
Drinks/week, mean (SD)	2.6 (8.1)	1.3 (4.9)	1.4 (6.1)	1.5 (4.8)
Drink				
Abstinence	63	68	66	66
Mild	25	27	30	29
Moderate	7.1	1.8	1.8	1.0
Heavy	5.1	2.6	1.8	3.9
Smoker				
Current	44	42	43	38
Ever	74	74	75	76
Marijuana use				
Current	20	18	20	17
Ever	56	53	53	51
Drug use				
Current	24	15	9	11
Ever	54	54	55	53
Metabolic				
BMI, median (IQR)				
BMI, median (IQR)	28 (23–34)	29 (24–33)	29 (24–34)	29 (24–33)
Waist circumference, cm, median (IQR)				
Waist circumference, cm, median (IQR)	94 (85–110)	100 (87–111)	98 (88–112)	96 (89–106)
HOMA-IR, median (IQR)				
HOMA-IR, median (IQR)	2.38 (1.27–3.82)	2.14 (1.46–3.99)	2.09 (1.26–4.19)	2.45 (1.65–5.26)
Diabetes	22	25	26	28
AST, IU/L, median (IQR)				
AST, IU/L, median (IQR)	38 (31–47)	22 (18–28)	20 (16–27)	19 (16–25)
ALT, IU/L, median (IQR)				
ALT, IU/L, median (IQR)	30 (24–45)	16 (12–21)	13 (11–19)	14 (11–18)
HIV-related				
Current CD4, cells/mm ³ , median (IQR)				
Current CD4, cells/mm ³ , median (IQR)	558 (429–778)	643 (432–798)	604 (437–788)	591 (420–846)
Undetectable HIV RNA	78	79	69	71
ART use	89	91	91	93
INSTI use	26	47	53	57

Definition of treatment periods are: pre-HCV, 1 to 2 years prior to report of HCV treatment; peri-HCV, within 1 year prior to report of HCV treatment; 1 year post-HCV, from report of treatment to 1 year after HCV treatment; and 2 years post-HCV, from 1 year up to 2 years after report of HCV treatment. Values are percent except where indicated.

Abbreviations: ALT, alanine transaminase; ART, antiretroviral therapy; AST, aspartate transaminase; BMI, body mass index; HCV, hepatitis C virus; HIV, human immunodeficiency virus; HOMA-IR, homeostasis model assessment; INSTI, integrase strand transfer inhibitor; IQR, interquartile range.

moderate to severe fibrosis range in the pre-HCV treatment period to the moderate fibrosis range, while the median APRI and FIB-4 values decreased but remained in the mild fibrosis range

and the moderate fibrosis range, respectively, throughout all 4 treatment periods.

ELF, APRI, and FIB-4 Trajectory Over the Pre-, Peri-, 1 Year Post-, and 2 Years Post-HCV Treatment Periods

In unadjusted analysis, we found a 3.3% per year rate of rise in the ELF score over the course of the pre-HCV treatment period, and a 2.2% and 3.6% per year rate of decline over the course of the peri-HCV treatment period and the 1 year post-HCV treatment period, respectively, followed by a 0.3% per year rate of rise up to the 2 years post-HCV treatment period, with only the decline over the 1 year post-HCV treatment period reaching statistical significance (Table 2). Similar findings were observed for the trajectory of APRI and FIB-4 over the treatment periods, but the declines in APRI and FIB-4 over both the peri- and 1 year post-HCV treatment periods were statistically significant.

We next adjusted for age, race, and changes in other factors thought to be most clinically associated with liver fibrosis biomarker changes (Table 2), primarily to see if those changes could explain the decline in the peri-HCV treatment period. Because changes in the potentially explanatory factors are relative to their values in the pretreatment period, results for that period are not shown. The unadjusted rates of change in the pretreatment period were 3.3% (95% CI, -0.6% to 7.4%; $P = .095$) for ELF, 10.0% (95% CI, -4.8% to 27.0%; $P = .19$) for APRI, and 4.2% (95% CI, -5.9% to 15.4%; $P = .43$) for FIB-4. During the peri-HCV treatment period, the decline in ELF was steeper after adjustment for changes in waist circumference, CD4, and INSTI use from the pre-HCV treatment period and was attenuated after adjustment for changes in alcohol use, but none of these adjustments produced an estimated ELF slope that was statistically significant during the peri-HCV treatment period. For APRI and FIB-4, adjustment for each factor led to small changes in the decline of APRI and FIB-4, and the declines remained statistically significant.

During the 1 year post-HCV treatment period, the decline in ELF was attenuated after adjustment for CD4 and INSTI use but remained statistically significant and substantially steeper only after adjustment for alcohol use. For APRI and FIB-4, adjustment for all factors retained statistical significance, but only adjustment for alcohol use led to substantially steeper declines.

During the 2 years post-HCV treatment period, adjustments for the change in alcohol use, waist circumference, CD4 count, and INSTI use did not substantially change ELF, APRI, and FIB-4 slope. Because the definition of FIB-4 includes age, we repeated the adjusted analysis for FIB-4 without adjusting for age, and found little change in the estimates (data not shown).

To facilitate comparison to results from a previous analysis [27], we performed a sensitivity analysis for the unadjusted analyses. This found strong evidence for a more rapid decrease in APRI during the first 6 months after treatment initiation

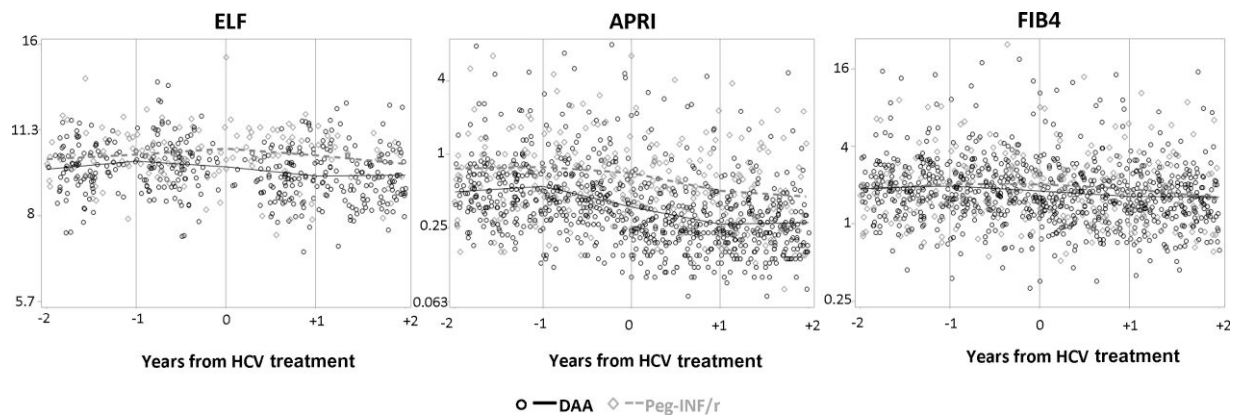


Figure 1. Liver fibrosis trajectory in the 116 women treated with HCV DAAs and the 42 women treated with pegylated interferon plus ribavirin across the pre-, peri-, 1 year post-, and 2 years post-HCV-treatment periods using ELF, APRI, and FIB4. Abbreviations: APRI, aspartate transaminase-to-platelet ratio index; DAA, direct-acting antiviral; ELF, enhanced liver fibrosis; FIB-4, Fibrosis-4; HCV, hepatitis C virus; Peg-IFN/r, pegylated interferon plus ribavirin.

than during the second 6 months ($P < .0001$); evidence was weaker but in the same direction for ELF ($P = .19$) and FIB-4 ($P = .26$). We therefore fit alternative models that changed the division of the last 2 periods to estimate annualized rates of change over the first 6 months and then from 6 months to 2 years after start of treatment. For ELF, these rates were -7.8% (95% CI, -14.0% to -1.0% ; $P = .025$) to 6 months and then -0.5% (95% CI, -2.6% to $+1.6\%$; $P = .65$) from 6 months to 2 years; for APRI the rates were -50.1% (95% CI, -59.2% to -39.1% ; $P < .0001$) to 6 months and then -1.6% (95% CI, -10.4% to $+8.1\%$; $P = .74$) from 6 months to 2 years; and for FIB-4 the rates were -15.5% (95% CI, -26.7% to -2.6% ; $P = .020$) to 6 months and then -3.1% (95% CI, -9.6% to $+3.9\%$; $P = .37$) from 6 months to 2 years.

ELF, APRI, and FIB-4 Trajectory in Women Treated With HCV DAAs Versus PEG-IFN Plus RBV

We next examined the trajectories of ELF, APRI, and FIB-4 in the 116 women treated with HCV DAAs and 42 women with HIV/HCV coinfection who had been treated with PEG-IFN plus RBV before 2009 (Figure 1). Compared to the DAA-treated women, those treated with PEG-IFN plus RBV had less favorable changes in the peri-HCV treatment period for ELF (2.4% increase vs 2.2% decline in DAA-treated women), APRI (10.8% decline vs 31.8% decline), and FIB-4 (0.6% decline vs 8.1% decline). The time by treatment interaction in the peri-HCV treatment period was statistically significant for APRI ($P = .027$). Other time by treatment interactions did not reach statistical significance.

DISCUSSION

In our study of liver fibrosis biomarker trajectories in women with HIV/HCV coinfection over a 4-year period before and after DAA treatment, we made several important observations.

While we found a rise in ELF in the pre-HCV treatment period, we unexpectedly observed declines in ELF that began within the 1-year period prior to HCV DAA treatment and then even steeper declines over the 1-year period post-HCV treatment before reversing course. Changes in factors that might influence liver fibrosis trajectories, including alcohol use, waist circumference, INSTI use, and CD4 count, had little effect on the observed liver fibrosis biomarker trajectory in the peri-HCV treatment period and subsequent periods. Similar findings were observed with APRI and FIB-4, but the declines were substantially and significantly steeper across both the peri- and 1-year post-HCV treatment periods, indicating that APRI and FIB-4 may be more affected by factors that could decrease liver inflammation than ELF.

Our study is notable in that we had serial measurements of ELF, APRI, and FIB-4 over several years. Our finding that decreases in moderate to heavy drinking, greater INSTI use, and higher CD4 counts in the peri-HCV treatment period compared to the pre-HCV treatment period had a small effect on the rate of decline in fibrosis biomarkers suggests that other unmeasured factors could explain this finding. It is also possible that there is a regression to the mean phenomenon where participants may have been targeted for treatment because of unusually high liver enzymes values near the beginning of the peri-HCV treatment period, with subsequent values tending to move toward more typical levels.

Consistent with prior studies that have evaluated mostly short-term changes in liver fibrosis post-SVR, we also found declines post-HCV treatment [15, 17, 18, 20]. The declines in APRI and FIB-4, however, were substantial and significant both in the peri- and immediate post-HCV treatment period, whereas the declines in ELF were significant only in the immediate post-HCV treatment period. These findings suggest that factors leading to decreases in liver inflammation begin in the peri-HCV treatment period and affect APRI and FIB-4 more than ELF. Furthermore, a study that examined fibrosis markers

Table 2. Unadjusted and Adjusted Liver Fibrosis Trajectory in the Peri-HCV Treatment Period, 1-Year Post-HCV Treatment Period, and 2-Year Post-HCV Treatment Period

	Peri-HCV Treatment	1 y Post-HCV Treatment	2 y Post-HCV Treatment
ELF			
Unadjusted	-2.2 (-6.1 to 1.7)	-3.6 (-7.0 to -0.1)*	0.3 (-2.9 to 3.7)
Adjusted for race, age + Δ drinks/wk	-1.2 (-5.5 to 3.3)	-6.0 (-9.8 to -2.0)**	2.9 (-0.9 to 6.7)
Adjusted for race, age + Δ WC	-3.0 (-7.6 to 1.9)	-4.4 (-8.8 to 0.1)	1.5 (-2.6 to 5.8)
Adjusted for race, age + Δ CD4	-3.0 (-7.1 to 1.3)	-2.6 (-6.5 to 1.4)	0.2 (-3.6 to 4.0)
Adjusted for race, age + Δ INSTI	-4.0 (-8.7 to 1.0)	-1.8 (-6.8 to 3.6)	-3.7 (-8.4 to 1.3)
APRI			
Unadjusted	-32 (-39 to -24)***	-28 (-35 to -20)***	3.5 (-9.5 to 18)
Adjusted for race, age + Δ drinks/wk	-31 (-38 to -21)***	-32 (-40 to -23)***	2.1 (-13 to 20)
Adjusted for race, age + Δ WC	-29 (-38 to -19)***	-30 (-39 to -20)***	3.1 (-14 to 23)
Adjusted for race, age + Δ CD4	-32 (-39 to -23)***	-26 (-35 to -17)***	-0.9 (-16 to 16)
Adjusted for race, age + Δ INSTI	-32 (-41 to -21)***	-30 (-41 to -17)***	7.5 (-14 to 34)
FIB-4			
Unadjusted	-8.1 (-15 to -0.4)*	-10.0 (-17 to -2.7)**	-0.3 (-9.5 to 9.8)
Adjusted for race, age + Δ drinks/wk	-10 (-18 to -2.6)*	-16 (-23 to -7.8)***	-2.0 (-12 to 9.6)
Adjusted for race, age + Δ WC	-9.9 (-18 to -1.3)*	-12 (-20 to -2.7)*	-3.3 (-14 to 9.3)
Adjusted for race, age + Δ CD4	-9.3 (-17 to -1.4)*	-12 (-19 to -3.6)**	-6.5 (-16 to 4.3)
Adjusted for race, age + Δ INSTI	-12 (-20 to -2.4)*	-12 (-22 to -1.1)*	-3.6 (-17 to 12)

Models adjusted for age, race/ethnicity plus change (Δ) in mean number of drinks per week, waist circumference, CD4 count logarithmically transformed, or INSTI use from the pre-HCV treatment period. **P* < .05, ***P* < .01, ****P* < .001.

Abbreviations: APRI, aspartate transaminase-to-platelet ratio; ELF, enhanced liver fibrosis; FIB-4, Fibrosis-4; HCV, hepatitis C virus; INSTI, integrase strand transfer inhibitor; WC, waist circumference.

to assess liver fibrosis post-HCV treatment in patients with HIV/HCV coinfection concluded that APRI and FIB-4 are not useful markers to monitor liver fibrosis, because liver inflammation is diminished after HCV cure [27]. Taken together, ELF may be a better marker of liver fibrosis and for monitoring changes in liver fibrosis during HCV treatment.

Finally, of clinical concern is that we observed a flattening of the declines even for ELF in the time period between 1 year and 2 years after HCV treatment. Importantly, our lower confidence bounds for ELF in both Table 2 and the sensitivity analysis are compatible with substantial declines during this post-HCV treatment period. A lack of substantial decline could indicate that either there was little longer-term fibrosis regression in this population or that ELF is not an ideal reflection of fibrosis but rather liver inflammation. A prospective biopsy-controlled study of patients with chronic liver disease suggested that the ELF score may be more strongly influenced by inflammatory liver injury than TE measurement of liver fibrosis [28]. By contrast, another report suggested that ELF can predict fibrosis progression when compared to liver biopsy [23]. However, liver biopsy may not be practical in a real-world setting where sampling and specimen reading error [29] may more likely occur. Longer-term monitoring of biomarkers of liver fibrosis is needed to understand trajectories after HCV cure.

Our study has some limitations. First, we examined a small sample size of women with HIV/HCV coinfection, but they contributed multiple time points over several years, allowing us to examine the trajectory of liver fibrosis biomarkers using

3 different serum markers. Second, we were unable to compare noninvasive biomarkers of fibrosis to liver biopsy, which might have helped discern whether changes in ELF, APRI, and FIB-4 were due to inflammation or not, but this is not practical in a study examining changes across multiple time periods.

Using serial measurements of ELF, APRI, and FIB-4 over a 4-year period in our cohort of women with HIV/HCV coinfection, we observed a rise in serum biomarkers of liver fibrosis followed by declines that unexpectedly began within the year before starting HCV treatment. The flattening of declines over the 1 to 2-year period after HCV cure suggests that continued monitoring of liver fibrosis and interventions to mitigate its progression in people with HIV after HCV cure remains essential. Further research is also needed to longitudinally evaluate the contribution of clinical and immunologic factors to liver fibrosis trajectory in patients with HIV after HCV cure.

Notes

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