Longitudinal Assessment of the Enhanced Liver Fibrosis Score in the Era of Contemporary HIV and HCV Treatment

Annelys Roque Gardner[a], Yifei Ma[b], Peter Bacchetti[c], Jennifer C. Price[b], Mark H. Kuniholm[d], Audrey L. French[e], Stephen Gange[f], Adaora A. Adimora[g], Howard Minkoff[h], Seble Kassaye[i], Igho Ofotokun[a], William Rosenberg[j], Andrea A.Z. Kovacs[k], Phyllis C. Tien[b,l]

[a]Department of Medicine, Emory University, Atlanta, Georgia, 30303, USA

[b]Department of Medicine, University of California, San Francisco, 94143 USA

[c]Department of Epidemiology and Biostatistics, University of California, San Francisco, CA 94143 USA

[d]Department of Epidemiology and Biostatistics, University at Albany, State University of New York, Rensselaer, NY

[e]Department of Medicine, Stroger Hospital, Cook County Health, Chicago, IL, 60612 USA

[f]Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, 21287, USA

[g]Department of Medicine, University of North Carolina, Chapel Hill, NC, 27599 USA

[h]Department of Obstetrics and Gynecology, State University of New York Downstate Health Sciences University, Brooklyn, NY, 11203, USA

[i]Department of Medicine, Georgetown University Medical Center, Washington, DC, 20007, USA

[j]Institute for Liver and Digestive Health, Division of Medicine, University College London, United Kingdom

[k]Department of Pediatrics, University of Southern California, Los Angeles, CA, 90033, USA

[l]Department of Veterans Affairs Medical Center, San Francisco, CA, 94121, USA

Total word count: 3493 words (abstract: 200 words)

Summary: Using serial measurements of ELF, APRI, and FIB-4 over a four- year period in women with HIV/HCV coinfection, we observed a rise in serum biomarkers of liver fibrosis followed by declines that began within the year before starting HCV treatment.

Address for correspondence:

Phyllis Tien, MD

University of California, San Francisco

VAMC, Infectious Disease Section, 111W

4150 Clement Street

San Francisco, CA 94121

Phone: 415-221-4810, ext 22577

Fax: 415-379-5523

E-mail: Phyllis.tien@ucsf.edu

Alternate Author for correspondence:

Annelys Roque Gardner, MD

annelys.roque.gardner@emory.edu

Acknowledgments: Data in this manuscript were collected by the Women's Interagency HIV Study (WIHS), now the MACS/WIHS Combined Cohort Study (MWCCS). The contents of this publication are solely the responsibility of the authors and do not represent the official views of the National Institutes of Health (NIH). MWCCS (Principal Investigators): Atlanta CRS (Ighovwerha Ofotokun, Anandi Sheth, and Gina Wingood), U01-HL146241; Baltimore CRS (Todd Brown and Joseph Margolick), U01-HL146201; Bronx CRS (Kathryn Anastos and Anjali Sharma), U01-HL146204; Brooklyn CRS (Deborah Gustafson and Tracey Wilson), U01-HL146202; Data Analysis and Coordination Center (Gypsyamber D'Souza, Stephen Gange and Elizabeth Golub), U01-HL146193; Chicago-Cook County CRS (Mardge Cohen and Audrey French), U01-HL146245; Chicago-Northwestern CRS (Steven Wolinsky), U01-HL146240; Northern California CRS (Bradley Aouizerat, Jennifer Price, and Phyllis Tien), U01-HL146242; Los Angeles CRS (Roger Detels and Matthew Mimiaga), U01-HL146333; Metropolitan Washington CRS (Seble Kassaye and Daniel Merenstein), U01-HL146205; Miami CRS (Maria Alcaide, Margaret Fischl, and Deborah Jones), U01-HL146203; Pittsburgh CRS (Jeremy Martinson and Charles Rinaldo), U01-HL146208; UAB-MS CRS (Mirjam-Colette Kempf, Jodie Dionne-Odom, and Deborah Konkle-Parker), U01-HL146192; UNC CRS (Adaora Adimora), U01-HL146194. The MWCCS is funded primarily by the National Heart, Lung, and Blood Institute (NHLBI), with additional co-funding from the *Eunice Kennedy Shriver* National Institute Of Child Health & Human Development (NICHD), National Institute On Aging (NIA), National Institute Of Dental & Craniofacial Research (NIDCR), National Institute Of Allergy And Infectious Diseases (NIAID), National Institute Of Neurological Disorders And Stroke (NINDS), National Institute Of Mental Health (NIMH), National Institute On Drug Abuse (NIDA), National Institute Of Nursing Research (NINR), National Cancer Institute (NCI),

National Institute on Alcohol Abuse and Alcoholism (NIAAA), National Institute on Deafness and Other Communication Disorders (NIDCD), National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), National Institute on Minority Health and Health Disparities (NIMHD), and in coordination and alignment with the research priorities of the National Institutes of Health, Office of AIDS Research (OAR). MWCCS data collection is also supported by UL1-TR000004 (UCSF CTSA), UL1-TR003098 (JHU ICTR), UL1-TR001881 (UCLA CTSI), P30-AI-050409 (Atlanta CFAR), P30-AI-073961 (Miami CFAR), P30-AI-050410 (UNC CFAR), P30-AI-027767 (UAB CFAR), and P30-MH-116867 (Miami CHARM). The study was also supported by the National Institute of Allergy and Infectious Diseases (K24 AI 108516 [PCT]), the National Institute of Diabetes and Digestive and Kidney Diseases (R01 DK 109823 [PCT]), the National Institute of Drug Abuse (R01 DA 044111 [Kovacs/Tien]), an American College of Gastroenterology Junior Faculty Development Award (JCP), and the University College London Hospitals National Institute for Health Research Biomedical Research Centre (WMR).

Conflict of Interests:

AA has received consulting fees from Merck, Viiv Healthcare, and Gilead Sciences; Gilead Sciences has provided her institution with funding for her research.

JCP has received consulting fees from Theratechnologies; Gilead Sciences and Merck have provided her institution with funding for her research.

PCT has investigator-initiated grants from Merck.

MHK reports consulting for Sanofi.

All other authors have no conflicts of interest to report.

Abstract

Background: The trajectory of liver fibrosis is not well-understood in the contemporary era of HIV and HCV therapy.

Methods: We assessed the Enhanced Liver Fibrosis (ELF) score, AST-to-platelet ratio (APRI) and 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 one-to-two-years before starting HCV treatment, within 1-year before starting (peri-HCV treatment), within 1-year after and from one-to-two-years post-HCV treatment in unadjusted and adjusted models including age, race, and changes from pre-treatment of factors that might affect fibrosis (e.g., alcohol, integrase strand inhibitor (INSTI) use, waist circumference, CD4 count).

Results: INSTI use nearly doubled from pre- to peri-treatment. In unadjusted analysis, there was a 3.33% 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 one 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

Introduction

Chronic hepatitis C virus (HCV) coinfection is common in people with HIV (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] Yet, 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 and 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 endpoints 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 monoinfection[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 non-invasive serum markers APRI and FIB-4, as well as transient elastography (TE), but whether the short-term declines observed may be more a result of decreases in liver inflammation than regression of liver fibrosis is unclear, since 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 (HA), 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 monoinfection, 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 monoinfection (n=26), pre-treatment but no post-treatment records (n=49), and post-treatment but no pre-treatment 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 one visit within 2 years prior to first reporting HCV treatment, and at least one 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 three biomarkers of extracellular matrix modelling measured from frozen sera that was stored at -70°C. An automated IMMUNO 1 immunoanalyzer (Siemens Medical Solutions Diagnostics, Tarrytown, New York) determined levels of TIMP-1, PIIINP, and HA via magnetic particle separation immunoassays as per the European Liver Fibrosis Study.[22] The TIMP-1 and PIIINP assays each use 2 monoclonal antibodies that bind to independent binding sites on their respective antigens. The HA assay uses HA 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: [(AST/ULN (upper limit of normal) of AST) x 100]/platelets (10^9/L).[25] FIB-4 was calculated using the equation [(age x AST)/(platelets [10^9/L] x $ALT^{1/2}$)].[26.] Severe fibrosis was defined as an APRI≥1.5 and FIB-4≥3.25, moderate fibrosis as APRI from 0.5-1.5 and FIB-4 from 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 [WC], body mass index [BMI]), diabetes mellitus (defined by self-report of anti-diabetes 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 yr post-HCV treatment), and from 1 to 2 years after treatment was first reported (2 yrs 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 post treatment, 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 four-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 yr post-, and 2 yrs post-HCV treatment periods, except for age which was included as a time-varying covariate. INSTI use status in the peri-, 1 yr post-, and 2 yrs 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 WC, number of drinks per week, CD4 count, and INSTI use while adjusting for patients' age and race. All three fibrosis biomarker measures were right skewed and therefore were normalized using log-transformation. The resulting regression coefficients (95% confidence intervals) were back-transformed to reflect the covariates' effects on the percentage rate of change per year. All the analyses were performed using STATA v16 (*StataCorp LP*, College Station, TX) and SAS 9.4 (*SAS Institute*, Cary, NC).

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 yr post-, and 2 yrs 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 yr post-HCV treatment periods, respectively, but rose slightly to 4.9% in the 2 yrs post-HCV treatment period. Additionally, more than half reported a history of tobacco, marijuana, and injection drug use (IDU), but among current users, only reports of current IDU showed substantial declines from the pre-HCV treatment to the 2 yrs post-HCV treatment period. The median BMI was in the overweight category (25 kg/m^2 – <30 kg/m^2) in all HCV treatment periods. WC appeared higher in the peri-HCV, 1 yr post-, and 2 yrs 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 yr post-HCV treatment period and subsequently increased again in the 2 yrs post-HCV treatment period.

Among the HIV characteristics, median CD4 count was above 500 cells/mm^3 in all treatment periods was higher in the peri-HCV, 1 yr post-, and 2 yrs 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 yr post-, and 2 yrs 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 yr post-, and 2 yrs 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 yr post-, and 2 yrs post-HCV treatment period, respectively. For FIB-4, values were the same as APRI in all four 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 yr post-, and 2 yrs post-HCV DAA treatment periods (Figure). The median ELF value declined from a borderline 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 yr post-, and 2 yrs 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, a 2.2% and 3.6% per year rate of decline over the course of the peri-HCV treatment period and the 1 yr post-HCV treatment period, respectively, followed by a 0.3% per year rate of rise up to the 2 yrs post-HCV treatment period, with only the decline over the 1 yr 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 yr 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 pre-treatment period, results for that period are not shown. The unadjusted rates of change in the pre-treatment period were 3.3% (95%CI -0.6% to 7.4%, p=0.095) for ELF, 10.0% (95%CI -4.8% to 27.0%, p=0.19) for APRI, and 4.2% (95%CI -5.9% to 15.4%, p=0.43) for FIB-4. During the peri-HCV treatment period, the decline in ELF was steeper after adjustment for changes in WC, 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 yr 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 yrs post-HCV treatment period, adjustments for the change in alcohol use, WC, 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).

In order 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 than during the second 6 months ($p<0.0001$); evidence was weaker but in the same direction for ELF ($p=0.19$) and FIB-4 ($p=0.26$). We therefore fit alternative models that changed the division of the last two 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%, $p=0.025$) to 6 months and then -0.5% (95%CI -2.6% to +1.6%, $p=0.65$) from 6 months to 2 years; for APRI the rates were -50.1% (95%CI -59.2% to -39.1%, $p<0.0001$) to 6 months and then -1.6% (95%CI -10.4% to +8.1%, $p=0.74$) from 6 months to 2 years; and for FIB-4 the rates were -15.5% (95%CI -26.7 to -2.6%, $p=0.020$) to 6 months and then -3.1% (95%CI -9.6% to +3.9%, $p=0.37$) from 6 months to 2 years.

ELF, APRI, and FIB-4 Trajectory in women treated with HCV DAAs vs 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). 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 ($p=0.027$). 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 four-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 one-year period prior to HCV DAA treatment and then even steeper declines over the one-year period post-HCV treatment before reversing course. Changes in factors that might influence liver fibrosis trajectories including alcohol use, WC, 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. 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 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 paper of patients with chronic liver disease suggested that the ELF score may be more strongly influenced by inflammatory liver injury than transient elastography measurement of liver fibrosis.[28] By contrast, another paper 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 timepoints over several years allowing us to examine the trajectory of liver fibrosis biomarkers using three different serum markers. Second, we were unable to compare non-invasive 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 four-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 one-to-two-year period after HCV cure suggests that continued monitoring of liver fibrosis and interventions to mitigate its progression in people with HIV post-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 living with HIV after HCV cure.

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Table 1. Characteristics of the 116 women with HIV/HCV coinfection at entry into the pre-HCV treatment (Tx) period (1 to 2 years prior to report of HCV treatment), peri-HCV Tx period (within 1 year prior to report of HCV treatment), 1 yr post-HCV Tx period (from report of treatment to 1 year after HCV treatment), and 2 yrs post-HCV Tx period (from 1 year up to 2 years after report of HCV treatment). Values are in percent or median (interquartile range) except where indicated.

		Pre-HCV Tx N=103	Peri-HCV Tx N=116	1 yr Post-HCV Tx N=115	2 yrs Post-HCV Tx 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		56 (51, 59)	57 (52, 60)	58 (53, 61)	59 (54, 62)
Lifestyle					
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%
Pot 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		28 (23, 34)	29 (24, 33)	29 (24, 34)	29 (24, 33)
Waist Circumference (cm)		94 (85, 110)	100 (87, 111)	98 (88, 112)	96 (89, 106)
HOMAIR		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)		38 (31, 47)	22 (18, 28)	20 (16, 27)	19 (16, 25)
ALT (IU/L)		30 (24, 45)	16 (12, 21)	13 (11, 19)	14 (11, 18)
HIV-related					
Current CD4 (cells/mm^3)		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%

Figure. 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.

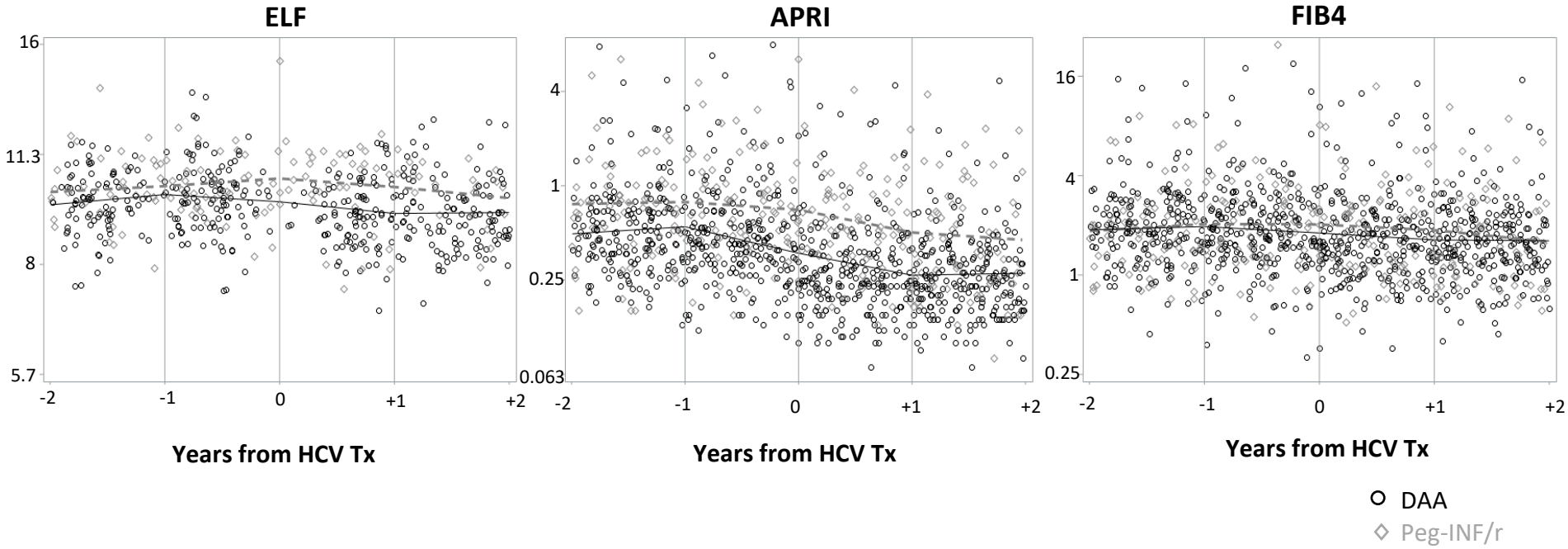

Table 2: Unadjusted and Adjusted Liver Fibrosis Trajectory in the Peri-HCV Treatment (Tx) period, 1-year Post-HCV Tx period, and 2-year Post-HCV Tx period. Models adjusted for age, race/ethnicity plus change (Δ) in mean number of drinks per week, waist circumference (WC), CD4 count logarithmically transformed, or INSTI use from the Pre-HCV Tx period.

	Peri-HCV Tx	1 yr Post-HCV Tx	2 yr Post-HCV Tx
ELF			
Unadjusted	-2.2% (-6.1%, 1.7%)	-3.6% (-7.0%, -0.1%)*	0.3% (-2.9%, 3.7%)
Adjusted for race, age +Δ drinks/wk	-1.2% (-5.5%, 3.3%)	-6.0% (-9.8%, -2.0%)**	2.9% (-0.9%, 6.7%)
Adjusted for race, age + Δ WC	-3.0% (-7.6%, 1.9%)	-4.4% (-8.8%, 0.1%)	1.5% (-2.6%, 5.8%)
Adjusted for race, age + Δ CD4	-3.0% (-7.1%, 1.3%)	-2.6% (-6.5%, 1.4%)	0.2% (-3.6%, 4.0%)
Adjusted for race, age + Δ INSTI	-4.0% (-8.7%, 1.0%)	-1.8% (-6.8%, 3.6%)	-3.7% (-8.4%, 1.3%)
APRI			
Unadjusted	-32% (-39%, -24%)***	-28% (-35%, -20%)***	3.5% (-9.5%, 18%)
Adjusted for race, age +Δ drinks/wk	-31% (-38%, -21%)***	-32% (-40%, -23%)***	2.1% (-13%, 20%)
Adjusted for race, age + Δ WC	-29% (-38%, -19%)***	-30% (-39%, -20%)***	3.1% (-14%, 23%)
Adjusted for race, age + Δ CD4	-32% (-39%, -23%)***	-26% (-35%, -17%)***	-0.9% (-16%, 16%)
Adjusted for race, age + Δ INSTI	-32% (-41%, -21%)***	-30% (-41%, -17%)***	7.5% (-14%, 34%)
FIB4			
Unadjusted	-8.1% (-15%, -0.4%)*	-10.0% (-17%, -2.7%)**	-0.3% (-9.5%, 9.8%)
Adjusted for race, age +Δ drinks/wk	-10% (-18%, -2.6%)*	-16% (-23%, -7.8%)***	-2.0% (-12%, 9.6%)
Adjusted for race, age + Δ WC	-9.9% (-18%, -1.3%)*	-12% (-20%, -2.7%)*	-3.3% (-14%, 9.3%)
Adjusted for race, age + Δ CD4	-9.3% (-17%, -1.4%)*	-12% (-19%, -3.6%)**	-6.5% (-16%, 4.3%)
Adjusted for race, age + Δ INSTI	-12% (-20%, -2.4%)*	-12% (-22%, -1.1%)*	-3.6% (-17%, 12%)

**p<0.05, **p<0.01; ***p<0.001*