Title

Moderate Alcohol Use Is Not Associated With Fibrosis Progression in Human Immunodeficiency Virus/Hepatitis C Virus—Coinfected Women: A Prospective Cohort Study

Journal

Clinical Infectious Diseases, 65(12)

ISSN

1058-4838

Authors

Kelly, Erin M
Dodge, Jennifer L
Bacchetti, Peter
et al.

Publication Date

2017-11-29

DOI

10.1093/cid/cix716

Peer reviewed

Clinical Infectious Diseases

MAJOR ARTICLE

Moderate Alcohol Use Is Not Associated With Fibrosis Progression in Human Immunodeficiency Virus/Hepatitis C Virus–Coinfected Women: A Prospective Cohort Study

Erin M. Kelly,[1] Jennifer L. Dodge,[2] Peter Bacchetti,[3] Monika Sarkar,[4] Audrey L. French,[5] Phyllis C. Tien,[4,6] Marshall J. Glesby,[7] Elizabeth T. Golub,[8] Michael Augenbraun,[9] Michael Plankey,[10] and Marion G. Peters[4]

[1]Department of Medicine, University of Ottawa, Ontario, Canada; Departments of [2]Surgery, [3]Epidemiology and Biostatistics, and [4]Medicine, University of California, San Francisco; [5]Department of Medicine, CORE Center/Stroger Hospital of Cook County, Chicago, Illinois; [6]Department of Veterans Affairs Medical Center, San Francisco, California; [7]Department of Medicine, Weill Cornell Medical College, New York, New York; [8]Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland; [9]Department of Medicine, State University of New York, Downstate Medical Center, Brooklyn; and [10]Department of Medicine, Georgetown University Medical Center, Washington, District of Columbia

(See the Editorial Commentary by Lo Re III on pages 2057–9.)

Background. Heavy alcohol use can lead to progressive liver damage, especially in individuals with chronic hepatitis C (HCV); however, the impact of nonheavy use is not clear. We studied long-term effects of modest alcohol use on fibrosis progression in a large cohort of women coinfected with human immunodeficiency virus (HIV)/HCV.

Methods. Alcohol intake was ascertained every 6 months and use categorized as abstinent, light (1–3 drinks/week), moderate (4–7 drinks/week), heavy (>7 drinks/week), and very heavy (>14 drinks/week). Fibrosis progression was defined as the change in Fibrosis-4 Index for Liver Fibrosis (FIB-4) units per year using random-intercept, random-slope mixed modeling.

Results. Among 686 HIV/HCV-coinfected women, 46.0% reported no alcohol use; 26.8% reported light use, 7.1% moderate use, and 19.7% heavy use (6.7% had 8–14 drinks/week and 13.0% had >14 drinks/week) at cohort entry. Median FIB-4 at entry was similar between groups. On multivariable analysis, compared to abstainers, light and moderate alcohol use was not associated with fibrosis progression (0.004 [95% confidence interval {CI}, –.11 to .12] and 0.006 [95% CI, –.18 to .19] FIB-4 units/year, respectively). Very heavy drinking (>14 drinks/week) showed significant fibrosis acceleration (0.25 [95% CI, .01–.49] FIB-4 units/year) compared to abstaining, whereas drinking 8–14 drinks per week showed minimal acceleration of fibrosis progression (0.04 [95% CI, –.19 to .28] FIB-4 units/year).

Conclusions. Light/moderate alcohol use was not substantially associated with accelerated fibrosis progression, whereas drinking >14 drinks per week showed increased rates of fibrosis progression. Women with HIV/HCV infection should be counseled against heavy alcohol consumption, but complete abstinence may not be required to prevent accelerated liver fibrosis progression.

Keywords. alcohol; fibrosis; hepatitis C; coinfection; FIB-4.

Chronic hepatitis C (CHC) infection and alcoholic liver disease are among the most common causes for advanced liver disease worldwide and frequently coexist. Heavy alcohol use has clearly been demonstrated to accelerate liver fibrosis progression [1–6], increasing cirrhosis and decompensated liver disease risk [7].

Although heavy alcohol use is clearly detrimental to the health of patients with CHC, it is unclear whether consumption of smaller quantities of alcohol impacts fibrosis progression. Many patients with CHC consume alcohol and are unable or unwilling to completely abstain. Some studies have suggested a linear dose-response on fibrosis progression even at lower quantities, whereas others have not clearly demonstrated a risk for fibrosis progression <20–50 g of alcohol per day [5, 8–13]. Patients coinfected with human immunodeficiency virus (HIV)/hepatitis C virus (HCV) have accelerated fibrosis progression compared with HCV-monoinfected individuals. Whether regular consumption of small quantities of alcohol further increases the rate of fibrosis progression is unknown. For this reason, we sought to examine the impact of moderate alcohol use on liver fibrosis progression in a well-characterized cohort of women coinfected with HIV and HCV.

PATIENTS AND METHODS

Population

The Women's Interagency HIV Study (WIHS) is a prospective, multicenter, longitudinal observational cohort of adult women infected with HIV or at high risk of acquiring HIV. Details of the WIHS cohort have been described elsewhere [14, 15]. Among the 3766 women enrolled in the first 2 recruitment waves (cohort 1 = 1994–1995; cohort 2 = 2001–2002), 18% were HIV/HCV coinfected at WIHS entry and included in this analysis (n = 686).

Received 29 December 2016; editorial decision 25 June 2017; accepted 15 August 2017; published online August 16, 2017.

Correspondence: E. M. Kelly, The Ottawa Hospital, General Campus, 501 Smyth, Box 255, Ottawa, ON, Canada, K1H8L6 (ekelly@toh.on.ca).

Clinical Infectious Diseases® 2017;65(12):2050–6

DOI: 10.1093/cid/cix716

The study was approved by each site's institutional review board and all women gave informed consent at entry. HCV infection was defined by positive serum HCV RNA at WIHS entry.

Data Collection

Patients were seen in follow-up every 6 months, where detailed sociodemographic (age, ethnicity, race, and past substance use), medical and behavioral data were collected through structured interviews, physical examination, and biologic specimen collection. Biologic specimens were collected every 6 months including liver enzymes, renal function, complete blood count, CD4 cell count, and HIV viral load. HIV RNA was measured using isothermal nucleic acid sequence-based amplification (NASBA/Nuclisens) method (bioMérieux, Durham, North Carolina) with a lower limit of detection of 80 copies/mL. Highly active antiretroviral therapy was defined by the contemporaneous Department of Health and Human Services guidelines [16]. Second- or third-generation enzyme-linked immunoassays were utilized for HCV antibody detection (Ortho-Diagnostic Systems, Rochester, New York) and confirmed by documenting HCV RNA seropositivity (Quantiplex 2.0 branched chain DNA-enhanced label amplification assay; Bayer-Versant Diagnostics, Emeryville, California) and by reverse-transcription polymerase chain reaction (COBAS Amplicor HCV Detection Kit, Roche Diagnostic Systems, Pleasanton, California). The presence of hepatitis B surface antigenemia was assessed within the first year of enrollment. Data including body mass index (BMI), history of hypertension, diabetes, and insulin resistance were collected at each study visit. Diabetes was defined as any fasting glucose measurement of >126 mg/dL, hemoglobin A1c measured at ≥6.5%, or self-report of taking antidiabetic medication.

Drug and Alcohol Use

Injection drug use (IDU) and non-IDU was assessed at the entry and subsequent follow-up visits. Alcohol intake was ascertained semiannually by average number of drinks per week during the preceding 6-month interval. Light use was defined as 1–3 drinks per week, moderate as 4–7 drinks per week, and heavy use as >7 drinks per week. Heavy users were substratified into 2 groups: 8–14 drinks per week, and >14 drinks per week, to reflect variable country-specific cutoffs for heavy use [17]. Participants were considered to be abstinent if no alcohol use was reported at WIHS entry and throughout all follow-up visits, and formed the reference group. Years of alcohol exposure within each category of use was cumulated from study entry throughout the course of the observation period, and the concurrent values of the resulting cumulative exposure variables were used as predictors of each Fibrosis-4 Index for Liver Fibrosis (FIB-4) measurement.

Fibrosis Measurements

Noninvasive fibrosis measurements including FIB-4 and AST to platelet ratio index (APRI) have been validated in patients with HIV/HCV coinfection as well as this cohort [18–22]. FIB-4, defined as (age × aspartate aminotransferase [AST]) / (platelets × alanine aminotransferase [ALT]), was calculated annually in WIHS participants. Standard cutoffs of FIB-4 were used to define no fibrosis (<1.5) and significant fibrosis (>3.25) for each measure. FIB-4 values were considered invalid if AST or ALT was >10 times the upper limit of normal or platelet counts were <25 000 10^6cells/L, as these extremes values are unlikely to be due to chronic liver fibrosis, and more likely to be caused by acute hepatitis or another disease process.

Primary Outcome

The primary outcome of this study was rate of fibrosis progression, defined as change in FIB-4 per year.

Statistical Analysis

Sociodemographic and clinical characteristics of WIHS women at study entry were described using mean (standard deviation [SD]), median (interquartile range [IQR]), and percentage (frequency). Entry characteristics were further stratified by baseline alcohol use and compared using *t* test, Wilcoxon rank-sum test, or χ^2 test, as appropriate. For descriptive purposes, average alcohol use was calculated as the median number of drinks per week during follow-up. Estimates of baseline and average alcohol use were compared and the proportion of women changing alcohol use categories from baseline was described.

We used statistical models that reflect the gradual, cumulative nature of fibrosis progression. We modeled all FIB-4 measurements together in a random-intercept, random-slope regression model. The random intercepts accounted for between-woman differences in FIB-4 at study entry, which allowed the model to focus on within-woman fibrosis progression during the study. We modeled the effect of alcohol consumption in terms of the woman's cumulative years as study entry that she spent in each nonabstinent alcohol consumption category up to each FIB-4 measurement, so that regression coefficients estimated the effect of alcohol consumption on the rate of fibrosis progression. Other covariates were modeled similarly, except for age and HIV viral load. Age is already a cumulative measure over time, so we used current age at the time of each FIB-4 measurement to model average rates of progression in the absence of any other factors that increase or decrease them. We used linear splines to allow these average rates to differ in different age ranges: <40, 40–45 inclusive, >45–50, >50–55, and >55. We modeled the effect of HIV viral load continuously using detectable $\log_{10}$ viral load years, defined as the area under the time-$\log_{10}$ viral load curve and >80 copies/mL; the coefficient for this variable therefore estimates the acceleration in fibrosis progression for each factor of 10 increase in HIV viral load. For all covariates, we carried the most recent measurement forward in time until a new measurement became available, but considered it to be missing after more than a year had passed since

the last available measurement. Patient follow-up was censored such that imputation of missing data never exceeded 1 year. To best focus on HIV/HCV-coinfected women, we excluded all observations that occurred after a woman started HCV treatment or had an undetectable HCV viral load. Forward stepwise selection ($P < .05$ for model inclusion) was used to build the multivariable model with alcohol use included as the primary independent factor of interest. Resulting β-coefficients and 95% confidence intervals (95% CIs) estimated the increase or decrease in the rate of FIB-4 progression per year. We also evaluated fibrosis progression using APRI; as results were similar regarding our primary independent variable, alcohol consumption, only results for FIB-4 are presented.

RESULTS

Study Population

Table 1 summarizes the cohort entry characteristics of the 686 women included in this analysis. Two women did not have entry alcohol use recorded and were excluded from Table 1 but included in fibrosis progression analysis. The mean age of the study population was 40 (SD, 6) years at entry. The majority (62.7%) of women were African American and had HCV genotype 1 (87.5%) with mean HCV viral load 14.2 $\log_{10}$ (SD, 2) IU/mL. Median HIV viral load was 18.0 (IQR, 2.7–88) IU/mL and median CD4 count at entry was 351 (IQR, 198–548) cells/μL. Nearly one-third (28.6%) of women were receiving antiretroviral therapy (ART) at WIHS entry. Median FIB-4 score at entry was 1.42 (IQR, 1.00–2.10), and 11% (n = 72) of women had evidence of significant fibrosis (FIB-4 >3.25). Median follow-up was 10.0 (IQR, 4.2–17.7) years. Within the entire cohort, a total of 15% (n = 103) received interferon-based HCV treatment and 13 achieved sustained virologic response.

At WIHS entry, 46% of women reported no alcohol use, and 27% reported light, 7% moderate, and 20% heavy alcohol use (>7 drinks per week) in the 6 months prior to WIHS entry. Among the 135 women who reported heavy alcohol use at WIHS entry, about one-third (n = 46) drank ≤14 drinks per week, whereas two-thirds (n = 89) reported >14 drinks per week. When compared to women abstinent at WIHS entry, those who consumed alcohol at cohort entry were more likely to smoke tobacco and report illicit drug use, both IDU and non-IDU. Women with higher entry categories of alcohol use were less likely to be on ART at study entry and had lower BMI.

Alcohol Use in Women's Interagency HIV Study Follow-up

Alcohol use varied through WIHS follow-up, with 30.5% increasing mean alcohol consumption, 14.5% decreasing, and

Table 1. Women's Interagency HIV Survey Entry Characteristics by Entry Alcohol Use Category

Variable	No.	All (N = 684)[a]	Average No. of Drinks per Week					*P* Value (Group)
			Abstinent (n = 316)	1–3 (n = 184)	4–7 (n = 49)	8–14 (n = 46)	>14 (n = 89)	
Mean age, y (SD)		39.7 (6)	39.6 (6)	40.3 (7)	40.4 (7)	38.8 (5)	39.4 (5)	**.049**
Race/ethnicity	680							.60
White[b]		17.4% (118)	17.5% (55)	18.1% (33)	6.1% (3)	23.9% (11)	17.2% (15)	
Hispanic		19.3% (131)	21.0% (66)	18.1% (33)	22.5% (11)	13.0% (6)	17.2% (15)	
African American[b]		62.7% (426)	60.5% (190)	63.2% (115)	71.4% (35)	63.0% (29)	65.5% (57)	
Other		0.7% (5)	1.0% (3)	0.6% (1)	0	0	0	
HCV genotype 1	554	87.5% (485)	85.7% (217)	89.1% (140)	89.5% (34)	90.9% (30)	88.7% (63)	.85
Mean HCV viral load, log IU/mL (SD)	686	6.2 (1)	6.2 (1)	6.1 (1)	6.1 (1	6.4 (1)	6.4 (1)	**<.001**
Median CD4 (IQR)	685	351 (198–548)	337 (176–548)	326 (197–506)	352 (235–555)	337 (176–548)	402 (249–633)	.2
Median HIV viral load × 10^3 (IQR), IU/mL	681	4.3 (3.4–4.9)	4.3 (3.2–4.9)	4.2 (3.5–4.8)	4.1 (3.6–4.9)	4.4 (3.8–5.1)	4.3 (3.7–5.1)	.71
ART use	682	28.6% (195)	36.1% (113)	30.0% (57)	16.3% (8)	13.3% (6)	11.2% (10)	**<.001**
Mean BMI (SD)	673	26.1 (6)	27.0 (6)	25.8 (6)	24.9 (5)	26.6 (5)	23.9 (4)	**.001**
Hypertension	686	22.7% (156)	21.2% (67)	22.8% (42)	24.5% (12)	26.1% (12)	25.8% (23)	.86
Diabetes	684	17.3% (118)	16.1% (51)	20.3% (37)	20.4% (10)	19.5% (9)	12.4% (11)	.5
Cigarette smoking	686	77.7% (533)	69.0% (316)	83.1% (153)	81.6% (40)	93.5% (43)	86.5% (77)	**<.001**
IDU	686	21.9% (150)	16.5% (52)	19.0% (35)	32.7% (16)	28.3% (13)	37.1% (33)	**<.001**
Non-IDU	686	44.9% (308)	21.5% (68)	54.8% (99)	69.4% (34)	65.2% (30)	84.3% (75)	**<.001**
Marijuana use	686	27.0% (185)	11.4% (36)	35.3% (65)	34.7% (17)	41.3% (19)	51.7% (46)	**<.001**
Median entry alcohol use (IQR)	684	0.5 (0–4.5)	0	1 (0.5–2)	6 (4.5–7)	10.5 (9–12)	33 (21–70)	**<.001**
Median FIB-4 score (IQR)	681	1.42 (1.0–2.1)	1.45 (1.05–2.08)	1.32 (0.89–2.02)	1.55 (1.01–1.36)	1.53 (1.09–2.16)	1.51 (0.99–2.26)	.5
Significant fibrosis (FIB-4 score >3.25)	681	10.6% (72)	9.9% (31)	10.9% (20)	8.1% (4)	10.9% (5)	13.6% (12)	.73

Data are presented as percentage (No.) unless otherwise indicated. Bold denotes $P < .05$.

Abbreviations: ART, antiretroviral therapy; BMI, body mass index; FIB-4, Fibrosis-4 Index for Liver Fibrosis; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IDU, injection drug use; IQR, interquartile range; SD, standard deviation.

[a]Missing entry data in 2 patients.

[b]Compared to African-American.

Table 2. Change in Alcohol Consumption in Women's Interagency HIV Study Follow-up by Entry Alcohol Use Groups

	Average No. (%) of Drinks/Week During Women's Interagency HIV Study				
Average No. of Drinks/Week at Baseline	0	1–3	4–7	8–14	> 14
0 (n = 316)	**159 (50.32)**	**125 (39.56)**	**14 (4.43)**	**9 (2.85)**	**9 (2.85)**
1–3 (n = 184)	*0 (0)*	**145 (78.8)**	**24 (13.04)**	**12 (6.52)**	**3 (1.63)**
4–7 (n = 49)	*0 (0)*	*25 (51.02)*	**17 (34.69)**	**5 (10.2)**	**2 (4.08)**
8–14 (n = 46)	*0 (0)*	*16 (34.78)*	*12 (26.09)*	**12 (26.09)**	**6 (13.04)**
>14 (n = 89)	*0 (0)*	*8 (8.99)*	*12 (13.48)*	*26 (29.21)*	**43 (48.31)**
Total (N = 684)	159	319	79	64	63

This includes averaged data from Women's Interagency HIV Study entry and follow-up so that only women who were abstinent from entry and every follow-up visit have average alcohol use of 0 (n = 159). Women with average use >0 but <1 were included in the 1–3 drinks/week category

Gray text denotes average alcohol use in follow-up greater than at entry, italic text denotes average alcohol use in follow-up less than at entry, and bolded black text denotes no change in average follow-up use as compared to entry use.

55.0% unchanged during overall follow-up. Seventy-seven percent of women reported at least 1 interval of alcohol use in WIHS, whereas the remaining 23% remained abstinent throughout follow-up. In most women, alcohol use in WIHS follow-up was comparable to alcohol use at cohort entry (Tables 2 and 3). Among women with light or moderate use at WIHS entry (1–7 drinks per week), 9.4% increased median alcohol use to >7 drinks per week in WIHS follow-up (22/233). Conversely, among the 135 women with >7 drinks per week use at WIHS entry, 48 (35.6%) decreased their average alcohol use in WIHS follow-up to ≤7 drinks per week (data not shown). A total of 590 women contributed median observation time of 4.5 (IQR, 2.0–8.0) years in the abstinent alcohol category; 436 women contributed median observation time of 2.0 (IQR, 1.0–4.0) years in the light use category; 252 women contributed median observation time of 1.0 (IQR, 0.5–2.0) years to the moderate alcohol use category; and 288 women contributed median observation time of 1.5 (IQR, 0.5–3.25) years to the heavy alcohol use group.

Predictors of Fibrosis Progression

Thirty percent (n = 182) of women without significant fibrosis at cohort entry developed cirrhosis (FIB-4 >3.25) in WIHS follow-up. Factors associated with higher rates of fibrosis progression on multivariable analysis included older age (0.17 FIB-4 units/year when age is >55 years vs –0.05 units/year when age is <40 years, difference of 0.22 [95% CI, .10–.34] units/year; $P < .001$) and HIV viral load (0.05 [95% CI, .02–.08] FIB-4 units/year faster progression for each 1 log increase in HIV viral load; $P < .001$) (Table 4). Compared to African Americans, Hispanic (0.25 [95% CI, .12–.38] FIB-4 units/year; $P < .001$) and white (0.17 [95% CI, .03–.31] FIB-4 units/year; $P = .02$) race/ethnicity were associated with faster fibrosis progression. Light or moderate alcohol use was not associated with faster rates of fibrosis progression as compared to periods with no consumption. Heavy alcohol use (>7 drinks per week) was suggestive of an increased rate of fibrosis progression (0.16 more FIB-4 units/

Table 3. Median Drinks in Women's Interagency HIV Study Follow-up[a] by Entry Alcohol Use Group

		Average No. of Drinks/Week During Study Follow-up	
Baseline No. of drinks per week	No. (%)	Median	(IQR)
0	316 (46.2)	0.00	(0.00–0.62)
1–3	184 (26.9)	0.85	(0.33–2.34)
4–7	49 (7.2)	3.00	(1.50–5.50)
8–14	46 (6.7)	5.55	(1.91–9.95)
>14	89 (13.0)	13.68	(8.29–26.00)
Total cohort	686	0.83	(0.02–4.22)

Abbreviation: IQR, interquartile range.

[a]Observation time (person-years [PY]) by alcohol use group (drinks per week): no alcohol, 3358 PY; 1–3 drinks, 1220 PY; 4–7 drinks, 353 PY; and ≥8 drinks, 690 PY.

Table 4. Factors Associated With Fibrosis Progression[a] in Women's Interagency HIV Study Follow-up

Variable	Estimated Average Rate of FIB-4 Progression, Units per Year (95% CI)	*P* Value
Within age range		
<40 y	–0.05 (–.18 to .07)	.41
40–45 inclusive y	0.09 (–.03 to .20)	.13
>45–50 y	0.07 (–.04 to .18)	.20
>50–55 y	0.13 (.02–.23)	**.02**
>55 y	0.17 (.05–.29)	**.007**
Race/ethnicity[b]		
Hispanic	0.25 (.12–.38)	**<.001**
White	0.17 (.03–.31)	**.02**
Log_{10} HIV viral load (per 1 log increase)	0.05 (.02–.08)	**.001**
Light alcohol use (1–3 drinks/week)[c]	0.004 (–.11 to .12)	.95
Moderate alcohol use (4–7 drinks/week)[c]	0.006 (–.18 to .19)	.95
Heavy alcohol use (>7 drinks/week)[c]	0.16 (–.03 to .34)	.09
8–14 drinks/week	0.04 (–.19 to .28)	.72
Heavier alcohol use (>14 drinks/week)[c]	0.25 (.01–.49)	**.04**

P values <.05 are denoted in bold.

Abbreviations: CI, confidence interval; FIB-4, Fibrosis-4 Index for Liver Fibrosis; HIV, human immunodeficiency virus.

[a]As measured by increase in FIB-4 units per year.

[b]Compared to African-American.

[c]Compared to abstinent.

year [95% CI, –.027 to .344]; $P = .09$) after controlling for age, race/ethnicity, and viral load. When heavy use was subcategorized, heavier alcohol use, defined as >14 drinks per week, was associated with more fibrosis progression on multivariable analysis (0.25 FIB-4 units/year [95% CI, .01–.49]; $P = .04$) whereas 8–14 drinks per week did not show accelerated fibrosis progression (0.04 more FIB-4 units/year [95% CI, –.19 to .28]; $P = .72$) (Table 4). Results were similar when fibrosis progression was evaluated with APRI instead of FIB-4 (data not shown).

DISCUSSION

Heavy alcohol use has clearly been shown to negatively impact health, accounting for 5.9% of all global deaths, and worsening >200 diseases including liver disease [23]. As such, many countries have guidelines for maximum daily/weekly alcohol consumption [17]. Even within the general population, there is no consensus regarding "safe" limits for alcohol. Further ambiguity exists regarding the safety of modest alcohol use in patients with established liver disease from disorders other than alcohol, including chronic HCV infection. National Health and Nutrition Examination Survey data [24] suggest that individuals with CHC have higher rates of alcohol use, with these individuals almost 3 times more likely to have >1 drink per day and 8 times more likely to have ≥3 drinks per day or binge drink (>5 drinks per day). Furthermore, some studies suggest that women are at higher risk for fibrosis progression and death with excessive alcohol use, possibly due to increased bioavailability [25–27]. Although many propose complete abstinence as the only safe option in those with chronic viral hepatitis, this may not be feasible for all patients with CHC, especially those with other comorbid illnesses including mental health and substance use disorders.

In this study, we found that light or moderate alcohol use (≤7 drinks per week) was associated with little change in fibrosis progression rate as measured by FIB-4 in long-term follow-up of HIV/HCV-coinfected women. Women with light or moderate alcohol use in follow-up had similar fibrosis progression rates as women abstinent from alcohol throughout the duration of follow-up. Conversely, women with heavy alcohol use (>7 drinks per week) showed trends toward greater fibrosis progression, compared with abstinent women, primarily driven by periods with >14 drinks per week. In addition to alcohol, fibrosis progression was also associated with Hispanic and white race/ethnicity (as compared to African American), older age, and higher HIV viral load [28–30]. We have previously shown that African American race is associated with decreased fibrosis progression and liver-related deaths in WIHS HIV/HCV-coinfected women [31]. Of interest, despite WIHS research clinicians recommending limiting or avoiding alcohol at semiannual visits, most women who consumed alcohol at WIHS entry continued to have periods of alcohol use in follow-up. This suggests that despite being enrolled in a long-term observational cohort study, patients did not change their drinking behaviors, limiting any potential bias in changing behaviors due to participation in a research study.

The impact of nonheavy alcohol use on fibrosis progression in CHC is not well described, especially in women. Definitions for nonheavy use fluctuate widely from study to study [8, 32, 33], and most studies do not employ sex-specific cutoffs. Many women were misclassified as moderate alcohol users when they should have been classified as being heavy alcohol users on the basis of guidelines for nonhazardous drinking in women without underlying liver disease. Not surprisingly, study conclusions vary, with some showing no impact of light alcohol use on fibrosis progression [8] and other suggesting accelerated fibrosis with alcohol use.

This is the first study specifically evaluating the impact of moderate alcohol use in HIV/HCV-coinfected women. Additionally, this is one of the few studies evaluating the long-term impact of ongoing nonheavy alcohol exposure on the natural history of CHC. Previous studies of alcohol in patients with HCV included few women, and even fewer women contributing data to heavy alcohol use groups. In this study, >40% of women had periods of heavy use, and almost 80% of women had at least some alcohol consumption during WIHS follow-up. We used conservative, sex-specific alcohol use categories, more reflective of current National Institute on Alcohol Abuse and Alcoholism guidelines [17], for the general population and better representative of "moderate" use. Follow-up time was long in this cohort, which helped us evaluate the long-term consequences of light alcohol use on fibrosis progression.

There are several limitations to this study. Current alcohol use was captured at study entry and in follow-up, but lifetime alcohol exposure was not collected. Abstinence was defined as no alcohol use in the 6 months prior to WIHS entry as well as throughout follow-up. Women categorized as abstinent may have had a prior history of alcohol use. Some of these women may represent "sick abstainers" that have ceased alcohol consumption due to the severity of their liver disease. This may explain the finding that entry fibrosis scores were similar between groups, when one would expect heavy users to have higher fibrosis scores as compared to abstinent patients. Nonetheless, the focus of this study was on fibrosis progression during study follow-up, when remote alcohol use would not be expected to impact current fibrosis progression rates. Moreover, our real-life cohort represents clinical practice where many patients have a history of prior alcohol use, which often cannot be accurately quantified. Alcohol intake was ascertained through self-report; women may have underreported actual usage. Short-term heavy alcohol use can transiently raise AST and FIB-4, and underreporting may lead to higher-than-expected fibrosis progression rates as measured by FIB-4. Although many women contributed data to the heavy use group (>7 drinks per week), considerably

fewer women had periods of heavy use as compared to light use and the time spent in the heavy use category was relatively short (median, 1 year). As such, our estimates are less precise in this group. Nonetheless, heavy alcohol use has clearly been established as predictive of fibrosis progression in other studies, and was not the focus of this analysis. Many women contributed significant data to light and moderate use categories (3358, 1220, 353, and 690 person-years of observation time, respectively). Our results are sufficiently precise, with confidence intervals centered around the null, to provide evidence that that modest alcohol use did not significantly increase rates of fibrosis progression with adequate observation time to reasonably adjust for confounding in our statistical analyses. Finally, FIB-4 is a noninvasive modality for estimating liver fibrosis, but is less accurate than liver biopsy or transient elastography [34–37]. However, it has been validated in patients with HIV/HCV coinfection, as well as specifically in this cohort [19, 20]

CONCLUSIONS

Alcohol use is common in HIV/HCV-coinfected women. Nonetheless, light and moderate alcohol use (≤7 drinks per week) was not shown to substantially increase liver fibrosis progression in this long-term cohort study, whereas heavy alcohol use was associated with accelerated liver damage. Women with HIV/HCV coinfection should be counseled to minimize alcohol consumption, but complete abstinence may not be required to prevent accelerated fibrosis progression.

Notes

Acknowledgments. Data in this manuscript were collected by the WIHS. We thank Eduard Poltavskiy for providing statistical assistance in this project.

Women's Interagency HIV Study. U01-AI-103408 (National Institutes of Health [NIH]); Bronx WIHS (Principal Investigator [PI], Kathryn Anastos), U01-AI-035004; Brooklyn WIHS (PIs, Howard Minkoff and Deborah Gustafson), U01-AI-031834; Chicago WIHS (PIs, Mardge Cohen and Audrey French), U01-AI-034993; Metropolitan Washington WIHS (PIs, Mary Young and Seble Kassaye), U01-AI-034994; Connie Wofsy Women's HIV Study, Northern California (PIs, Ruth Greenblatt, Bradley Aouizerat, and Phyllis Tien), U01-AI-034989; WIHS Data Management and Analysis Center (PIs, Stephen Gange and Elizabeth Golub), U01-AI-042590; Southern California WIHS (PIs, Alexandra Levine and Marek Nowicki), U01-HD-032632 (WIHS I–WIHS IV).

Disclaimer. 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).

Financial support. The WIHS is funded by the National Institute of Allergy and Infectious Diseases (NIAID) (grant numbers U01-AI-103401, U01-AI-103408, U01-AI-35004, U01-AI-31834, U01-AI-34994, U01-AI-103397, U01-AI-103390, U01-AI-34989, and U01-AI-42590), with additional co-funding from the Eunice Kennedy Shriver National Institute of Child Health and Human Development, the National Cancer Institute, the National Institute on Drug Abuse, and the National Institute of Mental Health. Targeted supplemental funding for specific projects is also provided by the National Institute of Dental and Craniofacial Research, the National Institute on Alcohol Abuse and Alcoholism, the National Institute on Deafness and Other Communication Disorders, and the NIH Office of Research on Women's Health. WIHS data collection is also supported by the University of California, San Francisco (UCSF) Clinical and Translational Science Awards (CTSA) (number UL1-TR000004); and Atlanta CTSA (number UL1-TR000454). The study was also supported by the UCSF Liver Center Biostatistics Core, NIH (grant number P30 DK026743) and by the NIAID (grant numbers R21 AI088351[MGP], K24 AI 108516, and R01 AI 087176 to P. C. T., which was administered by the Northern California Institute for Research and Education, and with resources of the Veterans Affairs Medical Center, San Francisco, California).

Potential conflicts of interest. All authors: No reported conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References

1. Benhamou Y, Di Martino V, Bochet M, et al; MultivirC Group. Factors affecting liver fibrosis in human immunodeficiency virus-and hepatitis C virus-coinfected patients: impact of protease inhibitor therapy. Hepatology **2001**; 34:283–7.
2. Martín-Carbonero L, Benhamou Y, Puoti M, et al. Incidence and predictors of severe liver fibrosis in human immunodeficiency virus-infected patients with chronic hepatitis C: a European collaborative study. Clin Infect Dis **2004**; 38:128–33.
3. Martinez-Sierra C, Arizcorreta A, Díaz F, et al. Progression of chronic hepatitis C to liver fibrosis and cirrhosis in patients coinfected with hepatitis C virus and human immunodeficiency virus. Clin Infect Dis **2003**; 36:491–8.
4. Mohsen AH, Easterbrook PJ, Taylor C, et al. Impact of human immunodeficiency virus (HIV) infection on the progression of liver fibrosis in hepatitis C virus infected patients. Gut **2003**; 52:1035–40.
5. Muga R, Sanvisens A, Fuster D, et al. Unhealthy alcohol use, HIV infection and risk of liver fibrosis in drug users with hepatitis C. PLoS One **2012**; 7:e46810.
6. Thomas DL, Seeff LB. Natural history of hepatitis C. Clin Liver Dis **2005**; 9:383–98, vi.
7. Mueller S, Millonig G, Seitz HK. Alcoholic liver disease and hepatitis C: a frequently underestimated combination. World J Gastroenterol **2009**; 15:3462–71.
8. Monto A, Patel K, Bostrom A, et al. Risks of a range of alcohol intake on hepatitis C-related fibrosis. Hepatology **2004**; 39:826–34.
9. Thomas DL, Astemborski J, Rai RM, et al. The natural history of hepatitis C virus infection: host, viral, and environmental factors. JAMA **2000**; 284:450–6.
10. Hézode C, Lonjon I, Roudot-Thoraval F, Pawlotsky JM, Zafrani ES, Dhumeaux D. Impact of moderate alcohol consumption on histological activity and fibrosis in patients with chronic hepatitis C, and specific influence of steatosis: a prospective study. Aliment Pharmacol Ther **2003**; 17:1031–7.
11. Chaudhry AA, Sulkowski MS, Chander G, Moore RD. Hazardous drinking is associated with an elevated aspartate aminotransferase to platelet ratio index in an urban HIV-infected clinical cohort. HIV Med **2009**; 10:133–42.
12. Papatheodoridis GV, Manesis EK, Manolakopoulos S, et al. Is there a meaningful serum hepatitis B virus DNA cutoff level for therapeutic decisions in hepatitis B e antigen-negative chronic hepatitis B virus infection? Hepatology **2008**; 48:1451–9.
13. Cheung O, Sterling RK, Salvatori J, et al. Mild alcohol consumption is not associated with increased fibrosis in patients with chronic hepatitis C. J Clin Gastroenterol **2011**; 45:76–82.
14. Barkan SE, Melnick SL, Preston-Martin S, et al. The Women's Interagency HIV Study. WIHS Collaborative Study Group. Epidemiology **1998**; 9:117–25.
15. Bacon MC, von Wyl V, Alden C, et al. The Women's Interagency HIV Study: an observational cohort brings clinical sciences to the bench. Clin Diagn Lab Immunol **2005**; 12:1013–9.
16. US Department of Health and Human Services. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Available at: http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf. Accessed 25 August 2016.
17. Arnett G. How do the UK's new alcohol guidelines compare with the rest of the world's? Available at: https://www.theguardian.com/news/datablog/2016/jan/08/how-do-the-uks-new-alcohol-guidelines-compare-with-the-rest-of-the-worlds. Accessed 25 August 2016.
18. Wai CT, Greenson JK, Fontana RJ, et al. A simple noninvasive index can predict both significant fibrosis and cirrhosis in patients with chronic hepatitis C. Hepatology **2003**; 38:518–26.
19. Sterling RK, Lissen E, Clumeck N, et al; APRICOT Clinical Investigators. Development of a simple noninvasive index to predict significant fibrosis in patients with HIV/HCV coinfection. Hepatology **2006**; 43:1317–25.
20. Bambha K, Pierce C, Cox C, et al. Assessing mortality in women with hepatitis C virus and HIV using indirect markers of fibrosis. AIDS **2012**; 26:599–607.
21. Vallet-Pichard A, Mallet V, Nalpas B, et al. FIB-4: an inexpensive and accurate marker of fibrosis in HCV infection. Comparison with liver biopsy and fibrotest. Hepatology **2007**; 46:32–6.

22. Tamaki N, Kurosaki M, Tanaka K, et al. Noninvasive estimation of fibrosis progression over time using the FIB-4 index in chronic hepatitis C. J Viral Hepat **2013**; 20:72–6.
23. World Health Organization. Global status report on alcohol and health 2014. Available at: http://www.who.int/substance_abuse/publications/global_alcohol_report/en/. Accessed 4 April 2017.
24. Armstrong GL, Wasley A, Simard EP, McQuillan GM, Kuhnert WL, Alter MJ. The prevalence of hepatitis C virus infection in the United States, 1999 through 2002. Ann Intern Med **2006**; 144:705–14.
25. Ashley MJ, Olin JS, le Riche WH, Kornaczewski A, Schmidt W, Rankin JG. Morbidity in alcoholics. Evidence for accelerated development of physical disease in women. Arch Intern Med **1977**; 137:883–7.
26. Neblett RC, Hutton HE, Lau B, McCaul ME, Moore RD, Chander G. Alcohol consumption among HIV-infected women: impact on time to antiretroviral therapy and survival. Int J Womens Health **2011**; 20:279–86.
27. Frezza M, di Padova C, Pozzato G, Terpin M, Baraona E, Lieber CS. High blood alcohol levels in women. The role of decreased gastric alcohol dehydrogenase activity and first-pass metabolism. N Engl J Med **1990**; 322:95–9.
28. Wiley TE, McCarthy M, Breidi L, McCarthy M, Layden TJ. Impact of alcohol on the histological and clinical progression of hepatitis C infection. Hepatology **1998**; 28:805–9.
29. Crosse K, Umeadi OG, Anania FA, et al. Racial differences in liver inflammation and fibrosis related to chronic hepatitis C. Clin Gastroenterol Hepatol **2004**; 2:463–8.
30. Sterling RK, Stravitz RT, Luketic VA, et al. A comparison of the spectrum of chronic hepatitis C virus between Caucasians and African Americans. Clin Gastroenterol Hepatol **2004**; 2:469–73.
31. Sarkar M, Bacchetti P, Tien P, et al. Racial/ethnic differences in spontaneous HCV clearance in HIV infected and uninfected women. Dig Dis Sci **2013**; 58:1341–8.
32. Lim JK, Tate JP, Fultz SL, et al. Relationship between alcohol use categories and noninvasive markers of advanced hepatic fibrosis in HIV-infected, chronic hepatitis C virus-infected, and uninfected patients. Clin Infect Dis **2014**; 58:1449–58.
33. Ostapowicz G, Watson KJ, Locarnini SA, Desmond PV. Role of alcohol in the progression of liver disease caused by hepatitis C virus infection. Hepatology **1998**; 27:1730–5.
34. Amorim TG, Staub GJ, Lazzarotto C, et al. Validation and comparison of simple noninvasive models for the prediction of liver fibrosis in chronic hepatitis C. Ann Hepatol **2012**; 11:855–61.
35. Resino S, Asensio C, Bellón JM, et al. Diagnostic accuracy of the APRI, FIB-4, and the Forns index for predicting liver fibrosis in HIV/HCV-coinfected patients: a validation study. J Infect **2011**; 63:402–5.
36. Shah AG, Smith PG, Sterling RK. Comparison of FIB-4 and APRI in HIV-HCV coinfected patients with normal and elevated ALT. Dig Dis Sci **2011**; 56:3038–44.
37. Schmid P, Bregenzer A, Huber M, et al; Swiss HIV Cohort Study. Progression of liver fibrosis in HIV/HCV co-infection: a comparison between non-invasive assessment methods and liver biopsy. PLoS One **2015**; 10:e0138838.