

Chronic hepatitis C virus infection and subsequent HIV viral load among women with HIV initiating antiretroviral therapy

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Objectives: One in four persons living with HIV is coinfecting with hepatitis C virus (HCV). Biological and behavioral mechanisms may increase HIV viral load among coinfecting persons. Therefore, we estimated the longitudinal effect of chronic HCV on HIV suppression after ART initiation among women with HIV (WWH).

Design: HIV RNA was measured every 6 months among 441 WWH in the Women's Interagency HIV Study who initiated ART from 2000 to 2015.

Methods: Log-binomial regression models were used to compare the proportion of study visits with detectable HIV RNA between women with and without chronic HCV. Robust sandwich variance estimators accounted for within-person correlation induced by repeated HIV RNA measurements during follow-up. We controlled for confounding and selection bias (because of loss to follow-up and death) using inverse probability-of-exposure-and-censoring weights.

Results: One hundred and fourteen women (25%) had chronic HCV before ART initiation. Overall, the proportion of visits with detectable HIV RNA was similar among women with and without chronic HCV [relative risk (RR) 1.19 (95% CI 0.72, 1.95)]. Six months after ART initiation, the proportion of visits with detectable HIV RNA among women with chronic HCV was 1.88 (95% CI 1.41–2.51) times that among women without HCV, at 2 years, the ratio was 1.60 (95% CI 1.17–2.19), and by 6 years there was no difference (1.03; 95% CI 0.60–1.79).

Conclusion: Chronic HCV may negatively impact early HIV viral response to ART. These findings reaffirm the need to test persons with HIV for HCV infection, and increase engagement in HIV care and access to HCV treatment among persons with HIV/HCV coinfection.

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Introduction

One in four persons living with HIV in the United States is coinfecting with hepatitis C virus (HCV) [1]. Quantifying the effect of HCV on HIV suppression is crucial. HIV suppression improves clinical outcomes and reduces HIV transmission [2,3]. Yet, biological and behavioral mechanisms may increase HIV viral load among people with HIV/HCV-coinfection. Common HIV coinfections, such as tuberculosis and herpes simplex virus, type 2, increase HIV viral replication [4–6]. Ongoing alcohol and drug use and decreased antiretroviral therapy (ART) adherence among coinfecting persons may also result in increased HIV viral load [7,8].

Published studies suggest that persons with HIV/HCV coinfection do not experience increased time to HIV suppression after ART initiation [9–17] but HCV may be associated with earlier failure of HIV viral control [18]. However, there are several limitations in studies quantifying the effect of HCV on HIV suppression after ART is begun. Many studies that found no association between HCV and HIV suppression did not distinguish between persons with chronic HCV (i.e. seropositive with detectable HCV RNA) and those who cleared infection (i.e. seropositive but RNA-negative) [9–14,18]; misclassification of HCV status could result in biased associations. Also, some studies did not account for potential confounding of the relationship between HCV and HIV suppression by alcohol or drug use [11,17].

Evidence regarding the effect of HCV on HIV suppression after ART initiation is especially lacking among women. Women respond differently to ART than men [19–23], often exhibiting more favorable immune responses [21–23] but experiencing greater drug toxicity [20] and more frequent treatment discontinuation [19]. To date, there is only one published study assessing the association between HCV and HIV suppression after ART initiation among women [24]. That study did not find an association between HCV status and HIV suppression, but did not distinguish between women with chronic HCV and women who cleared infection, and follow-up was limited to 1 year [24]. The effect of HCV on HIV viral response to ART among women warrants further investigation.

The objective of this study was to estimate the longitudinal effect of chronic HCV on HIV suppression after ART initiation among women for up to 15 years.

We hypothesized that women with chronic HCV would be more likely to have detectable plasma HIV RNA than women without HCV during the follow-up period.

Methods

Study population

We used data collected by the Women's Interagency HIV Study (WIHS) for this analysis. A full description of the WIHS cohort is provided elsewhere [25,26]. Briefly, the WIHS is a prospective cohort of women living with and at risk for HIV, with follow-up at 6-month intervals. At each visit, interviewer-administered questionnaires capture extensive medical, psychosocial, and drug-use information. ART use is defined as three or more antiviral medications approved by contemporaneous Department of Health and Human Services (DHHS) guidelines [27]. Between 1994 and 2014, 4982 women enrolled in the WIHS across 10 study sites; 3677 (74%) were living with HIV at enrollment and 24 (0.5%) acquired HIV during follow-up.

Women with HIV who initiated ART on or after 1 January 2000, and after they were enrolled in the WIHS, were eligible for the present analyses. Women who initiated ART prior to 2000 were excluded to allow assessment of HIV suppression with relatively modern ART regimens. Of the 640 eligible women, we excluded 100 (16%) who did not have HIV RNA measured prior to ART initiation, 29 (4%) without at least one HIV RNA measurement after initiating ART, and 23 (4%) missing HCV infection status. We also excluded 52 HCV-uninfected women less than 30 years of age at ART initiation. There were no women with chronic HCV who were less than 30 years of age at ART initiation and we did not want to bias our findings by extrapolating to women who did not exist in our data [28]. Therefore, the final study sample included 441 women. Demographic and clinical characteristics were similar between women included and excluded from our study, including the proportions with chronic HCV. However, excluded women were less likely to be black or have liver fibrosis, and more likely to have initiated ART between 2000 and 2005.

Chronic HCV was defined as the presence of HCV antibody and HCV RNA prior to ART initiation. HCV-seropositive women with undetectable HCV RNA were

classified as HCV-uninfected. In the WIHS, women are screened for HCV with enzyme immunoassays at one of the first three study visits after enrollment. Chronic infection is confirmed with HCV RNA among HCV-seropositive women. The average length of time between HCV testing and ART initiation was 6 years among participants and we were concerned that chronic HCV may be misclassified because of spontaneous HCV clearance, antiviral treatment, or incident HCV infections during this time. Therefore, we supplemented HCV results with follow-up HCV test results (available for over 80% of women) and HCV treatment initiation. Eleven women who were HCV-uninfected at enrollment had evidence of HCV antibodies and RNA prior to ART initiation and were classified as HCV-infected. Two women classified as HCV-infected at enrollment were reclassified as HCV-uninfected because of subsequent negative RNA tests. Lastly, four women reported HCV treatment prior to ART initiation. Three of the four women had HCV RNA testing performed after ART initiation and were still HCV-infected; we did not change their status. The fourth woman had undetectable HCV RNA before ART initiation and was reclassified as HCV-uninfected.

Our outcome of interest was detectable HIV RNA at each study visit after ART initiation. We defined detectable HIV RNA as >80 copies/ml to accommodate assays used during the study period, which had lower limits of detection ranging from 20 to 80 copies/ml.

Covariate assessment

Baseline covariates, measured at the last study visit prior to ART initiation, included age, race, year of ART initiation, history of injection drug use, CD4⁺ cell count, HIV RNA, and liver fibrosis. Age was included as a continuous variable using restricted quadratic splines with three knots placed at the 5th, 50th, and 95th percentiles [29]. Race was dichotomized as black or non-black and history of injection drug use was included as yes/no. Because our sample size was less than 500, we categorized several continuous variables: year of ART initiation, baseline CD4⁺ cell count, and baseline HIV RNA. Year of ART initiation was considered a proxy measure for ART regimen and categorized as 2000–2005, 2006–2010, and 2011–2015. Baseline CD4⁺ cell counts were grouped as less than 200, 200–499, at least 500 cells/ μ l, and HIV RNA was categorized as 4000 or less, 4001–10 000, and more than 10 000 copies/ml. Liver fibrosis was assessed by the FIB-4 index; scores were dichotomized as more than 1.45 and 1.45 or less to differentiate women with and without significant fibrosis [30–32].

We considered two time-varying covariates as predictors of loss to follow-up or death: alcohol and drug use. We categorized alcohol use as 0, 1–7, and more than 7 drinks per week since prior study visit. Women were categorized as current drug users if they reported using any illicit or recreational drugs since their last study visit. Time-varying

covariates were missing for 4% of follow-up visits; these were replaced with values carried forward from the previous visit.

Statistical methods

We used a log-binomial regression model to estimate the proportion of study visits with detectable HIV RNA during follow-up, and compared women with and without chronic HCV. Robust sandwich variance estimators were used to account for within-person correlation induced by repeated HIV RNA measurements over the follow-up period. We also planned a priori to include a product term between HCV status and time since ART initiation in a second log-binomial model. Therefore, we could assess whether the relationship between chronic HCV and detectable HIV RNA was a function of duration of ART.

Women were followed from the first study visit after ART use until the last visit prior to 30 September 2015, the last possible date on which data were available. Women were right-censored at the earliest occurrence of loss to follow-up, death, or last visit prior to 30 September 2015. Loss to follow-up was defined as two consecutively missed study visits. We also censored women with chronic HCV who initiated HCV treatment and HCV-uninfected women who had evidence of HCV antibody and HCV RNA during follow-up.

To control for confounding, we used time-fixed inverse probability-of-exposure weights [33,34]. These weights are fully described in the Supplemental Digital Content; <http://links.lww.com/QAD/B221>. Logistic regression was used to estimate the weights and included age, race, year of ART initiation, FIB-4, baseline HIV RNA, baseline CD4⁺ cell count, and history of injection drug use.

We created time-varying inverse probability-of-censoring weights to account for right-censoring because of death or loss to follow-up [35,36] (see Supplemental Digital Content; <http://links.lww.com/QAD/B221>). Pooled logistic regression models were used to estimate the censoring weights. The models included time, HCV status, race, age, and time-varying alcohol and drug use. Time was measured as the number of semiannual study visits since ART initiation and included in the models using restricted quadratic splines with knots at the 5th, 50th, and 95th percentiles [29].

Robust variance estimates tend to overestimate the variability of inverse probability-weighted estimators. We calculated 95% confidence intervals (CIs) for the weighted ratio measures using a nonparametric bootstrap with 200 resamples with replacement.

Sensitivity analyses

We conducted several sensitivity analyses to assess the robustness of our findings and reduce possible bias in our

estimated effects of chronic HCV on HIV RNA after ART initiation. In the first, we excluded women who reported single or dual antiretroviral use prior to ART initiation. For the second, we only included women who self-reported more than 95% adherence to ART during the first 6 months after initiation. This analysis allowed us to determine if the estimated effect of chronic HCV on HIV RNA could be explained by poorer ART adherence among women with chronic HCV. In the third sensitivity analysis, we reclassified women who were HCV-seropositive with undetectable HCV RNA to HCV-infected, as these women may share some of the same behaviors that lead to poorer control of HIV.

All data analyses were conducted with SAS version 9.4 (SAS Institute Inc., Cary, North Carolina, USA). The analysis was approved by the University of North Carolina at Chapel Hill Institutional Review Board.

Results

Of 441 women, 114 (26%) had chronic HCV before ART initiation (Table 1). The median age was 47 years

[interquartile range (IQR) 42–51] among women with chronic HCV and 41 years (IQR 36–47) among women without HCV. Two-thirds (67%) of all women were black and approximately one-third (34%) had less than a high school education. Three-quarters of women had previously used illicit drugs (75%) and the majority of women with chronic HCV (87%) had previously injected drugs. Nine percentage of women with chronic HCV were actively injecting drugs at baseline and 1% of women without HCV were.

Overall, half (55%) of women initiated ART from 2000 to 2005 and 22% initiated ART from 2006 to 2010. A greater proportion of women with chronic HCV initiated ART from 2000 to 2005 (70 versus 49% among HCV-uninfected). At baseline, the median CD4⁺ cell count was 303 cells/ μ l (IQR 188–440) and median HIV RNA was 4.20 log₁₀ copies/ml (IQR 3.27–4.79). These baseline measures did not differ between women with and without chronic HCV. HCV genotypes were available for 18 women with chronic HCV; 9 of these women (50%) were genotype 1a.

The median follow-up was 11 study visits or 5.6 years. Two hundred and twenty-nine (52%) women completed follow-

Table 1. Baseline characteristics of 441 HIV-infected women initiating antiretroviral therapy by hepatitis C virus status, Women's Interagency HIV Study, January 2000–September 2015.

	HCV+ (n = 114)		HCV- (n = 327)		Total (n = 441)	
	Median or n	IQR ^a or %	Median or n	IQR ^a or %	Median or n	IQR ^a or %
Age at ART initiation (years)	47	42, 51	41	36, 47	43	37, 49
Race/ethnicity						
White, non-Hispanic	18	16%	36	11%	54	12%
Black, non-Hispanic	77	68%	217	66%	294	67%
Other ^a	19	17%	74	23%	93	21%
Education ^b						
Less than high school	48	42%	103	32%	151	34%
Graduated high school	29	25%	109	33%	138	31%
Some college	37	32%	114	35%	151	34%
Annual household income <\$12,000	85	77%	163	51%	248	56%
Alcohol use ^c						
0 drinks per week	60	53%	150	46%	210	48%
One to seven drinks per week	32	28%	135	41%	167	38%
More than seven drinks per week	22	19%	42	13%	64	15%
Ever used noninjection drugs	109	96%	221	68%	330	75%
Ever injected drugs	99	87%	35	11%	134	30%
Chronic active HBV ^d	1	<1%	8	2%	9	2%
Year of ART initiation ^e						
2000–2005	80	70%	161	49%	241	55%
2006–2010	28	25%	70	21%	98	22%
2011–2015	6	5%	96	30%	102	23%
Single or dual antiretroviral use ^f	57	50%	92	28%	149	34%
CD4 ⁺ cell count at baseline	287.5	172, 392	313	194, 454	303	188, 440
HIV viral load at baseline ^g	4.16	3.11, 4.84	4.23	3.34, 4.77	4.20	3.27, 4.79
FIB-4 greater than 1.45	91	80%	70	21%	161	37%

ART, anti-retroviral therapy; HBV, hepatitis B virus; HCV, hepatitis C virus; IQR, inter-quartile range.

^a Other race/ethnicity includes Hispanic, Native American/Alaskan Native, Asian/Pacific Islander, and races/ethnicities categorized as other.

^b Education categories do not add to the total because of missing information.

^c Self-reported alcohol use within the last 6 months.

^d Chronic, active hepatitis B infection is defined as positive hepatitis B core antibody and positive hepatitis B surface antigen, and measured during

one of the first three study visits after enrollment.

^e ART is defined as use of three or more antiretroviral medications approved by contemporaneous DHHS guidelines.

^f Self-reported use of single or dual antiretroviral prior to ART initiation.

^g HIV viral load is reported in log₁₀ copies/ml.

Table 2. Estimated associations between hepatitis C virus infection and detectable HIV viral load among 441 women enrolled in the Women's Interagency HIV Study, January 2000–September 2015.

	HCV+ (<i>n</i> = 114)	HCV- (<i>n</i> = 327)	Overall (<i>n</i> = 441)
Total study visits	1509	4014	5523
Visits with detectable HIV viral load	708	1356	2064
Proportion of visits with detectable HIV viral load (95% CI)	0.47 (0.44, 0.49)	0.34 (0.32, 0.35)	0.37 (0.36, 0.38)
Crude risk ratio (95% CI)	1.39 (1.15, 1.68)	1	–
Weighted risk ratio (95% CI) ^{a,b}	1.19 (0.72, 1.95)	1	–

CI, confidence interval; HCV, hepatitis C virus

^aWeights account for the following set of time-fixed and time-varying covariates: age at ART initiation, race, history of injection drug use, year of ART initiation, CD4⁺ cell count at ART initiation, HIV viral load at ART initiation, FIB-4 at ART initiation, current alcohol use, current drug use, and time.

^b95% CI was estimated with a nonparametric bootstrap using 200 samples with replacement.

up alive, 86 (20%) died during follow-up, and 110 (25%) were lost to follow-up. Thirteen women with chronic HCV were censored because of HCV treatment initiation and three HCV-uninfected women were censored because of evidence of HCV acquisition during follow-up.

Table 2 depicts the crude and weighted risk ratios for detectable HIV RNA comparing women with and without chronic HCV. There were 5523 total study visits and HIV RNA was detected at 2064 visits (37%). The percentage of study visits with detectable HIV RNA was higher among women with chronic HCV (47 versus 34%). After weighting, the proportion of study visits with detectable HIV RNA among women with chronic HCV

was 1.19 (95% CI 0.72–1.95) times that of HCV-uninfected women.

The results of the log-binomial model with a product term between HCV status and time since ART initiation are depicted in Fig. 1. Approximately 6 months after ART initiation, the proportion of visits with detectable HIV RNA among women with chronic HCV was 1.88 (95% CI 1.41–2.51) times that among women without HCV, at 2 years the ratio was 1.60 (95% CI 1.17–2.18), and by 6 years, there was essentially no difference (1.03; 95% CI 0.60–1.79). The *P* value for a test of linear trend was 0.02, which indicates the observed trend of risk ratios by time was unlikely because of chance.

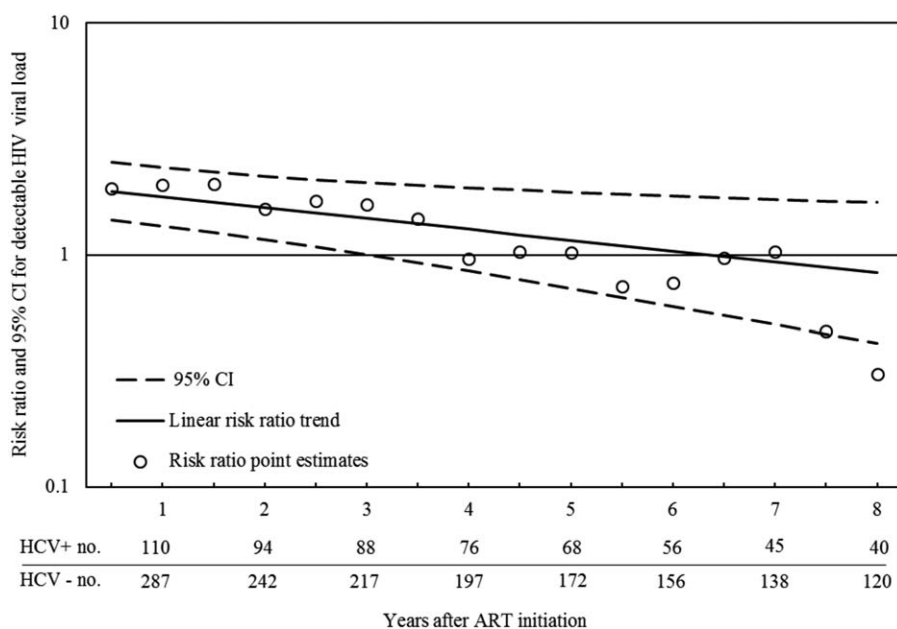


Fig. 1. Estimated association between chronic hepatitis C virus infection and detectable HIV RNA at each 0.5-year interval following antiretroviral therapy initiation among 441 HIV-infected women enrolled in the Women's Interagency HIV Study, January 2000–September 2015. The open circles represent the risk ratio point estimates. The solid black line represents the linear trend for the risk ratio point estimates and the dotted lines represent the 95% CI for the trend line. This CI was estimated with a nonparametric bootstrap using 200 samples with replacement. The line at 1 represents the null effect for a ratio measure. CI, confidence interval.

There were 149 women (34%) who reported single or dual antiretroviral use prior to initiation of an effective ART regimen. After excluding these women, the association between chronic HCV and HIV RNA after ART initiation was similar to the main analysis. The proportion of visits with detectable HIV RNA among women with chronic HCV was 1.46 times that among HCV-uninfected women (95% CI 0.74, –2.93). A similar trend in ratio measures over time was also observed ($P=0.04$).

We also observed similar results when we limited our sample to only those women who reported taking their ART medications as prescribed during the first 6 months of ART ($n=359$). The proportion of visits with detectable HIV RNA among women with chronic HCV was 1.05 (95% CI 0.62–1.78) times that among HCV-uninfected women. There was a similar trend in risk ratios over time as well ($P=0.05$); at 6 months the ratio was 1.68 (95% CI 1.14–2.44), at 3 years the ratio was 1.43 (95% CI 0.98–2.07), and by 6 years, there was no difference (0.95; 95% CI 0.53–1.69).

Lastly, we observed similar findings when we reclassified 33 women who were HCV antibody-positive with undetectable HCV RNA as HCV-infected. The proportion of visits with detectable HIV RNA among HIV/HCV-coinfected women was 1.29 times that among HIV-monoinfected women (95% CI 0.84–1.96). A similar trend in ratio measures over time was also observed ($P=0.07$).

Discussion

In this longitudinal study of women with HIV initiating ART, the proportion of study visits with detectable HIV RNA was similar among women with and without chronic HCV. However, women with chronic HCV were more likely to have detectable HIV RNA up to 2 years after ART initiation than women without HCV.

Behavioral and biological mechanisms may explain the increased risk for detectable HIV RNA among women with chronic HCV during the first few years after ART initiation. Women with HCV may have poorer ART adherence and use alcohol and drugs more frequently [7,8]. When we repeated our analysis among women reporting more than 95% adherence during the first 6 months after ART initiation, results were similar to the main analysis. We controlled for potential confounding of the relationship between chronic HCV and HIV RNA by history of injection drug use, and included time-varying drug and alcohol use in the models used to estimate inverse probability-of-censoring weights. Thus, the observed association between chronic HCV and detectable HIV RNA is not fully explained by behavioral

differences between women with and without chronic HCV. Persons living with HIV/HCV coinfection experience greater immune system dysregulation [37,38] and HCV has also been shown to replicate in extrahepatic lymphoid cells [39–41]. Therefore, biological interaction between HIV and HCV is possible, and could decrease ART effectiveness during the first few years after uptake.

Most of the previous studies assessing the effect of HCV on HIV treatment outcomes did not find that HCV negatively impacts HIV suppression [9–17]. Yet, a recent study by Hua *et al.* [18] found that HCV was associated with earlier failure of HIV control, which was defined as two consecutive detectable HIV RNA measurements 16 or more weeks after ART initiation. In that study, significantly more HIV/HCV-coinfected patients experienced viral failure by 48 weeks after ART initiation [18]. These results also provide evidence that HCV may negatively impact early HIV viral response to ART.

There are several key differences between the present study and previous research assessing the effect of HCV on HIV suppression after ART. Previous studies compared time to HIV suppression after ART initiation among persons with and without HCV [9–17]. WIHS data are interval censored at 6-month time periods, and the median time to first suppressed viral load in our analytic sample was approximately 6 months. Therefore, we could not replicate these analyses with our data. However, other studies have not assessed the association between HCV and HIV RNA using repeated measures of HIV RNA during follow-up, and our study provides a unique view of the longitudinal effect of chronic HCV on HIV RNA.

We defined HCV infection with confirmation of detectable HCV RNA. Approximately 15–25% of persons spontaneously clear their HCV infection (i.e. HCV RNA becomes undetectable), but remain HCV antibody-positive [42]. Previous studies often defined HCV by HCV antibody status only [9–14,18] and were not estimating the effect of chronic HCV infection on HIV RNA.

An additional distinction between previous research and the present study is that our analysis included only women. Women experience more frequent ART regimen discontinuation [19] and drug toxicity [20] than men. Despite this, only one previous study assessed the effect of HCV on HIV viral response after ART initiation among women. In unadjusted analyses, Marcus *et al.* [24] found that the cumulative incidence of HIV suppression 1 year after ART initiation was lower among HIV/HCV-coinfected women than among HIV-monoinfected women. After adjustment for confounding, there was no difference in HIV viral response by HCV status [24] but follow-up was limited to 1 year after ART initiation [22].

Our study has several limitations. We used observational data and the possibility of uncontrolled confounding remains. HCV may also potentiate hepatotoxicity after ART initiation [43,44], which could lead to more frequent regimen changes and interruptions in therapy among HIV/HCV-coinfected persons [45,46]. Although we controlled for clinical characteristics at ART initiation and year of ART initiation (as a proxy measure for ART regimen), we did not assess the frequency of ART regimen changes because of toxicity in our cohort. Drug toxicities and regimen changes could contribute to the increased risk for detectable HIV RNA among women with chronic HCV in our cohort.

Approximately 25% of our sample were lost to follow-up and 20% died. Our estimated measures of effect would be biased if there is differential loss to follow-up or death among women with chronic HCV or among women with detectable HIV RNA [47,48]. To reduce selection bias, we created inverse probability-of-censoring weights. If the models used to construct the censoring weights are correctly specified and the observed variables fully explain selection that is associated with the exposure and outcome, those who were censored would be exchangeable with those who remained under study in our weighted sample, and bias would be averted [49]. Nevertheless, the extent to which we achieved exchangeability is not testable in observational data.

There was also an average of 6 years between baseline HCV testing and ART initiation. This could result in poorer clinical outcomes among women with chronic HCV because of worsening liver function [37,38,50–53] and misclassification of HCV status. We included the FIB-4 index in our exposure weights to control for confounding by declining liver function among women with chronic HCV. We also minimized HCV misclassification by supplementing HCV tests at enrollment with follow-up results and self-reported HCV treatment initiation. Over 80% of women in our analytic sample had at least one follow-up result available. Only 1% of women who were HCV-infected at enrollment cleared their infection prior to ART initiation and were reclassified to HCV-uninfected, and 2% of women who were HCV-uninfected at enrollment were reclassified to HCV-coinfected. We were not able to account for women classified as HCV-infected at ART initiation who cleared HCV infection during follow-up.

The observed associations between chronic HCV and HIV RNA may not generalize to all women with HIV on ART in the United States. Our target population was women who initiated ART after they enrolled in the WIHS and after year 2000. We used these criteria in order to observe HIV RNA results at regular intervals, provide minimal missing information on confounders, and to assess the effect of chronic HCV on viral response

to relatively modern ART regimens. These criteria resulted in fewer than 500 women who were eligible for our study. Although women in the WIHS are representative of the HIV epidemic among women in the United States with respect to demographic characteristics [26], we cannot guarantee that the distribution of effect measure modifiers, like ART adherence, are similar. Therefore, the ability to generalize our findings to all women with HIV in the United States is limited [54].

Conclusion

The results of this study provide a unique view of the longitudinal effects of chronic HCV on HIV viral response to ART among women. Overall, the proportion of visits with detectable HIV RNA was similar between women with and without chronic HCV. However, women with chronic HCV were more likely to have detectable HIV RNA up to 2 years after ART initiation than women without HCV. This finding suggests that chronic HCV may negatively impact early HIV viral response to ART. Despite new treatment options for persons with HCV, 45–85% of those with HCV are unaware of their infection [55–58] and considerable barriers to HCV treatment remain [59,60]. Thus, our findings reaffirm the need to test persons with HIV for HCV infection, and increase engagement in HIV care and access to HCV treatment among persons with HIV/HCV coinfection.

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Conflicts of interest

There are no conflicts of interest.

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