CHRONIC HEPATITIS C AND HIV TREATMENT OUTCOMES AMONG WOMEN WHO INITIATE ANTIRETROVIRAL THERAPY

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ABSTRACT

Sarah J. Willis: Chronic hepatitis C and HIV treatment outcomes among women who initiate antiretroviral therapy
(Under the direction of Stephen R. Cole)

One in four persons living with HIV is coinfected with chronic hepatitis C virus (HCV). Biological interaction between HIV and HCV, and behaviors such as decreased antiretroviral therapy (ART) adherence and drug use, may negatively impact HIV treatment outcomes among persons with HIV/HCV-coinfection. Yet, previous research assessing the effect of HCV on HIV treatment outcomes produced inconsistent results. Evidence regarding the effect of HCV on HIV treatment outcomes is also lacking among women. Therefore, we estimated the effect of chronic HCV on HIV suppression and the effects of chronic HCV and depression on AIDS diagnosis or death among women who initiated ART while enrolled in the Women's Interagency HIV Study (WIHS).

We estimated the effect of chronic HCV on HIV suppression by comparing the proportion of study visits with detectable HIV RNA between women with and without chronic HCV. Among 441 women who initiated ART in 2000 or after, 114 (26%) had chronic HCV. Overall, the risk of having a visit with detectable HIV RNA was similar among women with and without chronic HCV (risk ratio (RR) 1.19; 95% confidence interval (CI) 0.72, 1.95)). However, 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 chronic HCV, at two years the ratio was 1.60 (95% CI 1.17, 2.19), and by six years there was no difference (RR 1.03; 95% CI 0.60, 1.79).

When assessing the effects of chronic HCV and depression on AIDS diagnosis or death among 957 women who initiated ART between 1995 and 2015, 200 women (21%) had chronic HCV. The incidence rates of AIDS diagnosis or death were 7.12 and 3.80 per 100 person-years for women with and without chronic HCV, respectively. Compared to women without chronic HCV and depression, the hazard ratio (HR) for AIDS diagnosis or death was 2.19 (95% CI 1.56, 3.07) for HCV-uninfected women with depression, 1.65 (95% CI 0.90, 3.01) for HCV-infected women without depression, and 3.02 (95% CI 1.49, 6.15) for HCV-infected women with depression.

To Joseph. Thank you for your patience and love.

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AIDS	acquired immune deficiency syndrome
aHR	adjusted hazard ratio
ALT	alanine aminotransferase
ART	antiretroviral therapy
AST	aspartate aminotransferase
CES-D	Centers for Epidemiologic Studies Depression Scale
CI	confidence interval
DAG	directed acyclic graph
HR	hazard ratio
HCV	hepatitis C virus
HIV	human immunodeficiency virus
IC	interaction contrast
IQR	interquartile range
IRR	incidence rate ratio
NNRTI	non-nucleoside reverse-transcriptase inhibitor
NRTI	nucleoside reverse-transcriptase inhibitor
PI	protease inhibitor
RNA	ribonucleic acid
RR	risk ratio
SD	standard deviation
WIHS	Women's Interagency HIV Study
US	United States

U/L	units per liter

CHAPTER 1: SPECIFIC AIMS

One in four people living with HIV in the United States (US) is coinfected with HCV.[1] HCV may adversely affect HIV disease in several ways after ART initiation, including diminished viral and immune responses, and accelerated progression to AIDS or death. Previous research assessing the effect of HCV on these HIV treatment outcomes produced inconsistent results. For example, most studies found that persons with HIV/HCV-coinfection do not experience increased time to HIV suppression [2-8] but HCV may be associated with earlier failure of HIV control.[9] Similarly, several studies have shown that HCV is associated with impaired CD4 cell recovery after ART initiation,[2-7,9] while other studies found no association.[8,10-12]

There are several limitations in studies quantifying the effect of HCV on HIV treatment outcomes that may explain inconsistent findings. Some of these studies did not distinguish between persons with chronic HCV (i.e., persons with detectable HCV RNA and antibody) and those who were seropositive only.[2,3,5,6,8-11] Misclassification of HCV status could result in biased measures of effect. In addition, some studies did not adjust for injection drug use and alcohol use in multivariable models.[6,8,10,11] Therefore, residual confounding due to no adjustment or incomplete adjustment of important confounders may exist.

The impact of HCV on HIV treatment outcomes has not been extensively explored among women. Women respond differently to ART than men,[13-17] often exhibiting more favorable immune responses [15-17] but experiencing greater drug toxicity [14] and more frequent treatment discontinuation.[13] However, only two studies have assessed the effect of HCV on HIV treatment outcomes among women.[4,12] Marcus *et al.* found that HIV/HCV-coinfected women

experienced increased all-cause mortality and slower CD4 cell recovery after ART initiation.[4] Therefore, women may be particularly vulnerable to adverse effects of HCV on HIV treatment outcomes.

Lastly, studies examining the effect of HCV on progression to AIDS or mortality have not considered the role of depression. Depression can decrease ART adherence [18-20] and accelerate progression to AIDS and mortality among HIV-monoinfected patients.[21-26] Depression is common among HIV/HCV-coinfected patients [27,28] and may, in fact, be more severe among HIV/HCV-coinfected patients than among HIV-monoinfected patients.[29,30] Therefore depression is an important and yet unexplored factor to consider in the effect of HCV on progression to AIDS or mortality.

The goal of this dissertation was to investigate whether chronic HCV negatively impacts HIV treatment outcomes among women.

1.1 Specific Aim 1

Our first aim was to estimate the longitudinal effect of chronic HCV on HIV suppression after ART initiation among women with HIV. We hypothesized that women with chronic HCV would be more likely to have detectable plasma HIV RNA levels throughout a fifteen-year follow-up period than women without chronic HCV would be.

1.2 Specific Aim 2

Our second aim was to estimate the effect of chronic HCV on progression to AIDS or all-cause mortality among women with HIV who initiate ART. We also sought to examine the joint effects of chronic HCV and depression on progression to AIDS or all-cause mortality among women with HIV who initiate ART. We hypothesized that when compared to women without chronic HCV, women with chronic HCV will experience reduced time to AIDS diagnosis or

death. In addition, reduced time to AIDS diagnosis or death will be greatest among women with chronic HCV who also experience depression.

CHAPTER 2: BACKGROUND

2.1 HIV infection in the US

By year-end 2014, 955,081 persons, or 0.3% of persons in the US were living with diagnosed HIV infection.[31] The number of newly diagnosed HIV infections is currently declining in the US. Between 2010 and 2014, the number of newly diagnosed HIV infections decreased from 43,978 in 2010 to 39,513 in 2014.[31] Survival after HIV diagnosis has also increased. Thirty-six month survival after diagnosis increased from 91% in 2006 to 94% in 2011.[31]

The improvements in the HIV epidemic are due, in large part, to effective HIV treatment. ART, which includes three or more therapies approved by the US Department of Health and Human Services, wer first used in the late 1990s. Adherence to these regimens increases survival and reduces HIV transmission. The HIV-CAUSAL Collaboration, which brings together 12 prospective cohort studies and data on over 62,000 persons living with HIV across Europe and the US, observed a 52% relative reduction in mortality (HR 0.48; 95% CI 0.41, 0.57) among patients who initiated ART, when compared to patients who did not.[32] ART use has also been shown to decrease transmission to sexual partners. In a large randomized controlled trial of HIV serodiscordant couples, a 96% reduction in HIV transmission to HIV-uninfected partners was observed among couples when the HIV-infected partner was using ART.[33]

2.2 HIV and HCV co-infection

One in four persons living with HIV in the US is coinfected with HCV,[1] and the prevalence of HCV among HIV-infected injection drug users is estimated to be between 50-90%.[34,35] Persons living with HIV/HCV-coinfection experience greater immune system

dysregulation and enhanced HCV replication leading to higher HCV viral loads.[36,37] HIV infection adversely impacts HCV disease progression among HIV/HCV-coinfected persons as well.[38-40] The rate at which HIV/HCV-coinfected patients progress to liver fibrosis is three times as high as the rate among HCV-monoinfected patients [41] and the time from HCV infection until cirrhosis is significantly shorter.[40]

The effects of HCV infection on HIV treatment outcomes are unclear. It is hypothesized that HCV may influence HIV disease in several ways including reduced HIV suppression [2-9] and delayed immune responses after ART initiation,[2-13] and accelerated progression to AIDS and mortality.[2-11, 42]

2.3 HCV and HIV suppression

Quantifying the effect of HCV on HIV suppression is crucial. HIV suppression improves clinical outcomes and reduces HIV transmission. However, biological and behavioral mechanisms may increase HIV viral load among people with HIV/HCV-coinfection. Other common HIV coinfections, such as tuberculosis and herpes simplex virus type 2, increase HIV viral replication.[43-45] Ongoing alcohol and drug use and decreased ART adherence among coinfected persons may also result in increased HIV viral load.[46,47]

Published studies suggest that persons with HIV/HCV-coinfection do not experience increased time to HIV suppression after ART initiation.[2-8] Yet, a recent study by Hua *et al*. 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.[9] In that study, significantly more HIV/HCV-coinfected patients experienced viral failure by 48 weeks after ART initiation than HIV-monoinfected patients.[9]

Importantly, studies assessing the relationship between HCV and HIV suppression have

not distinguished between persons with active chronic HCV (i.e., persons with detectable HCV RNA and antibody) and those who had cleared infection (i.e., persons who were HCV seropositive only).[2,3,5,6,8,9] In addition, some studies did not adjust for injection drug use and alcohol use in multivariable models.[6,8] Therefore, residual confounding due to no adjustment or incomplete adjustment of important confounders may exist. Many studies also had limited follow-up.[2,5,8]

2.4 HCV and CD4 cell response to ART

CD4 cell counts remain the strongest predictor of subsequent HIV disease progression, and an adequate CD4 cell response to ART is defined by an increase of 50 to 150 cells/mm^3 during the first year of treatment.[48] In subsequent years patients will experience increases of 50 to 150 cells/mm^3 until a steady state is reached.[48] HCV may negatively affect CD4 cell response to ART because HCV has been shown to replicate in cells outside of the liver and is associated with CD4 cell apoptosis.[49,50] Consequently, several studies do suggest that HCV coinfection is associated with smaller CD4 cell recovery after ART initiation.[2-7,9] A meta-analysis in 2005 found that the mean CD4 cell count increase among HIV/HCV-coinfected patients was 33 cells/mm^3 less than in HIV-monoinfected patients.[51] However, several studies have found no differences in CD4 cell count changes after ART initiation between HIV/HCV-coinfected patients and HIV-monoinfected patients,[8,10-12] or that the CD4 cell count differences decrease over time.[52,53] Limitations in studies quantifying the effect of HCV on CD4 cell response after ART initiation may explain inconsistent findings. Again, most studies did not distinguish between persons with active chronic HCV and persons that had HCV antibodies only. [2,3,5,6,8-11] Residual confounding due to no adjustment or incomplete adjustment for important confounders, including alcohol use and drug use, also may exist.[6,8,10,11]

2.5 HCV, depression, and HIV disease progression

Several studies have demonstrated that HCV has a harmful effect on HIV disease progression.[2,3,7,9,11] Stebbing *et al.* found an increased incidence of AIDS among patients with HIV/HCV-coinfection (adjusted HR (aHR) 1.52; 95% CI 1.07, 2.17) when compared to HIV-monoinfected patients.[11] In addition, Hua *et al.* observed an increased incidence of clinical AIDS or all-cause mortality among HIV/HCV-coinfected study participants (aHR 2.10; 95% CI 1.31, 3.37).[9] Yet, other studies did not find that HCV affects HIV disease progression.[5,8,10] For example, Rockstroh *et al.* did not observe an association between HCV and incidence of AIDS or death (adjusted incidence rate ratio 0.97; 95% CI 0.81, 1.16) among a cohort of patients initiating ART.[8]

To our knowledge, none of these studies accounted for depression in their analyses. However, depression is common among persons with HIV/HCV-coinfection and may be more severe among HIV/HCV-coinfected patients than among HIV-monoinfected patients. One in four people with HIV/HCV-coinfection experienced moderate to severe depression in recent studies.[27,28] After adjustment for alcohol consumption, drug dependence, and medical comorbidities, Libman *et al.* found higher mean scores on the Centers for Epidemiologic Depression Scale (CES-D) among HIV/HCV-coinfected patients when compared to HIV-monoinfected patients (24 vs. 19, $p<0.001$).[29] In a separate study of 18,349 patients with HIV in the Veterans Affairs medical system, 57% of HIV/HCV-coinfected patients and 46% of HIV-monoinfected patients had major depressive disorder ($p<0.0001$).[30]

Depression accelerates progression to AIDS or mortality among persons living with HIV.[21-26] In a recent study of women living with HIV, the mortality HR for depressive symptoms among women initiating ART was 3.38 (95% CI 2.15, 5.33), in comparison to women with no

depressive symptoms.[26] Depression is also associated with behavioral factors that worsen HIV outcomes, including decreased initiation of and adherence to ART [18-20] as well as use of alcohol and other substances.[54,55] Depression may also increase serum cortisol levels and norepinephrine, which may, in turn, stimulate HIV viral replication and trigger destruction of CD4 cells.[22,56]

To date, no published studies have assessed the joint effects of depression and HCV on progression to AIDS or mortality among persons with HIV. Given that HCV and depression are independently associated with these outcomes among HIV-infected patients, and that depression is common among HIV/HCV-coinfected patients, examining the joint effects of HCV and depression on these outcomes warrants investigation.

2.6 Effect of HCV on HIV treatment outcomes among women

The effects of HCV on HIV treatment outcomes have not been explored in detail among women. Women typically represent less than thirty percent of cohort studies investigating the effect of HCV on HIV disease progression and the sample size is too small to determine the effect of female sex on this relationship.[2,5,8-10] Women respond differently to ART than men, often exhibiting more favorable immune responses but experiencing greater drug toxicity and treatment discontinuation.[13-17] Female sex also is also associated with increased liver fibrosis among HIV/HCV-coinfected patients.[57,58] Only two studies explored the effect of HCV on HIV treatment outcomes among women. Al-Harthi *et al.* found that HIV/HCV-coinfection did not affect ART responses in the CD4 and CD8 T-cell compartments.[12] Conversely, Marcus *et al.* found that HIV/HCV-coinfected women experienced slower CD4 cell recovery and increased all-cause mortality after ART initiation, when compared to HIV-monoinfected women.[4] Therefore, investigating the effect of HCV among HIV-infected women warrants further investigation.

2.7 Significance

This research is significant because it will estimate the effect that HCV has on HIV treatment outcomes among women. Specifically, we will investigate the effects of HCV on HIV suppression and progression to AIDS or all-cause mortality among women who initiated ART. We will also assess the joint effects of HCV and depression on progression to AIDS or all-cause mortality among women who initiated ART. If HCV negatively impacts HIV disease, it would reaffirm the need to treat HIV/HCV-coinfected women with directly-acting antiviral HCV therapies. In addition, these results may highlight the need for improved access and engagement in effective medical and counseling interventions to treat depression and substance use among HIV/HCV-coinfected women.

2.8 Innovation

This is the first study to examine the joint effects of HCV and depression on HIV disease progression among women. Several studies suggest that HCV and depression are independently associated with accelerated progression to AIDS and/or death among persons living with HIV.[9,11,21-26] However, no published studies have examined whether HCV and depression act synergistically to accelerate progression to AIDS or death, even though depression is common among persons living with HIV and HCV.[27,28] Therefore, we plan to measure interaction between HCV and depression on the additive and multiplicative scales. If there is evidence of synergism, i.e., the combined effect of HCV and depression on progression to AIDS or all-cause mortality is greater than the independent effects of HCV or depression, it would emphasize the need for improved access and engagement in interventions to treat depression among women with HIV and HCV.

Causal inference methods will be used to estimate the effects of HCV on HIV treatment

outcomes. Marginal structural models allow us to estimate the marginal, or population-level, effects of HCV on HIV treatment outcomes. The estimated measures of effect would also mimic the results produced in randomized controlled trials if the statistical models are correctly specified, there is no unmeasured confounding, and selection and measurement bias are minimal. Marginal structural models are also appropriate for observational cohort data that include time-varying exposures and confounders.[59-61] In these settings, standard regression methods may produce biased results because their techniques to control for confounders block causal pathways of interest.[59-61] In Aim 2, we plan to assess the joint effects of HCV and depression on AIDS diagnosis or death using data from the WIHS. WIHS participants have follow-up visits at six-month intervals and depression is measured at every study visit. Therefore, depression status at the last study visit is both an exposure of interest and a confounder of depression status at the current study visit and the outcome, AIDS diagnosis or death.

Table 1. Studies examining the effect of HCV on HIV suppression after ART initiation

Study, Year	Study Type	Study Population	N	Result
Greub, 2000	Prospective cohort	HIV+ initiating ART	3,111	Time to HIV suppression (<400 copies/mL) and time to treatment failure did not differ by HCV status [Failure HR 0.98 (95% CI 0.81, 1.19)]
De Luca, 2002	Prospective cohort	HIV+ initiating ART	1,320	Time to HIV suppression (<500 copies/mL) did not differ by HCV status [HBV+/HCV+ HR 0.98 (95% CI 0.70, 1.38)] [HBV-/HCV+ HR 0.98 (95% CI 0.88, 1.17)]
Marcus, 2015	Retrospective cohort	HIV+ initiating ART, stratified by sex	1,088 women 10,623 men	Time to HIV suppression (<500 copies/mL) did not differ HCV and sex [Women HR 0.9 (95% CI 0.7, 1.1)] [Men HR 1.0 (95% CI 0.9, 1.1)]
Lincoln, 2003	Prospective cohort	HIV+ using ART	2,086	Prevalence of detectable viral load at 12 months after baseline did not differ by HCV status [HBV-/HCV+ OR 1.16 (95% CI 0.74, 1.81)] [HBV+/HCV+ OR 0.91 (95% CI 0.26, 3.17)]
Carmo, 2008	Retrospective cohort	HIV+ initiating ART	824	Time to HIV suppression (<400 copies/mL) did not differ by HCV [HR 0.81 (95% CI 0.56, 1.17)]
Weiss, 2006	Prospective cohort	HIV+ initiating ART	2.734	Prevalence of detectable VL (>500 copies/mL) was similar at 144 weeks [OR 1.1 (95% CI 0.8, 1.5)] and 288 weeks [OR 1.3 (95% CI 0.88, 2.00)] by HCV
Hua, 2013	Four RCTs combined	HIV+ initiating ART	3,041	HCV was associated with earlier viral failure [HR 1.43 (95% CI 1.07, 1.19)]
Rockstroh, 2005	Prospective cohort	HIV+ initiating ART	5,957	Time to HIV suppression (<500 copies/mL) did not differ by HCV [HR 1.13 (95% CI 0.84, 1.51)]

HCV – hepatitis C virus, HIV – human immunodeficiency virus, ART – antiretroviral therapy, HBV – hepatitis B virus, HR – hazard ratio, CI – confidence interval, OR – odds ratio, VL – viral load, RCT – randomized control trial

Table 2. Studies examining the effect of HCV on immunologic responses to ART

Study, Year	Study Type	Study Population	N	Result
Greub, 2000	Prospective cohort	HIV+ initiating ART	3,111	HCV seropositivity associated with smaller CD4 cell recovery after ART [HR ≥50 cells/μL increase 0.79 (95% CI 0.72, 0.87)]
De Luca, 2002	Prospective cohort	HIV+ initiating ART	1,320	Average CD4 cell recovery was at least 30 cells/mm^3 fewer among HCV+ after 36 months
Marcus, 2015	Retrospective cohort	HIV+ initiating ART, stratified by sex	1,088 women 10,623 men	Average increase in CD4 cell count one year after ART initiation was smaller among HCV+ men and women, when compared to HCV- men and women
Lincoln, 2003	Prospective cohort	HIV+ using ART	2,086	After 24 months, HCV+/HBV- patients had smaller CD4 cell count increases than HCV-/HBV- patients; no difference between HCV+/HBV+ and HCV-/HBV-.
Carmo, 2008	Retrospective cohort	HIV+ initiating ART	824	HCV seropositivity associated with smaller CD4 cell recovery after ART [HR>50 cells/mm^3 increase 0.68 (95% CI 0.49, 0.92)]
Weiss, 2006	Prospective cohort	HIV+ initiating ART	2.734	HCV+ patients attained lower absolute CD4 cell counts after ART at weeks 144 and week 288 than HCV- patients.
Hua, 2013	Four RCTs combined	HIV+ initiating ART	3,041	HCV associated with smaller mean CD4 cell count increase [-33.8(95% CI -52.2, -15.4)] and smaller CD4% increase [-1.16% (95% CI -1.43%, 0.89%)] after ART
Rockstroh, 2005	Prospective cohort	HIV+ initiating ART	5,957	No difference in CD4 cell count changes after ART initiation by HCV status [HR ≥50 cells/mm^3 increase 0.92 (95% CI 0.77, 1.11)]
Sulkowski, 2002	Prospective cohort	HIV+ initiating ART	1,955	Among patients who received ART and maintained HIV suppression, no differences in CD4 cell count increases at 1, 2, and 3 years of follow-up between HCV+ and HCV- were observed
Stebbing, 2005	Prospective cohort	HIV+	2,049	No differences in decline of CD4 cell counts between HCV seropositive and HCV seronegative patients after baseline
Al-Harthi, 2006	Prospective cohort	HIV+ initiating ART	294	Chronic HCV was not associated with differences in CD4 and CD8 T-cell compartments after ART initiation
Miller, 2005	Meta-analysis	HIV+ initiating ART	6,216	HCV was associated with a smaller increase in CD4 cell count after ART initiation [average increase -33.4 cells/mm^3 (95% CI -43.3, -23.5)]
Motta, 2012	Prospective cohort	HIV+ initiating ART	2,682	HCV was associated with a smaller increase in CD4 cell counts at 12 months after ART initiation [-38.4, p=0.005] but not at 24 months after ART initiation
Tsiara, 2013	Meta-analysis	HIV+ initiating ART	22,533	HCV was associated with a smaller increase in CD4 cell count between 3 and 12 months after ART initiation [average increase -34.86 (95% CI -52.89, -16.82)]. At 2 years, the difference decrease (average increase -13.43 (95% CI -26.04, -0.83)]

HCV – hepatitis C virus, HIV – human immunodeficiency virus, ART – antiretroviral therapy, HBV – hepatitis B virus, HR – hazard ratio, CI – confidence interval, RCT - randomized controlled trial

Table 3. Studies assessing the effect of HCV on progression to AIDS or death

Study, Year	Study Type	Study Population	N	Outcome	Result
Greub, 2000	Prospective cohort	HIV+ initiating ART	3,111	Time to AIDS or death	HCV associated with accelerated time to AIDS or death [HR 1.7 (95% CI 1.6, 2.30)]
De Luca, 2002	Prospective cohort	HIV+ initiating ART	1,320	Time to AIDS or death	HCV+, HBV- associated with accelerated time to AIDS or death [HBV+/HCV+ HR 1.62 (95% CI 0.64, 4.48)] [HBV-/HCV+ HR 1.57 (95% CI 1.01, 2.61)]
Marcus, 2015	Retrospective cohort	HIV+ initiating ART, stratified by sex	1,088 women 10,623 men	Time to AIDS Time to death	HCV not associated with AIDS in either sex but was associated with time to death among men [Men HR: 1.4 (95% CI 1.2, 1.6)] [Women HR: 1.3 (95% CI 0.7, 2.4)]
Lincoln, 2003	Prospective cohort	HIV+ using ART	2,086	Time to AIDS or death	HCV not associated with accelerated time AIDS or death [HR: 0.99 (95% CI 0.63, 1.56)]
Carmo, 2008	Retrospective cohort	HIV+ initiating ART	824	Time to AIDS or death	HCV not associated with accelerated time to AIDS or death [HR: 1.08 (95% CI 0.66, 1.77)]
Weiss, 2006	Prospective cohort	HIV+ initiating ART	2.734	Time to death	HCV was associated with accelerated time to death [HR 2.4 (95% CI 1.9, 3.0)]
Hua, 2013	Combined four randomized controlled trials	HIV+ initiating ART	3,041	Time to AIDS or death	HCV associated with accelerated time to AIDS or death [HR 2.10 (95% CI 1.31, 3.37)
Rockstroh, 2005	Prospective cohort	HIV+ initiating ART	5,957	Incidence of AIDS Incidence of death	HCV not associated with incidence of AIDS [IRR: 0.97 (0.81, 1.16)] HCV was associated with incidence of death [IRR: 1.41 (1.13, 1.76)]
Sulkowski, 2002	Prospective cohort	HIV+	1,955	Time to AIDS Time to death	HCV was not associated with AIDS or death [AIDS HR: 1.03 (95% CI 0.86, 1.23)] [Death HR: 1.05 (95% CI 0.85, 1.30)]
Stebbing, 2005	Prospective cohort	HIV+	2,049	Time to AIDS	HCV was associated with accelerated progression to AIDS [HR 1.57 (95% CI 1.07, 2.17)]
Chen, 2009	Meta-analysis	HIV+ initiating ART		Time to AIDS and time to death	HCV not associated with the risk of AIDS [RR 1.12 (95% CI 0.82, 1.51)] but was associated with death [RR 1.35 (95% CI 1.11, 1.63)]

HCV – hepatitis C virus, HIV – human immunodeficiency virus, ART – antiretroviral therapy, AIDS – acquired immune deficiency syndrome, HBV – hepatitis B virus, HR – hazard ratio, CI – confidence interval, IRR – incidence rate ratio, RR – risk ratio

CHAPTER 3: METHODS

3.1 Study population

We used data from the WIHS to investigate the effects of HCV on HIV treatment outcomes. The WIHS is a prospective cohort study designed to investigate HIV disease progression among women. WIHS participants were enrolled in 1994-1995, 2001-2002, and 2011-2012 in six consortia located in Bronx/Manhattan, NY; Brooklyn, NY; Los Angeles, CA; San Francisco/Bay Area, CA; Chicago, IL; and Washington, DC. In 2013 and 2014, new WIHS participants were recruited from Atlanta, GA, Chapel Hill, NC, Miami, FL, and Birmingham, AL/Jackson, MS. Figure 1 below is a map of the WIHS sites. To date, 4,982 women have been enrolled in the WIHS; 3,677 (74%) were living with HIV at enrollment and 24 (0.5%) acquired HIV during follow-up.

WIHS participants have follow-up visits at six-month intervals. Interviews at each visit capture extensive medical, psychosocial, drug use, and sexual behavior information. The medical history includes a medication inventory that is updated regularly to include newly available antiretroviral therapies. Interviewers are trained using standardized methods and WIHS Data Management and Analysis Center staff perform periodic assessments of the quality of the interviews. Blood is also drawn and analyzed at each study visit. Routine laboratory analyses include plasma HIV RNA and CD4 cell counts. Women also receive HCV antibody and HCV RNA testing during one of their first three study visits after enrollment in the WIHS. Approximately 900 (24%) of the women living with HIV were HCV antibody positive with detectable HCV RNA at baseline. Institutional review boards at each study site approve study procedures and all study participants

provide written informed consent.

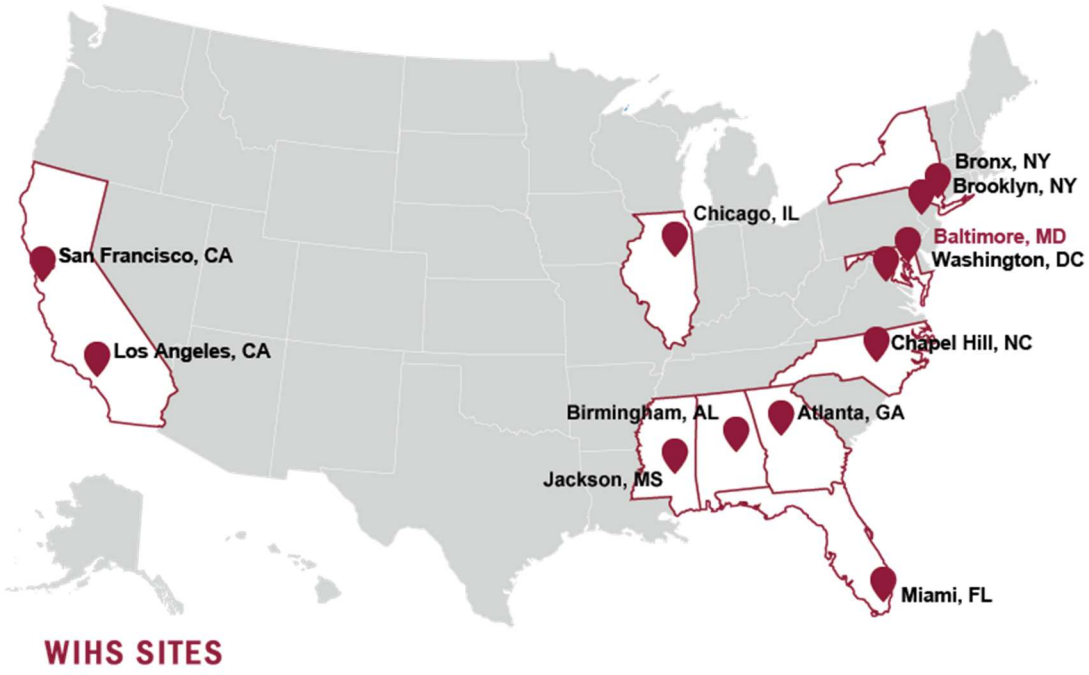

Figure 1. Location of WIHS clinical sites between 1994 and 2014

Women with HIV who enrolled in the WIHS are comparable with the HIV epidemic among women in the US.[62] The median age at WIHS enrollment was 37 years and two-thirds (60%) were African-American Non-Hispanic. Forty percent of women reported heterosexual sex and 20% reported injection drug use as a risk factor for HIV acquisition. HIV surveillance data from the Centers for Disease Control and Prevention indicate that 60% of women living with HIV in the US at the end of calendar year 2014 were Black, African American, 74% reported heterosexual sex, and 23% reported injection drug use as a risk factor for HIV acquisition.[31]

3.2 Study sample

The study sample includes women with HIV who initiated ART on or after the date they

enrolled in the WIHS. For the purposes of our analyses, ART was defined as three or more antiretroviral medications, one of which had to be a protease inhibitor (PI), a non-nucleoside reverse-transcriptase inhibitor (NNRTI), one of the nucleoside reverse-transcriptase inhibitors (NRTI) abacavir or tenofovir, an integrase inhibitor (e.g., raltegravir), or an entry inhibitor (e.g., Maraviroc or enfuvirtide). In the WIHS, the exact dates women start ART is typically unknown. Therefore, ART initiation dates are recorded as the date of the first study visit each woman reports ART use. Women who used monotherapy or dual therapies prior to ART initiation were included in our sample, however we repeated our analyses with these women were removed (see Section 3.6.2 below for more information). Eligible women must also have had HCV antibody and HCV RNA results available at WIHS enrollment.

For Aim 1, we excluded women who initiated ART prior to year 2000 because we wanted to assess HIV viral response to relatively modern ART regimens. There are 601 women within the WIHS cohort who meet these criteria; 144 (24%) had both HCV antibody and HCV RNA detected at baseline (Figure 2).

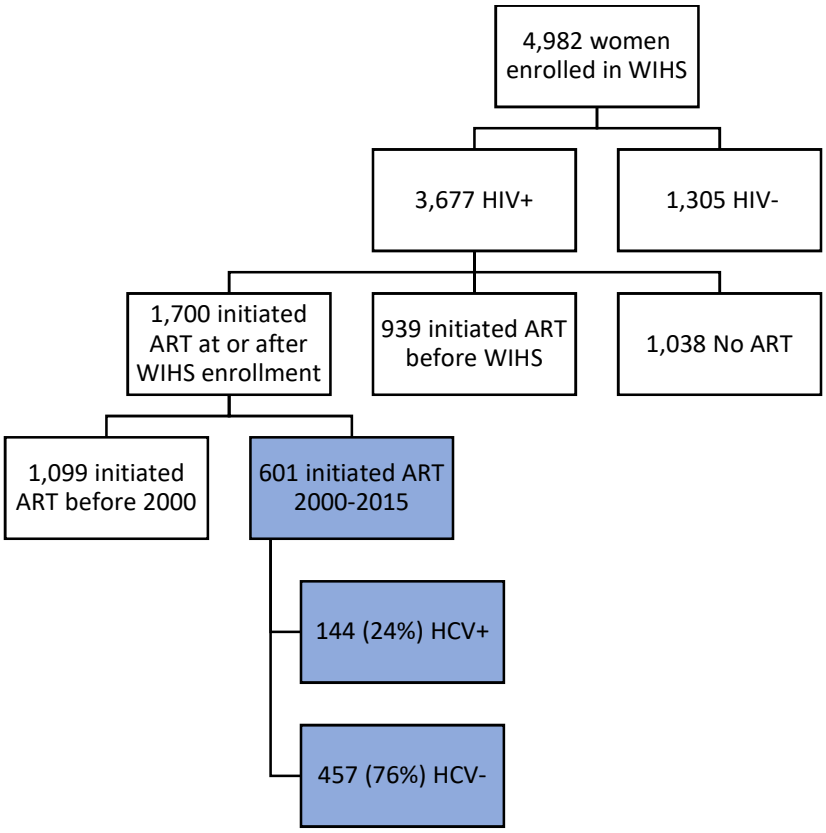

Figure 2. Chart of 4,982 women enrolled in the WIHS as of September 2015 and eligibility for Aim 1 analyses. The boxes shaded in blue represent women eligible for Aim 1 analyses. Women who are HCV+ have detectable HCV antibodies and HCV RNA.

As depicted in Figure 3 below, women were followed from the first study visit ART use was reported until the last study visit prior to September 30, 2015 (last day for WIHS visit 42), or censoring. Women were right-censored due to loss to follow-up or death. We also censored women with chronic HCV who initiated HCV treatment and HIV-monoinfected women with incident HCV infection during follow-up. We assessed the outcome of interest, HIV RNA, every six months during the 15-year follow-up period.

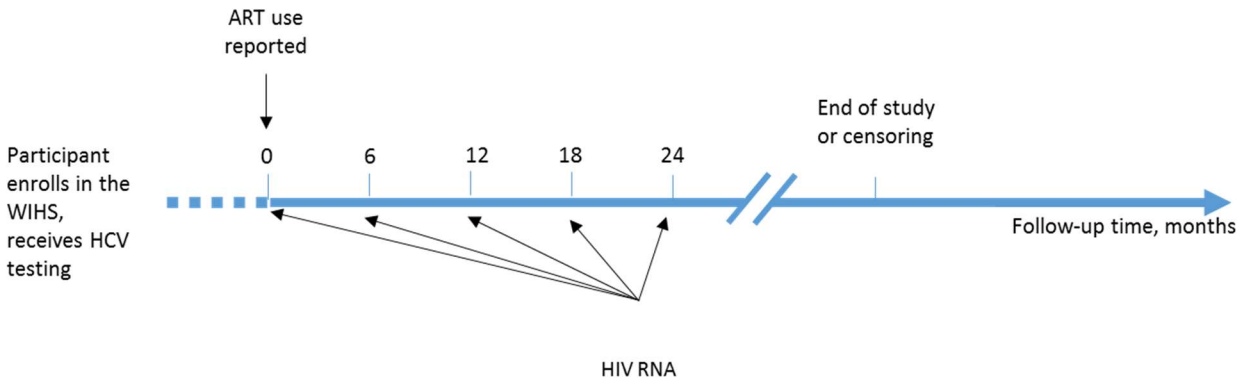

Figure 3. HIV RNA measurement after ART initiation among women living with HIV and enrolled in the WIHS, 2000 – 2015

For Aim 2, we selected all women who initiated ART on or after the date that they enrolled in the WIHS. We excluded women diagnosed with AIDS before ART initiation. There are 1,002 women who met these criteria, and 201 (20%) had both HCV antibody and HCV RNA detected at baseline (Figure 4).

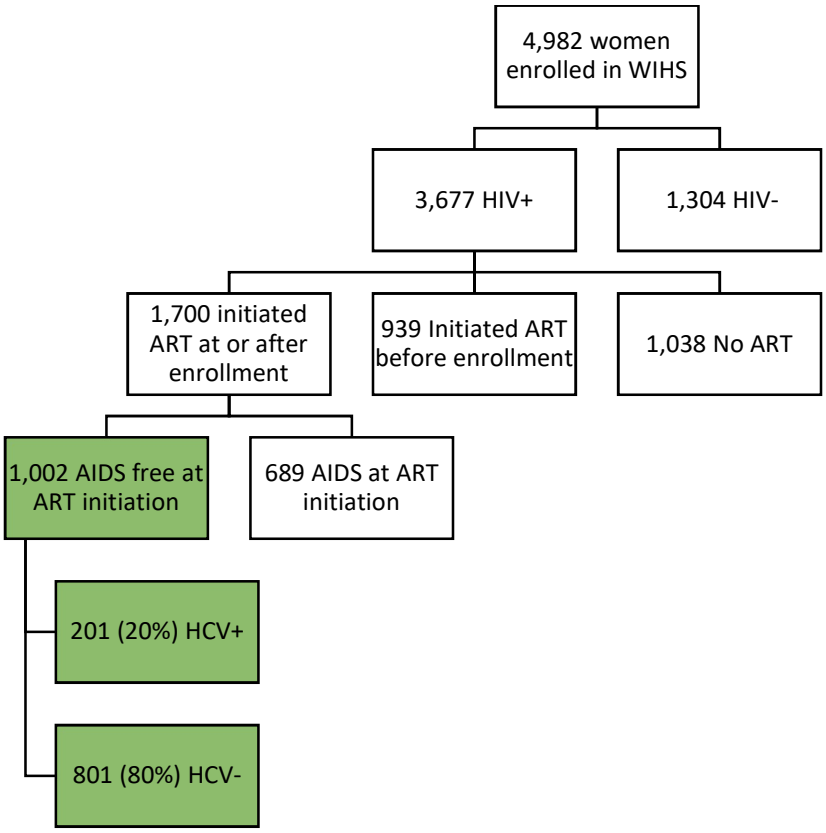

Figure 4. Chart of 4,982 women enrolled in the WIHS as of September 2015 and eligiblity for Aim 2 analyses. The boxes shaded in green represent women who are eligible for Aim 2 analyses. Women who are HCV+ have detectable HCV antibodies and HCV RNA.

In Aim 2, we followed women from the date of the first visit ART use was reported until the earliest occurrence of the following: date of the first visit with an AIDS diagnosis, date of death, censoring, or September 30, 2015 (last day for WIHS visit 42). We censored women who were lost to follow-up, women with chronic HCV who initiated HCV treatment, and HIV-monoinfected women with incident HCV infection during follow-up. To assess the joint effects of HCV and depression on progression to AIDS or mortality, we used the CES-D, collected every six months, to assess depression over time. For further information about data collection and the follow-up period, see Figure 5 below.

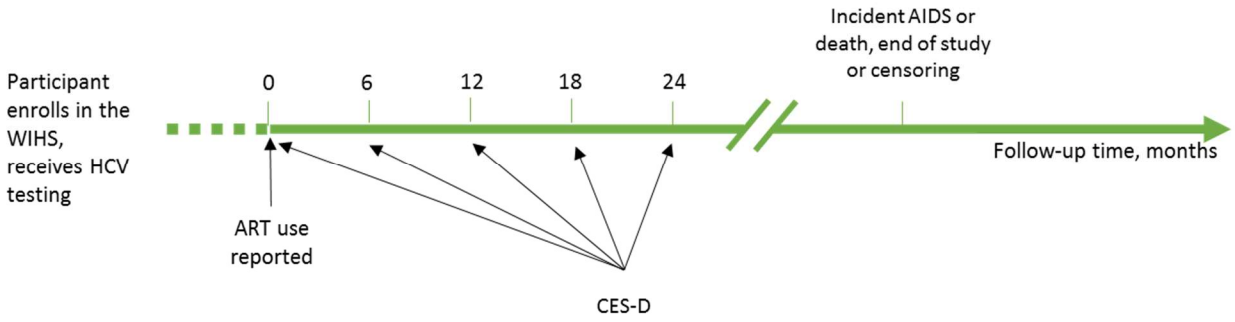

Figure 5. CES-D measurement after ART initiation among women living with HIV and enrolled in the WIHS, 1994-2015

3.3 Exposure assessment

The primary exposure of interest was chronic HCV. Women were tested for HCV antibodies with commercially available HCV enzyme immunoassays at one of the first three study visits upon enrollment. HCV RNA was measured using COBAS Amplicor HCV Monitor 2.0 (Roche Diagnostics) among women with HCV antibodies.[12] The presence of HCV RNA, with a positive HCV antibody, indicates that the participant has not cleared the HCV infection and that the infection is chronic. Therefore, we categorized women who had HCV antibodies and HCV RNA as having chronic HCV. Women who did not have HCV antibodies, and women who had HCV antibodies and undetectable HCV RNA, were categorized as not having chronic HCV. We excluded women who were missing HCV RNA results.

The average length of time between HCV testing and ART initiation was six years for the study sample in Aim 1 and three years for the study sample in Aim 2. We were concerned that chronic HCV status may have been misclassified due to spontaneous clearance of the virus, HCV treatment, or incident HCV infections during this time. Therefore, we supplemented HCV results at enrollment with follow-up HCV test results, which were available for over 80% of women, and self-reported information on HCV treatment initiation.

In Aim 2, we assessed the joint effects of HCV and depression on progression to AIDS or all-cause mortality. In the WIHS, depression is measured by the CES-D at all study visits. The CES-D was designed to measure current levels of depression symptomology in the general population.[63] The CES-D is not a diagnostic tool and does not measure the severity of illness.[63] The CES-D includes 20 questions and respondents are asked how often they've experienced each of these items in the past week. CES-D scores range from 0 to 60 and a score ≥16 indicates depression. We dichotomized depression and categorized scores 16-60 as "depressed" and 0-15 as "not depressed." Depression status may change at each study visit.

The scale has high sensitivity, ~99%, for persons experiencing acute depression when using a score of ≥16 for depression.[64] However, the specificity of the scale is lower. Among a patient population being treated for alcoholism, the specificity was approximately 85%.[64] In a recent study of low-income African-Americans being screened for perinatal depression, the specificity of the CES-D was 65%.[65]

3.4 Outcome assessment

For Aim 1, the outcome of interest was detectable HIV RNA measured at each study visit after ART initiation. We defined detectable HIV RNA as more than 80 copies of HIV RNA-1 circulating in one milliliter (mL) of plasma. This cut-off was chosen to accommodate the assays used during the study period, which had lower limits of detection ranging from 20 to 80 copies/mL. The WIHS uses a real-time polymerase chain reaction method to quantify HIV RNA.

For Aim 2, the outcome of interest was incident AIDS or death from any cause. In WIHS, participants are asked about health events that occurred since their last study visit. Participants are specifically asked about AIDS-defining illnesses, including candidiasis of the esophagus,

bronchi, trachea, or lungs; Kaposi sarcoma; cervical cancer; tuberculosis; etc. The first study visit at which an AIDS-defining illness is reported and recorded in the WIHS database.

In the WIHS, deaths can be reported by family members, friends, health care providers, obituaries, or through registry matches. If a death is reported by family members, friends, health care providers, etc., WIHS investigators request the death certificate to confirm the death occurred and record the date and cause of death. All women actively enrolled in the WIHS are also matched to the National Death Index and local vital statistics registries.

3.5 Covariate assessment

To accurately assess the effects of HCV on HIV treatment outcomes, we controlled for several covariates in multivariable models. Time-fixed covariates included age at ART initiation, race/ethnicity, year of ART initiation, history of injection drug use, socioeconomic, baseline CD4 cell count and baseline HIV viral load. We considered the following variables to represent socioeconomic status: years of education, marital status, type of residence, and annual household income. We selected years of education because it has direct relationships with economic outcomes, an indirect relationship with risk behaviors such as smoking,[66] and had the least amount of missing data (<0.2%) in our cohort.

Due to the length of time between chronic HCV testing and ART initiation we also included a marker for liver fibrosis, FIB-4. FIB-4 is calculated by the following formula:

$$\text{FIB-4} = \text{age (years)} \times \text{AST[U/L]}/\text{platelets}[10^9/\text{L}] \times (\text{ALT[U/L]})^{1/2}$$

where AST is aspartate aminotransferase, ALT is alanine aminotransferase, and U/L is units per liter. The FIB-4 score is dichotomized as >1.45 and ≤1.45 to differentiate between women with and without fibrosis.[67-69]

Time-fixed covariates were measured at the last study visit before ART initiation. The coding for each covariate differed by aim and are described in detail in Chapter 4 (Aim 1) and Chapter 5 (Aim 2).

We also considered the following time-varying covariates: drug use, alcohol use, smoking status, and adherence to ART. These covariates were measured at every study visit.

Drug use: Participants were asked if they have used any of the following drugs since their last study visit: marijuana, cocaine, crack, heroin, methamphetamine, hallucinogens, or club drugs. If the participant responded yes, the interviewer asked several questions that assessed their mode of use, e.g., smoking, sniffing, or injecting, how often they use the drug(s), and how much drug(s) is/are used at one time. Women were categorized as using drugs if they reported using any of these drugs since their last study visit

Alcohol use: At each visit, participants were asked if they had at least one drink containing alcohol since their last visit. If they responded yes, the interviewer asked them a series of questions to assess how frequently they drank alcohol and when they did, how much. Alcohol use was categorized as 0, 1-7, and >7 drinks per week since prior study visit.

Smoking status: Participants were asked if they smoked tobacco products since their last study visit. If they responded yes, the interviewer asked them to provide an average number of cigarettes or packs that they smoke each day. For this study, we dichotomized smoking as yes/no at each six-month visit.

Adherence to ART: We used suppressed HIV RNA as a proxy for adherence in multivariable regression models. We defined suppression 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.

Time-varying covariates were missing at less than or equal to 6% of visits with missing values replaced by values carried forward from the previous non-missing visit.

3.6 Statistical analysis

3.6.1 Statistical analysis for Aim 1

Log-binomial regression models were used to estimate the proportion of study visits with detectable HIV RNA during follow-up, and we compared women with chronic HCV to women 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 included a product term between chronic HCV status and time since ART initiation in a second log-binomial model to 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 ART use was reported until the last visit prior to September 30, 2015, the last possible date that data were available. Women were right-censored at the earliest occurrence of loss to follow-up, death, or last visit prior to September 30, 2015. Loss to follow-up was defined as two consecutively missed study visits and person-time was censored two visits after the last study visit in which they were seen.[70] We also censored women with chronic HCV who initiated HCV treatment and HIV-monoinfected women who had an incident HCV infection (detectable HCV antibody and HCV RNA during follow-up).

To control for confounding, we used stabilized time-fixed inverse-probability-of-exposure weights denoted as:

$$W_i^X = Pr(X_i = x)/Pr(X_i = x|V_i)$$

When applied to the observed data, these weights create a pseudo-population in which exposure is no longer associated with measured covariates. [59,71] The numerator of the exposure weight

represents the probability of having the exposure that participant *i* factually had; the denominator is the probability of having the exposure that participant *i* factually had conditional on V_i. V_i is a vector of covariate values at baseline for participant *i*, assumed to be sufficient to control for confounding. Logistic regression was used to estimate the denominator of the exposure weight and included age, race/ethnicity, year of ART initiation, FIB-4, history of injection drug use, baseline HIV viral load, and baseline CD4 cell count. See the directed acyclic graph (DAG) (Figure 6) below for the causal relationships between chronic HCV, detectable HIV RNA and these covariates.

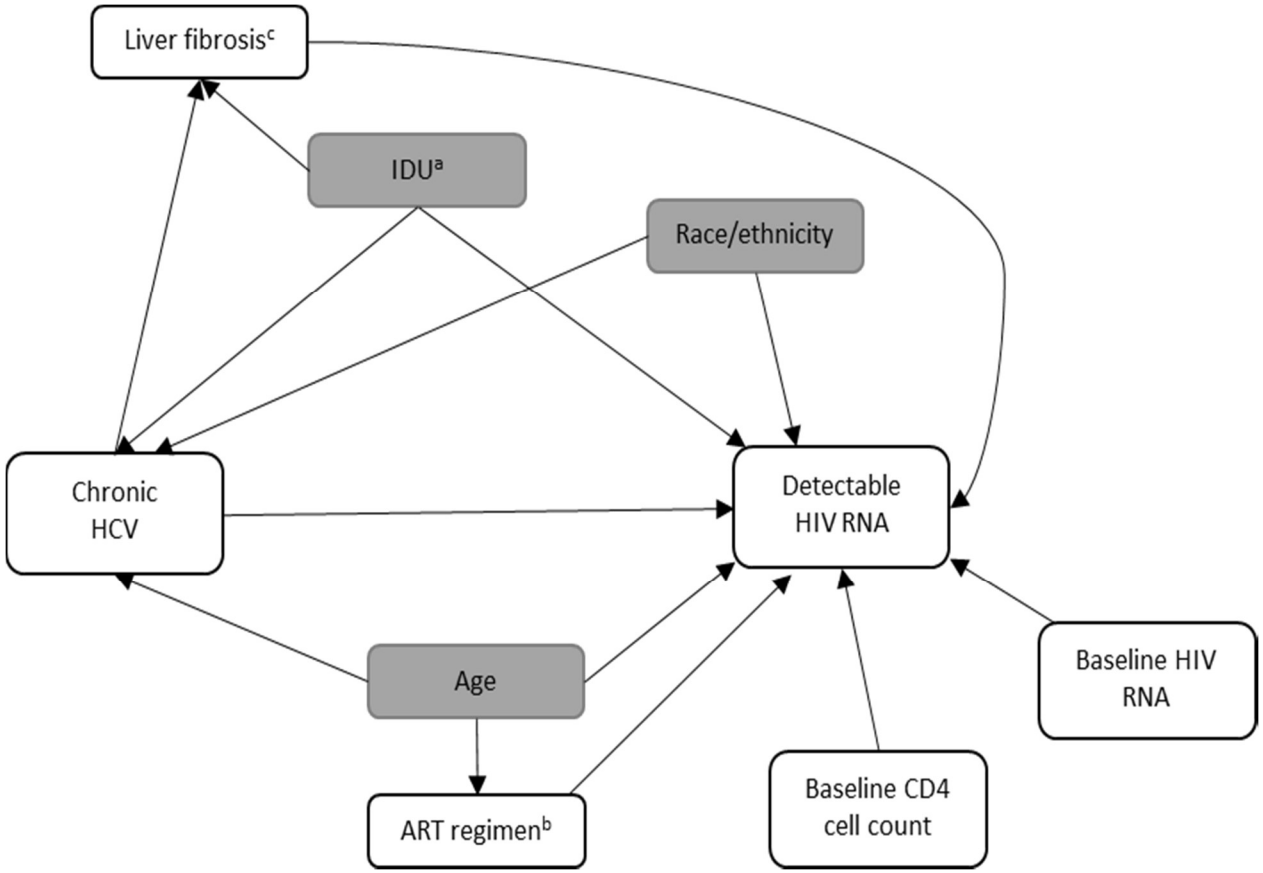

Figure 6. DAG depicting the causal relationship between chronic HCV and detectable HIV RNA This DAG represents the causal relationship between the exposure, chronic HCV, and the outcome, detectable HIV RNA. The directions of the arrows represent knowledge gathered from published literature. The shaded boxes represent potential confounders of the relationship between chronic HCV and detectable HIV RNA.

[a] History of injection drug use
[b] Year of ART regimen was used as a proxy measure for ART regimen
[c] Liver fibrosis was estimated by calculating FIB-4

We also created time-varying inverse-probability-of-censoring weights denoted as:

$$W_{ij}^{C} = \prod_{k=0}^{j+1} Pr(C_{ik} = 0|\bar{C}_{ik-1} = 0, X_i, V_i) / Pr(C_{ik} = 0|\bar{C}_{ik-1} = 0, X_i, \bar{V}_{ik-1})$$

These weights account for selection bias due to right-censoring.[72] We fit separate weight models for right-censoring due to death and right-censoring due to loss to follow-up. This allowed the parameter estimates to differ by censoring mechanism.[73] The numerator of each censoring weight represents the probability of remaining in the study at visit *k*, conditional on exposure and V_i. The denominators of the censoring weights are the conditional probability of remaining free from censoring, where $\bar{V}_{ik-1}$ is a vector of time-fixed and time-varying covariate histories measured up to visit *k*-1. Pooled logistic regression models were used to estimate the two censoring weights. The numerator models included time, chronic HCV status, age, race/ethnicity, and alcohol and drug use measured at the last study visit prior to ART initiation. The denominator models included time, chronic HCV status, age, race/ethnicity, and alcohol and drug use measured at visit *k*-1. 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.[74]

The exposure and censoring weights were combined: $W_{ij} = W_i^X \times W_{ij}^{C(death)} \times W_{ij}^{C(loss\ to\ follow-up)}$. The average of the estimated weights was 1.05 (standard deviation [SD], 1.78) and they ranged from 0.20 to 25.57. Robust variance estimates tend to overestimate the variability of inverse-probability-weighted estimators. Therefore, we obtained 95% confidence CIs for the weighted ratio measures using a nonparametric bootstrap with 200 resamples with replacement. The estimated weights in the 200 samples ranged from 0.06 to 535.95. We trimmed the weights at the 0.5th and 99.5th percentile to reduce the variability of the estimated effect of

chronic HCV on detectable HIV RNA.

3.6.2 Sensitivity analyses for Aim 1

We conducted several sensitivity analyses to reduce possible bias in our estimated effects of chronic HCV on HIV RNA after ART initiation. In the first sensitivity analysis, we excluded women who reported single or dual antiretroviral use prior to ART initiation because the relationship between chronic HCV and detectable HIV RNA may differ among women who previously received HIV treatment. For the second sensitivity analysis, we only included women who self-reported > 95% adherence to ART during the first six months after ART initiation. This analysis allowed us to determine if the estimated effect of chronic HCV on HIV RNA could be explained by differences in ART adherence. 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. For each sensitivity analyses we reconstructed the exposure and censoring weights for each subset (or reclassified) of women and reran the log-binomial regression models. Ninety-five percent CIs were obtained with nonparametric bootstrap with 200 resamples.

3.6.3 Statistical analysis Aim 2

In Aim 2, marginal structural Cox proportional hazards models were used to 1) assess the effect of chronic HCV on AIDS diagnosis or death and 2) assess the joint effects of depression and chronic HCV on AIDS diagnosis or death. We used marginal structural Cox proportional hazards regression, rather than standard regression methods, to appropriately adjust for time-varying confounders of the effect of time-varying depression on the outcome.[75]

We followed women from the date of the first visit they reported ART use until the earliest occurrence of the following: date of the first visit with an AIDS diagnosis, date of death,

censoring, or September 30, 2015 (last day for WIHS visit 42). Women were censored for loss to follow-up, which was defined as two consecutively missed study visits. Person-time was censored at two study visits after the last study visit in which they were seen.[70] We also censored HIV-monoinfected women who had evidence of incident HCV infection (detectable HCV antibody and HCV RNA) during follow-up and women with chronic HCV if they initiated HCV treatment during follow-up. The HCV treatments available throughout most of our follow-up period were interferon-based and depression was a significant and common side effect of these therapies.

The marginal structural Cox proportional hazards model for the effect of chronic HCV on AIDS diagnosis or death was defined as:

$$\lambda_{T^x}(t) = \lambda_0(t)\exp(\alpha_1 x(t))$$

where T_i^x represents the time from ART initiation until the earliest occurrence of AIDS diagnosis or death or censoring for participant *i* if they had been assigned chronic HCV status *x*, $\lambda_0(t)$ is the baseline hazard function and the parameter $\exp(\alpha_1)$ is the HR for the effect of chronic HCV on AIDS diagnosis or death.

The marginal structural Cox proportional hazards model for the joint effects of chronic HCV and depression on AIDS diagnosis or death was defined as:

$$\lambda_{T^{x\,1,\bar{x}_2}}(t) = \lambda_0(t)\exp(\alpha_1 x_1(t) + \alpha_2 x_2(t) + \alpha_3 x_1 x_2(t))$$

where $T_i^{x\,1,\bar{x}_2}$ represents the time from ART initiation until the earliest occurrence of AIDS diagnosis or death or censoring for participant *i,* if they had been assigned chronic HCV status x_1 and depression history $\bar{x}_2$ (overbar represents history). The parameter $\exp(\alpha_1)$ is the HR for the effect of chronic HCV on AIDS diagnosis or death among women without depression, the parameter $\exp(\alpha_2)$ is the HR for the effect of depression on AIDS diagnosis or death among

women without chronic HCV, and the parameter $\exp(\alpha_1 + \alpha_2 + \alpha_3)$ is the HR for the joint effect of chronic HCV and depression on AIDS diagnosis or death.

In both Cox models, we created stabilized time-fixed inverse-probability-of-exposure weights to control for confounding of the relationship between chronic HCV and AIDS diagnosis or death. These weights are defined as:

$$W_i^X = Pr(X_i = x)/Pr(X_i = x|V_i)$$

The components of these weights were described in Aim 1 above. Logistic regression was used to estimate the denominator of these weights and included age, race/ethnicity, education, history of injection drug use, year of ART initiation, FIB-4, and baseline CD4 cell count. Smoking was also included and was measured at the last visit prior to ART initiation. See Figure 7 below for the causal relationships between chronic HCV, HIV disease progression, and these covariates.

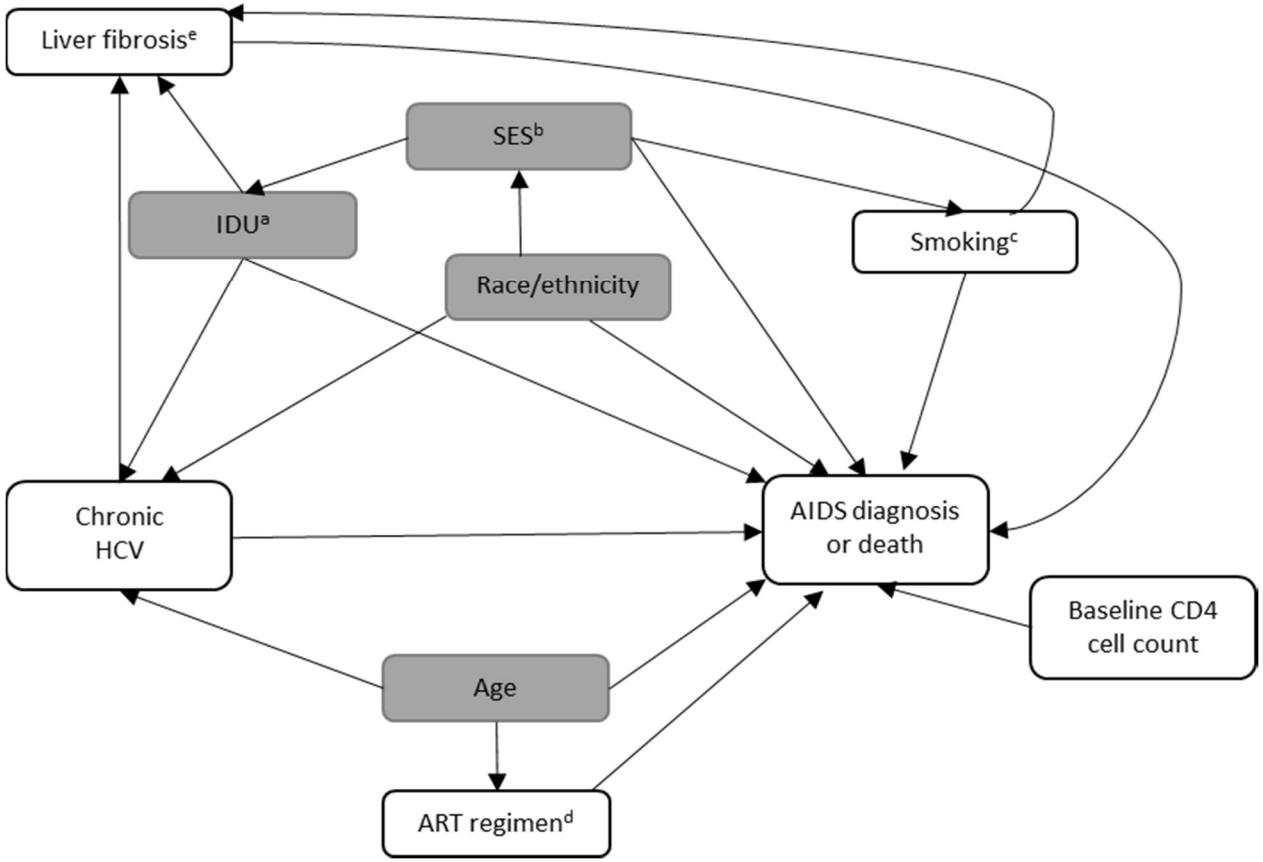

Figure 7. DAG depicting the causal relationship between chronic HCV and AIDS diagnosis or death This DAG represents the causal relationship between the exposure, chronic HCV, and the outcome, AIDS diagnosis or death. The directions of the arrows represent knowledge gathered from published literature. The shaded boxes represent potential confounders of the relationship between chronic HCV and AIDS diagnosis or death.

[a] History of injection drug use

[b] Socioeconomic status was measured by years of education at the last visit prior to ART initiation

[c] Smoking status was measured at the last visit prior to ART initiation

[d] Year of ART regimen was used as a proxy measure for type of ART regimen

[e] Liver fibrosis was estimated by calculating FIB-4

We also created time-varying inverse-probability-of-censoring weights to account for right-censoring due to loss to follow-up. These weights were defined as:

$$W_{ij}^{C} = \prod_{k=0}^{j+1} Pr(C_{ik} = 0|\bar{C}_{ik-1} = 0, X_i, V_i) / Pr(C_{ik} = 0|\bar{C}_{ik-} \ = 0, X_i, \bar{V}_{ik-1})$$

The components of these weights were described in Aim 1 above. Pooled logistic regression models were used to estimate these weights. The numerator model included time since ART initiation, chronic HCV, age, race/ethnicity, and alcohol and drug use measured at the last visit before ART use. The denominator model included time since ART initiation, chronic HCV, age, race/ethnicity, and alcohol and drug use measured at visit *k*-1. Time since ART initiation was included as a continuous variable using restricted quadratic splines with four knots at the 5th, 35th, 65th, and 95th percentiles in both models.[74]

In order to assess the joint effects of chronic HCV and depression on AIDS diagnosis or death, we needed to control for confounding of the relationship between depression (time-varying) and AIDS diagnosis or death. Therefore, we created time-varying inverse-probability-of-treatment weights for depression. These weights were defined as:

$$W_{ij}^{D} = \prod_{k=0}^{j} Pr[D_{ik}|\bar{D}_{ik-1}, X_i, V_{i0}, \bar{C}_{ik-1} = 0] / Pr[D_{ik}|\bar{D}_{ik-1}, X_i, \bar{V}_{ik-1}, \bar{C}_{ik-1} = 0]$$

D_{ik} represents the depression status of a participant at visit *k* and $\bar{D}_{ik-1}$ is the depression history of a given participant measured at visit *k*-1. X_i is chronic HCV. V_{i0} is a vector of baseline covariate values at for each participant *i* assumed to be sufficient to control for confounding between depression and AIDS diagnosis or death and $\bar{V}_{ik-1}$ is the vector of time-fixed and time-varying covariate histories measured up to visit *k*-1. $\bar{C}_{ik-1} = 0$ represents women who remain free from censoring at visit *k*-1. Pooled logistic regression models were used to estimate the

components of these weights. The numerator model included chronic HCV, age, race/ethnicity, education, baseline CD4 cell count, year of ART initiation, history of depression (indicator for depression status at the last visit and an indicator for depression status two visits prior), time since ART initiation and drug use, alcohol use, and smoking status measured at the last study visit before ART initiation. In the denominator model we included chronic HCV, age, race/ethnicity, education, baseline CD4 cell count, year of ART initiation, history of depression (measured at the last two study visits), time since ART initiation and drug use, alcohol use, smoking status, and HIV suppression measured at visit k-1. Time since ART initiation was included as a continuous variable in the models using restricted quadratic splines with four knots at the 5th, 35th, 65th, and 95th percentiles.[74]

See Figures 8 and 9 for the causal relationships between the exposures, chronic HCV and depression, covariates, and the outcome, AIDS diagnosis or death. In Figure 8 we demonstrate the causal relationship between chronic HCV, static depression (i.e., depression measured at one point in time), and AIDS diagnosis or death. However, depression was measured at every study visit and we explore the causal relationships between time-varying depression, time-varying substance use (alcohol use, drug use, and smoking), time-varying ART adherence and AIDS diagnosis or death in Figure 9.

In the model that assessed the effect of chronic HCV on AIDS diagnosis or death the weights were combined as $W_{ij} = W_i^X \times W_{ij}^C$. The average of these estimated weights was 0.99 (SD 1.04) and they ranged from 0.10 to 20.84. In the joint effects model, the weights were combined as $W_{ij} = W_i^X \times W_{ij}^D \times W_{ij}^C$. The average of the estimated weights was 1.00 (SD 1.10) and they ranged from 0.04 to 28.10. We used robust variance estimates to obtain 95% CIs for the weighted HRs.

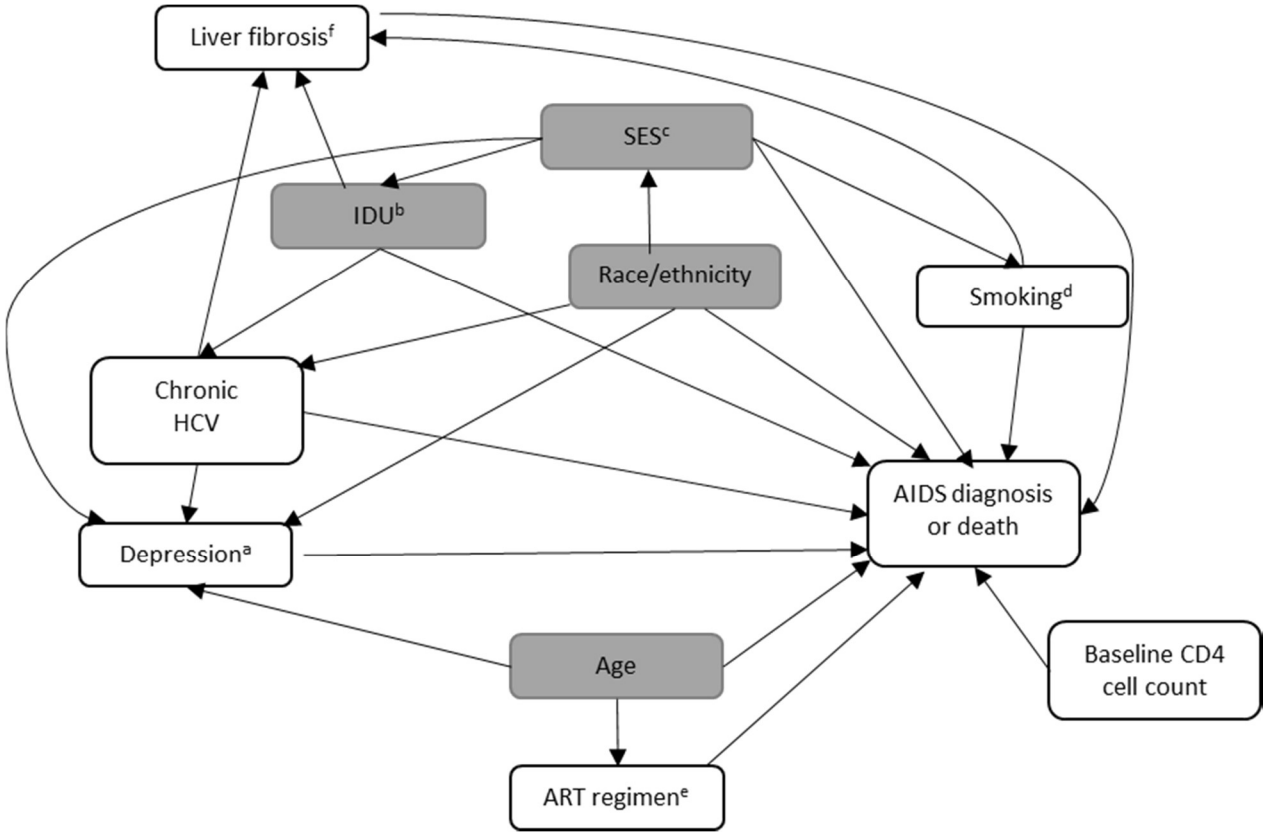

Figure 8. DAG depicting the causal relationships between chronic HCV, static depression, and AIDS diagnosis or death. This DAG represents the causal relationship between the exposures, chronic HCV and depression, and the outcome, AIDS diagnosis or death. The directions of the arrows represent knowledge gathered from published literature. The shaded boxes represent potential confounders of the relationship between chronic HCV, static depression, and AIDS diagnosis or death.

[a] Static depression

[b] History of injection drug use

[c] Socioeconomic status was measured by years of education at the last visit prior to ART initiation

[d] Smoking status was measured at the last visit prior to ART initiation

[e] Year of ART regimen was used as a proxy measure for ART regimen

[f] Liver fibrosis was estimated by calculating FIB-4

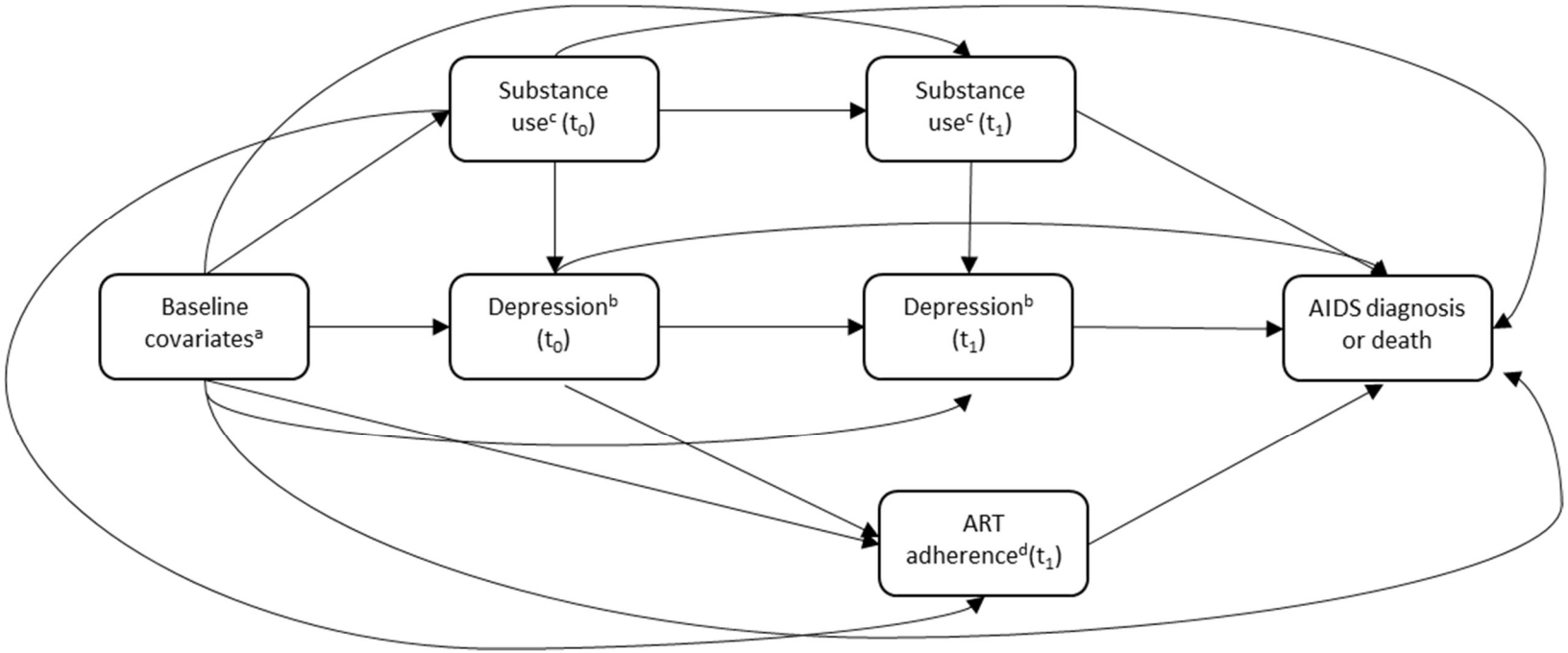

Figure 9. DAG depicting the causal relationships between time-varying depression and AIDS diagnosis or death This DAG represents causal relationships between depression measured at baseline (t_0), depression measured six months later (t_1), and the outcome, AIDS diagnosis or death. The directions of the arrows represent knowledge gathered from published literature. Potential confounders of the relationship between time-varying depression and AIDS diagnosis or death are also included.

[a] Baseline covariates include chronic HCV, age at ART initiation, race/ethnicity, year of ART initiation, history of injection drug use, socioeconomic status, and baseline CD4 cell count.
[b] Depression measured at baseline (t_0), last visit prior to ART initiation, and six months later (t_1)
[c] Substance use measured at baseline (t_0), last visit prior to ART initiation, and six months later (t_1). Substance use includes alcohol use, smoking, and injection and non-injection drug use.
[d] ART adherence is not measured at baseline (t_0), because it was prior to ART initiation. We depict ART adherence measured six months later (t_1).

Proportional hazards were assessed in the weighted Cox models with Wald chi-square tests on product terms between chronic HCV and time, and between depression and time. The Wald Chi-square tests on product terms between chronic HCV and time and between depression and time yielded *p*-values larger than 0.05. Therefore, these weighted models do not violate the proportional hazards assumption and we can assume the hazard ratios are constant over time.

We used the complement of the Kaplan Meier estimator to construct crude and weighted cumulative incidence curves for AIDS diagnosis or death.[76] We stratified these curves by chronic HCV and by the joint classification of chronic HCV and depression. The Kaplan Meier estimator of the survival function *S(t)* is below. Let d_j represent the number of AIDS diagnoses or deaths at time *j* and n_j represent the number of persons in the risk set at time *j*.

$$\hat{S}(t_i) = \prod_{j=1}^{i} \left(1 - \frac{d_j}{n_j}\right)$$

We also assessed interaction between chronic HCV and depression on the additive and multiplicative scales in the joint effects model. We used the complement of the Kaplan-Meier estimator to estimate the risk of AIDS diagnosis or death at five years and at ten years after ART initiation for each exposure group (i.e., no chronic HCV and no depression, no chronic HCV and depression, chronic HCV and no depression, and chronic HCV and depression).[76] We then calculated interaction contrasts (IC) to assess departure from the assumption of additive risks.[77] The IC is calculated as:

$$IC = R_{11} + R_{00} - R_{01} - R_{10}$$

In this study R_{11} represents the risk of AIDS diagnosis or death among women with chronic HCV and depression, R_{00} represents the risk among women with neither chronic HCV nor depression, R_{01} represents the risk among depressed women without chronic HCV, and R_{10} represents risk

among women with chronic HCV but no depression. We used a nonparametric bootstrap with 200 resamples with replacement to obtain 95% CIs for the ICs. Multiplicative interaction was assessed from the Wald chi-square test for the product term between chronic HCV and depression.

3.6.4 Sensitivity analyses for Aim 2

We conducted two sensitivity analyses to assess the robustness of our findings. More than half of the women in our study sample initiated ART prior to the year 2000 and our findings may not be relevant to current clinical practice because current ART regimens are more effective and have fewer side effects than older regimens. Therefore, we restricted our analytic sample to women who initiated ART after the year 2000 in our first sensitivity analysis. For this analysis, we reconstructed the exposure and censoring weights for this subset of women and reran both Cox models.

In our second sensitivity analysis, we used a higher CES-D score for depression, ≥22. The scale has high sensitivity, ~99%, for persons experiencing acute depression.[64] However, the specificity of the CES-D is lower. Among a patient population being treated for alcoholism, the specificity was approximately 85%.[64] In a recent study of low-income African-Americans being screened for perinatal depression, the specificity of the CES-D was 65%.[65] Given the specificity of the CES-D in these populations, we were concerned we may overestimate depression in our study sample. Thus, we used a higher cut-off on the CES-D to represent depression to potentially reduce the number of women who may be misclassified as depressed in our analysis.

CHAPTER 4: CHRONIC HEPATITIS C VIRUS INFECTION AND SUBSEQUENT HIV VIRAL LOAD AMONG WOMEN WITH HIV INITIATING ANTIRETROVIRAL THERAPY[1]

4.1 Introduction

One in four persons living with HIV in the US is coinfected with HCV.[1] Quantifying the effect of HCV on HIV suppression is crucial. HIV suppression improves clinical outcomes and reduces HIV transmission.[32,33] 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.[43-45] Ongoing alcohol and drug use and decreased ART adherence among coinfected persons may also result in increased HIV viral load.[46,47]

Published studies suggest that persons with HIV/HCV-coinfection do not experience increased time to HIV suppression after ART initiation [2-8,78-80] but HCV may be associated with earlier failure of HIV viral control.[9] 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);[2-8,9] misclassification of HCV status could result in biased

[1]This is a non-final version of an article published in final form in AIDS. The citation for the final article is as follows: Willis SJ, Cole SR, Westreich D, Edmonds A, Hurt CB, Albrecht S, *et al.* Chronic hepatitis C virus infection and subsequent HIV viral load among women with HIV initiating antiretroviral therapy. AIDS. 2018; 32:653-661. The article is available at: https://journals.lww.com/aidsonline/Citation/2018/03130/Chronic_hepatitis_C_virus_infection_and_subsequent.14.aspx

associations. Also, some studies did not account for potential confounding of the relationship between HCV and HIV suppression by alcohol or drug use.[5,80]

Evidence regarding the effect of HCV on HIV suppression after ART initiation is especially lacking among women. Women respond differently to ART than men,[13-17] often exhibiting more favorable immune responses [15-17] but experiencing greater drug toxicity [14] and more frequent treatment discontinuation.[13] To date, there is only one published study assessing the association between HCV and HIV suppression after ART initiation among women.[4] 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 one-year.[4] 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 without HCV during the follow-up period.

4.2 Methods

4.2.1 Study population

We used data collected by the WIHS for this analysis. A full description of the WIHS cohort is provided elsewhere.[62,81] Briefly, the WIHS is a prospective cohort of women living with and at risk for HIV, with follow-up at six-month intervals. At each visit, interviewer-administered questionnaires capture extensive medical, psychosocial, and drug use information. ART was defined as three or more antiretroviral medications, one of which had to be a PI, a NNRTI, one of the NRTIs abacavir or tenofovir, an integrase inhibitor, or an entry inhibitor.

Between 1994 and 2014, 4,982 women enrolled in the WIHS across ten study sites; 3,677 (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 January 1, 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.[82] 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- 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 six years among participants and we were concerned that chronic HCV may be misclassified due to 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 due to 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 20-80 copies/mL.

4.2.2 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.[74] Race was dichotomized as Black or non-Black and history of injection drug use was included as yes/no. Because our sample size was <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 <200, 200-499, ≥500 cells/μL, and HIV RNA was categorized as ≤4000, 4001-10,000, and >10,000 copies/mL. Liver fibrosis was assessed by the FIB-4 index; scores were dichotomized as >1.45 and ≤1.45 to differentiate women with and without significant fibrosis.[67-

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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 >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.

4.2.3 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 HCV to women without 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 September 30, 2015, the last possible date that data were available. Women were right-censored at the earliest occurrence of loss to follow-up, death, or last visit prior to September 30, 2015. Loss to follow-up was defined as two consecutively missed study visits. We also censored HIV/HCV-coinfected women who initiated HCV treatment and HIV-monoinfected 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, denoted as $W_i^X = Pr(X_i = x)/Pr(X_i = x|V_i)$. These weights are fully described in Appendix 1. Logistic regression was used to estimate the denominator of the exposure weight and included

age, race, year of ART initiation, baseline HIV-RNA, baseline CD4 cell count, FIB-4, and history of injection drug use.

We created time-varying inverse-probability-of-censoring weights to account for right-censoring (see Appendix 1).[72] Pooled logistic regression models were used to estimate the two censoring weights. The numerator models included time, HCV status, age, race, and baseline alcohol and drug use. The denominator models included time, HCV status, age, race, and time-varying alcohol and drug use measured at visit *k*-1. 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.[74]

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

4.2.4 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 > 95% adherence to ART during the first six 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, US). The analysis was approved by the University of North Carolina at Chapel Hill Institutional Review Board.

4.3 Results

Of 441 women, 114 (26%) had chronic HCV before ART initiation (Table 4). 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 percent 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 2000-2005 and 22% initiated ART from 2006-2010. A greater proportion of women with chronic HCV initiated ART from 2000-2005 (70% vs. 49% among HCV-uninfected). At baseline, the median CD4 cell count was 303 cells/μL (IQR 188, 440) and median HIV RNA was 4.20 $\log_{10}$ 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 twenty-nine (52%) women completed follow-up alive, 86 (20%) died during follow-up, and 110 (25%) were lost to follow-up. Thirteen women with chronic HCV were censored due to HCV treatment initiation and three HCV-uninfected women were censored due to evidence of HCV acquisition during follow-up.

Table 5 depicts the crude and weighted risk ratios for detectable HIV RNA comparing

women with and without chronic HCV. There were 5,523 total study visits and HIV RNA was detected at 2,064 visits (37%). The percentage of study visits with detectable HIV RNA was higher among women with chronic HCV (47%, vs. 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 Figure 10. Approximately 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 two years the ratio was 1.60 (95% CI 1.17, 2.18), and by six years there was essentially no difference (RR 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 due to chance.

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 six 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 six months the ratio was 1.68 (95% CI 1.14, 2.44), at two

years the ratio was 1.43 (95% CI 0.98, 2.07), and by six years there was no difference (RR 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).

4.4 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 two 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.[46,47] When we repeated our analysis among women reporting >95% adherence during the first six 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 [36,37] and HCV has also been shown to replicate in

extrahepatic lymphoid cells.[49,83,84] 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.[2-8,78-80] Yet, a recent study by Hua *et al*. 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.[9] In that study significantly more HIV/HCV-coinfected patients experienced viral failure by 48 weeks after ART initiation.[9] 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.[2-8,78-80] WIHS data are interval censored at six-month time periods, and the median time to first suppressed viral load in our analytic sample was approximately six 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.[85] Previous studies often defined HCV by HCV antibody status only [2-9] 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 only included women. Women experience more frequent ART regimen discontinuation [13] and drug toxicity [14] 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*. found that the cumulative incidence of HIV suppression one year after ART initiation was lower among HIV/HCV-coinfected women than among HIV-monoinfected women.[4] After adjustment for confounding, there was no difference in HIV viral response by HCV status but follow-up was limited to one year after ART initiation.[4]

Our study has several limitations. We used observational data and the possibility of uncontrolled confounding remains. HCV may also potentiate hepatoxicity after ART initiation, [86,87] which could lead to more frequent regimen changes and interruptions in therapy among HIV/HCV-coinfected persons.[88,89] 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 due to 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.[90,91] 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.[92]

Nevertheless, the extent to which we achieved exchangeability is not testable in observational data.

There was also an average of six years between baseline HCV testing and ART initiation. This could result in poorer clinical outcomes among women with chronic HCV due to worsening liver function [36-41] 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 US. 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 US with respect to demographic characteristics [62] 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 US is limited.[93]

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 two 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 [94-97] and considerable barriers to HCV treatment remain.[98,99] 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.

Table 4. Baseline characteristics of 441 HIV-infected women initiating ART by HCV 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 [b]	19	17%	74	23%	93	21%
Education [c]						
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 [d]						
0 drinks per week	60	53%	150	46%	210	48%
1 – 7 drinks per week	32	28%	135	41%	167	38%
>7 drinks per week	22	19%	42	13%	64	15%
Ever used non-injection drugs	109	96%	221	68%	330	75%
Ever injected drugs	99	87%	35	11%	134	30%
Chronic active HBV [e]	1	<1%	8	2%	9	2%
Year of ART initiation [f]						
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 [g]	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 [h]	4.16	3.11, 4.84	4.23	3.34, 4.77	4.20	3.27 4.79
FIB-4 > 1.45	91	80%	70	21%	161	37%

[a] Interquartile range

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

[c] Education categories do not add to the total due to missing information

[d] Self-reported alcohol use within the last six months

[e] 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.
[f] ART is defined as use of three or more antiretroviral medications approved by contemporaneous DHHS guidelines
[g] Self-reported use of single or dual antiretroviral prior to ART initiation.
[h] HIV viral load is reported in $\log_{10}$ copies/mL.

Table 5. Estimated associations between HCV infection and detectable HIV RNA among 441 women enrolled in the Women's Interagency HIV Study, January 2000-September 2015

	HCV+ (n=114)	HCV- (n=327)	Overall (n=441)
Total study visits	1,509	4,014	5,523
Visits with detectable HIV viral load	708	1,356	2,064
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	--

[a] Weights 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.

[b] 95% CI was estimated with a nonparametric bootstrap using 200 samples with replacement.

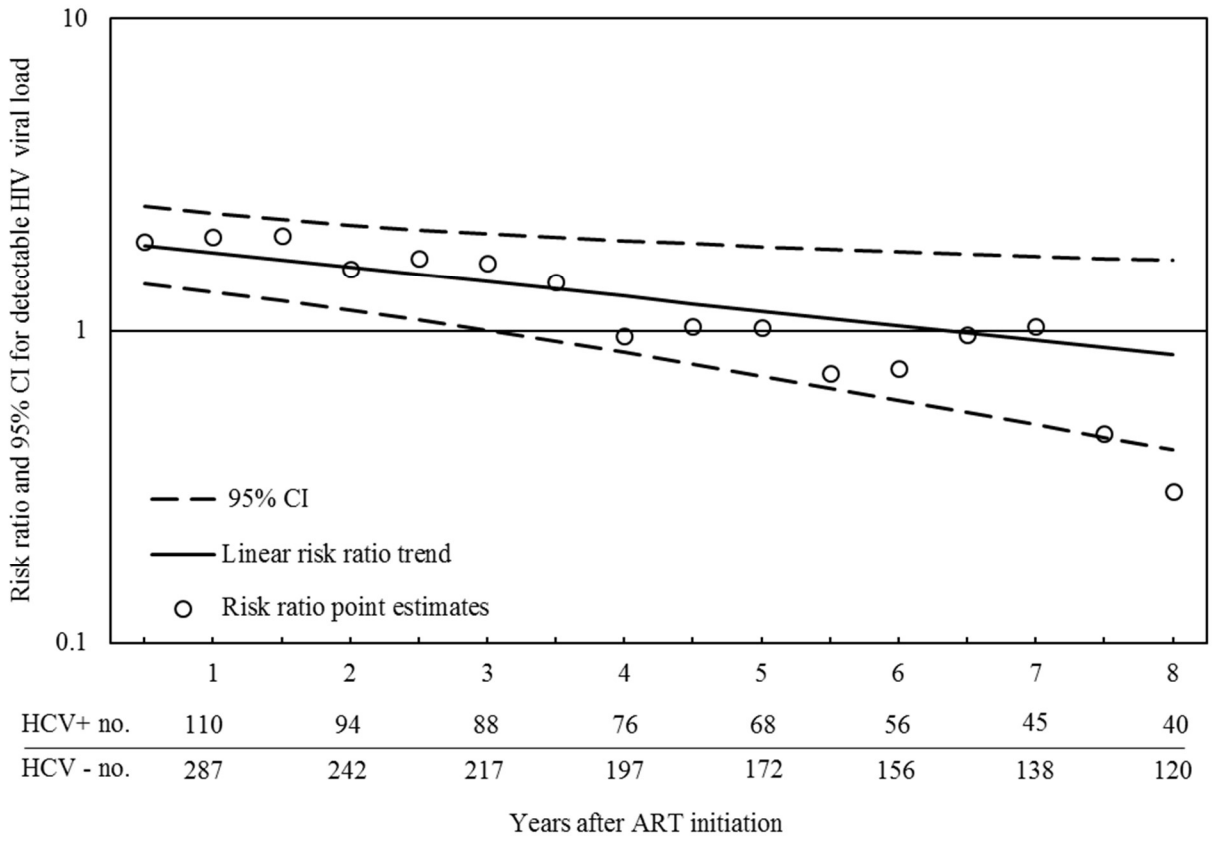

Figure 10. Estimated association between chronic HCV infection and detectable HIV RNA at each 0.5-year interval following ART initiation among 441 HIV-infected women enrolled in the Women's Interagency HIV Study, January 2000-September 2015. The open circles represent the risk ratio point estimates. 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.

CHAPTER 5: CHRONIC HEPATITIS C VIRUS INFECTION, DEPRESSION, AND PROGRESSION OF HIV DISEASE AMONG WOMEN INITIATING ANTIRETROVIRAL THERAPY

5.1 Introduction

One in four persons with HIV in the US are coinfected with HCV.[1] Untreated HCV may negatively impact HIV disease by accelerating progression to AIDS and mortality.[2-7,9,11] Studies examining the effect of HCV on HIV disease progression have not yet considered the role of depression.

Depression is common and possibly more severe among persons with HIV/HCV-coinfection than among HIV-monoinfected persons.[28,29,100] After adjustment for drug and alcohol use, Libman *et al*. observed higher mean scores on the CES-D among HIV/HCV-coinfected patients than in HIV-monoinfected patients.[29] Yoon *et al*. found that HCV was associated with depression severity among persons with HIV, even after removing somatic items from their depression measure.[28]

Depression accelerates progression to AIDS and mortality among persons with HIV-monoinfection.[21,22,26,101] In a recent study of women with HIV initiating ART, the mortality HR among women with depression (defined as CES-D score >16) was 3.38 (95% CI 2.15, 5.33), in comparison to women with no depression.[26] Depression is often associated with behaviors that worsen HIV treatment outcomes including decreased initiation and adherence to ART,[18-20] and use of alcohol and other substances.[54,55]

Understanding the combined effects of HCV and depression on HIV disease progression is critical. If the joint effects of depression and HCV are greater than we would expect given

their independent effects, persons living with HIV/HCV-coinfection may need additional psychosocial support and interventions to identify and treat depression. Therefore, our objectives were to estimate the effect of chronic HCV on progression to AIDS or all-cause mortality among women with HIV who initiate ART, and to examine the joint effects of chronic HCV and depression on progression to AIDS or all-cause mortality among women with HIV initiating ART.

5.2 Methods

5.2.1 Study population

Data from the WIHS were used for this analysis. A full description of the WIHS is provided elsewhere.[62] Briefly, the WIHS is a prospective cohort study of women living with and at risk for HIV, with follow-up at six-month intervals. Interviewer-administered questionnaires capture medical, psychosocial, and behavioral information and biological specimens are collected at each visit. Between 1994 and 2014, 4,982 women enrolled in the WIHS; 3,677 (74%) were living with HIV at enrollment and 24 (0.5%) acquired HIV during follow-up.

Women with HIV who initiated ART after they enrolled in the WIHS and who were not diagnosed with AIDS prior to ART initiation were eligible for this analysis (n=1,002). For this study, ART was defined as three or more antiretroviral medications, one of which had to be a PI, a NNRTI, one of the NRTIs abacavir or tenofovir, an integrase inhibitor, or an entry inhibitor. We excluded 10 (1%) women who did not have at least one visit after ART initiation, 10 (1%) who did not have data available at ART initiation, and 25 (2%) women missing HCV RNA results. Therefore, 957 (96%) women were included in analyses.

Chronic HCV was defined as the presence of HCV antibodies and HCV RNA prior to ART initiation. Women with HCV antibodies but undetectable HCV RNA were considered

HCV-uninfected. Women are tested for HCV during one of their first three study visits after enrollment and the average length of time between HCV testing and ART initiation was three years among women eligible for this analysis. To reduce the likelihood of misclassifying chronic HCV, we supplemented HCV results with follow-up testing, if available. Nine HCV-uninfected women had evidence of HCV antibodies and RNA prior to ART initiation and were classified as HCV-infected. One HCV-infected woman was classified as HCV-uninfected due to a subsequent negative RNA result before ART initiation.

Depression was measured by the CES-D at each study visit. CES-D scores range from 0 to 60, and a score ≥16 indicates risk for depression.[63,64] For each visit, we categorized CES-D scores 16-60 as "depressed" and 0-15 as "not depressed."

The outcome of interest was AIDS diagnosis or death from any cause. In the WIHS, participants are asked about health events that occurred since their last study visit. Participants are specifically asked about AIDS-defining illnesses, including candidiasis of the esophagus, bronchi, trachea, or lungs; Kaposi sarcoma; tuberculosis; etc. The date and specific AIDS-defining illnesses are recorded in the WIHS database. WIHS participants are also routinely matched to the National Death Index and local vital statistics registries.

5.2.2 Covariate assessment

Baseline covariates were measured at the last study visit prior to ART initiation and included age, race/ethnicity, year of ART initiation, history of injection drug use, education, liver fibrosis, and CD4 cell count. Age and CD4 cell count were included in models as continuous variables using restricted quadratic splines with four knots at the 5th, 35th, 65th, and 95th percentiles.[74] Race/ethnicity was categorized as non-Hispanic White, non-Hispanic Black, and all other races/ethnicities (Hispanic, Asian/Pacific Islander, Native American/Alaskan, and races

categorized as other). History of injection drug use was dichotomized as yes/no. Year of ART initiation was categorized as 1995-1999, 2000-2004, 2005-2009, or 2010-2015, and education was classified as less than high school degree, high school degree, or some college/college degree. Liver fibrosis was measured by FIB-4 and dichotomized as >1.45 and ≤1.45 to differentiate between women with and without fibrosis, respectively.[67]

We also considered several time-varying covariates, which were measured at every study visit: drug use, alcohol use, smoking status, and HIV suppression. Women were categorized as using drugs if they reported any illicit or recreational drug use since their last study visit. Alcohol use was categorized as 0, 1-7, or >7 drinks per week since prior study visit. Women who reported smoking cigarettes or other tobacco products since their last visit were considered to be current smokers. HIV suppression was used as a proxy measure for ART adherence. We defined suppression as ≤80 HIV copies/mL to accommodate assays used during the study period, which had lower limits of detection ranging from 20 to 80 copies/mL. Time-varying covariates were missing at 5-6% of visits and were replaced by values carried forward from previous visits.

5.2.3 Statistical methods

Women were followed from the date of the first study visit they reported ART use until the earliest occurrence of the following: date of the first study visit with an AIDS diagnosis; date of death; or censoring. Women were censored due to loss to follow-up, evidence of incident HCV infection, or HCV treatment initiation. Loss to follow-up was defined as two consecutively missed study visits. Women who initiated any HCV treatment during follow-up were censored because most of the treatments available were interferon-based, and depression was a common side effect of these therapies. Women who remained in the study were administratively censored at their last visit prior to September 30, 2015, the last date data were available.

Marginal structural Cox proportional hazards models were used to 1) assess the effect of chronic HCV on AIDS diagnosis or death, 2) assess the joint effects of depression and chronic HCV on AIDS diagnosis or death, and 3) create crude and weighted cumulative incidence curves. We used marginal structural Cox proportional hazards regression, rather than standard regression methods, to appropriately adjust for time-varying confounders of the effect of time-varying depression on the outcome.[75] There is a detailed description of these models in Appendix 1.

We created stabilized time-fixed inverse-probability-of-exposure weights to control for confounding of the relationship between chronic HCV and AIDS diagnosis or death.[59,71] Appendix 2 provides more detail about these weights. Logistic regression models were used to estimate the weights and included age, race/ethnicity, education, history of injection drug use, year of ART initiation, FIB-4, and baseline CD4 cell count. Smoking was also included and was measured at the last visit prior to ART initiation.

Inverse-probability-of-censoring weights were created to account for right-censoring due to loss to follow-up (Appendix 2).[72] Pooled logistic regression models were used to estimate these weights and included time since ART initiation, chronic HCV, age, race/ethnicity, and time-varying alcohol and drug use, measured at the prior visit. Time since ART initiation was included as a continuous variable in the models using restricted quadratic splines with four knots at the 5^{th}, 35^{th}, 65^{th}, and 95^{th} percentiles.[74]

We also created time-varying inverse-probability-of-depression weights to control for confounding of the relationship between depression and AIDS diagnosis or death in the joint effects model (Appendix 2). These weights were necessary to assess interaction between chronic HCV and depression, rather than modification of the effect of chronic HCV on AIDS diagnosis

or death, by depression.[102] Pooled logistic regression models were used to estimate these weights. The models included chronic HCV, age, race/ethnicity, education, baseline CD4 cell count, year of ART initiation, time since ART initiation and time-varying drug use, alcohol use, HIV suppression, smoking status, and history of depression (measured at the prior two study visits).

We verified proportionality of hazards in the weighted Cox models by Wald chi-square tests on product terms between chronic HCV and time, and depression at baseline and time (both *p*-values > 0.05).

To assess additive interaction between chronic HCV and depression in the joint effects model, we calculated risk of AIDS diagnosis or mortality and ICs at 5 and at 10 years after ART initiation.[77] We used a nonparametric bootstrap with 200 resamples with replacement to obtain 95% CIs for the ICs. Multiplicative interaction was assessed from the Wald chi-square test for the product term for chronic HCV and depression in the joint effects model.

5.2.4 Sensitivity analyses

We conducted two sensitivity analyses to assess the robustness of our findings. More than half of the women in our study sample initiated ART prior to the year 2000 and our findings may not be relevant to current clinical practice because current ART regimens are more effective and have fewer side effects than older regimens. Therefore, we restricted our analytic sample to women who initiated ART after the year 2000 in our first sensitivity analysis.

In our second sensitivity analysis we used a higher CES-D score for depression, ≥22. Despite the high sensitivity when using scores ≥16 as the cut-off for depression (~99%), the specificity is lower.[65] Thus, we sought reduce the number of women who would be misclassified as depressed in our analysis.

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

5.3 Results

Of the 957 women with HIV, 200 (21%) had chronic HCV prior to ART initiation (Table 6). The median age was 38 years (IQR 33, 44) and more than half of the women self-identified as Black non-Hispanic (58%). About half (54%) of the women reported an annual household income <$12,000 and one-third (35%) did not have a high school degree. A large minority of the women (41%) had depression at the visit prior to ART initiation. Most women with chronic HCV (85%) had previously injected drugs and two-thirds (68%) of all women reported using non-injected drugs in the past. The median CD4 cell count at ART initiation was 330 cells/mm^3 (IQR 207, 471) and more than half (58%) of the women initiated ART between 1995 and 1999.

Women experienced 7182 person-years during follow-up, in which 316 were diagnosed with AIDS or died during follow-up (Table 7). The incidence rates of AIDS diagnosis or death were 7.12 and 3.80 per 100 person-years for women with and without chronic HCV, respectively. In addition, 298 (31%) women were lost to follow-up, 5 (<1%) HCV-uninfected women had an incident HCV infection, and 34 (4%) women with chronic HCV initiated HCV treatment during follow-up. The weighted HR for AIDS diagnosis or death was 1.68 (95% CI 1.03, 2.74) when comparing women with chronic HCV to women without chronic HCV.

In the joint effects model the weighted HR for AIDS diagnosis or death was 2.19 (95% CI 1.56, 3.07) comparing HCV-uninfected women with depression to HCV-uninfected women without depression (Table 8). The weighted HR was 1.65 (95% CI 0.90, 3.01) comparing HCV-infected women without depression to HCV-uninfected women without depression. Lastly, the

weighted HR was 3.02 (95% CI 1.49, 6.15) when comparing women with chronic HCV and depression to women with neither HCV or depression.

Unweighted and weighted 20-year cumulative incidence curves for AIDS diagnosis or death, stratified by chronic HCV, and chronic HCV and depression, are presented in Figures 11 and 12, respectively. In Figure 11, the cumulative incidence of AIDS diagnosis or death was higher in women who had chronic HCV. In the joint classification of chronic HCV and depression (Figure 12), women with chronic HCV and depression had the highest cumulative incidence of AIDS diagnosis or death.

At 5 years, the IC was 0.09 (95% CI -0.27, 0.33) and at 10 years the IC was 0.05 (95% CI -0.31, 0.33). Because both ICs are greater than zero and each exposure increases the risk of the outcome (Table 9), there may be synergism between HCV and depression on progression to AIDS diagnosis or death. However, the IC CI are imprecise and include the null value. The *p*-value for the product term between HCV and depression was 0.71, which indicates no departure from multiplicativity of effects.

The magnitude of the HRs were attenuated when we limited our study sample to the 398 women who initiated ART after the year 2000. The weighted HR for the association between chronic HCV and AIDS diagnosis or death was 1.57 (95% CI 0.71, 3.47). In the joint effects model, the weighted HR comparing non-depressed women with chronic HCV to non-depressed women without chronic HCV was 1.17 (95% CI 0.39, 3.52). When comparing women with depression and chronic HCV to women with neither chronic HCV nor depression, the weighted HR was similar, 2.59, but less precise (95% CI 0.93, 7.22).

The results from the joint effects model were similar when we classified women with CES-D scores ≥ 22 as depressed. Compared to HCV-uninfected women without depression, the

HR for AIDS diagnosis or death was 2.21 (95% CI 1.55, 3.17) for HCV-uninfected women with depression, 1.74 (95% CI 1.02, 3.00) for HCV-infected women without depression, and 3.18 (95% CI 1.29, 8.35) for HCV-infected women with depression.

5.4 Discussion

Women with chronic HCV and depression experienced accelerated progression to AIDS diagnosis or death, when compared to women with neither chronic HCV or depression. In addition, women with depression who did not have chronic HCV also experienced accelerated progression to AIDS diagnosis or death. Results from the joint effects model indicate that in the absence of depression, women with chronic HCV have an increased hazard of AIDS diagnosis or death, however this HR was somewhat weaker and less precise.

Our findings support previous research regarding the harmful effects of depression on HIV disease progression.[21,22,26,101] Depression is often associated with behavioral factors that worsen HIV outcomes, including decreased ART adherence [18-20] and alcohol and drug use.[54,55] Even after controlling for time-varying drug use, alcohol use and HIV suppression, we found that women who experienced depression, regardless of chronic HCV status, had a 2 to 3-fold increase in the hazard of AIDS diagnosis or death.

Several studies observed accelerated progression to AIDS or death among persons living with HIV/HCV-coinfection when compared to HIV-monoinfected patients.[2-7,9,11] Yet, other studies have not found that HCV affects HIV disease progression.[8,10] Previous studies assessing the effect of HCV on HIV disease progression did not report the prevalence of depression in their study populations. It is possible that varying frequencies of depression in these populations could explain discrepant findings.

We did not find evidence of interaction between chronic HCV and depression on the

additive scale or on the multiplicative scale. Given that both exposures had an effect on AIDS diagnosis or death, would expect to see interaction on at least one scale.[103] The ICs at five and at ten-years after ART initiation are greater than zero and both HCV and depression increased the risk for AIDS diagnosis or death. This indicates possible synergism between HCV and depression on the additive scale but our sample size and the imprecision of the estimated measures of effect preclude certainty.

This study is not without limitations. Despite the extensive information available for women enrolled in the WIHS, there may be unmeasured confounders that could bias our results. Additionally, more than half of the study participants initiated ART prior to the year 2000. Currently available ART regimens are more effective and tolerable than the regimens many women in the study were initially using. When we restricted our analysis to women who initiated ART after the year 2000 (n=398), the HRs demonstrated somewhat attenuated increases in disease progression among HIV/HCV-coinfected women, with CIs that were much wider because of the reduced sample size.

Our primary exposure, chronic HCV, was a prevalent exposure and the duration of infection was unknown. It is likely that women living with HCV for longer periods of time will experience worse HIV outcomes, given the natural history of HCV infection.[37,40,41] However, women with HIV who survived with HCV-coinfection and were eligible for our analysis could introduce survivor bias.[104] Although we could not control for duration of HCV infection in our analyses, we included FIB-4 in our exposure weights to control for confounding by liver fibrosis among HIV/HCV-coinfected women.

Importantly, we used marginal structural models to assess the effects of chronic HCV and depression on HIV treatment outcomes. Previous studies assessing the effect of HCV on HIV

disease progression have not used this approach. A benefit of these models is that they may reduce selection bias due to lost to follow-up through the use of inverse-probability-of-censoring weights.[71,72] In addition, these models were necessary to assess the joint effects of chronic HCV and depression because depression was time-dependent. Standard regression methods can produce biased results for time-varying exposures and confounders because their control of confounding blocks causal pathways of interest.[60,61] In the WIHS, depression status was collected at every study visit. Therefore, depression status at the last study visit was both an exposure of interest and a potential confounder of depression status at the current study visit and the outcome.

In conclusion, we observed accelerated progression to AIDS or all-cause mortality among women with depression, particularly among women who also had chronic HCV. These findings highlight the need for improved access and engagement in interventions to treat depression among persons with HIV/HCV-coinfection.

Table 6. Baseline characteristics of 957 women with HIV who initiated ART by chronic HCV status, Women's Interagency HIV Study, May 1995 - September 2015

	Chronic HCV (n=200)		No chronic HCV (n=757)		Total (n=957)	
Characteristic	Median or n	IQR[a] or %	Median or n	IQR[a] or %	Median or n	IQR[a] or %
Age at ART initiation (years)	42	38, 47	37	32, 43	38	33, 44
Race/ethnicity						
White, non-Hispanic	36	18.0%	102	13.5%	138	14.4%
Black, non-Hispanic	121	60.5%	434	57.3%	555	58.0%
Other[b]	43	21.5%	221	29.2%	264	27.6%
Chronic HBV infection[c]	5	2.5%	21	2.8%	26	2.7%
Annual household income ≤ $12,000	135	67.5%	385	50.9%	520	54.3%
Education						
Less than high school degree	78	39.0%	258	34.1%	336	35.1%
High school degree	63	31.5%	229	30.3%	292	30.5%
Some college or college degree	59	29.5%	270	35.7%	329	34.4%
Alcohol use (drinks per week)[d]						
0	120	60.0%	396	52.3%	516	53.9%
>0-7	50	25.0%	299	39.5%	349	36.5%
>7	30	15.0%	62	8.2%	92	9.6%
Depression[e]	91	45.5%	304	40.2%	395	41.3%
Current smoker	140	70.0%	275	36.3%	415	43.4%
Injection drug use (ever)	169	84.5%	68	9.0%	237	24.8%
Non-injection drug use (ever)	182	91.0%	472	62.4%	654	68.3%
HIV viral load[f]	3.60	2.63, 4.50	3.97	3.08, 4.66	3.91	3.00, 4.64
CD4 cell count	312	203, 447	339	209, 474	330	207, 471
Single or dual antiretroviral use prior to ART	135	67.5%	443	58.5%	578	60.4%
FIB-4 > 1.45	118	59.0%	178	23.5%	296	30.9%
Year of ART initiation[g]						
1995-1999	137	68.5%	422	55.7%	559	58.4%
2000-2004	41	20.5%	149	19.7%	190	19.9%
2005-2009	17	8.5%	78	10.3%	95	9.9%
2010-2015	5	2.5%	108	14.3%	113	11.8%

[a] Interquartile range

[b] Other race/ethnicity includes Hispanic, Native American/Alaskan Native, Asian/Pacific Islander, and races/ethnicities categorized as other

[c] Chronic hepatitis B virus infection is defined as positive hepatitis B core antibody and positive hepatitis B surface antigen measured during one of the first three study visits after enrollment

[d] Self-reported alcohol use within the last six months

[e] CES-D score ≥16
[f] HIV viral load is reported in $\log_{10}$ copies/mL
[g] Antiretroviral use is defined as three or more antiretroviral medications, one of which has to be a PI, a NNRTI, one of the NRTIs abacavir or tenofovir, an integrase inhibitor, or an entry inhibitor.

Table 7. Estimated associations between chronic HCV and AIDS diagnosis or all-cause mortality among 957 women with HIV who initiated ART in the Women's Interagency HIV Study, May 1995 - September 2015

	Chronic HCV (n=200)	No chronic HCV (n=757)	Overall (n=957)
Outcome events	93	223	316
AIDS diagnosis	54	182	236
Death	39	41	80
Person-years	1306.7	5875.31	7182.03
Incidence rate per 100 person-years	7.12	3.80	4.40
Crude hazard ratio (95% CI)	1.76 (1.38, 2.25)	1.	--
Weighted hazard ratio [a] (95% CI)	1.68 (1.03, 2.74)	1.	--

[a] Weights account for the following set of time-fixed and time-varying covariates: age at ART initiation, race/ethnicity, year of ART initiation, history of injection drug use, education, liver fibrosis, baseline CD4 cell count, smoking status, alcohol and drug use, and time.

Table 8. Unweighted and weighted joint effects of chronic HCV and depression on AIDS diagnosis or all-cause mortality among 957 women with HIV who initiated ART in the Women's HIV Interagency HIV Study, May 1995 - September 2015

		AIDS diagnosis or all-cause mortality	Person-years[a]	Incidence rate[b]	HR (95% CI)	Interaction *p*-value[c]
Unweighted[d]	HCV-, no depression	113	3771.33	3.00	1	0.56
	HCV-, depression	110	2103.98	5.23	1.71 (1.31, 2.22)	
	HCV+, no depression	40	682.37	5.86	1.81 (1.26, 2.60)	
	HCV+, depression	53	624.35	8.49	2.67 (1.93, 3.71)	
Weighted[e]	HCV-, no depression	132	4357.27	3.03	1	0.71
	HCV-, depression	129	1942.61	6.64	2.19 (1.56, 3.07)	
	HCV+, no depression	33	577.30	5.72	1.65 (0.90, 3.01)	
	HCV+, depression	48	554.24	8.66	3.02 (1.49, 6.15)	

[a] In the unweighted model we classified all of a woman's person-time "depressed" or "not depressed" based upon her depression status at the last visit before ART use was reported. In the weighted model we classified the time between a women's last visit and current visit as "depressed" or "not depressed" based upon a woman's depression status at the current study visit.

[b] Incidence rate per 100 person-years

[c] *p*-value for the interaction term between the joint exposures, HCV and depression

[d] Depression was measured at last visit before ART use was reported in the unweighted model

[e] Weights account for the following set of time-fixed and time-varying covariates: age at ART initiation, race/ethnicity, year of ART initiation, history of injection drug use, history of depression, education, liver fibrosis, baseline CD4 cell count, suppressed HIV RNA, smoking, alcohol and drug use, and time.

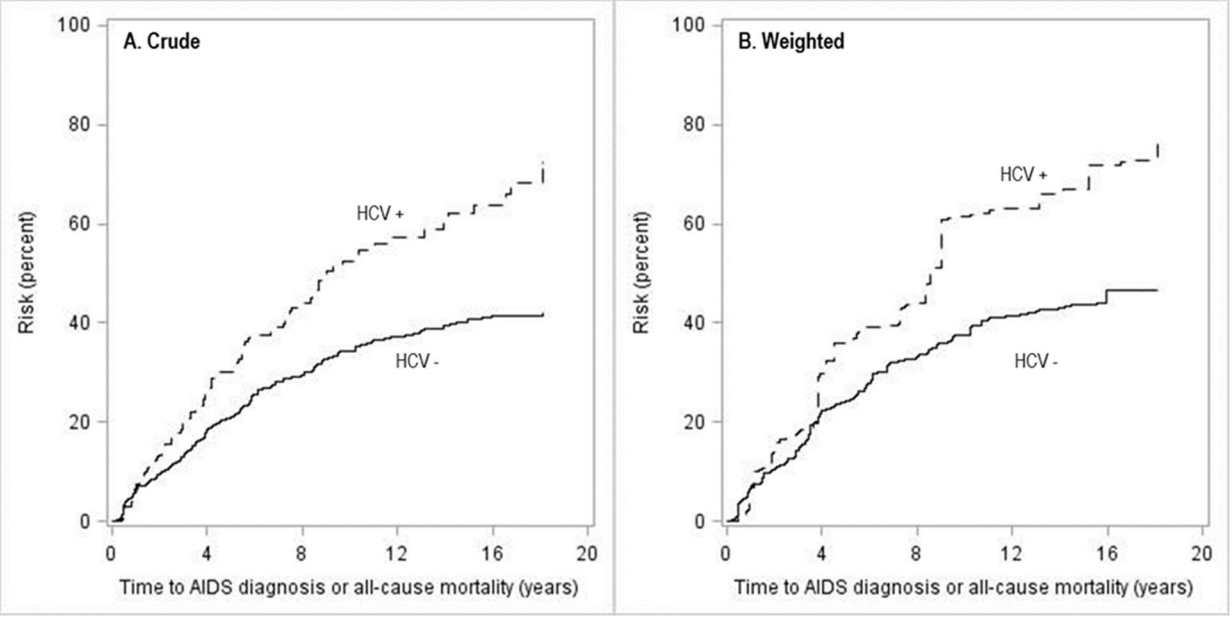

Figure 11. Crude and weighted Kaplan-Meier survival curves for AIDS diagnosis or all-cause mortality, stratified by chronic HCV, among 957 women with HIV who initiated ART between May 1995 and September 2015. Panel A depicts the crude survival curves and panel B depicts the inverse-probability-of-treatment-and-censoring weighted curves. The curves in panel B reflect weighted pseudopopulations in which confounding has been removed, in expectation. Weights account for the following set of time-fixed and time-varying covariates: age at ART initiation, race/ethnicity, year of ART initiation, history of injection drug use, education, liver fibrosis, baseline CD4 cell count, alcohol and drug use, and time.

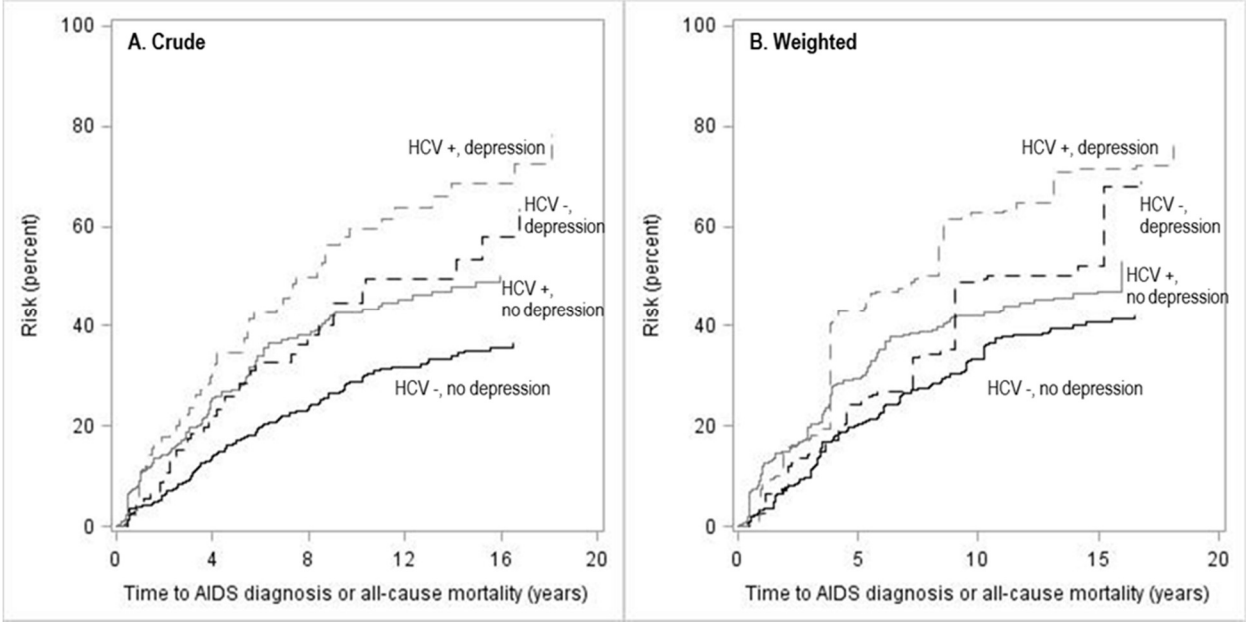

Figure 12. Crude and weighted Kaplan-Meier survival curves for AIDS diagnosis or all-cause mortality, stratified by chronic HCV and depression, among 957 women with HIV who initiated ART between May 1995 and September 2015. Panel A depicts the crude survival curves and panel B depicts the inverse-probability-of-treatment-and-censoring weighted curves. The curves in panel B reflect weighted pseudopopulations in which confounding has been removed, in expectation. The grey lines represent survival curves for women with HCV and the black lines represent women without HCV. The dotted curves indicate depression. Weights account for the following set of time-fixed and time-varying covariates: age at ART initiation, race/ethnicity, year of ART initiation, history of injection drug use, history of depression, education, liver fibrosis, baseline CD4 cell count, suppressed HIV RNA, smoking, alcohol and drug use, and time.

Table 9. Estimated risk, risk difference, and risk ratios for AIDS diagnosis or all-cause mortality among 957 women with HIV who initiated ART in the Women's HIV Interagency HIV Study, May 1995 - September 2015

		Risk	Risk difference	Risk ratio
5 years after ART initiation	HCV-, no depression	0.21	0	1
	HCV-, depression	0.30	0.09	1.45
	HCV+, no depression	0.25	0.04	1.20
	HCV+, depression	0.43	0.23	2.10
10 years after ART initiation	HCV-, no depression	0.33	0	1
	HCV-, depression	0.43	0.09	1.27
	HCV+, no depression	0.49	0.15	1.46
	HCV+, depression	0.63	0.30	1.88

CHAPTER 6: DISCUSSION

6.1 Summary

The goal of this dissertation was to investigate the effects of chronic HCV on HIV treatment outcomes among women initiating ART. Specifically, we assessed the longitudinal effect of chronic HCV on HIV suppression, and the effect of chronic HCV on progression to AIDS or all-cause mortality among women. We also examined the joint effects of chronic HCV and depression on progression to AIDS or all-cause mortality. This research was motivated by the prevalence of HCV among persons with HIV, i.e., one in four persons living with HIV in the US is coinfected with HCV, and by inconsistent results in previous studies assessing the relationships between HCV and HIV treatment outcomes.

In Chapter 4, we demonstrated that women with chronic HCV were more likely to have detectable HIV RNA up to two years after ART initiation than women without HCV. The association between chronic HCV and detectable HIV RNA disappeared by approximately six years after ART initiation. We hypothesized that chronic HCV may negatively impact HIV suppression due to biological and behavioral mechanisms. For example, other common HIV co-infections, such as herpes simplex virus type 2, increase HIV replication.[43-45] In addition, drug and alcohol use and decreased adherence to ART among persons with HIV/HCV-coinfection may also result in increased HIV viral load.[46,47] We repeated our analysis among women who reported >95% adherence to ART regimens within the first six months after initiation and the results were similar to those using the entire analytic sample. The results of this sensitivity analysis indicate that the observed association between HCV and HIV RNA is not fully

explained by differences in ART adherence among women with HIV/HCV-coinfection.

In Chapter 5, we observed accelerated progression to AIDS diagnosis or death among women with chronic HCV and depression, when compared to women with neither chronic HCV nor depression. In addition, HIV-infected women with depression who did not have chronic HCV also experienced accelerated progression to AIDS diagnosis or death. We did not find evidence of interaction between chronic HCV and depression on the additive or multiplicative scales. Yet our measures of interaction were imprecise, due to the limited sample size.

6.2 Limitations

One of the primary limitations in our analyses was the long length of time between HCV testing and ART initiation among women in our analytic samples. The average length of time between HCV testing and ART initiation was six years in our Aim 1 sample and three years in our Aim 2 sample. Therefore, misclassification of chronic HCV at ART initiation due to incident HCV infections, spontaneous clearance of the virus, and HCV treatment could have occurred. We sought to overcome this limitation by supplementing baseline HCV testing, which typically occurs during a woman's first three WIHS visits, with follow-up HCV testing, if available. Follow-up HCV test results were available for over 80% of the women in our samples. After reviewing the follow-up results, 1% of women with chronic HCV at enrollment cleared their infection prior to ART initiation, and 2% of women who were HCV-uninfected at enrollment were reclassified as HCV-coinfected in Aim 1. In Aim 2, 1% of women who were HCV-infected at enrollment cleared their infection prior to ART and <1% of women who were HCV-uninfected at enrollment had an incident HCV infection.

A second limitation of our analyses was the frequency of loss to follow-up among women in our samples. We defined loss to follow-up as two consecutively missed study visits and we

did not allow women to rejoin the analysis sample even if they returned at a subsequent WIHS visit. In Aim 1, 25% of the sample was censored due to loss to follow-up and in Aim 2, 30% of the sample was censored due to loss to follow-up. Longitudinal analytic methods assume censoring is not informative, i.e., not related to the exposure or outcome of interest. However, we expect that loss to follow-up was related to chronic HCV status, and to detectable HIV RNA in Aim 1 and AIDS diagnosis or death in Aim 2. Therefore, our estimated measures of effect would be biased by selection bias.[90,91] To reduce 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 outcomes, those who were lost to follow-up would be exchangeable with those who remained under study in our weighted sample, and bias would be averted.[92] Nevertheless, the extent to which we achieved exchangeability is not testable in observed data.

The observed associations between chronic HCV and HIV treatment outcomes may have limited generalizability to all HIV-infected women who are initiating ART. In Aim 1, the target population was women who initiated ART after they enrolled in the WIHS and after year 2000. These criteria resulted in fewer than 500 women who were eligible for our study. Although women in the WIHS are generally representative of the HIV epidemic among women in the US with respect to demographic characteristics,[62] we cannot guarantee that the distributions of effect measure modifiers, such as ART adherence, are similar. Thus, the magnitude of the estimated effect of chronic HCV on detectable HIV RNA may be larger or smaller in other cohorts of women, if the proportion of women who adhere to ART is larger or smaller than in our cohort.[93] In Aim 2, more than half of the study participants initiated ART prior to the year 2000. Currently available ART regimens are more effective and tolerable than the regimens many women in the

study were initially using. Therefore, the results in Chapter 5 may not generalize to women who recently initiated ART.

Our analyses may also be limited by unmeasured and residual confounding. Despite the extensive information available for women enrolled in the WIHS, there may be unmeasured factors that could bias our estimated measures of effect. In addition, we collapsed categories of race/ethnicity, number of alcoholic drinks per week, etc. These categorizations of confounders could result in residual confounding of the relationships between chronic HCV and HIV treatment outcomes. Lastly, measurement error may limit the validity of our analyses. In Aim 1, chronic HCV status may have been incorrectly measured due to the long length of time between WIHS enrollment and ART initiation. In Aim 2, one component of the outcome, AIDS diagnosis, was self-reported and women may have misunderstood or misreported their diagnoses.

6.3 Strengths

A primary strength of these analyses was the high-quality data from the WIHS. The WIHS is a longitudinal cohort study designed to assess the progression of HIV disease among women. Detailed interviews about medical, psychosocial, drug use, and sexual behavior information, as well as biological specimens are collected from participants every six months. The WIHS also strives to minimize missing data. For example, HIV RNA measurements were missing for less than 4% of the visits included in our Aim 1 analyses and time-varying covariate data were missing for 5-6% of visits in Aim 2. The WIHS has also been collecting these data since 1994. This allowed us to examine the effect of chronic HCV on HIV suppression for up to 15 years after ART initiation (median follow-up was 5.5 years) and the effect of chronic HCV on progression of HIV disease for up to 20 years after ART initiation (median follow-up was 5.8 years). In contrast, several previous studies assessing the effect of chronic HCV on HIV

suppression focused on the time to first suppressed HIV RNA measurement and follow-up was limited to between 12 and 24 months after ART initiation.[2,5,8,10]

The distinction between women with chronic HCV infection and those with HCV antibodies only (resolved HCV infection) was a second strength of these analyses. Active chronic HCV infection is defined by detectable HCV RNA and HCV antibodies. Approximately 15-25% of persons exposed to HCV will clear infection but continue to have an HCV antibody response.[85] Previous studies assessing the relationships between HCV and HIV treatment outcomes did not collect data on HCV RNA or had substantial missing HCV RNA results. They defined HCV by HCV antibody status only [2,3,5,6,8-11] and were not estimating the effects of active HCV infection on HIV treatment outcomes.

A third strength of these analyses were causal inference methods. No previous studies assessing the effects of chronic HCV on HIV treatment outcomes have used these methods. In Aim 1, we used inverse-probability-of-treatment-and-censoring weights to control for confounding and selection bias due to loss to follow-up and death. In Aim 2, we included inverse-probability-of-depression weights in the Cox proportional hazards model to assess the joint effects of chronic HCV and depression on progression to AIDS diagnosis or death. These weights were appropriate for our data, which included depression measurements at every study visit. Depression status at the last study visit was both an exposure of interest and a confounder of depression status at the current study visit and AIDS diagnosis or death.

6.4 Future directions for research and policy

Limited research has focused on the effects of chronic HCV on HIV treatment outcomes among women. Women respond differently to ART than men,[13-17] often exhibiting more favorable immune responses[15-17] but experiencing greater drug toxicity[14] and more frequent

treatment discontinuation.[13] However, in the one previous study that examined the association between HCV and HIV treatment outcomes in women, no association between and HCV and HIV suppression and no association between HCV and HIV disease progression were detected.[4] Therefore, the analyses presented here need to be repeated among larger cohorts of women to determine if they are reproducible.

Another area of exploration is estimating the effect of chronic HCV on CD4 cell count after ART initiation among women. HCV may negatively affect CD4 cell response to ART because HCV has been shown to replicate in cells outside of the liver and is associated with CD4 cell apoptosis.[49,50] Several studies do suggest that HCV coinfection is associated with impaired CD4 cell recovery after ART initiation.[2-8] However, other studies have found no differences in CD4 cell changes after ART initiation between HIV/HCV-coinfected patients and HIV-monoinfected patients,[9-13] or that the CD4 cell count differences decrease over time.[52,53] Therefore we plan to estimate the effect of HCV on changes in CD4 cell counts over a five-year period after ART initiation among HIV-infected women. We plan to use inverse-probability-of-treatment-and-censoring-weighted linear regression models to estimate the absolute change in CD4 cell counts from baseline to 5 years after ART initiation. We will compare the mean change in CD4 cell counts between women who are coinfected with HCV and those who are not at six months, one year, and at five years after ART initiation.

A third area of exploration is to determine whether successful treatment of chronic HCV alleviates the negative effects of chronic HCV on HIV treatment outcomes we observed. Directly-acting antiviral therapies for chronic HCV are now available and more than 90% of patients treated with these therapies achieve sustained virologic response, or cure. Persons living with chronic HCV often report poorer health-related quality of life than the general US

population.[105-107] Results from clinical trials of directly-acting antiviral therapies indicate there are secondary benefits to treatment which include improvement in mental health, fatigue, and work productivity.[108,109] Therefore, it would be noteworthy if HIV-infected women who are successfully treated for chronic HCV also experience similar HIV treatment outcomes as women who have HIV-monoinfection.

6.5 Conclusions

In conclusion, we observed an increased proportion of visits with detectable HIV viral load among women with HCV-coinfection up to two years after ART initiation. We also observed accelerated progression to AIDS or all-cause mortality among women with depression and chronic HCV. These findings suggest that HCV may negatively impact HIV treatment outcomes. Ensuring access to and improving engagement in HIV care should continue to be a chief concern for women with chronic HIV/HCV-coinfection.

APPENDIX 1: CHAPTER 4 INVERSE PROBABILITY OF TREATMENT AND CENSORING WEIGHTS

To control for confounding of the relationship between chronic HCV and detectable HIV RNA, we used stabilized time-fixed inverse-probability-of-exposure weights denoted as:

$$W_i^X = Pr(X_i = x)/Pr(X_i = x|V_i)$$

These weights create a pseudo-population in which chronic HCV is no longer associated with measured covariates, assuming no statistical model misspecification.[59,71] The numerator of the exposure weight represents the probability of having the exposure that participant *i* factually had; the denominator is the probability of having the exposure that participant *i* factually had conditional on V_i. V_i is a vector of covariate values at baseline for participant *i*, assumed to be sufficient to control for confounding. Logistic regression was used to estimate the denominator of the exposure weight.

Time-varying inverse-probability-of-censoring weights are denoted as:

$$W_{ij}^C = \prod_{k=0}^{j+1} Pr(C_{ik} = 0|\bar{C}_{ik-} = 0, X_i, V_i) / Pr(C_{ik} = 0|\bar{C}_{ik-1} = 0, X_i, \bar{V}_{ik-1})$$

These weights account for selection bias due to right-censoring from loss to follow-up and death.[72] We fit separate weight models for right-censoring due to death and loss to follow-up to allow the parameter estimates to differ for each censoring mechanism.[73] The numerator of the censoring weights represent the probability of remaining in the study at visit *k*, conditional on exposure and V_i. The denominators of the censoring weight are the conditional probability of remaining free from censoring, where $\bar{V}_{ik-}$ is a vector of time-fixed and time-varying covariate histories measured up to visit *k*-1. Pooled logistic regression models were used to estimate the censoring weights.

The log binomial regression models were weighted by the product of the treatment and censoring weights ($W_{ij} = W_i^X \times W_{ij}^{C_{loss\ to\ follow-up}} \times W_{ij}^{C_{death}}$). The average of the estimated weights was 1.05 (standard deviation: 1.78) and they ranged from 0.20 to 25.57. We obtained 95% confidence intervals (CIs) for the weighted ratio measures using a nonparametric bootstrap with 200 resamples with replacement. The estimated weights in the 200 samples ranged from 0.06 to 535.95. We trimmed the weights at the 0.5th and 99.5th percentile to reduce the variability of the estimated effect of chronic HCV on detectable HIV RNA.

APPENDIX 2: MARGINAL STRUCTURAL COX PROPORTIONAL HAZARDS MODELS

Model 1. Let T_i^x represent the time from ART initiation until the earliest occurrence of AIDS diagnosis or death or censoring due to lost to follow-up, incident HCV infection, or HCV treatment initiation for participant *i* if they had been assigned chronic HCV status *x*. Then the marginal structural Cox proportional hazards model for the effect of chronic HCV on AIDS diagnosis or death is defined as:

$$\lambda_{T^x}(t) = \lambda_0(t)\exp(\alpha_1 x(t))$$

where $\lambda_0(t)$ is the baseline hazard function and the parameter $\exp(\alpha_1)$ is the HR for the effect of chronic HCV on AIDS diagnosis or death.

Model 2. Let $T_i^{x_1,\bar{x}_2}$ represent the time from ART initiation until the earliest occurrence of AIDS diagnosis or death or censoring due to lost to follow-up, incident HCV infection, or HCV treatment initiation for participant *i,* if they had been assigned chronic HCV status x_1 and depression history $\bar{x}_2$ (overbar represents history). The marginal structural Cox proportional hazards model for the joint effects of chronic HCV and depression on AIDS diagnosis or death is defined as:

$$\lambda_{T^{x_1,\bar{x}_2}}(t) = \lambda_0(t)\exp(\alpha_1 x_1(t) + \alpha_2 x_2(t) + \alpha_3 x_1 x_2(t))$$

where the parameter $\exp(\alpha_1)$ is the HR for the effect of chronic HCV on AIDS diagnosis or death among women without depression, the parameter $\exp(\alpha_2)$ is the HR for the effect of depression on AIDS diagnosis or death among women without chronic HCV and the parameter $\exp(\alpha_1 + \alpha_2 + \alpha_3)$ is the HR for the joint effect of chronic HCV and depression on AIDS diagnosis or death.

These models were weighted by inverse-probability-of-treatment-and-censoring weights to control for confounding and selection bias. These weights are described in Appendix 3.

APPENDIX 3: CHAPTER 5 INVERSE PROBABILITY OF TREATMENT AND CENSORING WEIGHTS

To control for confounding of the relationship between chronic HCV and AIDS diagnosis or death, we used stabilized time-fixed inverse-probability-of-exposure weights denoted as:

$$W_i^X = Pr(X_i = x)/Pr(X_i = x|V_i)$$

These weights create a pseudo-population in which chronic HCV is no longer associated with measured covariates, assuming no statistical model misspecification.[59,71] The numerator of the exposure weight represents the probability of having the exposure that participant *i* factually had; the denominator is the probability of having the exposure that participant *i* factually had conditional on V_i. V_i is a vector of covariate values at baseline for participant *i*, assumed to be sufficient to control for confounding. Logistic regression was used to estimate the denominator of the exposure weight.

Time-varying inverse-probability-of-censoring weights are denoted as:

$$W_{ij}^C = \prod_{k=0}^{j+1} Pr(C_{ik} = 0|\bar{C}_{ik-1} = 0, X_i, V_i)/\, Pr(C_{ik} = 0|\bar{C}_{ik-1} = 0, X_i, \bar{V}_{ik-1})$$

These weights account for selection bias due to right-censoring.[71,72] The numerator of the censoring weight represents the probability of remaining in the study at visit *k*, conditional on exposure and V_i. The denominator of the censoring weight is the conditional probability of remaining free from censoring, where $\bar{V}_{ik-1}$ is a vector of time-fixed and time-varying covariate histories measured up to visit *k*-1. Pooled logistic regression models were used to estimate the censoring weights.

The second objective of these analyses was to assess the joint effects of chronic HCV and depression on AIDS diagnosis or death. We sought to examine interaction between chronic HCV and depression on the outcome, rather than effect modification of

chronic HCV on the outcome by depression. To do so, we needed to control for confounding of the relationship between depression and AIDS diagnosis or death, as we did for confounding of the relationship between chronic HCV and AIDS diagnosis or death. In addition, depression is a time-dependent exposure. Therefore, we created time-varying inverse-probability-of-depression weights to control for confounding and to appropriately handle the time-dependent nature of depression. These weights were defined as:

$$W_{ij}^{D} = \prod_{k=0}^{j} Pr[D_{ik}|\bar{D}_{ik-1}, X_i, V_{i0}, \bar{C}_{ik-1} = 0] / Pr[D_{ik}|\bar{D}_{ik-1}, X_i, \bar{V}_{ik-1}, \bar{C}_{ik-1} = 0]$$

D_{ik} represents the depression status of a participant *i* at visit *k* and $\bar{D}_{ik-1}$ is the depression history of a given participant measured at visit *k*-1. X_i is chronic HCV. V_{i0} is a vector of baseline covariate values at for each participant *i* assumed to be sufficient to control for confounding between depression and AIDS diagnosis or death and $\bar{V}_{ik-1}$ is the vector of time-fixed and time-varying covariate histories measured up to visit *k*-1. $\bar{C}_{ik-1} = 0$ represents women who remain free from censoring at visit *k*-1.

The marginal structural Cox proportional hazards model assessing the effect of chronic HCV on AIDS diagnosis or death was weighted by the product of the inverse-probability-of-treatment weights and inverse-probability-of-censoring weights. The marginal structural Cox proportional hazards model assessing the joint effects of chronic HCV and depression on AIDS diagnosis or death was weighted by the product of all three weights described above.

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