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The Effects of Hepatitis C Infection and Treatment on All-cause Mortality Among People Living With Human Immunodeficiency Virus

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Background. Persons living with human immunodeficiency virus (HIV; PLwH) are commonly co-infected with hepatitis C virus (HCV). Most co-infected individuals can achieve a sustained HCV virologic response after treatment with direct-acting antivirals (DAA). However, the effect of HCV co-infection and DAA treatment on mortality after initiating antiretroviral therapy (ART) is unknown for PLwH.

Methods. We analyzed data from the Women's Interagency HIV Study and the Multicenter AIDS Cohort Study. Participants included those who had prevalent HIV or seroconverted during follow-up; all were antiretroviral-naive and acquired immunodeficiency syndrome (AIDS)-free prior to their first visit after 1 October 1994. The follow-up lasted 10 years or until 30 September 2015. We used parametric g-computation to estimate the effects of HCV infection and DAA treatment on mortality had participants initiated ART at study entry.

Results. Of the 3056 eligible participants, 58% were female and 18% had HCV. The estimated 10-year all-cause mortality risk in the scenario in which no PLwH had HCV was 10.4% (95% confidence interval [CI] 6.0–18.0%). The 10-year mortality risk difference for HCV infection was 4.3% (95% CI 0.4–8.9%) and the risk ratio was 1.4 (95% CI 1.0–1.9). The risk difference for DAA treatment was -3.8% (95% CI -9.2–0.9%) and the risk ratio was 0.8 (95% CI 0.6–1.1).

Conclusions. HCV co-infection remains an important risk factor for mortality among PLwH after initiating ART according to modern guidelines, and DAAs are effective at reducing mortality in this population. HCV prevention and treatment interventions should be prioritized to reduce mortality among PLwH.

Keywords. hepatitis C virus; human immunodeficiency virus; antiretroviral therapy; direct-acting antivirals.

With modern antiretroviral therapy (ART), life expectancies for people living with human immunodeficiency virus (HIV; PLwH) are approaching those of HIV seronegative individuals [1]. While acquired immunodeficiency syndrome (AIDS)-related causes of death continue to decline [2], liver-related complications have emerged as a major source of mortality, largely driven by co-infections with viral hepatitides [3].

In the United States, an estimated 25% of PLwH are co-infected with HCV [4]. However, the effect of HCV on mortality among PLwH remains unclear. In the current era of effective and less-toxic ART, studies have estimated that the all-cause mortality rates are up to 2-fold higher among those individuals with HIV/HCV co-infections [5, 6], but other studies have found more modest effects [7, 8]. Most studies investigating the role of HCV co-infections on mortality among PLwH were conducted prior to the ART guidelines recommending treatment for all PLwH [9]. These studies also pre-date direct-acting antiviral (DAA) medications, which are capable of producing sustained HCV virologic responses (SVRs) in more than 97% of individuals [10], irrespective of the9ir HIV status [11].

Though DAA treatment is considered curative, it may not fully reverse the effects of HCV infection, and thus infection and treatment effects may differ [12]. Although data are accumulating that indicate DAAs reduce the complications of HCV infection [13, 14] and improve survival [15, 16], treatment does not immediately reverse liver fibrosis. Therefore, mortality risks may remain elevated in successfully-treated individuals.

Without estimates of the long-term impacts of HCV co-infections and DAA treatments on mortality, it is difficult for clinicians and policy-makers to properly prioritize HCV care among PLwH. We thus estimated the long-term effects of HCV infection and DAA treatment on all-cause mortality among PLwH under modern guidelines, which suggest ART initiation regardless of CD4 cell count. We estimated each effect using parametric g-computation: a method for modelling the effect of

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an exposure or treatment in a cohort where all of the simulation parameters are estimated directly from the cohort data [17].

METHODS

Study Sample

Our data came from the Women's Interagency HIV Study (WIHS) [18, 19] and the Multicenter AIDS Cohort Study (MACS) [20]. Briefly, the WIHS is an ongoing US-based cohort study of HIV-infected and -uninfected women, and the MACS is an ongoing US-based cohort study of HIV-infected and -uninfected men who have sex with men. MACS began in 1984, with additional recruitment waves in 1987, 2001, and 2010 at 4 urban locations. WIHS began in 1994 at 6 urban locations, with additional recruitment waves in 2001, 2011, and 2013, eventually expanding to 10 urban and suburban sites. In both studies, laboratory procedures, clinical examinations, and interviews are conducted at semi-annual study visits. Information collected through interviews includes self-reported medication use along with demographic, socioeconomic, and behavioral characteristics. The laboratory procedures include measures of CD4 cell counts, HIV ribonucleic acid (RNA) tests, HCV antibody (Ab) and RNA tests, and non-invasive markers of liver fibrosis.

Individuals included in our cohort were HIV-infected at study entry or seroconverted during follow-up. Visits occurring after the opening of WIHS recruitment (1 October 1994) were included. All participants were ART-naive and without an AIDS diagnosis prior to their first eligible study visit. Follow-up began at the first eligible study visit after HIV diagnosis and continued until the first of: loss to follow-up, death, 10 years after the first eligible visit, or 30 September 2015. A participant was considered lost to follow-up at the time of their second missed study visit.

Definitions

In both studies, HCV Ab was assessed at baseline by an enzyme immunoassay. Specimens with reactive Ab results underwent HCV RNA testing by real-time polymerase chain reaction assays. Those with detectable HCV RNA were considered to have chronic HCV (HCV+).

The definition of ART was guided by the November 2014 US Department of Health and Human Services guidelines [21]. Once a participant reported initiating ART, they were assumed to remain on it for the duration of the study (the intent-to-treat assumption). ART was split into 2 variables based on time of initiation: ART initiated prior to 1 October 2001 (when tenofovir, a key component of many modern ART regimens [9], was approved) was considered early ART, while ART initiated after that date was considered modern ART.

Ascertainment of Death

Both studies perform death registry searches to obtain information on the mortality of participants. Dates and causes of death are obtained either directly from the National Death Index (https://www.cdc.gov/nchs/ndi/index.htm) or through copies of death certificates obtained by study investigators.

Confounders

Confounders were chosen using a causal diagram [22] constructed prior to data analysis. Time-fixed confounders included age, sex, race and ethnicity, injection drug use, heavy alcohol use [23], and smoking status. Time-varying confounders included CD4 cell count and HIV RNA. For the effect of DAA treatment (but not HCV infection, see the statistical analysis section), hepatic fibrosis was also included as a time-fixed confounder after categorization into 3 levels: FIB-4 [24] ≥ 3.25 or an aspartate aminotransferase (AST) to Platelet Ratio Index (APRI) [25] ≥ 1 was classified as cirrhosis; FIB-4 < 1.45 and APRI < 0.7 (together) was classified as no significant fibrosis; and other combinations were classified as non-cirrhotic fibrosis. We chose APRI cutoffs based on a meta-analysis [25] that suggested the improved performance of these cutoffs for the classification of cirrhosis and of no significant fibrosis, as compared to the commonly-used cutoffs of 2 and 0.5, respectively. Further details on variable measurements and operationalization are in the Supplementary Appendix.

Statistical Analysis

We estimated 3 effects in this study. First, we compared 10-year all-cause mortality under a scenario in which all PLwH had HCV at study entry with a scenario in which no PLwH had HCV at study entry. Second, we compared mortality among people with observed HIV/HCV co-infection with mortality under a scenario in which none of those individuals had HCV co-infection. Finally, we compared mortality among people with observed HIV/HCV co-infections with mortality under a scenario in which all co-infected individuals had received DAA treatment at the time of their study entry. To ensure that these results are useful in modern contexts, we estimated each effect under a scenario where all people in the study initiated modern ART at the time of their study entry.

We estimated each effect with the parametric g-computation algorithm (hereafter referred to as g-computation) [26]. G-computation is an extension of direct standardization which involves conducting 2 data-intensive microsimulations within a single cohort [17, 27]. In each microsimulation, exposure or treatment is set to a given level for every individual (for example: all individuals with HCV receive DAAs), and survival is simulated under that exposure or treatment regimen using models estimated from the study population. The results from each microsimulation are compared to provide an estimate of the effect of interest. In contrast to traditional microsimulations, all of the model parameter estimates are obtained from the study population rather than from external sources [17]. Unlike traditional regression approaches, g-computation remains valid in the presence of time-varying confounding impacted by prior exposure [26].

In our implementation of g-computation, we modeled the conditional distributions of mortality and the time-varying confounders, with logistic regressions pooled over time for binary variables and linear regressions pooled over time for continuous variables. Using these models, we simulated and compared the time-varying confounder histories and survival curves under each HCV infection or treatment scenario. Confidence intervals were estimated using the nonparametric bootstrap with 1000 samples. Full details are in the Supplementary Appendix.

We used multiple imputation to handle missing data with a multivariate normal imputation model [28] (the amount missing for each variable is presented in Table 1, and ranged from none to 30% missing [baseline fibrosis]). We incorporated multiple imputation into the bootstrap with the Boot MI algorithm [29], with 20 imputed datasets per bootstrap sample.

Though most of the period covered in this study predates DAAs, with strong assumptions we can estimate the effect of DAAs using data available from the MACS and WIHS. We estimated this effect under the assumptions that DAAs work quickly,

Table 1. Characteristics of the Study Population at Baseline, Women's Interagency HIV Study and Multicenter AIDS Cohort Study, 1994–2015

	Total		HCV+		HCV-		Missing HCV	
	N = 3056		n = 543		n = 2411		n = 102	
	n	%	n	%	n	%	n	%
Age (median, IQR)	38	(32; 44)	40	(35; 44)	37	(31; 43)	40	(33; 49)
Race								
White (Non-Hispanic)	1113	36.4	109	20.1	980	40.7	24	23.5
African American	1339	43.8	321	59.1	957	39.7	61	59.8
Hispanic	529	17.3	107	19.7	409	17.0	13	12.7
Other	74	2.4	6	1.1	64	2.7	4	3.9
Missing	1		0		1		0	
Female sex	1777	58.1	460	84.7	1231	51.1	86	84.3
CD4 count (median, IQR)	417	(258; 607)	379	(217; 586)	422	(270.5; 605.5)	471	(333; 684.5)
Missing	169		16		139		14	
Detectible HIV viral load[a]	2393	95.1	487	95.5	1829	95.0	77	93.9
Missing	539		33		486		20	
IDU								
Never	2313	76.5	102	19.0	2156	90.4	55	53.9
Former	491	16.2	300	55.8	162	6.8	29	28.4
Current	220	7.3	136	25.3	66	2.8	18	17.6
Missing	32		5		27		0	
Heavy alcohol use[b]	377	12.7	102	19.4	252	10.7	23	23.0
Missing	77		18		57		2	
Smoking								
Never	918	30.4	58	10.8	837	35.2	23	22.8
Former	693	23.0	77	14.4	601	25.2	15	14.9
Current	1406	46.6	400	74.8	943	39.6	63	62.4
Missing	39		8		30		1	
BMI > 30 kg/m^2	617	22.2	105	20.8	482	22.1	30	32.6
Missing	273		37		226		10	
HBsAg positive	130	4.4	17	3.2	109	4.6	4	7.0
Missing	103		4		54		45	
Fibrosis status[c]								
No significant fibrosis	1621	76.2	225	49.0	1362	84.6	34	56.7
Non-cirrhotic fibrosis	304	14.3	127	27.7	162	10.1	15	25.0
Cirrhosis	203	9.5	107	23.3	85	5.3	11	18.3
Missing	928		84		802		42	
ART								
Initiated pre–October 2001	1296	42.4	229	42.2	1034	42.9	33	32.4
Initiated post–October 2001	613	20.1	52	9.6	537	22.3	24	23.5

Abbreviations: AIDS, acquired immunodeficiency syndrome; ART, antiretroviral therapy; BMI, body mass index; HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IDU, injection drug use; IQR, interquartile range.

[a]Lower limit of detection varied over time, and ranged from 500 copies/ml to 20 copies/ml.

[b]Defined as more than 7 drinks per week for women and more than 14 drinks per week for men [23].

[c]Cirrhosis was defined as (1) FIB-4 ≥ 3.25 or (2) AST to Platelet Ratio Index ≥ 1; no significant fibrosis was defined as FIB-4 < 1.45 and APRI < 0.7; other combinations were classified as non-cirrhotic fibrosis.

have few side effects that impact mortality, and completely eliminate the effect of HCV besides any effect on fibrosis already present at the time of study entry/DAA initiation. Under these assumptions, an individual without HCV with a given degree of liver fibrosis at baseline should have the same mortality risk as a similar co-infected individual after successful treatment of their HCV infection (conditional on a sufficient set of confounders). Baseline fibrosis was thus included as a confounder when estimating the effect of DAA treatment, so fibrosis was held constant when we changed whether a person received DAAs. In contrast, we did not include fibrosis as a confounder for the effect of HCV infection, because fibrosis is the primary mechanism through which HCV causes mortality and, thus, should change when infection status changes. Rather than assuming all people with HIV/HCV co-infection would achieve SVR with DAAs, we assumed DAAs were effective in 96% of co-infected individuals [30] (details in the Supplementary Appendix).

Sensitivity Analyses

First, the effect of HCV infection among all PLwH was estimated with a marginal structural model fit with inverse probability weighting [31]. The models used in this analysis are distinct from those needed for g-computation, so concordance between the results provides confidence in the model specifications. Further details are provided in the Supplementary Appendix.

Second, subjects may have been enrolled long after HCV acquisition, and the time of HCV acquisition is unknown in this study. As such, subjects with prolonged infections had more advanced liver fibrosis, on average, than those with recently-acquired infections, and there was also a possibility of selection bias. Additionally, PLwH without HCV co-infections must have had other conditions that contributed to their fibrosis (eg, steatosis), and thus may not represent the experience co-infected persons would have if successfully treated with DAAs. To provide estimates that are potentially less impacted by such biases, we estimated the effects of HCV infection and treatment in a population restricted to participants without significant fibrosis.

Third, to address possible confounding by hepatitis B virus (HBV) co-infections, we conducted sensitivity analyses for each effect restricted to those negative for HBV antigen at baseline. We used this restriction (rather than standardization or adjustment) due to the small number of HBV/HCV co-infected individuals in the study population leading to issues of non-positivity [32].

RESULTS

Study Sample

Overall, 3056 people were eligible for the study, of whom 543 (18%) had HCV at baseline. The study population was 58% female (85% of those with HCV were female). The median follow-up time was 7.5 years (interquartile range: 2, 10). People with HIV/HCV co-infections had more advanced liver fibrosis by FIB-4 and APRI and lower median CD4 cell counts; they were also more likely to inject drugs, use alcohol heavily, and smoke at baseline than those without HCV. ART was initiated by 63% of study participants during follow-up. Of those initiating ART, 32% did so after 1 October 2001 (constituting modern ART). Additional characteristics of the study population are presented in Table 1 (the characteristics of the populations from the MACS and WIHS are presented separately in Supplementary Tables 1 and 2), and the modelled and observed natural course are presented in Supplementary Table 3 and Supplementary Figure 1.

Estimated Effects of Hepatitis C Virus Infection and Direct-acting Antiviral Treatment

The 10-year risk difference (RD) for all-cause mortality comparing the scenario in which all PLwH had HCV at study entry to the scenario in which none had HCV at study entry was 4.3% (95% confidence interval [CI]: 0.4%, 8.9%), and the risk ratio (RR) was 1.4 (95% CI: 1.0, 1.9) (Table 2; Figure 1a). This risk difference corresponds to a 10-year number needed to harm (NNH) of 23, indicating that if 23 PLwH initiated ART at study entry and had HCV, we would expect one additional death over 10 years compared with none of them having HCV. The 10-year RD comparing all-cause mortality among people with observed HIV/HCV co-infection to the scenario in which none of those individuals had HCV at study entry was 5.3% (95% CI: 0.6%,

Table 2. Predicted Effects of HCV Infection and DAA Treatment on 10-Year All-cause Mortality if All Subjects Initiated ART at Baseline, Women's Interagency HIV Study and Multicenter AIDS Cohort Study, 1994-2015

Effect	Population	Exposure/Treatment	Risk[a] (95% CI)	Risk Difference[a] (95% CI)	Risk Ratio (95% CI)
HCV Infection	All PLwH	HCV+	14.69 (8.10–24.36)	4.34 (0.42–8.92%)	1.42 (1.04–1.86)
		HCV-	10.35 (6.04–17.60)	Ref	Ref
HCV Infection	PLwH and HCV	HCV+	18.56 (10.67–30.34)	5.29 (0.57–10.47)	1.40 (1.04–1.81)
		HCV-	13.27 (8.36–22.08)	Ref	Ref
HCV Treatment	PLwH and HCV	All HCV treated	14.88 (9.17–24.39)	-3.80 (-9.22%–0.89)	0.80 (0.61–1.06)
		No HCV treated	18.68 (10.81–30.54)	Ref	Ref

Abbreviations: AIDS, acquired immunodeficiency syndrome; ART, antiretroviral therapy; CI, confidence interval; HIV, human immunodeficiency virus; HCV, hepatitis C virus; PLwH, people living with HIV; Ref, referent category.

[a]Expressed as a percentage.

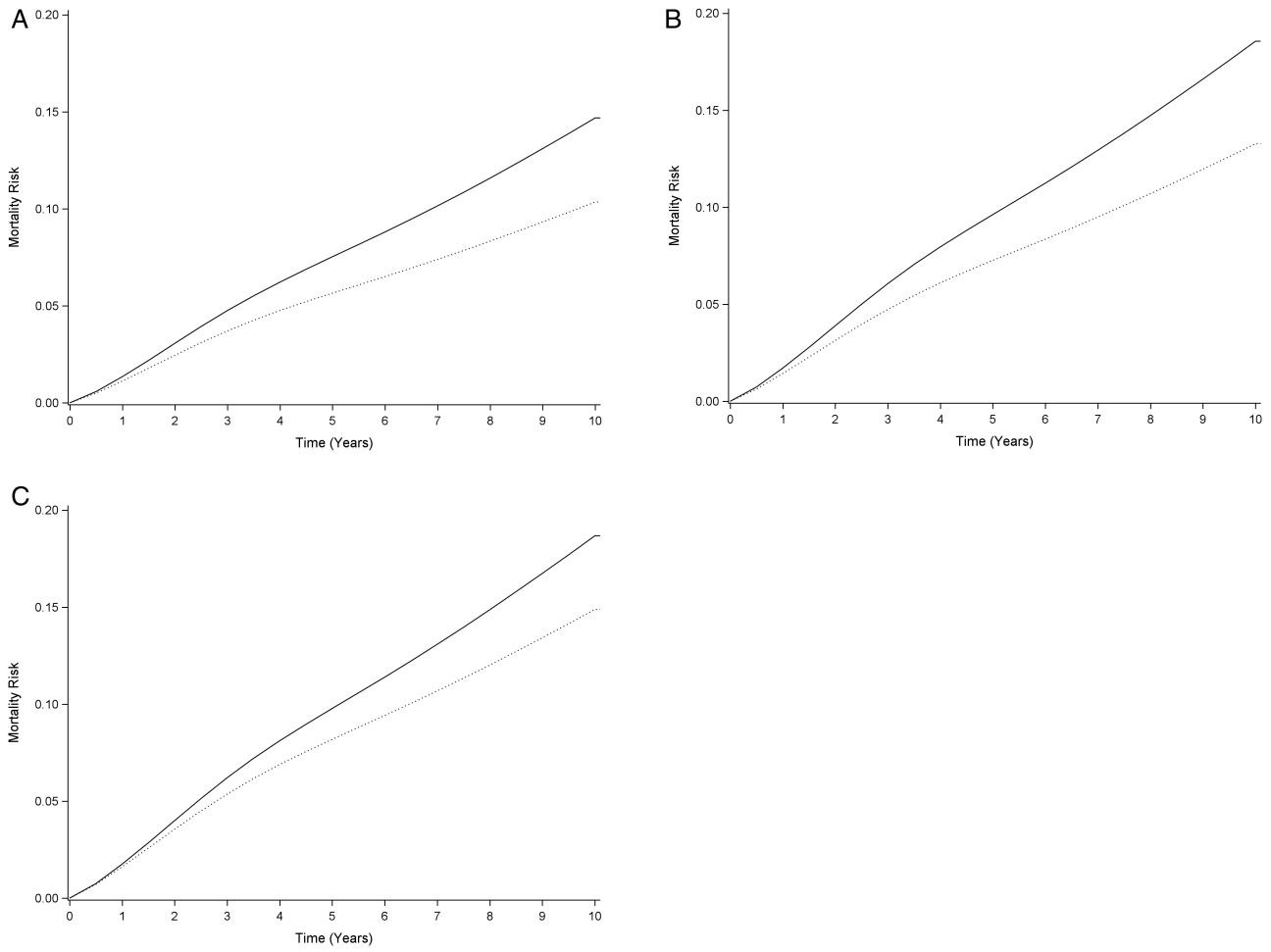

Figure 1. Predicted 10-year all-cause mortality had all subjects initiated modern ART at baseline, using data from the Women's Interagency HIV Study and Multicenter AIDS Cohort Study, 1994–2015. (*A*) The effect of HCV infection among PLwH. The solid line depicts the scenario in which all PLwH had HCV at study entry. The dashed line depicts the scenario in which no PLwH had HCV at study entry. (*B*) The effect of HCV infection among people with observed HIV/HCV co-infection. The solid line depicts he scenario in which all of these individuals had HCV at study entry. The dashed line depicts the scenario in which none of these individuals had HCV at study entry. (*C*) The effect of DAA treatment among people with observed HIV/HCV co-infection. The solid line depicts the scenario in which none of these individuals were treated with DAAs at study entry. The dashed line depicts the scenario in which all of these individuals were treated with DAAs at study entry. Abbreviations: AIDS, acquired immunodeficiency syndrome; ART, antiretroviral therapy; DAA, direct-acting antivirals; HIV, human immunodeficiency virus; HCV, hepatitis C virus; PLwH, people living with HIV.

10.5%) and the RR was 1.4 (95% CI: 1.0; 1.8) (Table 2; Figure 1b). The corresponding 10-year NNH was 19.

The 10-year RD for all-cause mortality comparing the scenario in which all people with observed HIV/HCV co-infection were treated with DAAs at study entry to the scenario in which none of those individuals were treated was -3.8% (95% CI: -9.2%, 0.9%), corresponding to a RR of 0.8 (95% CI: 0.6, 1.1) (Table 2; Figure 1c). This risk difference corresponds to a 10-year number needed to treat of 26.

Sensitivity Analyses

The estimated effect of HCV infection from the marginal structural model was similar to that from g-computation, but the CI was wider (RD 4.1%, 95% CI -7.4–25.0%, compared to RD 4.3%, 95% CI: 0.4–8.9%, respectively). After restricting to those without significant fibrosis, the estimated effects of HCV infection and DAA treatment were similar to those in the main analysis (RDs 3.7% and -4.1%, compared with 4.3% and -3.8%, respectively). When restricted to those without HBV co-infection, the effects of HCV infection among all PLwH and among people with HIV/HCV co-infections, as well as the effect of DAA treatment, were stronger (RDs 4.9%, 6.1%, and -4.5%, compared with 4.3%, 5.3%, and -3.8%, respectively; Supplementary Table 4).

DISCUSSION

In the modern ART era, it is imperative to identify those interventions that alleviate the sources of mortality that most impact PLwH. We estimated the effects of HCV infection and DAA treatment on mortality risk among PLwH after initiating modern ART according to current guidelines. Our results suggest that successful interventions to prevent and treat HCV would likely improve survival in this population. The estimated

beneficial effect of DAA treatment among people with HIV/HCV co-infection was smaller than the harmful effect of HCV infection in the same population, likely due to the fact that liver fibrosis does not immediately revert after SVR.

Because we estimated the effects after ART initiation at study enrollment, our study provides evidence that is useful for clinicians and policy-makers to properly address HCV after patients enter care for HIV. By using data from large, long-running observational cohorts, we estimated effects on 10-year all-cause mortality, a time-frame that captures the slow, progressive nature of HCV. With the liver fibrosis data collected by the cohorts, we were able to separately estimate the effects of HCV infection and a well-defined DAA treatment intervention [12].

The RR attributable to HCV infection that we estimated (1.4) is similar to the pooled RR of 1.35 reported by a 2009 meta-analysis [33]. Despite the numerical similarity, our results carry a different interpretation. Notably, prior studies account for ART use either with regression adjustment or by restricting their study populations to those who had initiated ART, thus providing estimates that are conditional on observed ART. Our estimates, obtained using g-computation, can instead be interpreted as the effect of HCV infection had all study participants initiated modern ART upon study enrollment, regardless of what ART use was actually observed, and thus may be more directly applicable in the era of modern ART guidelines suggesting that all PLwH receive ART.

Our estimated effect of HCV treatment is smaller than previous estimates among PLwH from the pegylated interferon (PEG-IFN) era, where hazard ratios for mortality comparing those who achieved SVR on PEG-IFN plus ribavirin to those who did not achieve SVR or were not treated ranged from 0.12 [34] to 0.22 [35]. PEG-IFN has severe side effects and toxicity among people with HIV/HCV co-infections [36]. Those who were successfully treated with a PEG-IFN-plus-ribavirin regimen were able to tolerate the drugs and complete the course of therapy, and thus likely differed from those for whom treatment was unsuccessful on important, unmeasured factors related to treatment adherence and success. Therefore, these prior results may be subject to bias due to confounding. Our estimated DAA treatment effect is also smaller than the hazard ratios of 0.43 and 0.44 reported in short-term studies in the general population on the effect of DAA treatment [15] and the effect of SVR after DAA treatment [16], respectively. Because those studies specifically excluded PLwH, they cannot be directly compared with our results, as risk factors for and causes of mortality differ between PLwH and the general population.

Our results are subject to limitations. First, we assumed that people with HIV/HCV co-infections who were successfully treated with DAAs would have the same survival rates as PLwH without HCV, conditional on fibrosis and confounders. However, PLwH who do not have HCV but do have moderate-to-severe fibrosis (or cirrhosis) must have other factors contributing to liver scarring, such as steatosis. Some of these contributing factors were measured and controlled for in the analysis, but others likely remain, so our estimated effect of DAAs may be conservative. The estimated effect of DAAs from a sensitivity analysis restricted to PLwH without significant fibrosis yielded similar results to the main analysis, so the aforementioned bias may be small. Second, we did not account for the possibility of fibrosis reversion after successful DAA treatment [13]. Reversion should reduce mortality after HCV treatment, further suggesting that our estimated treatment effect is conservative. We likewise did not account for reinfection after successful treatment or for incident infections after baseline. Third, the variables used in our analysis are subject to measurement errors. In particular, substance use may be subject to recall bias, and fibrosis was assessed using indirect markers that are not well-validated among individuals without HCV. Fourth, our estimates may be biased if the models for mortality or the time-varying confounders were inaccurate. Though we used several methods to assess the fit of the models, the possibility of model inaccuracies remains. Fifth, the effect of DAAs may depend on the time between infection and treatment, so our results may not immediately generalize to other populations, such as those with recently acquired HCV. However, the results of our sensitivity analysis that was restricted to those without significant fibrosis (who were likely to have more recently-acquired infections) did not differ substantially from the results of the primary analysis. Lastly, our study featured a much higher proportion of female participants than the current population of PLwH in the United States [37], possibly limiting the generalizability of our results [38].

Though the validity of our analysis depends on strong assumptions, our results provide valuable estimates of the effect of HCV infection and treatment early in the DAA era. Given our findings, we believe that HIV care providers should make strong efforts to address HCV co-infection in their patients and that policy-makers and insurers should expand access to DAAs and prioritize HCV interventions for PLwH. As person-time accrues in the DAA era, future studies should directly estimate the effect of DAAs on long-term mortality among people with HIV/HCV co-infection.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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