Clinical Infectious Diseases
MAJOR ARTICLE

Impact of Hepatitis C Virus Cure on Depressive Symptoms in the Human Immunodeficiency Virus-Hepatitis C Virus Coinfected Population in Canada

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Background. Depression is common in people with human immunodeficiency virus (HIV) and hepatitis C virus (HCV), with biological and psychosocial mechanisms at play. Direct acting antivirals (DAA) result in high rates of sustained virologic response (SVR), with minimal side-effects. We assessed the impact of SVR on presence of depressive symptoms in the HIV-HCV coinfected population in Canada during the second-generation DAA era (2013–2020).

Methods. We used data from the Canadian CoInfection Cohort (CCC), a multicenter prospective cohort of people with a HIV and HCV coinfection, and its associated sub-study on food security. Because depression screening was performed only in the sub-study, we predicted Center for Epidemiologic Studies Depression Scale-10 classes in the CCC using a random forest classifier and corrected for misclassification. We included participants who achieved SVR and fit a segmented modified Poisson model using an interrupted time series design, adjusting for time-varying confounders.

Results. We included 470 participants; 58% had predicted depressive symptoms at baseline. The median follow-up was 2.4 years (interquartile range [IQR]: 1.0–4.5.) pre-SVR and 1.4 years (IQR: 0.6–2.5) post-SVR. The pre-SVR trend suggested depressive symptoms changed little over time, with no immediate level change at SVR. However, post-SVR trends showed a reduction of 5% per year (risk ratio: 0.95 (95% confidence interval [CI]: .94–.96)) in the prevalence of depressive symptoms.

Conclusions. In the DAA era, predicted depressive symptoms declined over time following SVR. These improvements reflect possible changes in biological pathways and/or better general health. If such improvements in depression symptoms are durable, this provides an additional reason for treatment and early cure of HCV.

Keywords. HIV-HCV coinfection; depressive symptoms; direct acting antivirals; HCV cure; sustained virologic response.

Both hepatitis C virus (HCV) and human immunodeficiency virus (HIV) infections are associated with neuropsychiatric manifestations, mainly depression [1, 2]. Among people with either HIV or chronic HCV, prevalence of depression ranges from 20% to 30% [1, 3, 4]. Depression is reported to be even higher in the HIV-HCV coinfected population [5]. Depression mechanisms related to HIV and HCV are both biological and psychosocial. HIV and HCV affect the central nervous system directly, which causes immune activation leading to depression [1, 6]. In addition, pro-inflammatory cytokines like tumor necrosis factor α (TNF-α) and interleukin 1 (IL-1) and altered neurotransmitter action like dopamine and serotonin play roles in inducing depression [1, 6, 7]. There are also many known psychosocial pathways to depression including social stresses caused by stigma, discrimination, and lack of social and financial support [1, 2]. Among HCV-HIV coinfected persons, ongoing substance use is a common additional risk factor and may also be affected by presence of depressive symptoms [8].

Depression was a well-described major side effects of earlier interferon (IFN)-ribavirin based HCV antiviral treatments, with some studies showing more than 20% of those treated developed depression [9]. This led to those with current or past psychiatric illness often not being prescribed IFN therapy [10]. However, after 2013, second-generation IFN-free direct acting antiviral (DAA) regimens now result in >95% rates of sustained virologic response (SVR), even among HIV-HCV coinfected

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persons [11, 12]. Importantly, there is no evidence of any significant psychiatric side effects associated with DAA treatment [13–15]. HCV treatment guidelines have thus been updated, and depression is no longer a contraindication for treatment [16].

These changes in prescribing practices provide us with the opportunity to assess the potential impact of HCV treatment on depressive symptoms over time. We may expect lower depressive symptoms post-cure via biological pathways due to HCV viral clearance. However, coinfected populations continue to face challenges including discrimination, socioeconomic burden, substance use, increasing risk of overdoses, and poor mental health, mitigating the benefits of HCV cure. Thus, it is important to examine longitudinally whether HCV cure leads to change in the level of depressive symptoms and moreover whether such a change persists over time. This will provide evidence for healthcare providers to appropriately monitor and manage depression. Evidence of possible improvement in mental health after cure could encourage individuals hesitant to start treatment to do so. Thus, in this study we evaluated the impact of SVR on presence of depressive symptoms in the HIV-HCV coinfected population in Canada during the second-generation DAA era (2013–2020).

METHODS

Study Population

We used data from the Canadian Co-Infection Cohort (CCC), an open multicenter prospective cohort study, established in 2003 and described in detail elsewhere [17]. Briefly, the CCC recruits from 18 urban and semi-urban centers across 6 Canadian provinces (Quebec, British Columbia, Alberta, Ontario, Nova Scotia, and Saskatchewan). Eligibility criteria include ≥16 years of age, documented HIV infection, and evidence of HCV infection (HCV RNA positivity and/or HCV seropositivity). As of July 2020, the study had recruited 2018 participants. Participants are followed longitudinally, with visits every 6 months. Sociodemographic and behavioral data are collected by a standardized self-administered questionnaire at each visit. Clinical data including HIV and HCV treatment dates, medications, comorbidities, and psychiatric diagnoses are collected via medical chart reviews and HIV and HCV related blood tests performed.

We also used data from a sub-study conducted within the CCC, the Food Security and HIV-HCV coinfection study (FS sub-study), to predict the presence of depressive symptoms in the parent CCC. Participants for the FS sub-study were recruited from the CCC (n = 725) with a maximum of 5 visits integrated into CCC visits from 2012 to 2015. In the sub-study, described elsewhere [18], depression screening was performed using the Center for Epidemiologic Studies Depression Scale-10 (CES-D-10) that assesses presence and severity of depressive symptoms in the past week [19]. A score ≥10 is widely considered to represent the presence of depressive symptoms indicative of being at risk for clinical depression; this cutoff has been validated in HIV populations in Canada [20].

MEASUREMENT

Exposure

The exposure of interest was successful HCV treatment or cure in individuals treated with DAA regimens. Successful treatment or SVR was defined as an undetectable viral load (HCV RNA) 12 weeks after the end of treatment. We included participants who were HCV RNA positive, were treated, and then achieved SVR during the second-generation (IFN free) DAA era. The second-generation DAA era was defined from when the first second-generation DAA, Simeprevir, was approved for use by Health Canada, 25 November 2013, and continued until end of study period, 15 July 2020.

Outcome

The outcome of interest was presence of depressive symptoms indicative of being at risk for major depression, hereafter referred to as depressive symptoms. CCC participants are not screened for depression as part of usual study procedures (baseline or follow-up), however depression screening was performed in the FS sub-study. Because the FS sub-study was conducted between 2012 and 2015, we only had such measurements for about 1.5 years in the second-generation DAA era, thus, insufficient data with which to conduct an analysis using measured depressive symptoms. Thus, to obtain a measure of depressive symptoms in the full CCC, we developed a random forest (RF) classifier using the CES-D-10 to classify presence/absence of depressive symptoms derived from the FS sub-study as the outcome (target of prediction), and sociodemographic, behavioral, and clinical characteristics from the parent CCC as predictors [21]. We used the CES-D-10 score cutoff of 10, such that "CES-D-10 class = 1" corresponds to a score ≥10 for presence and "CES-D-10 class = 0" corresponds to a score <10 for absence of depressive symptoms indicative of being at risk for clinical depression. The details of the RF classifier development are in Appendix A and Supplementary Table 1. Using this RF classifier, the CES-D-10 classes were predicted for each CCC visit included in this analysis. We addressed outcome misclassification for the predicted depressive symptoms using the predictive value-based record-level correction method [22]. In this method, we applied the positive predictive value (PPV) and negative predictive value (NPV) estimated for the RF algorithm; PPV: 0.74 (95% confidence interval [CI]: .68–.80) and NPV: 0.76 (95% CI: .69–.82). The procedure included simulation of corrected outcome at each visit by repeated Bernoulli trials with probability equal to PPV for those classified as CES-D-10 class = 1 and 1-NPV for those classified as CES-D-10 class = 0 [22].

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Confounders

We considered time-varying confounders, which were selected a priori [23–25]. These confounders were measured at each biannual visit and included advanced fibrosis/cirrhosis, HIV viral load, CD4 cell count, current injection drug use, current alcohol use, recent incarceration, and antidepressant use. We dichotomized 3 confounders: advanced fibrosis/cirrhosis (aspartate aminotransferase [AST] to Platelet Ratio Index (APRI) ≥ 1.5 and/or end stage liver disease diagnosis), HIV viral load (at 50 copies/mL), CD4 cell count (at 250 cells/μL). Though using continuous measures may have improved precision, these dichotomizations were chosen to reflect clinical cutoffs for assessment of fibrosis stage and HIV control. In addition, we opted to adjust for HIV viral load directly rather than antiretroviral therapy status, as these 2 factors are correlated, and viral load would be more relevant regarding biological mechanisms underlying HIV and depression [1]. At least 1 confounder value was missing in 38% of the included visits. We assessed if this missingness was informed by other covariates by using logistic regressions with the missing data indicator as the outcome for each confounder and found missingness to be informed by other covariates in 2 confounders, recent incarceration, and alcohol use. We used multiple imputation by chained equations (MICE) to address this missing data in the confounders [26]. We created 5 imputed datasets using logistic regression for these binary confounder variables.

Statistical Analysis

Primary Analysis

We used a segmented regression model with interrupted time series (ITS) design to evaluate the impact of SVR on depressive symptoms. In an ITS, a time series of a particular outcome of interest is used to establish an underlying trend, which is "interrupted" by an exposure at a known point in time, with a clear differentiation between the pre-exposure and post-exposure periods [27]. In this analysis, the extrapolation of the pre-exposure outcome trend acts as a counterfactual for the post-exposure trend for each individual. It is assumed that, since the same individual is observed before and after the exposure, this design accounts for known and unknown confounders that do not vary with time [27, 28]. The pre-exposure period included time from cohort entry when participants were HCV RNA positive to treatment initiation in the second-generation DAA era. The post-exposure period included time after the ascertainment of SVR for each individual. We did not include the time between DAA initiation and SVR ascertainment in the analysis. Based on subject matter knowledge, we hypothesized that depressive symptoms may have an immediate decrease at SVR as well as a decrease over time. The causal diagram can be seen in Appendix B, Supplementary -Figure 1. Subgroup analyses were performed to explore possible difference by sex (male, female), race (White, Indigenous), employment status (employed, not employed), and baseline liver disease (no liver disease, with liver disease).

We used generalized estimating equations (GEEs) with robust standard errors, which account for correlation between repeated measurements on the same participant over time. GEEs are a population-level approach and provides population-averaged estimates of the parameters (as opposed to the individual-level analysis provided by mixed effect models) [29]. We used an exchangeable working correlation structure in these models, which assumes positive correlation between repeated measurements over time for an individual. The segmented modified Poisson model, which involves using a robust variance estimation, was defined as below [27]. We developed these models with and without outcome misclassification correction. The model can be seen in Appendix C.

Sensitivity Analyses

We conducted planned sensitivity analyses to assess robustness of the results, specifically due to 2 possible methodological challenges for ITS: lead time bias and non-linear effect. Lead time bias is possible in this analysis as depressive symptoms may change in anticipation of the exposure, SVR [28]. To check for lead time bias, we moved the time axis to set the exposure 1 year before SVR ascertainment. To address the possibility that the effect may not be linear on the log scale, we developed adjusted models with polynomials (squared and cubic transformations of time) and also with restricted cubic spline with 5 knots—see further details in Appendix D [30]. We then used the quasi-likelihood under the independence model criterion

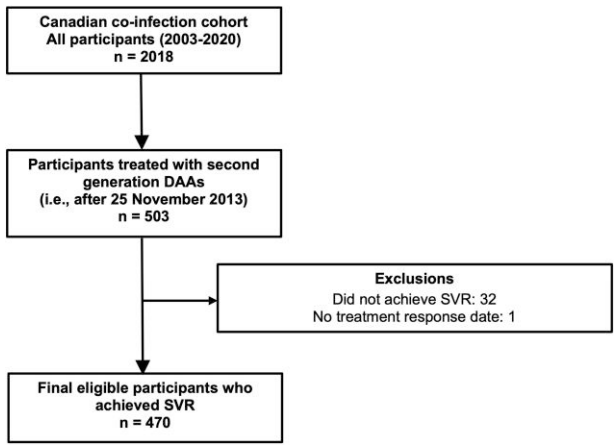

Figure 1. Flowchart of participants included in the analytical sample. The Canadian Co-Infection Cohort (CCC) had recruited 2018 HIV-HCV coinfected participants (HCV RNA positive/HCV seropositive) until July 2020. In our analysis, we included 503 participants who were treated with IFN-free second-generation direct acting antiviral (DAA) regimens after 25 November 2013, when the first second-generation DAA, Simeprevir, was approved for use by Health Canada. Of the participants who were treated, we excluded those who did not achieve sustained virologic response (SVR) (n = 32) and did not have a treatment response date (n = 1). Thus, in the final analytical sample we included a total of 470 participants who had achieved SVR. Abbreviations: HCV, hepatitis C virus; HIV, human immunodeficiency virus; IFN, interferon.

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Table 1. Baseline Characteristics of the Included Participants (n = 470)

Baseline Characteristics	Participants (n = 470) n (%) or Median (IQR)
Predicted presence of depressive symptoms (CES-D-10 score ≥ 10)	272 (58%)
Age (y)	47 (41–52)
Gender–male	321 (68%)
Self-reported race/ethnicity	
White	323 (69%)
Indigenous (First Nations, Inuit, and Metis)	107 (23%)
Asian	14 (3%)
Black	17 (4%)
Hispanic/Latinx	7 (2%)
Living situation–homeless	48 (10%)
Education–high school educated and less	344 (73%)
Employment–not employed	317 (68%)
Monthly income–≤ $1500 CAD	356 (76%)
Revenue source–welfare	233 (50%)
Sexual orientation–heterosexual	319 (68%)
Immigrant to Canada	42 (9%)
Marital status–single	329 (70%)
Previous IFN-based HCV treatment	69 (15%)
Injection drug use in the past 6 months	159 (34%)
Alcohol use in the past 6 months	243 (52%)
Incarceration in the past 6 months	31 (7%)
Liver disease–APRI score ≥ 1.5 and/or liver disease diagnosis	90 (19%)
Hepatitis B infection	17 (4%)
HIV viral load–>50 copies/mL	121 (26%)
CD4 count–≤250 cells/uL	107 (23%)
Antidepressant prescribed in the past 6 months	40 (9%)

Abbreviations: APRI, AST to platelet ratio index; AST, aspartate aminotransferase; CAD, Canadian dollars; CD4, cluster of differentiation 4 receptor; CES-D-10, Center for Epidemiologic Studies Depression Scale-10; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IFN, interferon; IQR, interquartile range.

(QIC) for model selection among the linear and the non-linear models [31]. Additionally, we conducted a sensitivity analysis exploring depressive symptom trends for those who did not respond to DAAs, by comparing the trends before and after the date of no-response ascertainment. All primary and sensitivity analyses were performed using Stata v.17 [32].

RESULTS

Participant Characteristics

The flowchart for participants in the final analytical sample is shown (Figure 1). We included 470 participants who achieved SVR in the DAA era. Baseline characteristics are shown in Table 1. Participants were vulnerable and could face potential barriers to HCV and mental health care. They were predominantly male (68%) and unemployed (68%); 23% were Indigenous, 50% were on welfare as their primary revenue source, 73% had no post-secondary education, and 34% were current injection drug users. At baseline, 58% of the cohort had predicted depressive symptoms indicative of a risk of depression.

Primary Analyses

The results of the primary analyses are shown in Table 2 and illustrated in Figure 2*A*. The median follow-up was 2.4 years (interquartile range [IQR]: 1.0–4.5) pre-SVR and 1.4 years (IQR: 0.6–2.5) post-SVR. After correcting for outcome misclassification, the pre-treatment trends show an adjusted risk ratio (aRR) of 1.01 (95% CI: 1.01–1.02), which indicates little change in the annual rate of predicted depressive symptoms over time prior to treatment. The model does not show any immediate level change at SVR (aRR) of 1.01 (95% CI: .97–1.04). However, the post-SVR trends shows a decrease in depressive symptoms over time, of 5% per year (aRR of 0.95 (95% CI: .94–.96)). There were no major differences noted between the various subgroups (sex, race, employment status, and liver disease) in the pre-treatment initiation and changes at SVR. There was some difference noted in the post-SVR downward trend by sex and race; however, sample sizes were limited, precluding definitive conclusions (see Appendix E, Supplementary Table 3).

Sensitivity Analyses

The results of the sensitivity analysis used to assess possible lead time bias are shown in Table 3 and illustrated in Figure 2*B*. The trends are similar for pre-treatment period as the primary analysis. There is an increase in the immediate level of depressive symptoms prevalence 1-year pre-SVR (aRR: 1.06 (1.02–1.10)), showing no evidence of lead time bias. The second

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Table 2. Impact of SVR on Depressive Symptoms in the HIV-HCV Coinfected Population: Primary Analysis Models With and Without Outcome Misclassification Correction (n = 470)

Sr. No.	Models	Risk Ratios (95% CI)		
		Pre-Treatment Trends Per Year	Level Change at SVR	Post-SVR Trends Per Year
I	Unadjusted models			
A	No misclassification correction	1.01 (.99–1.04)	1.01 (.93–1.09)	0.92 (.88–.96)
B	Misclassification correction	1.01 (1.00–1.01)	1.01 (.97–1.04)	0.95 (.94–.96)
II	Adjusted models[a]			
A	No misclassification correction	1.02 (.99–1.04)	1.01 (.94–1.10)	0.92 (.88–.96)
B	Misclassification correction	1.01 (1.01–1.02)	1.01 (.97–1.04)	0.95 (.94–.96)

Abbreviations: AST, aspartate aminotransferase; CD4, cluster of differentiation 4 receptor; CI, confidence interval; HCV, hepatitis C virus; HIV, human immunodeficiency virus; SVR, Sustained virologic response.

[a]Adjusted for time-varying confounders: Advanced fibrosis/cirrhosis (AST to platelet ratio index [APRI] ≥1.5 and/or end stage liver disease diagnosis), detectable HIV viral load (>50 copies/mL), low CD4 cell count (≤250 cells/μL), current injection drug use, current alcohol use, incarceration in the past 6 months, and antidepressant use.

sensitivity analysis did not support non-linearity of the effect on the log scale: the linear model was selected based on the lowest values of the QIC statistic. These results of the non-linearity sensitivity analysis are shown in Supplementary Table 2 in Appendix B. The results for the sensitivity analysis with DAA non-responders are shown in Supplementary Table 4 and Supplementary Figure 2 in Appendix F. In DAA non-responders, the pre-treatment probability trend was stable over time, with no evidence of immediate change at date of no-response ascertainment. However, the probability trend post-no-response indicates a gradual increase in depressive symptoms over time.

DISCUSSION

We measured using segmented regression models the impact of HCV cure on predicted depressive symptoms. Although depressive symptoms changed little over time in the leadup to DAA treatment, we observed a gradual decline in prevalence of depressive symptoms over time post-SVR among patients coinfected with HIV. There was no evidence of immediate change at SVR. The improvement after cure may reflect changes in biological pathways leading to HCV-related depression due to viral clearance and/or improved general physical health.

The use of DAAs has increased and improved HCV treatment among people with a history of depression or with current depressive symptoms. Several studies have assessed health-related quality of life post-SVR with DAAs and have shown a modest improvement after HCV cure [33, 34]. This is in line with our observation of decline of depressive symptoms over time, which are strongly correlated with health-related quality of life [35].

Several studies have compared depressive symptoms at baseline and at SVR-12. In a study by Moez et al, Beck depression inventory (BDI) scores were found to be lower (reduced depression severity) at SVR-12 compared to baseline [36]. Similar results were observed in a few other studies [14, 15, 37]. In contrast, in a prospective study with psychiatric assessments at baseline and at SVR-12, scores were shown to have increased post-treatment, with 32% developing moderate to severe depression [38]. The authors suggested an explanation for this increase might include biological mechanisms related to increased levels of IFN, the higher percentage of women in the cohort, continued stigma, other comorbid conditions, and persisting unemployment [38, 39]. Similar results were seen in other studies [40, 41]. All the above studies, however, were conducted in HCV monoinfected populations. Only 1 study to our knowledge was among HIV-HCV coinfected people, which showed a decline in BDI scores from baseline to 1–8 weeks after end of DAA treatment [42]. There are several possible methodological reasons for these conflicting results, like different sample sizes (eg, n = 150 (Moez. et al) vs n = 47 (Khalil et al), different depression scales, and varying measurement time points (between 4 and 12 weeks of treatment; not all at SVR, eg, Egmond et al) [36, 38, 41]. Additionally, none of the studies examined depression in the time frame beyond SVR, and thus very little is known about post-SVR depressive symptoms trends and persistence in both HCV monoinfected and HIV-HCV coinfected populations.

One major strength of our study is we used longitudinal data collected in numerous, diverse patients. Using a quasi-experimental design, ITS, we were able to obtain robust marginal effect estimates of the impact of SVR on depressive symptoms in the coinfected population. We believe our estimates are generalizable to HIV-HCV coinfected patients engaged in care in Canada, as CCC participants are recruited from primary and tertiary care clinics in urban and semi-urban areas across 6 provinces in Canada. We also conducted multiple sensitivity analyses and adjusted for time-varying confounders.

Our study, however, does have some limitations. The depressive symptoms were predicted via an RF algorithm and not measured directly in the cohort. Misclassification was therefore

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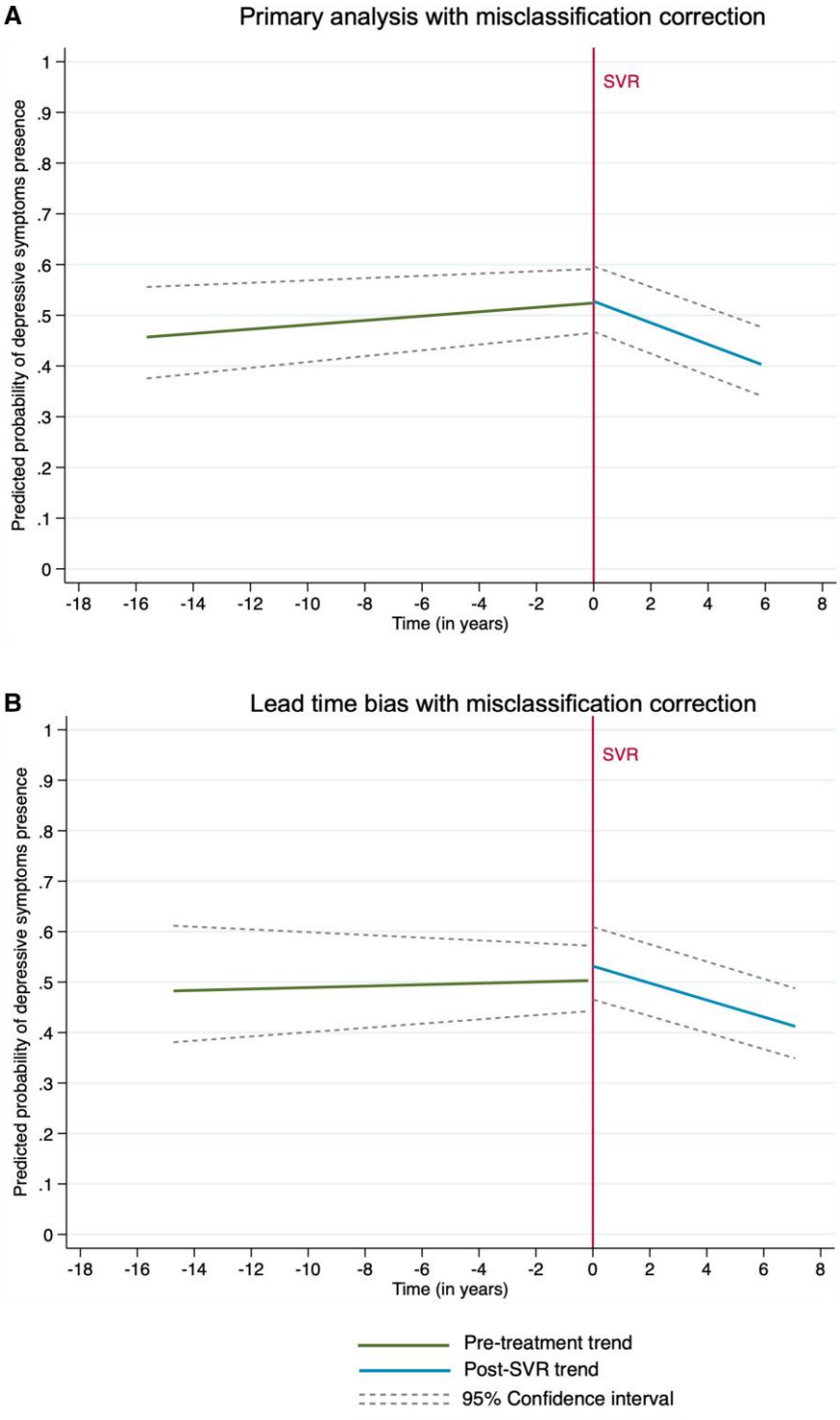

Figure 2. Impact of sustained virologic response (SVR) on depressive symptoms in the HIV-HCV coinfected population (*A*). Results of the primary analysis model with outcome misclassification correction. The graph shows that pre-treatment the probability trend for presence of depressive symptoms was stable over time. There was no evidence of immediate change at SVR; however, the probability trends post-SVR indicate a gradual decline in depressive symptoms over time (*B*). Results of the sensitivity analysis model to assess lead time bias with outcome misclassification correction. In this model, we lagged SVR by 1 year to assess possibility of lead time bias. The graph shows a stable pre-treatment trend like the primary analysis. The increase in the immediate level of depressive symptoms prevalence 1-year pre-SVR, provides evidence for no lead time bias in this analysis, meaning depressive symptoms did not seem to improve in anticipation of the cure. Abbreviations: HCV, hepatitis C virus; HIV, human immunodeficiency virus.

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Table 3. Sensitivity Analysis to Assess Possible Lead Time Bias: Models With and Without Outcome Misclassification Correction (n = 332)

Sr. No.	Models	Risk Ratios (95% CI)		
		Pre-Treatment Trends per Year	Level Change at SVR	Post-SVR Trends per Year
I	Unadjusted models			
A	No misclassification correction	1.01 (.98–1.03)	1.10 (.99–1.22)	0.93 (.89–.98)
B	Misclassification correction	1.00 (.99–1.01)	1.10 (1.01–1.10)	0.96 (.95–.98)
II	Adjusted models[a]			
A	No misclassification correction	1.01 (.98–1.04)	1.10 (.99–1.23)	0.93 (.90–.97)
B	Misclassification correction	1.01 (.99–1.01)	1.06 (1.02–1.10)	0.96 (.95–.98)

Abbreviations: AST, aspartate aminotransferase; CD4, cluster of differentiation 4 receptor; CI, confidence interval; HIV, human immunodeficiency virus; SVR, sustained virologic response.

[a]Adjusted for time-varying confounders: Advanced fibrosis/cirrhosis (AST to Platelet Ratio Index (APRI) ≥ 1.5 and/or end stage liver disease diagnosis), detectable HIV viral load (>50 copies/ml), low CD4 cell count (≤250 cells/μl), current injection drug use, current alcohol use, incarceration in the past 6 months and antidepressant use.

expected, and we corrected for it. We predicted the depressive symptoms based on a screening questionnaire, CES-D-10, and not a major depression diagnosis. Thus, this study does not provide an effect estimate for depression but rather for depressive symptoms that are indicative of a depression risk. Furthermore, we predicted the CES-D-10 classes based on the validated cutoff of 10 and not a CES-D-10 continuous score. The continuous score prediction algorithm could only explain a small portion of the outcome variability. This could have been because the FS sub-study sample was relatively small and did not capture the full range of the continuous scale. We used an ITS because an appropriate control group was difficult to find. Those not treated may be inherently different from those treated, and in the DAA era, very few of those treated fail to achieve SVR. Finally, the crucial assumption of the ITS design that the extrapolated pre-exposure trend is considered the counterfactual trend, makes it vulnerable to unmeasured time-varying confounding, which we tackled by adding known time-varying confounders; however, some residual confounding could still be possible. Finally, the median post-SVR follow-up was 1.4 years, so the durability of the observed effect is yet to be explored. Persisting psychosocial and economic burdens post-cure such as stigma and discrimination in social, professional as well as healthcare settings could still lead to shame, suffering and lack of disease-related education and recurrence of depressive symptoms over the long term [43].

In conclusion, following SVR, there appears to be a continuous decline in the presence of depressive symptoms in highly vulnerable patients coinfected with HCV and HIV. This finding suggests that the health benefits of curing HCV extend beyond improving liver disease and provides additional rationale for treating HCV in all chronically infected persons.

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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Consent to participate. Informed consent was obtained from all individual participants included in the study.

Ethics approval. This study was approved by the Research Ethics Board of the McGill University Health Centre (2021-6985). The CCC and the FS Sub-Study were approved by the Research Ethics Board of the McGill University Health Centre (2006-1875, BMB-06-006t, 2013-994) and the research ethics boards of participating institutions. The study was conducted according to the Declaration of Helsinki.

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