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Effect of Clinically Relevant Depressive Symptoms on Hepatitis C Virus (HCV) Treatment Initiation in the HIV-HCV Co-Infected Population in Canada

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CIHR IRSC Canadian Institutes of Health Research / Instituts de recherche en santé du Canada

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BACKGROUND AND OBJECTIVE

- Hepatitis C virus (HCV) treatment has evolved from interferon (IFN)-based regimens to safer IFN-free direct acting antiviral (DAA) regimens.
- IFN-based regimens were associated with neuropsychiatric side effects including mild/severe depression, leading to lower treatment among those with psychiatric illness[1].
- The second-generation DAA regimens have fewer side effects, importantly psychiatric side effects[2]; however, patient-level barriers to treatment initiation persist[3].
- With high depression prevalence reported in the HIV-HCV co-infected population, presence of clinically relevant depressive symptoms can be one such barrier[4].

Objective

Examine the effect of clinically relevant depressive symptoms on time to HCV treatment initiation among HIV-HCV co-infected persons during the IFN (2003-2011) and second-generation DAA eras (2013-2020).

1. Schaefer 2002; 2. Sundberg 2018; 3. Saeed 2017; 4. Fialho 2017

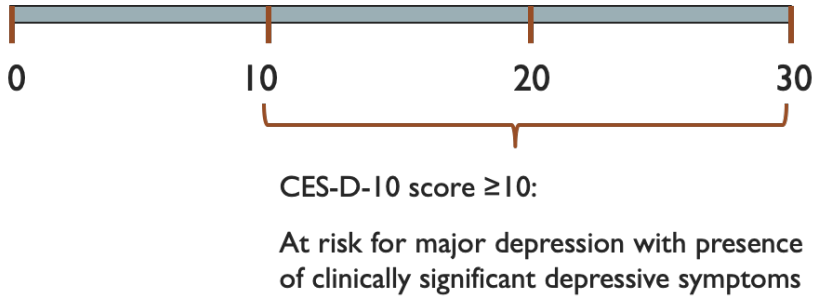
DATA SOURCES

Canadian Co-infection Cohort (CCC)

- Multicenter prospective cohort study with visits every 6 months - ongoing since 2003.
- HIV-infected participants with evidence of HCV infection - 2018 participants as of July 2020.

Food Security and HIV-HCV co-infection study (FS sub-study)

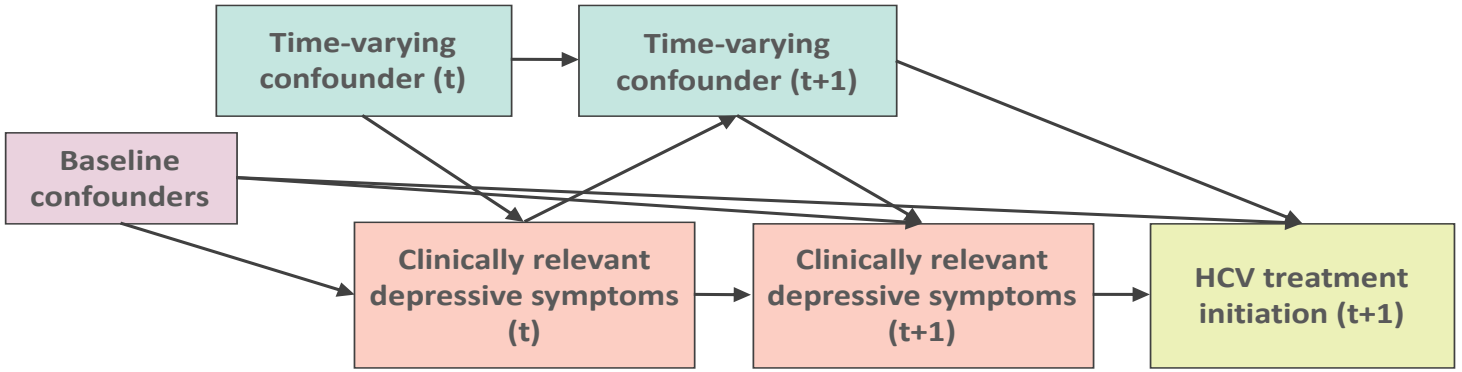
- Sub-study initiated in 2012 until 2015, with visits integrated into the CCC - Total 725 participants.
- Depression screening was performed using Center for Epidemiologic Studies Depression Scale-10 (CES-D-10):
  - 10 item Likert scale, score range: 0-30
  - CES-D-10 classes (1/0) at score 10



Definition of the two HCV treatment eras

- **IFN era**: From beginning of CCC, April 28, 2003 to the approval of the first 1st generation DAA, boceprevir, on August 1, 2011.
- **DAA era**: From the approval of the first 2nd generation DAA, simeprevir, on November 25, 2013 to the end of available CCC data, July 15, 2020.

METHODS



Clinically relevant depressive symptoms: Predicted by a random forest (RF) classifier

Eligible CCC participants

- Included if HCV RNA positive
- Followed up until treatment initiation or censoring due to loss to follow-up, withdrawal, death or end of study period

Multiple imputation for missing confounder values

- Multiple imputation by chained equations (MICE) - 5 imputed datasets

Overall HCV treatment initiation rate per 100 person-years

Effect of depressive symptoms on time to HCV treatment initiation

- Marginal structural Cox proportional hazards models accounting for baseline and time varying confounders
- Accounted for death as a competing risk using inverse probability censoring weights
- Exposure misclassification was addressed using predictive value-based record-level correction
- Positive predictive value: 0.74 (95% CI: 0.68-0.80) and Negative predictive value: 0.76 (95% CI: 0.69-0.82) for the RF classifier

RESULTS AND CONCLUSION

Treatment era	Participants (N)	Baseline depressive symptoms (%)	Treatment initiations (N)	Treatment initiation rate per 100 person-years (95% CI)	Effect of depressive symptoms on HCV treatment initiations			
					No misclassification correction		Misclassification correction	
					HR	95% CI	HR	95% CI
IFN era	590	55	126	8.5 (7.2-10.2)	0.63	0.43-0.93	0.81	0.69-0.95
DAA era	1127	60	566	20.5 (18.8-22.2)	1.42	1.17-1.71	1.19	1.10-1.27

Abbreviations: IFN = Interferon; DAA = Direct acting antiviral; N = number; HR = hazard ratio; CI = Confidence interval; **Baseline confounders:** Age, gender, race, education, sexual orientation, previous HCV treatment, immigration status, marital status and province; **Time-varying confounders:** Living situation, employment, monthly income, revenue source, injection drug use, alcohol use, smoking, incarceration, liver fibrosis stage, HIV viral load, CD4 count and antidepressant use

Conclusion

- There was high baseline prevalence of clinically relevant depressive symptoms among participants in both IFN and DAA eras.
- Treatment initiation rates more than doubled from the IFN to the DAA era.
- Our results suggest that depressive symptoms are no longer a barrier to HCV treatment initiation in the DAA era.
- The relatively higher rates of initiation among individuals with depressive symptoms in the DAA era could be because a backlog of patients who were unable to tolerate IFN are now accessing treatment.