Relationship Between Depressive Symptoms and Adherence to Direct-Acting Antivirals: Implications for Hepatitis C Treatment Among People Who Inject Drugs on Medications for Opioid Use Disorder

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Abstract

Background

Interferon-based regimens exacerbated depressive symptoms, which interfered with treating hepatitis C virus (HCV) among people who inject drugs (PWID). Direct-acting antivirals (DAA) are not associated with worsening depressive symptoms; however, the impact of depressive symptoms on adherence remains little known. We examined the association between depressive symptoms and adherence to DAA among HCV-infected PWID. A secondary aim was to identify the optimal cut-off for major depressive disorder for this population.

Methods

Participants were 150 HCV-infected PWID on maintenance treatment enrolled in a randomized clinical trial testing three HCV care models. Severity of depressive symptoms were assessed using the Beck Depression Inventory-II (BDI-II) at baseline and every 4 weeks during treatment. Current major depressive disorder at baseline was diagnosed by the Mini-International Neuropsychiatric Interview. Adherence was measured during treatment (weeks 1-12) using electronic blister packs

Results

BDI-II scores ≥18 were identified as the optimal threshold for diagnosing major depressive disorder. Participants with BDI scores ≥18 at baseline had significantly lower adherence rates at weeks 1 to 4 of treatment compared to those with BDI scores <18 (b = -0.23, 95% CI: 0.45-0.01, p=0.044), but not in any other time intervals (weeks 5-8, b = -0.03, 95% CI: -0.32, 0.26, p= 0.825; weeks 9-12, b = -0.33, 95% CI -0.70, 0.02, p=0.066).

Conclusions

Elevated depressive symptoms were associated with lower adherence to DAA only during the first 4 weeks of HCV treatment. Neither severe depressive symptoms nor major depressive disorder appears to be a barrier to DAA adherence among PWID.

Keywords: Depression; Mental Health; HCV; People Who Inject Drugs; Injecting Drug Use; Adherence

1. Introduction

Depressive disorders are highly prevalent among people who inject drugs (PWID) (Goldner, Lusted, Roerecke, Rehm, & Fischer, 2014). According to a recent systematic review, the prevalence of major depressive disorder (MDD) among PWID is 28.7% (Colledge et al., 2020), which is 4-fold higher than the general adult population, and approximately 59.7% experience moderate to severe symptoms of depression (Colledge et al., 2020). In addition, hepatitis C virus (HCV) is one of the most common comorbidities among PWID (Levitt, Mermin, Jones, See, & Butler, 2020) as approximately 69-77% PWID have been infected with HCV (Nelson et al., 2011), which is also is associated with an increased risk of having a depressive disorder (Adinolfi, Nevola, Rinaldi, Romano, & Giordano, 2017).

Depressive symptoms are important contributors to morbidity and mortality among PWID (Levintow et al., 2019; So-Armah et al., 2019). Depression has been associated with an increased risk of ongoing illicit drug use, conducting illegal activities, and sharing injecting equipment among PWID (Lemstra, Rogers, Thompson, Moraros, & Buckingham, 2011; Risser, Cates, Rehman, & Risser, 2010; Teesson et al., 2015). PWID who experience elevated depressive symptoms are at increased risk for a drug overdose (Pabayo, Alcantara, Kawachi, Wood, & Kerr, 2013; Tobin & Latkin, 2003). Among PWID infected with HCV, elevated symptoms of depression have been related to higher levels of healthcare-seeking barriers (Li et al., 2020). Furthermore, recent evidence has demonstrated that having a diagnosis of depression decreased the likelihood of contacting a health care provider to make an appointment after an HCV-positive result (Stephens, Young, & Havens, 2017) or initiating HCV treatment (Talal et al., 2018) in HCV-infected PWID.

When treating HCV with early interferon-based regimens, depressive symptoms were exacerbated (Udina et al., 2012) and associated with lower treatment uptake or treatment failure among PWID (Grebely et al., 2010; Mravčík et al., 2013). The new direct-acting antivirals (DAAs) are highly effective, have few side effects (Asselah et al., 2020), and also appear to facilitate a decrease in depressive symptoms (Goñi Esarte et al., 2019; Juanbeltz et al., 2018; Pericot-Valverde et al., 2020; Sundberg, Lannergård, Ramklint, & Cunningham, 2018). Nevertheless, an optimal level of adherence is still necessary to optimize rates of sustained virologic response (i.e., HCV cure)(Norton et al., 2020). Prior studies have explored the association between a history of depression or elevated depressive symptoms and adherence to DAAs among PWID, none found an association between adherence to medication and depressive symptoms or history of depression (Back et al., 2019; Brown et al., 2020; Mason et al., 2017; Petersen et al., 2016; Ward et al., 2021). However, these studies relied on suboptimal measures of adherence including pill count (Back et al., 2019; Brown et al., 2020; Petersen et al., 2016; Ward et al., 2021), which results in an increased work burden and an increased risk of mathematical error, or self-reported questionnaires (Mason et al., 2017), which are subject to recall bias or social desirability(Burton, Voluse, Patel, & Konkle-Parker, 2018). Moreover, assessment tools used to determine depressive symptomatology varied across the studies, including medical history of depression (Back et al., 2019; Brown et al., 2020), self-reported lifetime history of depression (Mason et al., 2017), or the Center for Epidemiological Studies-Depression scale (CESD-D) but with different cut-offs (≥8(Petersen et al., 2016) or ≥16 (Ward et al., 2021)). Finally, these studies only explored the association between pre-treatment depressive symptoms or diagnosis of depression and overall adherence (Back et al., 2019; Brown et al., 2020; Mason et al., 2017; Petersen et al., 2016; Ward et al., 2021). Recent studies have shown

that the severity of depressive symptoms decreases during HCV treatment with DAAs (Goñi Esarte et al., 2019; Juanbeltz et al., 2018; Pericot-Valverde et al., 2020; Sundberg et al., 2018). Thus, it seems clinically relevant to examine whether depressive symptoms during the course of treatment, rather than only before treatment, are associated with adherence during treatment.

We sought to investigate the relationship between depressive symptoms and adherence to DAAs among PWID using validated instruments for depression assessments and utilizing electronic blister packs for accurate measurement of treatment adherence. Thus, the first aim of this study is to determine the optimal cut-off score for diagnosing major depressive disorder (MDD) with the Beck Depression Inventory (BDI-II) in comparison to Mini-International Neuropsychiatric Interview (MINI) diagnosis among PWID infected with HCV. The second aim was to utilize this cut-off point to examine the association between elevated depressive and objectively measured adherence to DAAs among a sample of HCV-infected PWID on medications for opioid use disorder (MOUD).

2. Materials and Methods

2.1 Participants

150 PWID on MOUD were enrolled in a randomized parent clinical trial, called PREVAIL, (ClinicalTrials.gov NCT01857245) that tested the three models the effectiveness of three models of care for HCV treatment: self-administered individual treatment (SIT), group treatment (GT), and directly observed therapy (DOT). Participants were recruited at 3 OAT programs in Bronx, New York. In the parent trial, participants were deemed eligible if they met the following criteria (1) were aged ≥18 years; (2) had HCV genotype 1; (3) were able to speak English or Spanish; (4) were psychiatrically stable, that is, not having severe psychotic symptoms and not being at risk of injuring or harming themselves or others based on the

clinician's judgment experienced in treating PWID; (4) agreed to receive HCV treatment on-site in their OAT program; and (5) were never treated for HCV with DAAs(or treatment experienced with interferon-based regimens after December 2014). All participants provided written informed consent and the study protocol was approved by the Institutional Review Board.

Research visits were conducted at baseline, every 4 weeks during the first 12 weeks of treatment, at the end of treatment, and 4, 12, and 24 weeks after treatment. A detailed description of the PREVAIL study is published elsewhere (Matthew J. Akiyama et al., 2018; M. J. Akiyama et al., 2019). During these visits, the computer-assisted self-interview (ACASI) was used to record participants' responses to surveys.

Participants in the PREVAIL study received the following DAA regimens based on the AASLD/ISDA guidelines: telaprevir/pegylated interferon/ribavirin (TVR/PEG/RBV), sofosbuvir/pegylated interferon/ribavirin (SOF/PEG/RBV), sofosbuvir/ribavirin (SOF/RBV), sofosbuvir/ledipasvir (SOF/LDV) or sofosbuvir/simeprevir (SOF/SIM). First-generation DAAs (i.e., SOF/RBV, TVR/RBV/PEG, and SOF/RBV/PEG) contained ribavirin, interferon, or ribavirin and interferon, which are known to exacerbate depressive symptoms. Thus, for the analyses exploring the association between adherence and both MDD and depressive symptoms during treatment, the sample was limited to those participants who received a combination of second generation DAAs (N=115), which are SIM/SOF and SOF/LDV regimens. One participant receiving second-generation DAAs did not return any blister pack, resulting in a total sample size of N=114.

2.2 Measures

2.2.1 Baseline characteristics

At baseline, all participants completed a questionnaire asking about basic sociodemographic characteristics, including age, gender, race/ethnicity, and education. The Addiction Severity Index-Lite (ASI-Lite)(Cacciola, Alterman, McLellan, Lin, & Lynch, 2007) was used to document self-reported use of alcohol and other drugs within the 30 days prior to baseline. Urine specimens were tested for amphetamines, benzodiazepines, cocaine, opioids, and oxycodone using an enzyme multiplied immunoassay technique. Data about MOUD medication and psychiatric comorbidities prior to starting treatment were obtained through chart review. Baseline demographic and clinical characteristics, as well as self-reported drug use and urine toxicology tests are presented in Table 1.

2.2.2 Depression and depressive symptoms

Both instruments were administered during the research visits using ACASI.

The BDI-II is a 21-item self-reported inventory designed to measure the presence and severity of depressive symptoms over the last 2 weeks. Each item is item is scored on a 4-point scale ranging from 0 to 3. BDI-II with total score ranges from 0 to 63, with higher scores indicating higher levels of depressive symptoms (Beck, Ward, Mendelson, Mock, & Erbaugh, 1961). The BDI was completed at baseline, then every 4 times during treatment (weeks 4, 8, and 12).

The MINI was considered the gold standard.(Sheehan et al., 1998) The M.I.N.I. is a structured and standardized diagnostic interview developed for the diagnosis of mental diagnosis according to DSM-IV-TR and the International Statistical Classification of Diseases and Related Health Problems (ICD-10). The MINI was administered at baseline.

2.2.3 Adherence

HCV medication adherence was continuously during treatment (weeks 1 to 12) using electronic blister packs which accurately record the specific time and date that participants pop-up the medication. Adherence was calculated by using daily timeframe approach, which implies that the patient received credit for daily adherence only if medication was popped out of the blister pack within the prescribed day. Blister pack data was used to calculate mean adherence scores for weeks 1-4, 5-8, and 9-12 (total doses removed every days/days).

2.3 Data analyses

Descriptive statistics were used to summarize baseline demographic characteristics, self-reported drug use, and urine toxicology results. To determine BDI's cut-off point, we used Youden index [sensitivity + specificity-1] based on the Receiver Operating characteristics (ROC) Curve. The following predictive accuracy indices of BDI-II were calculated based on the optimal cut-off: area under the curve (AUC), sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV).

We conducted multivariable linear regression analyses to test significance of associations between adherence to DAAs and depressive symptoms during treatment. Specifically, tested were the time-by-time associations between BDI scores controlling for three treatment groups (SIT, GT, and DOT): at baseline, week 4, and week 8 with average adherence scores during weeks 1-4, weeks 5-8, and weeks 9-12, respectively so that the time frames align each other. To test the association between baseline MINI-diagnosis of MDD and adherence to DAAs, t-tests were conducted comparing average adherence during weeks 1-4, weeks 5-8, and weeks 9-12 between those with and without baseline MINI-diagnosis of MDD. Finally, we compared average adherence scores at weeks 1-4, weeks 5-8, and weeks 9-12, between participate with

BDI≥ 18 and < 18 for each corresponding time interval, using t-tests. Statistical analyses were conducted using SAS v9.4 (SAS Inc., Cary, NC, USA), and statistical significance was declared if a two-sided p-value<.05.

3. **Results**

Table 1 presents participants' characteristics at baseline (N=150). Briefly, participants' mean age was 51.2 (SD=10.6) years old and 35.3% were female. The majority of the sample was Latino/Hispanic (56%), 26.7 % were African-Americans, and 8% were White. Sixty-six percent of the participants had a diagnosis of a comorbid psychiatric condition before treatment.

Figure 1 displays the ROC curve generated for MDD diagnosis by BDI-II compared to the MINI diagnosis. AUC for detecting MDD was 0.81, indicating that the BDI-II-based diagnosis has good accuracy. A score ≥18 was identified as the optimal cut-off score to detect MDD with 0.85 sensitivity, 0.66 specificity, 0.27 PPV, and 0.96 NPV. The diagnostic accuracy of the BDI for MDD is shown in Table 2. Using the cut-off of ≥18 to diagnose MDD, the BDI identified 61 participants with MDD.

The average adherence level for the PREVAIL study cohort on DAAs (N=114) was 81.1% (SD=17.1), 79.3% (SD=18.8), and 77.3% (SD=21.1) for weeks 1 to 4, 5 to 8, and 9 to 12, respectively. The average BDI scores for these participants were 18.0 (SD=14.0) for baseline, 13.3 (SD =12.2) for week 4, and 12.7 (SD=12.3) for week 8. A significant inverse treatment adjusted association between continuous BDI scores at baseline and adherence rates during treatment weeks 1 to 4 was observed (b = -0.23, 95% CI : -0.45, -0.01, p = 0.044), showing that higher BDI scores at baseline were significantly associated with lower adherence rates during treatment weeks 1 through 4. No significant association was found between BDI scores and

adherence during weeks 5-8 (b = -0.03, 95% CI: -0.32, 0.26, p = 0.825), or week 9-12 (b = -0.33, 95% CI: -0.70, 0.02, p = 0.066).

We also observed a significant association between having BDI scores ≥18 at baseline and adherence rates at weeks 1 through 4. Specifically, participants with BDI scores ≥18 at baseline had significantly lower adherence rates during weeks 1-4 compared to those with BDI scores <18 (75.21 (SD = 19.9) vs. 85.38 (SD =13.4); p = 0.0035). However, no significant association was found between having BDI scores ≥18 at week 4 and week 8 and adherence rates during weeks 5-8 (79.4 (SD = 19.1) vs. 79.68 (SD =19.0); p = 0.954), or weeks 9-12 (72.4 (SD = 23.1) vs. 79.3 (SD =20.1); p = 0.218), respectively.

Finally, participants with a MINI-MDD diagnosis and those without had no difference in adherence rates at any of the three time frames [(weeks 1-4, 81.1 (SD = 14.0) vs 81.1 (SD=17.5), p = 0.998); (weeks 5-8, 77.5 (SD = 20.1) vs 79.5 (SD=18.7), p = 0.722), or (weeks 9-12, 66.4 (SD = 27.2) vs 79.3 (SD=19.4), p = 0.140)].

4. Discussion

The principal findings from this study are: (1) elevated depressive symptoms at baseline were associated with lower DAAs adherence rates, but only at treatment weeks 1 through 4; (2) high adherence rates to DAAs were observed, regardless of participants having elevated depressive symptoms; and (3) ≥18 was identified as the optimal cut-off score for detecting MDD among HCV-infected PWD on MOUD.

An important and novel finding was that elevated depressive symptoms before treatment were significantly inversely associated with DAA adherence rates only during the first 4 weeks of treatment among our sample of PWID on MOUD. This finding contradicts earlier studies conducted in samples of HCV-infected PWD treated with DAAs which did not show a

significant association between depressive symptoms and adherence to HCV medication.(Back et al., 2019; Brown et al., 2020; Mason et al., 2017; Petersen et al., 2016; Ward et al., 2021) Three rationales might account for this finding. First, recent studies have shown that depressive symptoms decline after initiating HCV treatment (Sundberg et al., 2018; Tang et al., 2016), including ours involving the PREVAIL sample (Pericot-Valverde et al., 2020). In this study, the decline in depressive symptoms that occurred after initiating treatment might have attenuated the association between adherence and depressive symptoms. It may also be possible that earlier studies did not find an association between adherence due to the approach used to test the association. In those studies, baseline depressive symptoms were compared with overall adherence rates through the entire treatment period or used arbitrary values to determine elevated depressive symptoms (Petersen et al., 2016; Ward et al., 2021). Third, the relationship between adherence and depressive symptoms may be related to common confounding factors that are associated with both phenomena. For example, psychological experience of stigma has been known to hinder diagnosis and successful treatment (Butt, 2008; Marinho & Barreira, 2013) and is negatively associated with depressive symptoms and disorders (Golden, Conroy, Marie O'Dwyer, Golden, & Hardouin, 2006) among persons living with HCV. Taken together, our finding suggests that elevated depressive symptoms only become a risk for DAA non-adherence in the early weeks of treatment, and do not support the assumption that depressive symptoms or having a diagnosis of depression may impede overall DAA adherence. However, It should be highlighted, that this is an important finding as a recent study has showed that nonadherence during the first weeks of treatment is associated with HCV treatment failure (Heo et al., 2021). Thus, it is possible that patients with elevated depressive symptoms may need counseling added to their HCV treatment in the initial weeks of treatment.

Second, we observed high and comparable adherence rates to DAAs in this sample of HCV-infected PWID actively injecting drugs regardless of having a diagnosis of MDD or elevated depressive symptoms, except for the first four weeks of treatment. This finding is consistent with prior research showing that DAA adherence is comparably high among patients with and without depression before treatment (Back et al., 2019; Mason et al., 2017). This study adds novel data to demonstrate that having a MDD before treatment or a possible MDD diagnosis, based on the cutoff score of ≥18, during the last 8 weeks of treatment has no impact on adherence to DAAs among PWID actively using drugs. Having depression or other psychiatric conditions has traditionally been a concern among providers to treat HCV among patients due to the potential to worsen psychiatric symptoms and expected low adherence(Hauser & Kern, 2015). Using PREVAIL trial data, we demonstrated in a prior study that DAA therapy among active PWID does not exacerbate depressive symptoms (Pericot-Valverde et al., 2020). In this study, we showed that elevated depressive symptoms do not impact adherence to DAA therapy. Taken together, our findings further support that PWID infected with HCV should be treated regardless of having a diagnosis of depression or elevated depressive symptoms as these comorbidities are unlikely to interfere with their medication adherence.

Finally, this study found that a cut-off score ≥18 is the optimal score to identify and classify those HCV-infected PWID on MOUD with or without MDD, which was used in this study to test the association between adherence to DAAs and a possible diagnosis of depression. This finding is similar to earlier studies that explored the best cut-offs of BDI to diagnose depressive disorder among people living with HCV (Fábregas et al., 2012; Golub et al., 2004). More specifically, Fabregas(Fábregas et al., 2012) found the same cut-off of 18 in a sample of HCV patients, including a portion with a history of injection drug use. Golub et al (Golub et al.,

2004) found 19 as the optimal cut-off threshold in a cohort of young adult (18-35 years) PWID living with HCV. It should be noted that these values are significantly higher than the threshold of 12-13 chosen for adults from the general population.(Lasa, Ayuso-Mateos, Vázquez-Barquero, Díez-Manrique, & Dowrick, 2000) Given the potential for extreme differences in characteristics between patients, using the specific BDI cut-off for the particular patient profile, in this case HCV infected PWID on MOUD in our study, is necessary.

Limitations of this study should be taken into consideration. First, the diagnosis of MDD was determined using the ACASI, a computer interface that asks questions and records patients' answers, not through a structured, clinical interview conducted by a clinician. It should be noted that ACASI reduces the possibility of interviewer bias and data entry errors. Second, the generalizability of our findings is limited by the fact that we recruited participants from an urban setting. Finally, we did not adjust p-values for multiple tests due to the nature of the present secondary analyses. However, we believe that the estimated effect sized along with re 95% CI's could serve as valuable information for future confirmatory studies.

5. Conclusion

In conclusion, prior studies reported no association between adherence to DAAs and depressive symptoms among PWID, but these earlier studies are limited by only exploring depressive symptoms pre-treatment; and relying on suboptimal measures of adherence. Thus, the association between depressive symptoms experienced over the course of HCV treatment and continuous adherence to DAAs remains unexplored. The current study sought to explore the relationship between depressive symptoms and adherence to DAAs among PWID using validated instruments for depression assessments and utilizing electronic blister packs for accurate measurement of treatment adherence. Overall, our study demonstrates that PWID with

elevated depressive symptoms have similarly high adherence rates to DAAs than those without, except for the first 4 weeks of treatment. Future studies are needed to identify the mechanisms underlying the relationship between adherence and depressive symptoms at early treatment stages . Taken together, as evidenced in earlier research, DAA HCV treatment should never be withheld from PWID even when they experience psychiatric comorbidities before or during treatment period.

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Figure 1. Receiver operating characteristics (ROC) curve of the BDI-II for detecting MDD. The X-axis represents the false positive rate (FPR), i.e., 1-specificity, which is the proportion of incorrectly BDI-identified positives among those who are true negatives diagnosed based on MINI. The Y-axis represents the true positive rate (TPR), i.e., sensitivity, which is the proportion of correctly BDI-identified positives among those who are true postives diagnosed based on MINI.

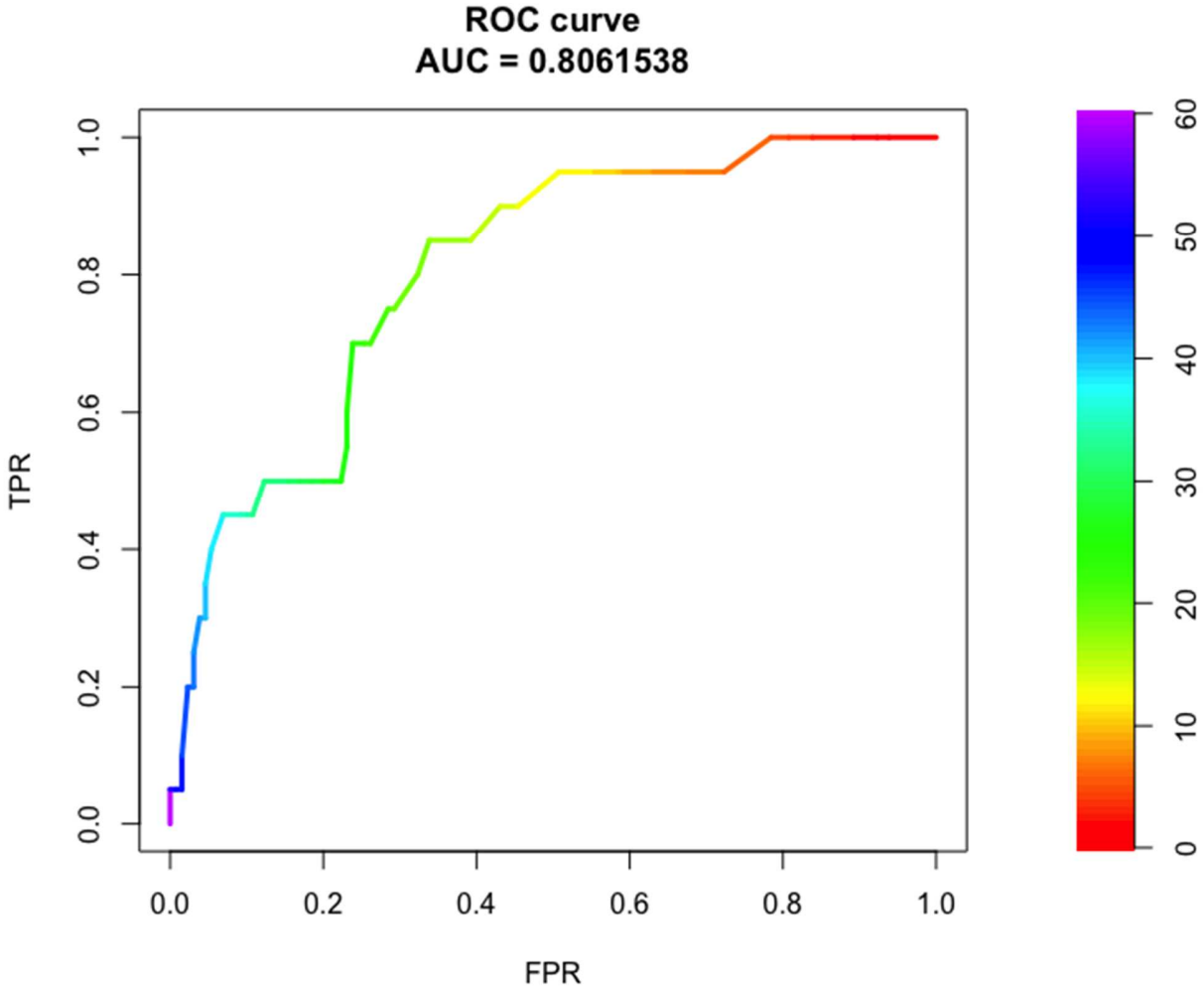

Table 1. PREVAIL Participants' characteristics

Characteristic	All PREVAIL participants (N=150)	Received DAAs (N=114)*
Sociodemographics	M(SD)/N(%)	M(SD)/N(%)
Age	51.2 (10.6)	52.1 (10.1)
Gender		
Male	97 (64.7)	69 (60.5)
Female	53 (35.3)	45 (39.5)
Race/ethnicity		
Black/African American	40 (26.7)	33 (28.9)
Hispanic/Latino	84 (56.0)	61 (53.5)
White	12 (8.0)	11 (9.6)
Other	14 (9.3)	19 (7.9)
Educational attainment		
Less than HS	64 (42.7)	44 (38.6)
≥HS graduate/GED	86 (57.3)	70 (61.4)
Medication for opioid use disorder		
Methadone	147 (98.0)	112 (98.2)
Buprenorphine	3 (2.0)	2 (1.8)
Drug use		
Self-reported drug use (prior 30 days)		
Alcohol to intoxication	36 (24.0)	25 (21.9)
Heroin	28 (18.6)	19 (16.7)
Opiates/analgesics	33 (22.0)	25 (21.9)
Sedatives/hypnotics/tranquilizers	33 (22.0)	24 (21.1)
Cocaine	36 (24.0)	26 (22.8)
Amphetamine	4 (3.0)	3 (2.6)
Urine drug screen		
Any drug	76 (50.7)	56 (49.1)
Opiate/Oxycodone	37 (24.6)	30 (26.3)
Cocaine	44 (29.5)	30 (26.3)
Benzodiazepine	23 (15.3)	14 (12.3)
Amphetamine	0 (0.0)	0 (0.0)
Psychiatric comorbidities		
Any	99(66.0)	72 (63.2)
Depression	73(48.7)	57 (50.0)
Anxiety	42(28.0)	32 (28.1)
Bipolar	22(14.7)	18 (15.8)
Post-traumatic stress disorder	13(8.7)	11 (9.6)
Obsessive compulsive disorder	1(0.7)	1 (0.9)

Note: M= mean; SD = standard deviation; HS = high school; GED = general educational diploma; *participants who received DAAs with adherence data available.

Table 2. Diagnostic accuracy of the BDI-II for major depressive disorder among our sample of HCV-infected PWID on MOUD

	Diagnosis for MDD (M.I.N.I)		Total
	Present	Absent	
BDI <18	3	86	89
BDI ≥18	17	44	61
Total	20	130	150

Note: BDI = Beck depression Inventory; MDD = Major depressive disorder; MINI = Mini-International Neuropsychiatric Interview