1-1-2019

Impacts Of Hepatitis C Virus Infection Treatment For Patients In Treatment For Opioid Use Disorder

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Abstract

Hepatitis C virus (HCV) infection is common among patients with opioid use disorder (OUD), a population who faces barriers to HCV treatment access. Co-located treatment for HCV within an opioid treatment program (OTP) addresses gaps in the HCV care continuum. Few reports have analyzed outcomes related to OUD, such as OUD treatment retention, associated with onsite HCV treatment. Patients (N=89) treated for chronic HCV infection in a Connecticut OTP from January 2014 through July 2017 were compared to control patients (N=199) with HCV-based ICD10 coding (B18.2) who were not treated during the same period. All patients received opioid agonist treatment (OAT) as part of an OTP. To assess the period following HCV treatment, a look-back period from September 2017 through September 2018 was included. Outcomes include (1) retention in OUD treatment from January 2014 through September 2018, analyzed first using logistic regression and subsequently using survival analysis based on OTP loss to follow-up dates; (2) urine analysis (UA) results screening for non-prescribed opioids during the look-back period, analyzed using ordered logistic regression; (3) changes in a behavior and symptom scale based on the BASIS-24 validated instrument, analyzed using linear regression. After adjusting for all baseline covariates, patients who initiated and completed HCV treatment had 2.2 (95% CI: 1.1, 4.5) increased likelihood of remaining in the OTP compared to patients in the control group. There were no differences between the two groups in terms of UA results of non-prescribed opioids or changes in BASIS-24 scores. Results indicate that the co-located model of concurrent HCV and OUD treatment is associated with improved OTP treatment retention following HCV treatment. This naturalistic study confirms prior findings that co-located treatment models are feasible and effective, and suggests that this model has an important and needed impact on keeping patients engaged in OAT.

Acknowledgements

Thank you to the APT Foundation leadership and informational technology team for your patience and trust in this project, especially Lynn Madden, Declan Barry, Robert Freeman, and Ehab Hussein. Thank you to Kenneth Morford for comments and suggestions.

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Introduction

In October 2018, the United States 115th Congress passed the "Substance Use Disorder Prevention that Promotes Opioid Recovery and Treatment (SUPPORT) for Patients and Communities Act."[1] This act, specifically Section 7141, included language that linked infectious diseases with widespread illicit drug use, and further appropriated funds for increased surveillance and education efforts related to infectious diseases spread through drug use.[2] Though this link is evident to practitioners who have worked at the intersection of infectious diseases and drug use for decades, the signal in the form of federal statute is noteworthy.

Hepatitis C virus (HCV) infection is a significant contributor to morbidity and mortality in the US. In 2012, deaths related to hepatitis C surpassed deaths related to any of 60 other nationally-notifiable infectious diseases reportable to the Centers for Disease Control and Prevention (CDC), including Human Immunodeficiency Virus (HIV).[3] Though other groups are at risk for HCV infection, persons who use or inject drugs are often deemed the most vulnerable to new HCV infections, given that the infection is primarily spread through infected blood. The CDC estimates that injection drug use is the most common means of transmission in the US, despite the substantial challenges related to the classification and detection of acute and chronic cases.[4, 5] It is increasingly recognized that rising HCV incidence is closely tied with widespread injection drug use.[6] The American Association for the Study of Liver Disease (AASLD) and Infectious Diseases Society of America (ISDA) recommend ongoing testing and linkage-to-care, if applicable, for persons who inject drugs (PWID).[7] The advent of direct acting antiviral treatment (DAA) revolutionized HCV treatment with decreased treatment duration, improved side effect profile, and greater likelihood of establishment of sustained virologic response (SVR),

or viral cure.[8] It is well-established that it is feasible, using DAA treatment, to achieve SVR in PWID.[9,10]

Researchers have also demonstrated that HCV treatment is effective at achieving SVR within 12 weeks (SVR 12) in patients who concurrently receive treatment with opioid agonist medications for the treatment of opioid use disorder (OUD). In a randomized control trial conducted across 12 countries, drug use at baseline and during treatment did not affect SVR 12 or adherence to HCV treatment among patients receiving opioid agonist treatment (OAT).[11] Though the possibility of HCV cure among PWID who also receive OAT has been demonstrated, there remain barriers for this population in accessing education about the natural history of HCV infection, screening, and treatment. The understanding of these barriers through qualitative inquiry has been conducted in the pre-DAA era of HCV treatment in the Enhancing Treatment for Hepatitis C in the Opioid Substitution Setting (ETHOS) study in Australia, in which researchers noted barriers of feeling well, concerns about efficacy of treatment, family responsibilities, and unstable housing.[12] A recent qualitative study in the post-DAA era interviewed 30 Australian PWID with serologic evidence of chronic HCV infection; participants discussed themes of lack of symptoms directly attributable to HCV infection, lack of accurate information about HCV treatment and treatment access, and lack of models of care that could support the unique needs of PWID.[13] Several participants in this study specifically proposed the concurrent receipt of medication for OUD and HCV at their opioid treatment program (OTP) as a way to establish a "routine."[13] Such a solution addresses gaps in the HCV care continuum, obviating the need for offsite referrals for follow-up ribonucleic acid (RNA) confirmatory testing, treatment workup, and management of the treatment regimen at a separate location. At the same OTP that is the context for the present study, Butner et al. observed a 98% SVR 12 rate

for a small sample of patients who received concurrent OUD and HCV treatment in a co-located model of care.[14] Another potential effective solution to addressing gaps in the HCV care continuum for this population is the use of telemedicine for HCV treatment within an OTP setting, should on-site integrated primary care services not be feasible and/or sustainable.[15]

In studies on the general effectiveness of HCV treatment among PWID and among those who receive treatment for OUD in the form of opioid agonists, either in a co-located model of treatment or not, the primary outcome of interest is most typically SVR 12. There is considerably less literature examining the potential effect of DAA treatment for HCV on OUD outcomes, most notably of retention in care in an OTP. In a six-year observational study in Taiwan, Chen et al. record retention in care using a time-spanning method and found that patients with OUD and HCV infection had better retention in care.[16] Such observations are not easily transferable to the American medical system in which OTPs are not typically located within the psychiatric department of hospitals, as in Taiwan, but rather are located in the community and generally separate from other healthcare services. It is also critical to note that authors were looking at patients with HCV infection, not those patients who had been treated and cured; the study pre-dated the approval of DAAs.[16]

Study Objectives and Hypotheses

The objective of this study is to examine OUD outcomes among a population of patients treated with DAAs for HCV treatment while concurrently receiving OAT in a comprehensive OTP. I examined the association between HCV treatment and the OUD outcomes of (1) retention in the OTP, (2) urine analysis (UA) results screening for non-prescribed opioids, and (3) changes in results of a behavior and symptom scale based on the Behavior and Symptom Identification

Scale of 24 questions (BASIS-24) validated instrument. The primary hypothesis is that patients who have initiated and completed treatment for chronic HCV infection and receive co-located treatment for OUD will have improved retention in care in the OTP as compared to those who are infected with HCV but untreated and receive treatment for OUD. Secondary hypotheses are that patients treated for chronic HCV infection will have lesser proportions of positive urine drug analyses for non-prescribed opioids as well as improved scores in a behavior and symptom survey instrument over time compared to those who did not receive HCV treatment.

I intend to use the data analysis to inform an existing effective model of HCV treatment co-located with treatment for OUD. Though this model is highly effective in curing patients with HCV infection and treating the chronic illness of addiction, there remain patients who are diagnosed with HCV yet do not receive treatment and have co-occurring substance use disorder. Through my analyses, I hope to identify characteristics of HCV-treated patients who are retained in the OTP, have lower proportions of positive UAs for non-prescribed opioids, and have improved scores in a behavior and symptom survey instrument. I clearly note that the goal of this study is not to identify characteristics of those who do or do not initiate HCV treatment itself in a co-located model of treatment with OUD; for such a study objective, prospective and more-detailed data would be required. Should OUD outcomes improve among those receiving co-located treatment for HCV, this could potentially further validate the co-located model of care and prompt other OTPs to incorporate HCV screening and treatment into their programs, if feasible. It could also add to the growing literature that patients with OUD receiving OAT should be considered HCV treatment candidates.

Methods

Study Setting

The APT Foundation is a not-for-profit addiction treatment program with integrated primary care services that serves patients at several locations in South Central Connecticut.[17] A full description of the medical model and clinical processes for treatment of chronic HCV provided at APT Foundation has been described elsewhere by clinician-researchers at the practice.[18] In brief, however, the APT Foundation provides an open access model to patients seeking OAT as part of a comprehensive OTP including intensive outpatient services, residential treatment, onsite psychiatric care, and onsite primary medical care.[19] Patients treated with methadone or buprenorphine receive a physical and psychiatric evaluation by providers upon intake into the OTP, including an opt-out HCV antibody screening. Patients with positive HCV antibody tests are notified and receive HCV RNA confirmatory testing. If RNA confirmatory testing is positive, patients receive further workup for and counseling about treatment options. Patients are treated with DAAs under the management of APT Foundation clinicians and staff. Though data on patients' insurance status are not available in this study, it is notable that in Connecticut, the state Medicaid program does not restrict coverage of DAAs based upon sobriety, specialty provider, and/or degree of fibrosis.[20] For all patients who participate in the OTP, unique treatment plans are developed by clinicians for the daily, weekly, or monthly administration of methadone or buprenorphine.[18]

Upon intake to the OTP, all patients are asked to complete a BASIS-24 instrument. The BASIS-24 is a validated behavioral health assessment tool developed and licensed by McClean Hospital, a Harvard Medical School affiliate.[21,22] The BASIS-24 survey results are subdivided into six sub-scores and one overall score. The BASIS-24 instrument also includes questions

related to demographic characteristics, including age, sex, marital and employment status, among others. Patients complete the BASIS-24 during the intake process and each year thereafter. Due to the possibility that patients may have multiple treatment episodes at APT Foundation, it is possible that patients do not have documented BASIS-24 survey results for each year of their participation in the program or have more than one result per year.

This study was approved by the Institutional Review Board of Yale University Human Investigation Committee and the Board of Directors at the APT Foundation.

Study Design and Sample

This study was a retrospective, observational case-control study. I chose the beginning of the study period at 1/1/2014 to reflect the Food and Drug Administration approval of DAAs and their entrance to the market beginning in late 2013 as well as patient accessibility of these medications.[23] The cutoff date of 7/8/2017 for the selection of patients who had been treated for chronic HCV was arbitrary. The study's look-back period for the secondary outcome of proportion of positive urine drug analyses for non-prescribed opioids was a 12-month period between 9/30/2017 and 9/30/2018. This gap in time from the end of the HCV treatment period (7/8/2017) to the beginning of the look-back period (9/30/2017) allows for the possibility that a patient could have completed treatment on the last day of the study period, allowing for 12 weeks of follow-up by which to measure SVR 12.

Patients were included in the treatment group if they initiated treatment for HCV infection between 1/1/2014 and 7/8/2017. All patients in the treatment group have documented dates of treatment completion and SVR 12 in a clinical registry of HCV-treated patients. A clinician at the APT Foundation provided me with this clinical registry according to the time

parameters I set. Patients were excluded from the treatment group if they did not receive concurrent OAT at the APT Foundation at the time in which they initiated HCV treatment. Therefore, patients who were enrolled in primary care only or primary care only at the time of HCV treatment initiation were excluded. Patients who received treatment for OUD at locations other than APT Foundation were excluded from the study.

The lead information technology (IT) staff member at APT Foundation provided a data set of all patients with a documented ICD10 code for chronic viral hepatitis, B18.2, during the time period 1/1/2014 to 7/8/2017 who were also enrolled in the OTP. ICD 10 coding for chronic viral hepatitis does not differentiate between patients with chronic viremia and those who have a positive HCV antibody but do not have viremia. A condition for treatment with DAAs is documentation of chronic viremia. Using SAS Version 9.4 (SAS Institute Inc., Cary, NC) and with the assumption that all patients treated for chronic HCV infection have ICD10 code B18.2, I removed the patients in the treatment group (provided to me from the clinical registry of treated patients) from the ICD 10 B18.2 data set. The remaining patients became the control group of the study. I then excluded any patient who was enrolled only in primary care services during the study period. After a medical chart review of all patients in the control group, I removed patients who had chart documentation of treatment for HCV elsewhere and/or prior to the study period.

Study Variables and Analytic Approach

The lead IT staff member at APT Foundation provided all BASIS-24 scores for all patients in the study. As patients' demographic data was linked to their BASIS-24 survey results and as the date of completion was critical to the study's aims, the BASIS-24 surveys with missing dates of completion, or dates of completion prior to the beginning of the study period

(1/1/2014), were removed from the data set. This removal of BASIS-24 survey results as described was completed for both the treatment and control groups. All baseline demographic covariates as well as behavior and symptom indicators were derived from patients' BASIS-24 survey result closest following the beginning of the study period (1/1/2014).

I also received all recorded dates of loss to follow-up for all patients in the study during the period 1/1/2014 to 9/30/2018. Notably, this time period spans the initial study period as well as the study lookback period. Retention for the purpose of this study was defined as the absence of a recorded date of loss to follow-up during the period 1/1/2014 to 9/30/2018. Though patients may have had multiple episodes of treatment at the APT Foundation during this time, the present study was concerned only with the patients' status in the OTP at the conclusion of the study period (9/30/2018). I also lack information on reasons for patient loss to follow-up. Using the dates of loss to follow-up, I coded retention as a binary variable, either retained at the conclusion of the study (9/30/2018) or not.

Clinical data were abstracted by comprehensive chart review of the study look-back period, 9/30/2017 to 9/30/2018. Prior to completing the chart review, I met with APT Foundation leadership, clinicians, as well as research and IT staff to develop a data dictionary of clinically-meaningful measures. The outcome variable of proportion of positive urine drug analyses for non-prescribed opioids was derived through the following process: first, I examined the chart during the look-back period for any prescription validation documentation for synthetic opioids, then queried the electronic record system for all UA results during the look-back period. Patients typically have anywhere between 8 to 20 UAs over one year, each of which screen for 15 analytes.[24] I entered the fraction of positive UAs for opioids over the total number of UAs in an Excel sheet to arrive at a proportion. If a patient had a prescription validation entered into the

clinical chart by a master's level clinician for a synthetic opioid at any point during the look-back period, positive results for opioids in the UAs were not factored into the calculation. The same process was completed for the proportion of positive UAs for non-prescribed benzodiazepines and cocaine during the study look-back period. Therefore, I did not count urine toxicology for prescribed opioids or benzodiazepines as positive urine toxicology analysis. Prescription validations for both opioids and benzodiazepines were also recorded as binary variables in the data abstraction. I included a documentation of the type of OAT a patient received during the look-back period. In addition, I included the covariate "counsel" as a patient having use of counseling services beyond the program's requirement of one group or individual session per month at any point during the look-back period**.** This was meant to capture added counseling treatment services above and beyond usual care. The electronic medical chart system does not, however, capture the use of counseling services external to the OTP. I included a covariate for the use of psychiatric services at APT Foundation during the look-back period as evidenced by a documentation of a medical visit coded in psychiatric services. Lastly, I included a covariate for use of intensive outpatient (IOP) services during the study period as evidenced by a documentation of IOP services.

All study data were de-identified using a formula to code the patient identification number before conducting analyses. All data cleaning and statistical analyses were conducted in SAS Version 9.4. Bivariate analyses used chi-square tests for binary and categorical variables, and t-tests for continuous variables. Retention was analyzed first as a binary outcome variable in a logistic regression model, using a backward stepwise elimination strategy to arrive at the most parsimonious model. I conducted a subsequent Kaplan-Meier survival analysis with retention according to the dates of loss to follow-up. To conduct this analysis, I set a length of follow-up

variable as the time between the date of loss to follow-up and the date of the first BASIS-24 survey in the study period. If a patient did not have a date of loss to follow-up, I set the censor date as the last day of the study period (9/30/2018). I then conducted a Cox proportional hazards model, though notably there was a violation of the proportional hazards assumption and this will be discussed in the subsequent section. The secondary outcome variable of the proportion of positive UAs for non-prescribed opioids was a continuous variable, ranging from 0 to 1, with 0 meaning no positive screens and 1 meaning all positive screens during the study look-back period. The data, however, were more interpretable if I categorized the proportions into quartiles. Therefore, I conducted an ordered logistic regression with the categorized positive UA proportions as the outcome variable using a backward stepwise elimination strategy. I also completed the same categorization for the covariate of positive UA proportions for benzodiazepines and cocaine screens. The last outcome of interest, change in BASIS-24 scores over the study period, was first conducted using t-tests for each of the sub-scores and overall score for the "pre" and "post" period. Results closest to a score of 0 indicate less frequent symptoms or difficulty while a score of 4 indicates more frequent symptoms or difficulty. Therefore, when analyzing differences, greater negative values for differences over time would indicate patient improvement based on BASIS-24 scoring. As described, the initial BASIS-24 survey date closest to 1/1/2014 was used as the "pre" results; the BASIS-24 survey date closest to the last day of the study period (9/30/2018) was used as the "post" result. I analyzed the differences first using t-tests for all sub-scores and overall score, then conducted a linear regression with the overall score as the outcome variable.

Results

Description of the Sample and Bivariate Analyses

According to the exclusion and inclusion criteria for the treatment and control groups as described, there were 89 patients in the treatment group and 199 patients in the control group. Patients in the treatment group were an average age of 42.8 (±11.5) years at the beginning of the study period and were primarily non-Hispanic white males. Of the treatment group, 42.5% completed high school or attained a GED, 59.1% were never married, 68.2% did not report working in the past 30 days, and 92.1% reported not being a student in the past 30 days. Patients in the control group resemble patients in the treatment group according to the covariates included in this study. The average age of those in the control group is 43.9 (±11.9) at the beginning of the study period. Though the control group was also largely composed of non-Hispanic white males, the ratio of males to females was more balanced in the control group and there was a greater percent of patients who reported Hispanic race/ethnicity in the control as compared to the treatment group. Of the control group, 39.8% reported completing high school or attaining a GED, 50.5% were never married, 75.3% reported not working in the past 30 days, and 94.4% reported not being a student in the past 30 days. According to bivariate analyses of demographic characteristics included in this study, there were no significant differences between the treatment and control groups (Table 1). Data on the total patient population enrolled in the OTP at APT Foundation during this time period would be useful for comparative purposes but are not available for the present study.

Table 1. Baseline demographic characteristics according to HCV treatment status using BASIS-24 survey results closest following 1/1/2014[a, b]

	HCV Treatment		
Characteristic	**Treatment (N = 89)**	**Control (N=199)**	**P[c]**
Age (years)	42.8 (±11.5)	43.9 (±11.9)	0.466
Sex			0.107
Male	61 (69.3)	115 (52.3)	
Female	27 (30.7)	79 (40.7)	
Race/Ethnicity			0.180
Non-Hispanic White	60 (76.9)	132 (72.1)	
Non-Hispanic Black	9 (11.5)	12 (6.6)	
Hispanic	7 (9.0)	27 (14.8)	
Other	2 (2.2)	12 (6.6)	
Education			0.148
Some high school or less	19 (21.8)	64 (32.7)	
High school graduate/GED	37 (42.5)	78 (39.8)	
Some college or more	31 (35.6)	54 (27.6)	
Marital status			0.356
Married	12 (13.6)	28 (14.1)	
Separated, divorced or widowed	24 (27.3)	70 (35.4)	
Never married	52 (59.1)	100 (50.5)	
Employment in past 30 days			0.420
No	60 (68.2)	146 (75.3)	
Yes <30 hours	16 (18.2)	25 (12.9)	
Yes >30 hours	12 (13.6)	23 (11.9)	
Student in past 30 days			0.460
No	81 (92.1)	184 (94.4)	
Yes	7 (8.0)	11 (5.6)	

[a] Table values are mean ± SD for continuous variables and n (column %) for categorical variables
[b] Numbers may not sum to total due to missing data, and percentages may not sum to 100% due to rounding
[c] P-value is for t-test (continuous variables) or χ^2 test (categorical variables

Across depression/functioning, self-harm, emotional lability, substance use, and overall scores, scores for the treatment group were closer to 0 than the control group, which indicates less frequent symptoms or difficulty. Bivariate analysis of baseline BASIS-24 survey results (Table 2) revealed significant differences, with the treatment group showing improved scores for the sub-scores of depression/functioning (p=0.002) and self-harm (p=0.003) compared to the control group.

Table 2. Baseline behavior and symptom indicators according to HCV treatment status using BASIS-24 survey results closest following 1/1/14[a]

	HCV Treatment		
Sub-scales and overall scores	**Treatment (N = 89)**	**Control (N=199)**	**P[b]**
Depression/functioning	1.3 (± 0.9)	1.7 (± 1.1)	0.002
Relationships	1.8 (± 1.1)	1.7 (± 1.1)	0.692
Self-Harm	0.2 (± 0.4)	0.4 (± 0.7)	0.003
Emotional lability	1.4 (± 0.9)	1.6 (± 1.0)	0.132
Psychosis	0.5 (±0.7)	0.5 (± 0.8)	0.844
Substance Abuse[c]	1.7 (± 1.3)	1.9 (± 1.2)	0.161
Overall	1.2 (± 0.7)	1.4 (± 0.8)	0.059

[a] Table values are mean ± SD
[b] P-value is for t-test
[c] BASIS-24 survey instrument uses this terminology, which has been removed according to the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5)

Results for both demographic and psychological or behavioral data were used as covariates for the following analyses of retention and proportion of positive urine analyses for non-prescribed opioids. These covariates were derived from one BASIS-24 survey administered and completed on a single day.

Retention

I first began with an analysis of retention as a binary variable, either remaining in the OTP at the end of the study period (9/30/2018) or not, using logistic regression. In an unadjusted association, patients in the treatment group had 1.5 (95% confidence interval [CI], 0.9 to 2.5) increased likelihood of remaining in the OTP compared to patients in the control group. After adjusting for all covariates in the model, patients who had been treated for HCV had 2.2 (95% CI, 1.1 to 4.5) increased likelihood of remaining in the OTP compared to the control group, and this was significant at p=0.024. I then completed a backward stepwise elimination strategy to

find the most parsimonious model, removing gender, student status, and the BASIS-24 overall measure. In this model, HCV-treated patients had 2.1 (95% CI, 1.0 to 4.0) increased likelihood of remaining in the OTP compared with the control group and this was significant at p=0.039. Patient age, depression/functioning, psychosis, and substance use measures were all significant predictors in this model. Table 3 includes the results for both models.

Table 3. Results of logistic regression: adjusted model and best-fitting model of the association between retention and HCV treatment

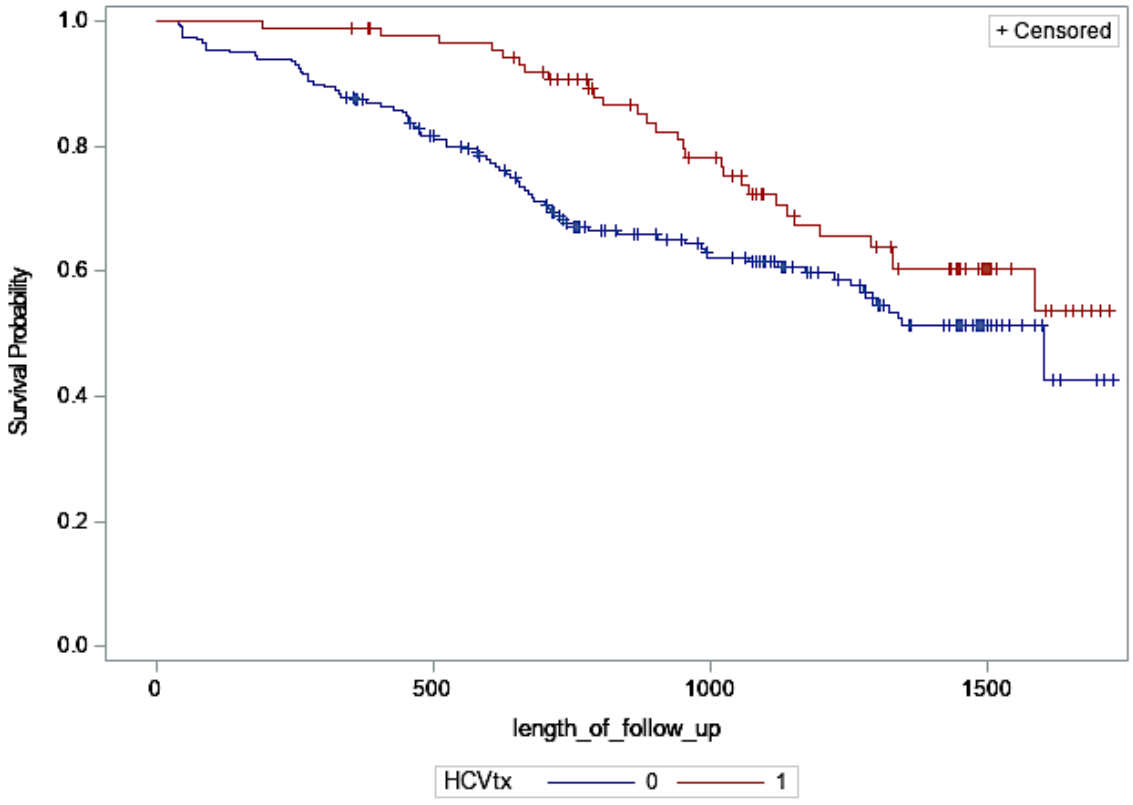
	Model 1 (All variables)		Model 2 (Best-fitting)	
Variable	**OR (95% CI)**	**p**	**OR (95% CI)**	**p**
HCV treatment (Reference: no)	2.2 (1.1, 4.5)	0.024	2.1 (1.0, 4.0)	0.039
Age	1.1 (1.0, 1.1)	<0.001	1.1 (1.0, 1.1)	<0.001
Sex			--	
Female	Reference	--	Reference	--
Male	0.9 (0.5, 1.7)	0.768	--	--
Race/Ethnicity				
Non-Hispanic White	Reference	--	Reference	--
Non-Hispanic Black	1.4 (0.4, 5.6)	0.613	1.5 (0.4, 5.9)	0.526
Hispanic	0.8 (0.3, 2.0)	0.682	0.8 (0.3, 1.9)	0.605
Other	2.5 (0.7, 9.3)	0.173	2.5 (0.7, 9.4)	0.172
Education				
High school grad/GED	Reference	--	Reference	--
Some high school or less	0.8 (0.4, 1.6)	0.445	0.8 (0.4, 1.6)	0.507
Some college or more	0.5 (0.3, 1.1)	0.079	0.5 (0.3, 1.1)	0.089
Marital status				
Never married	Reference	--	Reference	--
Separated/divorced or widowed	0.7 (0.3, 1.5)	0.395	0.7 (0.4, 1.5)	0.401
Married	1.9 (0.8, 4.9)	0.171	1.9 (0.7, 4.8)	0.185
Employment in past 30 days				
No	Reference	--	Reference	--
Yes <30 hours	2.0 (0.8, 5.2)	0.157	2.0 (0.8, 5.1)	0.150
Yes >30 hours	1.8 (0.7, 4.5)	0.244	1.8 (0.7, 4.6)	0.226
Student in past 30 days (Reference: no)	1.9 (0.5, 6.9)	0.341	--	--
Depression/Functioning	2.4 (0.6, 10.0)	0.236	1.7 (1.1, 2.7)	0.029
Relationships	0.9 (0.5, 1.4)	0.591	0.8 (0.6, 1.1)	0.125
Self-harm	1.2 (0.6, 2.2)	0.672	1.2 (0.7, 2.1)	0.490
Emotional lability	1.6 (0.8, 3.0)	0.179	1.5 (1.0, 2.2)	0.073
Psychosis	0.7 (0.4, 1.2)	0.193	0.6 (0.4, 1.0)	0.034
Substance abuse[a]	0.6 (0.4, 0.9)	0.006	0.6 (0.4, 0.8)	<0.001
Overall	0.5 (0.0, 10.6)	0.667	--	--

[a] BASIS-24 survey instrument uses this terminology, which has been removed according to the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5)

I next analyzed retention using the dates of loss to follow-up of patients in the sample. As noted, length of follow-up was defined as the difference between the patient's date of loss to

follow-up and their first BASIS-24 survey date in the study period; if a patient did not have a date of loss to follow-up, the censor date was set to the last day of the study period (9/30/2018). Using univariate analysis, I found that the average length of follow-up for the treatment group was 1,114.2 (±389.2) days, while the average for the control group was 896.0 (±459.3) days. This is approximately 3.1 years of follow-up for the treatment group and 2.5 years for the control group. As these results were promising, I conducted a Kaplan-Meier survival analysis with the data. The survival curves indicated that the HCV treatment group had a higher probability of being retained over the duration of the study (1/1/14 to 9/30/18) compared with the control group; according to the log-rank test, the difference in the survival curves was significant at p= 0.025 (Figure 1).

Figure 1. Kaplan-Meier survival curves modeling the probability of loss to follow-up from the OTP by HCV treatment status over the period 1/1/2014 to 9/30/2018



I then conducted a Cox proportional hazards regression. I first tested the time interaction term between the HCV treatment variable and length of follow-up; this interaction term, however, was significant (p=0.003), providing evidence of non-proportionality. Though the survival curves did not meet the statistical test for proportionality, I conducted a Cox proportional hazards regression as a supplemental analysis. In an unadjusted model, those who were treated for HCV were 0.6 (95% CI, 0.4 to 1.0) times as likely to be lost to follow-up compared to those in the control group; this was significant at p=0.027. I then included a model with all baseline covariates; in the full adjusted model, those who were treated for HCV were 0.4 (95% CI, 0.3 to 0.7) times as likely to be lost to follow-up compared to those in the control group. Patient age, "other" race/ethnicity, and the BASIS-24 substance use measure were significant predictors in this model. Removing variables using a stepwise backward elimination strategy caused the hazard ratio to increase and become less statistically significant. For this reason, it appears that the full model provides the best-fitting model for this Cox proportional hazards regression (see Table 4).

Table 4. Results of Cox proportional hazards regression modeling for loss to follow-up from OTP

	Full model (All variables)	
Variable	**HR (95% CI)**	**p**
HCV treatment (Reference: no)	0.4 (0.3, 0.7)	0.001
Age	1.0 (0.9, 1.0)	<0.001
Sex		
Female	Reference	--
Male	1.0 (0.6, 1.6)	0.974
Race/Ethnicity		
Non-Hispanic White	Reference	--
Non-Hispanic Black	0.9 (0.3, 2.6)	0.797
Hispanic	1.2 (0.7, 2.2)	0.541
Other	0.4 (0.1, 1.0)	0.044
Education		
High school grad/GED	Reference	--
Some high school or less	1.1 (0.7, 1.9)	0.669
Some college or more	1.5 (0.9, 2.5)	0.163
Marital status		
Never married	Reference	--
Separated/divorced or widowed	1.3 (0.8, 2.3)	0.335
Married	0.7 (0.3, 1.3)	0.232
Employment in past 30 days		
No	Reference	--
Yes <30 hours	0.7 (0.3, 1.4)	0.276
Yes >30 hours	0.8 (0.4, 1.5)	0.411
Student in past 30 days (Reference: no)	1.0 (0.4, 2.5)	0.946
Depression/Functioning	0.5 (0.2, 1.4)	0.200
Relationships	1.1 (0.8, 1.6)	0.624
Self-harm	0.9 (0.6, 1.5)	0.817
Emotional lability	0.7 (0.4, 1.1)	0.091
Psychosis	0.7 (0.8, 1.7)	0.490
Substance abuse[a]	0.6 (1.2, 2.0)	0.003
Overall	2.0 (0.2, 18.6)	0.533

[a] BASIS-24 survey instrument uses this terminology, which has been removed according to the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5)

Proportion of Positive Urine Analysis Results for Non-Prescribed Opioids

A description of patients with clinical data during the study look-back period of 9/30/2017 to 9/30/2018 are described below (Table 5). It is possible that a patient was not lost to follow-up prior to 9/30/2017 but still had incomplete clinical data, such as a small number or lack of UAs from which to derive our proportion measure, during the look-back period. I included all relevant data for all patients despite this possibility. According to bivariate analysis, there were significant differences between the treatment and control groups for both type of OUD treatment and proportion of positive UAs for non-prescribed benzodiazepines and cocaine. A greater percentage of patients in the treatment group were treated with buprenorphine; 13.6% of the treatment group compared to 3.7% of the control group. The mean value for proportion of positive UAs for non-prescribed benzodiazepines and cocaine was 0.2 (±0.3) for the treatment group and 0.3 (±0.4) for the control group; this difference was significant at p=0.011.

Table 5. Clinical indicators according to HCV treatment status from medical chart review 9/30/2017 to 9/30/2018[a, b]

	HCV Treatment		
Variable	**Treatment (N=66)**	**Control (N=135)**	**P[c]**
OUD Treatment			0.009
Methadone	57 (86.4)	130 (96.3)	
Buprenorphine	9 (13.6)	5 (3.7)	
Urine analysis (Proportion positive)			
Non-prescribed opioids	0.2 (±0.3)	0.2 (± 0.3)	0.361
Non-prescribed benzodiazepines and cocaine	0.2 (± 0.3)	0.3 (± 0.4)	0.011
Prescription validation			
Opioids			0.079
Yes	8 (12.1)	7 (5.2)	
No	58 (87.9)	128 (94.8)	
Benzodiazepines			0.365
Yes	12 (18.2)	18 (13.3)	
No	54 (81.8)	117 (86.7)	
Counseling Beyond Requirements	42 (63.6)	79 (58.5)	0.486
Psychiatric Services Use	22 (33.3)	28 (20.7)	0.052
Intensive Outpatient Use	4 (6.1)	9 (6.7)	0.870

[a] Table values are mean ± SD for continuous variables and n (column %) for categorical variables
[b] Numbers may not sum to total due to missing data, and percentages may not sum to 100% due to rounding
[c] P-value is for t-test (continuous variables) or χ^2 test (categorical variables)

As described by Table 5, there was not a significant difference according to bivariate analysis between the treatment and control groups for the proportion of positive UA results for non-prescribed opioids over the 12-month study look-back period. HCV treatment providers at APT Foundation, however, had an a priori assumption based on clinical experiences that patients in the treatment group would be less likely to have ongoing illicit opioid use. Thus, I attempted to conduct a linear regression using proportion of positive UAs for non-prescribed opioids. To increase the interpretability of the data, I decided to categorize the outcome variable into quartiles and then completed an ordered logistic regression. Bivariate analysis of the categorized UA proportions according to HCV treatment is represented in Table 6.

Table 6. Bivariate analysis with categorized proportion of positive urine analysis results for non-prescribed opioids from 9/30/2017 to 9/30/2018[a, b]

	HCV Treatment		
Variable	**Treatment (N=66)**	**Control (N=132)**	**P[c]**
Proportion positive urine analyses for non-prescribed opioids			0.603
< 25%	48 (72.7)	92 (69.7)	
25-49%	10 (15.2)	15 (11.4)	
50-74%	4 (6.1)	11 (8.3)	
≥ 75%	4 (6.1)	14 (10.6)	

[a] Table values are n (row %)
[b] Numbers may not sum to total due to missing data, and percentages may not sum to 100% due to rounding
[c] P-value is for χ^2 test

Results from the ordered logistic regression with the outcome as categorized proportions of positive UA results for non-prescribed opioids do not indicate a positive significant difference between the treatment and control groups. In the unadjusted model, patients in the treatment

group have 1.2 (95%CI, 0.7 to 2.4) increased likelihood of having a lower category of positive UA results for non-prescribed opioids compared to the control group. After including all covariates – the original baseline covariates according to earliest BASIS-24 date in the study period as well as all of the clinical covariates collected in chart review – the treatment group had 0.5 (95%CI, 0.2 to 1.3) increased likelihood of having a lower category of positive UA results for non-prescribed opioids compared to the control group. I did not arrive at a model in which there was a significant association between treatment and control groups for this outcome variable even after using stepwise elimination of non-significant covariates. The model was also not significant when only baseline characteristics (i.e., the baseline BASIS-24 survey results with demographic information) were included in the model. I also transformed the outcome variable to be dichotomous (greater or less than 50%); using this as the outcome variable in a simple logistic regression did not produce a significant difference between the treatment and control groups.

Interestingly, the only significant predictor variable in the logistic regression described above was the proportion of positive UAs for non-prescribed benzodiazepines and cocaine. Based on this finding, I conducted an exploratory analysis using the proportion of non-prescribed benzodiazepines and cocaine as an outcome variable. I first categorized the variable into quartiles, and conducted bivariate analysis (Table 7). Using an ordered logistic regression, the unadjusted association found that patients in the treatment group had 1.9 (95%CI, 1.0 to 3.4) increased likelihood of having a lower category of positive UAs for non-prescribed benzodiazepines and cocaine compared to the control group; this association was significant at p=0.040. The adjusted association that included all covariates, including the proportion of positive UAs for non-prescribed opioids, was also significant. According to the adjusted

analysis, patients in the treatment group had 3.0 (95%CI, 1.2 to 7.4) increased likelihood of having a lower category of positive UAs for non-prescribed benzodiazepines and cocaine compared to the control group; this was significant at p=0.019. Though this was an exploratory analysis, these results indicate that a decreased presence of other substances (like non-prescribed benzodiazepines and cocaine) may be a potential outcome after a patient is treated with HCV treatment. This will be further discussed in the subsequent section.

Table 7. Bivariate analysis with categorized proportion of positive urine analysis results for non-prescribed benzodiazepines and cocaine from 9/30/2017 to 9/30/2018[a, b]

	HCV Treatment		
Variable	**Treatment (N=66)**	**Control (N=132)**	**P[c]**
Proportion positive urine analyses for non-prescribed benzodiazepines and cocaine			0.081
< 25%	43 (65.2)	70 (53.0)	
25-49%	11 (16.7)	15 (11.4)	
50-74%	5 (7.6)	16 (12.1)	
≥ 75%	7 (10.6)	31 (23.5)	

[a] Table values are n (row %)
[b] Numbers may not sum to total due to missing data, and percentages may not sum to 100% due to rounding
[c] P-value is for χ^2 test

Change in BASIS-24 Scores

The final outcome measure for this study was the change in BASIS-24 scores over the time of the study period (1/1/2014 to 9/30/2018). For the "post" BASIS-24 survey result date, as described, I used the survey date that was closest to the last day of the study period (9/30/2018) for patients in the treatment and control groups. See Table 2 for baseline BASIS-24 survey results and recall that, in bivariate analysis, scores for depression/functioning and self-harm were both positively significant for the treatment as compared to the control group. Table 8 demonstrates the same bivariate analyses but using BASIS-24 scores closest to the conclusion of

the study period. In the "post" period, I observed positive significant differences for depression/functioning, emotional lability, substance use, and overall scores. Patients in the treatment group, for example, scored a mean of 1.1 (±0.9) for depression/functioning while patients in the control group scored a mean of 1.4 (±1.0) for the same measure; this was highly significant at p=0.008.

Table 8. Follow-up behavior and symptom indicators according to HCV treatment status using most recent to 9/30/2018 BASIS-24 survey results [a]

	HCV Treatment		
Sub-scales and overall scores	**Treatment (N = 89)**	**Control (N=199)**	**P[b]**
Depression/functioning	1.1 (± 0.9)	1.4 (± 1.0)	0.008
Relationships	1.8 (± 1.2)	1.7 (± 1.1)	0.620
Self-Harm	0.2 (± 0.5)	0.2 (± 0.5)	0.345
Emotional lability	1.1 (± 0.9)	1.4 (± 1.0)	0.025
Psychosis	0.4 (±0.6)	0.5 (± 0.8)	0.178
Substance abuse[c]	1.2 (± 1.1)	1.5 (± 1.1)	0.018
Overall	1.0 (± 0.7)	1.2 (± 0.8)	0.043

[a] Table values are mean ± SD
[b] P-value is for t-test
[c] BASIS-24 survey instrument uses this terminology, which has been removed according to the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5)

I completed analysis on the difference in differences for the BASIS-24 survey results of the treatment and control groups from the "pre" to the "post" periods. As demonstrated in Table 9, I observed a significant difference between the treatment and control groups only for the sub-score of self-harm. Patients in the treatment group had a mean difference of -0.0 (±0.5) while patients in the control group had a mean difference of -0.2 (±0.6); this was significant at p=0.031. It appears that the significant difference observed in the self-harm score reflects greater

improvement in the control group, contrary to our study hypothesis of seeing improved differences of BASIS-24 scores for the treatment group over time.

Table 9. Change in behavior and symptom indicators according to HCV treatment status using BASIS-24 survey results closest following 1/1/2014 and most recent to 9/30/2018 [a]

	HCV Treatment		
Sub-scales and overall scores	**Treatment (N = 89)**	**Control (N=199)**	**P[b]**
Δ Depression/functioning	-0.2 (± 1.0)	-0.3 (± 1.0)	0.557
Δ Relationships	-0.0 (± 1.4)	-0.0 (± 1.1)	0.912
Δ Self Harm	-0.0 (± 0.5)	-0.2 (± 0.6)	0.031
Δ Emotional lability	-0.3 (± 0.9)	-0.2 (± 1.1)	0.399
Δ Psychosis	-0.1 (±0.5)	0.0 (± 0.7)	0.190
Δ Substance abuse[c]	-0.5 (± 1.4)	-0.4 (± 1.1)	0.481
Δ Overall	-0.2 (± 0.7)	-0.2 (± 0.7)	0.968

[a] Table values are mean ± SD
[b] P-value is for t-test
[c] BASIS-24 survey instrument uses this terminology, which has been removed according to the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5)

Finally, I attempted to conduct a linear regression with the outcome variable as the difference in the overall score between the "pre" and "post" BASIS-24 scores according to HCV treatment status. However, when testing for normality of the difference overall variable, it did not meet the Shapiro-Wilk statistical test for normality. I do not believe that categorizing this variable in order to perform a logistic regression would be clinically meaningful, as the negative differences are not easily interpreted for practical purposes. I will discuss limitations of this particular outcome variable and its analysis in the subsequent section.

Conclusion

Limitations

The data in this study – including all documentation of patients with ICD code B18.2, patient loss to follow-up dates, and BASIS-24 data –were not originally collected for the purpose of a research study but rather for clinical and reporting purposes internal to the APT Foundation. Though the APT Foundation and its clinical and research staff contribute to academic research in meaningful ways, the primary purpose of the organization is to meet the medical, psychiatric, and social needs of its patients. Therefore, the community-level data derived for this study is subject to limitations given that research protocols did not prospectively guide the collection and organization of the data. Nevertheless, the data used for this study represent realistic conditions of a comprehensive OTP in which primary care services, including the treatment of chronic HCV, are integrated.

The data derived from my chart review process, though it was designed for this research study and developed with the input of APT Foundation leadership and staff, are also subject to limitations given that only one researcher conducted the chart review. There is the possibility of human error in collecting the variables for the chart review. Specifically, for example, it is possible that I missed a prescription validation for either synthetic opioids and/or benzodiazepines and therefore did not factor this into the calculation of proportion positive urine drug analysis results for either variable. It is also possible that the prescription validations for either synthetic opioids and/or benzodiazepines were not documented in the chart during the study period and thus were not included and/or factored into the calculation of proportion of positive results. Indeed, for all variables included in the chart review, the study is limited by placing an arbitrary look-back period (9/30/2017 to 9/30/2018) on the capture of these variables.

I decided upon the look-back period, however, given the 12-week separation of time with the conclusion of the HCV treatment period (7/8/2017) as well as my timing of the chart review data collection.

An additional limitation concerning the collection of clinical data from medical charts is that it may have been advantageous for the purpose of our study to collect data from a period *prior* to the beginning of the study period for all patients. This would have allowed for the comparison of our secondary outcome variable, proportion of positive UAs for non-prescribed opioids, throughout the entire study period. It also may have allowed for the adjustment of regression models with the baseline covariates included in the chart review (e.g., proportion of positive UAs for non-prescribed benzodiazepines and cocaine, use of psychiatric services). Future studies seeking to analyze OUD outcomes among persons treated for HCV while being treated with OAT should incorporate such baseline covariates.

Studies of HCV infection all must address the inherent challenges in researching this infection given its natural history. I compared patients who initiated and completed treatment for chronic HCV infection, with patients who had a documented ICD10 code 18.2 and, according to chart review, had not been treated previously, elsewhere, or during the study period at the APT Foundation for chronic HCV infection. The inclusion and exclusion criteria I applied to the data, in addition to limiting our sample sizes for the treatment and control groups, also present several limitations. As in the collection of covariates, the chart review process is subject to human error and therefore it is possible that I failed to exclude certain patients in our control group who had been treated for chronic HCV. It is also possible that a patient could have opted out of initial HCV antibody testing during the intake process into the OTP but gone on to develop chronic infection during the study period. The patient as well as APT Foundation clinicians would, then,

not be aware of infection status. Though this is not specifically a limitation of the current study, I am aware that there are patients in the general OTP patient population who may have HCV infection but are not included in the data set of patients with documented ICD codes for B18.2. It is also possible that I included patients in our control group who had positive HCV antibody results and were HCV treatment naïve but had not developed chronic infection that would benefit from DAA treatment. Due to the nature of the study setting, however, I decided that ICD B18.2 coding and a stringent chart review to remove patients who had previously been treated for chronic HCV was sufficient for the purpose of this study.

The measurement of retention in the present study is also limited given that, though it is possible for patients in the sample to have multiple treatment episodes during the time period, I was provided with one patient loss to follow-up date per patient, if applicable. I was also not provided any information about the reasons for patient loss to follow-up. Though this information would contribute to understanding about patient retention in an OTP, it was not needed for the purpose of this study. I was concerned only with patient status at the conclusion of the study period (9/30/2018). For clinicians and staff at the OTP, a patient's status as retained in the OTP – rather than information about their loss to follow-up – is arguably more crucial information in the management of OUD and ancillary services in an OTP.

A final set of limitations concerns the BASIS-24 survey results. Due to the nature of the study sample and the setting in which it occurred, it is possible that patients have incomplete BASIS-24 data. As noted, it is possible that patients have incomplete BASIS-24 results, or results that do not adhere to the timeline which APT Foundation sets for the completion of such surveys, due to the possibility that patients may have multiple treatment episodes during the study period. It is also possible that patients have only one BASIS-24 score throughout the study

period, making a comparison of "pre" and "post" BASIS-24 results unfeasible. Among all patients included in the study and after removing all BASIS data with missing dates and/or dates from the time period prior to 1/1/14, there were approximately 51 unique patients with only one BASIS score. This calls into question the internal validity of using the pre/post analysis. It does not, however, affect the use of the BASIS survey data as baseline covariates in the above analyses. In addition, I selected BASIS-24 dates of completion according to the confines of my arbitrary study period and it may have been advantageous to select them based upon the treatment group's HCV treatment dates (i.e., start and end of treatment, date of SVR12). I ultimately did not select such dates to align with the selection of BASIS-24 completion dates because of the difficulty in matching similar control group times. More complex statistical methods would be required in a future study to accomplish that aim.

Discussion

There are several key distinctions between the present study and other studies related to the treatment of chronic HCV infection among a population of persons who concurrently receive OAT for OUD. The first and central difference is that my study does not seek to understand why patients do and do not initiate treatment for chronic HCV infection. The outcomes I analyzed in our study – retention in care in an OTP, proportion of positive urine drug analyses for non-prescribed opioids, and change in behavior and symptom indicators – do not allow me to speculate on reasons why patients with chronic HCV infection did or did not initiate HCV treatment with DAAs. Though I had baseline demographic data prior to the initiation of treatment for both groups, I did not use these covariates to model the *outcome* of HCV treatment. I therefore cannot speculate on predictors of whether or not a patient who initiates or completes

HCV treatment. Such an endeavor may be best suited first for qualitative inquiry, and the work of Wright and colleagues in the Australian context provides an excellent recent example.[13] Anecdotally, from the process of chart review in the present study, I note that clinicians who regularly engage with these patients may also be a source of information for qualitative inquiry on this topic. Clinicians may provide insights on their own attitudes regarding the counseling of patients about HCV treatment, and about common barriers that their patients encounter when deciding whether or not to initiate HCV treatment. This research question, though not my own, is of utmost importance to those working at the intersection of drug use and HCV infection, as increased HCV treatment among this population could help to restrain rising rates of infection.[25]

The second distinction between this and other similar studies is that I do not include SVR 12 as a study outcome. It has been established that patients who receive HCV treatment concurrently with OAT can achieve SVR 12 rates similar to a general patient population. I sought to understand how co-located treatment can affect other clinical outcomes. The present study demonstrated that, after adjusting for all baseline covariates, patients who undergo and complete HCV treatment have 2.2 (95% CI, 1.1 to 4.5) increased likelihood of remaining in the OTP compared to patients in the control group. My analysis also showed that, when using the dates of loss to follow-up of the treatment and control groups, those treated for chronic HCV infection have a significantly higher probability of not being lost to follow-up from the OTP compared to the control group. Remaining in the OTP allows a patient to continue his/her OAT and, if needed, receive counseling support and psychiatric services, and attend to other medical concerns in primary care. There is also recent evidence that, in a Canadian sample of PWID who had been treated for HCV infection and who received OAT daily, there was a non-significant reduction in the risk of HCV reinfection at 52 weeks post SVR 12.[26] A major concern among

state Medicaid programs and other insurance payers, given the high (though declining) cost of treatment, is the risk of reinfection among patients treated with DAAs.[27] This is especially true for patients treated with DAAs who also inject drugs and/or receive treatment for OUD in the form of opioid agonists. Though further studies are needed, the use of a co-located model of treatment for both OUD and HCV may be an effective way of retaining patients in care for OUD – which could thereby reduce the risk of HCV reinfection and help the patient to manage his/her OUD.

A final consideration concerns my findings regarding the outcome of proportion positive urine drug analysis results for non-prescribed opioids. In the analyses I conducted, I found that patients in the treatment group did not have significantly greater odds of having lower proportions of positive UAs for non-prescribed opioids over a 12-month period. The analysis of such an outcome for the treatment of OUD with opioid agonists has been accomplished in similar ways previously, though not to my knowledge in the context of those being concurrently treated for chronic HCV.[28] As the treatment of OUD is conceptualized by many in the addiction medicine field as the treatment of a chronic illness with accompanying natural fluctuations, it may not be appropriate and/or useful to measure proportion of positive UAs for non-prescribed opioids as outcome variable of OUD treatment. The use of other illicit substances while receiving treatment with opioid agonists is an emerging field of study.[29] I included a measurement of positive UAs for non-prescribed benzodiazepines and cocaine as a covariate in the study. Though this was not a hypothesized outcome for the present study, I conducted an exploratory analysis in which this covariate was the outcome of interest with the primary predictor variable of HCV treatment. Results demonstrated that patients who were treated for HCV had significantly greater odds of having lower proportions of positive UAs for non-

prescribed benzodiazepines and cocaine, even after adjusting for all baseline covariates. This could potentially suggest that, among patients receiving concurrent OAT, the time period following HCV treatment could reduce the practice of use of non-prescribed benzodiazepines and cocaine. This result is limited, however, because it only reflects a 12-month period following treatment; in addition, I combined non-prescribed benzodiazepines and cocaine into one variable whereas they may have been better suited as two variables. The results of this exploratory analysis require further investigation in future, prospective studies on the effects of HCV treatment within a co-located model of care with treatment for OUD.

Although this study is limited in ways described above, I demonstrated that HCV treatment among patients receiving concurrent treatment for OUD has positive effects on retention in an OTP. Ultimately, additional baseline covariates and/or qualitative interviews of patients at baseline (i.e., prior to HCV treatment) are needed to generate definitive evidence about what mechanisms are involved in accounting for the longer retention in the OTP, as well as what patient characteristics and/or practices predict greater retention after completing HCV treatment. As noted, further research into the role of non-opioid substances on both HCV and OUD treatment outcomes is required for this patient population. A co-located model of care for patients in treatment for chronic HCV and OUD can be a highly effective mechanism not only for curing one's HCV infection, but also for continuing on in the management of one's addiction in a supportive environment.

References

[1] H.R.6 - SUPPORT for Patients and Communities Act. Congress.gov website. https://www.congress.gov/bill/115th-congress/house-bill/6/text. Accessed December 4, 2018.
[2] 42 U.S. Code § 247b–15. Surveillance and education regarding infections associated with illicit drug use and other risk factors. Cornell Law School Legal Information Institute website. https://www.law.cornell.edu/uscode/text/42/247b-15. Accessed March 15, 2019.
[3] Ly KN, Hughes EM, Jiles RB, Holmberg SD. Rising mortality associated with hepatitis C virus in the United States, 2003–2013. *Clinical Infectious Diseases*. 2016; *62*(10): 1287-1288. doi: 10.1093/cid/ciw111.
[4] Hepatitis C Questions and Answers for Health Professionals. Centers for Disease Control and Prevention. https://www.cdc.gov/hepatitis/hcv/hcvfaq.htm#b1. Updated April 30, 2018. Accessed October 30, 2018.
[5] Hepatitis C, Acute 2016 Case Definition. Centers for Disease Control and Prevention website. https://wwwn.cdc.gov/nndss/conditions/hepatitis-c-acute/case-definition/2016/. Accessed December 6, 2018. See also Hepatitis C, Chronic 2016 Case Definition. Centers for Disease Control and Prevention website. https://wwwn.cdc.gov/nndss/conditions/hepatitis-c-chronic/case-definition/2016/. Accessed December 6, 2018.
[6] Zibbell JE, Asher AK, Patel RC, et al. Increases in Acute Hepatitis C Virus Infection Related to a Growing Opioid Epidemic and Associated Injection Drug Use, United States, 2004 to 2014. *Am J Public Health*. 2017;108(2):175-181. doi:10.2105/AJPH.2017.304132.
[7] HCV Testing and Linkage to Care. HCV Guidance: Recommendations for Testing, Managing, and Treating Hepatitis C, American Association for the Study of Liver Disease and Infectious Diseases Society of America. Updated May 24, 2018. https://www.hcvguidelines.org/evaluate/testing-and-linkage. Accessed October 30, 2018.
[8] Ara AK, Paul JP. New Direct-Acting Antiviral Therapies for Treatment of Chronic Hepatitis C Virus Infection. *Gastroenterol Hepatol (N Y)*. 2015;11(7):458–466.
[9] Grebely J, Hajarizadeh B, Dore GJ. Direct-acting antiviral agents for HCV infection affecting people who inject drugs. *Nature Reviews Gastroenterology & Amp; Hepatology*. 2017; 14:641.
[10] Grebely J, Dalgard O, Conway B, et al. Sofosbuvir and velpatasvir for hepatitis C virus infection in people with recent injection drug use (SIMPLIFY): an open-label, single-arm, phase 4, multicentre trial. *The Lancet Gastroenterology & Hepatology*. 2018;3(3):153-161. doi:10.1016/S2468-1253(17)30404-1.
[11] Dore GJ, Altice F, Litwin AH, et al. Elbasvir–grazoprevir to treat hepatitis c virus infection in persons receiving opioid agonist therapy: A randomized trial. *Annals of Internal Medicine*. 2016;165(9):625-634. doi:10.7326/M16-0816.
[12] Treloar C, Rance J, Dore GJ, Grebely J, the ETHOS Study Group. Barriers and facilitators for assessment and treatment of hepatitis C virus infection in the opioid substitution treatment setting: insights from the ETHOS study. *Journal of Viral Hepatitis*. 2014;21(8):560-567. doi:10.1111/jvh.12183.
[13] Wright C, Cogger S, Hsieh K, Goutzamanis S, Hellard M, Higgs P. "I'm obviously not dying so it's not something I need to sort out today": Considering hepatitis C treatment in the era of direct acting antivirals. *Infection, Disease & Health*. November 2018. doi:10.1016/j.idh.2018.10.006.
[14] Butner JL, Gupta N, Fabian C, Henry S, Shi JM, Tetrault JM. Onsite treatment of HCV infection with direct acting antivirals within an opioid treatment program. *Journal of Substance Abuse Treatment*. 2017;75(Supplement C):49-53. doi:10.1016/j.jsat.2016.12.014.
[15] Talal AH, Andrews P, Mcleod A, et al. Integrated, Co-located, Telemedicine-based Treatment Approaches for Hepatitis C Virus (HCV) Management in Opioid Use Disorder Patients on Methadone. *Clinical Infectious Diseases*. October 2018:ciy899-ciy899. doi:10.1093/cid/ciy899.

[16] Chen H-M, Lu T-H, Chang K-C, Lee K-Y, Cheng C-M. Opioid users with comorbid hepatitis C spent more time in agonist therapy: A 6-year observational study in Taiwan. *Addictive Behaviors*. 2017;72(Supplement C):133-137. doi:10.1016/j.addbeh.2017.03.028.
[17] About Us. APT Foundation website. https://aptfoundation.org/about-us/. Accessed March 15, 2019.
[18] Butner JL, Gupta N, Fabian C, Henry S, Shi JM, Tetrault JM. Onsite treatment of HCV infection with direct acting antivirals within an opioid treatment program. *Journal of Substance Abuse Treatment*. 2017;75(Supplement C):49-53. doi:10.1016/j.jsat.2016.12.014.
[19] Madden LM, Farnum SO, Eggert KF, et al. An investigation of an open-access model for scaling up methadone maintenance treatment. *Addiction*. 2018;113(8):1450-1458. doi:10.1111/add.14198.
[20] Hepatitis C: State of Medicaid Access Report Card for Connecticut. Harvard Law School Center for Health Law and Policy Innovation and National Viral Hepatitis Roundtable website. https://stateofhepc.org/wp-content/themes/infinite-2/reports/HCV_Report_Connecticut.pdf. 2017. Accessed March 15, 2019.
[21] BASIS-24. McLean Hospital website. http://www.ebasis.org/basis24.php. Accessed March 15, 2019.
[22] Eisen SV, Normand S-L, Belanger AJ, Avron Spiro, David Esch. The Revised Behavior and Symptom Identification Scale (BASIS-R): Reliability and Validity. *Medical Care*. 2004; 42(12):1230-1241. See also Eisen SV, Gerena M, Ranganathan G, Esch D, Idiculla T. Reliability and Validity of the BASIS-24© Mental Health Survey for Whites, African-Americans, and Latinos. *The Journal of Behavioral Health Services & Research*. 2006;33(3):304. doi:10.1007/s11414-006-9025-3.
[23] FDA approves Sovaldi for chronic hepatitis C. United States Department of Health and Human Services website. https://www.hhs.gov/hepatitis/blog/2013/12/09/fda-approves-sovaldi-for-chronic-hepatitis-c.html. December 9, 2013. Accessed March 21, 2019.
[24] Of note, the analytes screening for opiates and oxycodone were reviewed concurrently and merged as the "non-prescribed opioids" measure, while the analytes screening for benzodiazepines and cocaine were reviewed concurrently and merged as the "non-prescribed benzodiazepines and cocaine" measure. As an example, if a patient had a prescription validation for a benzodiazepine during the time period, a total of 8 UAs – 5 of which were positive for benzodiazepines, 2 of which were positive for cocaine, and 1 of which was positive for opiates – the recorded proportion for non-prescribed opioids would be 1/8 or 0.125 and for non-prescribed benzodiazepines and cocaine would be 2/8 or 0.250.
[25] For an example of research about "treatment as prevention" modeling, see Metzig C, Surey J, Francis M, et al. Impact of Hepatitis C Treatment as Prevention for People Who Inject Drugs is sensitive to contact network structure. *Scientific Reports*. 2017;7(1):1833. doi:10.1038/s41598-017-01862-6.
[26] Rossi C, Butt ZA, Wong S, et al. Hepatitis C virus reinfection after successful treatment with direct-acting antiviral therapy in a large population-based cohort. *Journal of Hepatology*. 2018;69(5):1007-1014. doi:10.1016/j.jhep.2018.07.025. For a recent review on reinfection literature, see Falade-Nwulia O, Sulkowski MS, Merkow A, Latkin C, Mehta SH. Understanding and addressing hepatitis C reinfection in the oral direct-acting antiviral era. *Journal of Viral Hepatitis*. 2018;25(3):220-227. doi:10.1111/jvh.12859.
[27] Overview of Cost, Reimbursement, and Cost-Effectiveness Considerations for Hepatitis C Treatment Regimens. American Association for the Study of Liver Diseases and the Infectious Diseases Society of America HCV Guidance. https://www.hcvguidelines.org/evaluate/cost. Updated September 21, 2017. Accessed December 17, 2018. See also Highleyman, L. "Surprising price break for newly-approved hepatitis C drug." August 16, 2017. BETA website. https://betablog.org/surprising-price-break-newly-approved-hepatitis-c-drug/. Accessed December 16, 2018.
[28] Accurso AJ, Rastegar DA. The Effect of a Payer-Mandated Decrease in Buprenorphine Dose on Aberrant Drug Tests and Treatment Retention Among Patients with Opioid Dependence. *Journal of Substance Abuse Treatment*. 2016;61: 74-79. doi:10.1016/j.jsat.2015.09.004.
[29] For one example of this work, see Franklyn AM, Eibl JK, Gauthier G, Pellegrini D, Lightfoot NE, Marsh DC. The impact of benzodiazepine use in patients enrolled in opioid agonist therapy in Northern and rural Ontario. *Harm Reduction Journal*. 2017;14(1):6. doi:10.1186/s12954-017-0134-5.