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MAJOR ARTICLE

Integrated, Co-located, Telemedicine-based Treatment Approaches for Hepatitis C Virus Management in Opioid Use Disorder Patients on Methadone

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Background. Despite high hepatitis C virus (HCV) prevalence, opioid use disorder (OUD) patients on methadone rarely engage in HCV treatment. We investigated the effectiveness of HCV management via telemedicine in an opioid substitution therapy (OST) program.

Methods. OUD patients on methadone underwent biweekly telemedicine sessions between a hepatologist and physician assistant during the entire HCV treatment course. All pretreatment labs (HCV RNA, genotype, and noninvasive fibrosis assessments) were obtained onsite and direct-acting antivirals were coadministered with methadone using modified directly observed therapy. We used multiple correspondence analysis, least absolute shrinkage and selection operator, and logistic regression to identify variables associated with pursuit of HCV care.

Results. Sixty-two HCV RNA–positive patients (24% human immunodeficiency virus [HIV] infected, 61% male, 61% African American, 25.8% Hispanic) were evaluated. All patients were stabilized on methadone and all except 4 were HCV genotype 1 infected. Advanced fibrosis/cirrhosis was present in 34.5% of patients. Of the 45 treated patients, 42 (93.3%) achieved viral eradication. Of 17 evaluated patients who were not treated, 5 were discontinued from the drug treatment program or did not follow up after the evaluation, 2 had HIV adherence issues, and 10 had insurance authorization issues. Marriage and a mental health diagnosis other than depression were the strongest positive predictors of treatment pursuit, whereas being divorced, separated, or widowed was the strongest negative predictor.

Conclusions. HCV management via telemedicine integrated into an OST program is a feasible model with excellent virologic effectiveness. Psychosocial and demographic variables can assist in identification of subgroups with a propensity or aversion to pursue HCV treatment.

Keywords. viral hepatitis; telemedicine; predictors of HCV treatment uptake; substance use; virtual HCV treatment integration.

Hepatitis C virus (HCV) infection is a leading cause of chronic liver disease, cirrhosis, and liver cancer, affecting 71 million people globally and approximately 5 million in the United States [1,2]. Although the incidence of HCV has declined or has remained stable during the period prior to 2011, large annual increases in incidence have occurred subsequently [3–6]. Persons with substance use disorder (PWSUD) have the highest HCV incidence and prevalence [7, 8]. Conventionally, HCV management in PWSUD has primarily been through offsite referral to an HCV specialist. However, only a minority of PWSUD referred will actually undergo an HCV evaluation [9, 10]. As a large majority of PWSUD remain undiagnosed and untreated [9], new models of care are needed to eliminate HCV from the PWSUD population [11].

Integrated care, either virtually or physically, for behavioral and medical conditions affecting PWSUD has been advocated but has been difficult to achieve [3, 12, 13]. Telemedicine, 2-way videoconferencing between a patient and a physician geographically separated, is a potential strategy for treatment integration at sites where opioid use disorder (OUD) patients on methadone routinely congregate, including opioid substitution therapy (OST) programs [3]. OST programs offer a variety of services such as nursing, counseling, social support, and education that can be leveraged to provide a supportive environment for integration of medical care. Recent advancements in HCV diagnostics and therapeutics have facilitated HCV treatment integration and onsite treatment delivery. For example, the development of all-oral, direct-acting antivirals (DAAs) for HCV treatment has resulted in substantially shorter treatment duration, dramatically improved efficacy, and reduced medication-related adverse effects. Development of point-of-care fibrosis assessments has also facilitated integration of HCV and substance use treatment [14].

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In this study, we sought to leverage the supportive environment of the OST program to evaluate virtual integration of HCV management utilizing telemedicine. Our primary aim was HCV treatment effectiveness delivered via telemedicine to OUD patients on methadone. Our rationale was that integrated, onsite delivery of HCV care would foster treatment pursuit among this difficult-to-engage population. As a secondary objective, we sought to evaluate the positive and negative social determinants of pursuit of HCV management.

METHODS

The PET-C Study (Prevention, Evaluation and Treatment of HCV) was a study designed to assess the willingness of OUD patients on methadone to undergo HCV education and treatment [15], outcomes of HCV-related education [16], and the effectiveness of telemedicine-based HCV management [17]. After approval of all-oral DAA regimens, we initiated onsite HCV evaluation and treatment via telemedicine combined with coadministration of DAAs and methadone (Figure 1). The study protocol was approved by the OST program's institutional review board (IRB).

HCV Telemedicine Evaluations

After completion of 2 HCV educational sessions, we obtained blood onsite to assess HCV RNA levels. HCV RNA–positive individuals were subsequently offered an HCV evaluation by telemedicine. Inclusion criteria required at least 3 months' enrollment in the OST program and coverage by medical insurance.

Telemedicine consultations occurred between a hepatologist (A. H. T.) and an OST program–employed advanced practitioner (AP) (P. A.) who served as the telepresenter. Telemedicine appointments occurred at a prespecified day and time each week utilizing a regulatory-compliant system (Cisco, San Jose, California). Schedule adjustments were made for patients who attended on alternative days. To minimize routine patient care activities, telemedicine evaluations were interspersed between routinely evaluated patients.

The initial encounter consisted of a standard medical evaluation, a physical examination performed by the AP, and a treatment plan formulated by both practitioners. The AP authored the majority of the medical note; the hepatologist subsequently completed the documentation and assigned medical charges, which were then submitted electronically. Additional laboratory assessments, all obtained onsite, included HCV genotype, FibroSure (LabCorp, Research Triangle Park, North Carolina), and hepatitis B virus serology. Two weeks after the initial encounter, laboratory results were reviewed, and DAAs were ordered electronically for treatment-eligible patients. If indicated, cirrhotic patients were referred for hepatocellular carcinoma and esophageal variceal surveillance.

HCV Medications

DAAs, consistent with professional society guidelines [18], were coadministered with methadone. "Take-home" doses were provided for days when patients did not attend the program.

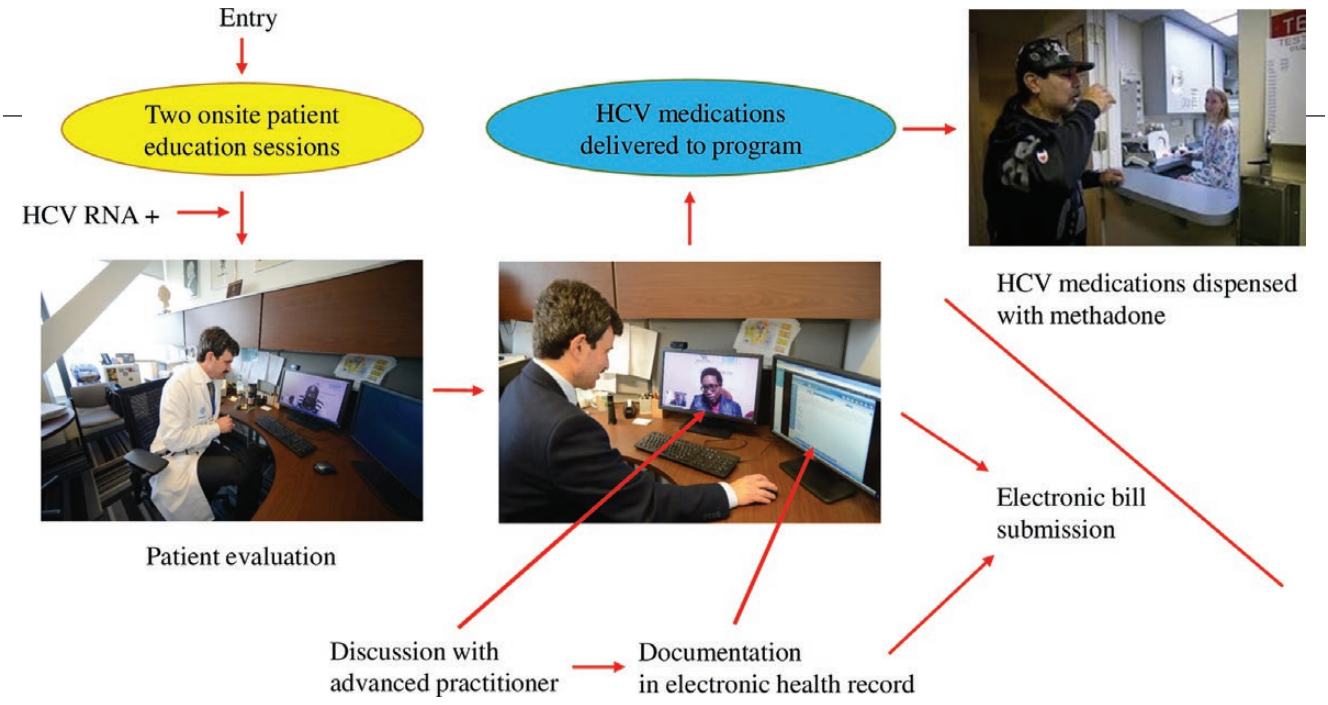

Figure 1. Study flow. Patients initially underwent 2 educational sessions. Subsequently, hepatitis C virus (HCV) RNA–positive patients underwent an HCV evaluation via telemedicine with the hepatologist and with the advanced practitioner as the telepresenter. Relevant documentation and billing were completed in the electronic health record, and medications for eligible participants were ordered and procured through a specialty pharmacy. Medications were subsequently delivered to the clinic and dispensed with methadone. Charges for the medical encounter were submitted electronically to third-party payers. Abbreviation: HCV, hepatitis C virus.

Treatment Course

During treatment, biweekly telemedicine evaluations occurred with assessment of medication adherence and medication-related adverse events. At posttreatment weeks 4 and 12, we assessed HCV RNA status. Viral eradication, the primary study endpoint, was defined as undetectable HCV RNA 12 weeks after treatment cessation.

Positive and Negative Factors for HCV Treatment Engagement

Variables associated with demographics, social functioning, medical history, and substance use treatment were obtained from participants' medical records.

Statistical Analysis

Statistical analysis was performed using R software (http://www.r-project.org/). Categorical variables were summarized as counts and/or percentages, and continuous variables by their means and standard deviations, as appropriate. The number of cases entering the analysis equaled 59 individuals, of whom 55 individuals provided complete data. The reasons for excluding 3 patients are listed in Supplementary Table 1. Missing values of social function variables in the remaining 4 cases were imputed using the R package missMDA [19] (missing at random assumption was considered plausible). Four demographic variables, 9 variables related to participants' medical conditions, and 10 categorical social function variables were potential candidates for inclusion in the statistical analysis. Multiple correspondence analysis (MCA) was used to analyze the pattern of relationships of the social function variables through the R package FactoMineR [20]. The k-means algorithm was applied on the first 2 principal dimensions obtained from MCA to assign patients into different clusters. We initially applied MCA on the social functioning variables and obtained 14 principal dimensions (Supplementary Table 2) with the first principal dimension (SFI.Dim1) explaining 13.81% of the total variance, and the second principal dimension (SFI.Dim2) explaining 12.61% of the total variance.

Following the recommendations by Gifi [21], we retained the first 2 principal dimensions of social function information and applied the k-means algorithm to assign patients into 3 different clusters. To determine the number of clusters, we use the elbow plot method that consists of plotting the within sum of squares as a function of different numbers of clusters k. The location of a bend in the plot provides the appropriate number of clusters.

To identify motivators of treatment engagement, logistic regression with least absolute shrinkage and selection operator penalty was applied using demographic and medical information as well as to all 14 principal dimensions of social function information variables (R package "glmnet" [22]). Following Jolliffe [23], we included all principal dimensions in the model. The outcome variable was binary: 1 if the patient was treated, 0 if not. The corresponding penalty parameter was selected using 5-fold cross-validation and had a value of 0.108. Then logistic regression was implemented to assess the effect of the factors chosen on treatment status.

RESULTS

Patient Characteristics

Sixty-two OUD patients on methadone underwent telemedicine-based HCV evaluations. Approximately one-quarter of subjects were human immunodeficiency virus (HIV) infected, most were male (61.3%) with a mean age of 57.5 ± 9.9 years, 61.3% were African Americans, and 74.2% were non-Hispanic (Table 1). Most (67.2%) were HCV genotype 1a infected. Fibrosis stage was approximately equivalently distributed, with one-third with no or minimal fibrosis and 34% with moderate fibrosis and 34% with either advanced fibrosis or cirrhosis (Figure 2). The social function variables are illustrated in Table 2.

Treatment Regimen

Forty-five patients were prescribed DAA-based treatment, with 19 (42.2%) receiving 8 weeks and 25 (55.6%) receiving 12 weeks. One participant discontinued treatment prematurely (week 4) due to nausea and abdominal discomfort. Treatment regimens are illustrated in Table 1. Reasons for not receiving HCV treatment included discontinuation from the OST program in 3 patients (17.7%) (ie, relocation out of the area, incarceration), insurance issues in 10 (58.8%) (ie, not completing appropriate registration, switching insurance plans, or plan absence of telemedicine coverage), nonadherence to third-party payer requirements for additional testing in 2 (11.8%) (ie, additional blood tests or urine toxicology screens), and denials due to HIV adherence issues in 2 (11.8%). Specifically, both participants failed to demonstrate antiretroviral adherence resulting in undetectable HIV RNA, which was deemed necessary for approval of DAA therapy. In no cases were DAAs denied due to illicit drug use or based upon fibrosis stage. Three patients who did not complete the medical evaluation were excluded from the analysis (Supplementary Table 1).

Antiviral Efficacy, Adverse Effects, and Adherence

Of patients who received at least one DAA dose, 42 (93.3%) achieved viral eradication. Importantly, nonresponse is likely attributable to early treatment discontinuation or reinfection rather than virological ineffectiveness. Besides one early discontinuation, the 2 additional nonresponders were likely reinfected, as each had negative HCV RNA between posttreatment weeks 2 and 4 with positive values on or after posttreatment week 12.

In terms of adverse effects, at treatment week 2, 42.2% of participants reported insomnia while 17.8% reported drowsiness. By treatment week 8, the prevalence of insomnia increased to 56.0% while that of drowsiness decreased

Table 1. Summary of Demographic, Medical, and Treatment Variables

			All Patients			Treated Patients			Untreated Patients		
Category	Variable	Level	Size	Mean or Count	(SD or %)	Size	Mean or Count	(SD or %)	Size	Mean or Count	(SD or %)
Demographic information	Age[a]		62	57.5	(9.9)	45	56.3	(10.0)	17	60.8	(9.1)
	Weight, kg		62	78.9	(17.6)	45	80.9	(18.7)	17	73.6	(13.4)
	Height, cm		62	169.8	(8.6)	45	170.5	(9.2)	17	168.1	(6.5)
	BMI, kg/m^2		62	27.4	(6.0)	45	27.9	(6.3)	17	26	(4.7)
	Sex	Female	62	24	(38.7)	45	16	(35.6)	17	8	(47.1)
		Male		38	(61.3)		29	(64.4)		9	(52.9)
	Race	African American	62	38	(61.3)	45	27	(60.0)	17	11	(64.7)
		Other[b]		24	(38.7)		18	(40.0)		6	(35.3)
	Ethnicity	Hispanic	62	16	(25.8)	45	11	(24.4)	17	5	(29.4)
		Non-Hispanic		46	(74.2)		34	(75.6)		12	(70.6)
Medical information	HCV RNA, $\log_{10}$		62	6.4	(0.6)	45	6.29	(0.556)	17	6.50	(0.6)
	Stage[c]		59	0.5	(0.3)	45[d]	0.46	(0.2)	14	0.52	(0.3)
	Grade[c]		59	0.3	(0.2)	45[d]	0.31	(0.2)	14	0.36	(0.2)
	HCV genotype	1a	61	41	(67.2)	45	29	(64.4)	16	12	(75.0)
		1b, 2b, or 3		20	(32.8)		16	(35.6)		4	(25.0)
	HIV	No	62	47	(75.8)	45	35	(77.8)	17	12	(19.4)
		Yes		15	(24.2)		10	(22.2)		5	(8.1)
	Comorbidity	Kidney and urologic	62	9	(14.5)	45	9	(20.0)	17	0	(0.0)
		Mixed[e]		29	(46.8)		20	(44.4)		9	(14.5)
		None		10	(16.1)		8	(17.8)		2	(3.2)
		Pulmonary		14	(22.6)		8	(17.8)		6	(9.7)
Treatment information	Therapeutic agent	Sofosbuvir/velpatasvir	45	…	…	45	2	(4.4)	…	…	…
		Sofosbuvir/ledipasvir		…	…	45	35	(77.8)		…	…
		Sofosbuvir/ribavirin		…	…	45	1	(2.2)		…	…
		Ombitasvir/paritaprevir/ dasabuvir/ribavirin		…	…	45	2	(4.4)		…	…
		Elbasvir/grazoprevir		…	…	45	5	(11.1)		…	…
	Treatment duration, wk	4		…	…	45	1	(2.2)		…	…
		8		…	…		19	(42.2)		…	…
		12		…	…		25	(55.6)		…	…
	Final treatment outcome	Nonresponder		…	…	45	3	(6.7)		…	…
		Viral eradication		…	…		42	(93.3)		…	…

Categorical variables are summarized as count (%) and continuous variables as mean (SD).

Abbreviations: BMI, body mass index; HCV, hepatitis C virus; HIV, human immunodeficiency virus; SD, standard deviation.

[a]Ages are calculated as differences (in years) between date of birth and 1 March 2015.

[b]"Other" includes white, Native American, and others (as shown in the data).

[c]Assessed by FibroSure, LabCorp, Research Triangle Park, North Carolina.

[d]One subject had liver biopsy approximately 5 years prior to study entry.

[e]"Mixed" means mixed combinations of endocrine, eye, kidney/urologic, neurologic, musculoskeletal, and pulmonary diseases.

to 4.0% (Figure 3). Other medication-related adverse effects that occurred in 40% of patients included gastrointestinal (ie, nausea, vomiting, diarrhea, constipation, bloating, gas), neurologic (ie, headache, dizziness, nightmares, changes in mood, numbness/tingling), or rash. One patient had ribavirin-induced severe anemia. No IRB-defined serious adverse effects occurred during the study.

In terms of adherence, 20% of patients reported at least one missed dose during the initial 2 weeks of treatment. Approximately 10% of patients at treatment weeks 4, 6, and 8 reported missing at least one DAA dose (Figure 4).

Social Health Determinants of HCV Evaluation Pursuit

The characteristics of the patients in different clusters are illustrated in Table 3 and Supplementary Figure 1. Cluster distribution by treatment status is illustrated in Supplementary Figure 2. In general, patients in all 3 clusters have relatively poor social function; however, patients in each cluster present with a

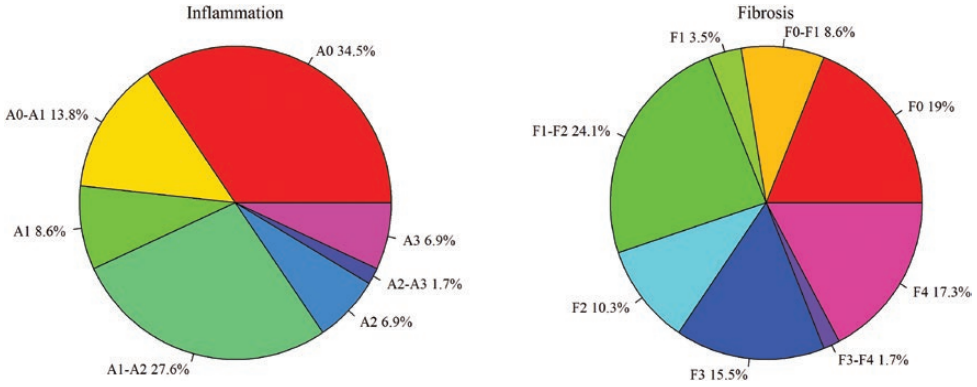

Figure 2. Distribution of inflammatory grade (*A*) and fibrosis stage (*B*). Results obtained from hepatitis C virus FibroSure test from LabCorp (Research Triangle Park, North Carolina). Inflammation was defined as activity grade (range): A0, no activity (0.00–0.17); A0–A1 (>0.17–0.29); A1, minimal activity (>0.29–0.36); A1–A2 (>0.36–0.52); A2, moderate activity (>0.52–0.60); A2–A3 (>0.60–0.63); A3, severe activity (>0.63–1.00). Fibrosis was defined as fibrosis stage (range): F0, no fibrosis (0.00–0.21); F0–F1 (>0.21–0.27); F1, portal fibrosis (>0.27–0.31); F1–F2 (>0.31–0.48); F2, bridging fibrosis with few septa (>0.48–0.58); F3, bridging fibrosis with many septa (>0.58–0.72); F3–F4 (>0.72–0.74); F4, cirrhosis (>0.74–1.00).

unique combination of social function characteristics that distinguishes them from individuals in the other 2 clusters. For example, patients in cluster 1 are more likely to have a diagnosis of depression and to have a developmental disability, while they also tend to be divorced, separated, or widowed and to have an educational level of at least a high school diploma equivalency (GED). In contrast, individuals in cluster 3 are more likely to never have been married and not to have developmental

Table 2. Social Function Variables

		All Patients		Treated Patients		Untreated Patients	
Social Function Variable	Level	Count	(%)	Count	(%)	Count	(%)
Marital status[a]	Divorced/separated/widowed	20	(32.8)	12	(27.3)	8	(47.1)
	Married	16	(26.2)	13	(29.5)	3	(17.6)
	Never married	25	(41.0)	19	(43.2)	6	(35.3)
Employment status	Employed	4	(6.4)	3	(6.7)	1	(5.9)
	Unemployed and disabled	33	(53.2)	23	(51.1)	10	(58.8)
	Unemployed and not disabled	25	(40.3)	19	(42.2)	6	(35.3)
Highest educational level	GED or above	36	(58.1)	27	(60.0)	9	(52.9)
	No GED/some high school	26	(41.9)	18	(40.0)	8	(47.1)
Patient-reported living situation	Homeless/shelter	16	(25.8)	13	(28.9)	3	(17.6)
	Living alone	22	(35.5)	16	(35.6)	6	(35.3)
	Living with someone	24	(38.7)	16	(35.6)	8	(47.1)
History of IDU	No	23	(37.1)	17	(37.8)	6	(35.3)
	Yes	39	(62.9)	28	(62.2)	11	(64.7)
Other illicit drug #1	Cocaine	39	(62.9)	30	(66.7)	9	(52.9)
	No or other drugs[b]	23	(37.1)	15	(33.3)	8	(47.1)
Other illicit drug #2	No	38	(61.3)	27	(60.0)	11	(64.7)
	Yes[c]	24	(38.7)	18	(40.0)	6	(35.3)
Forensic history[a]	No	23	(39.0)	16	(36.4)	7	(46.7)
	Yes	36	(61.0)	28	(63.6)	8	(53.3)
Psychiatric history	Depression	16	(25.8)	11	(24.4)	5	(29.4)
	No	33	(53.2)	25	(55.5)	8	(47.1)
	Other[d]	13	(21.0)	9	(20.0)	4	(23.5)
Developmental disability	No	58	(93.5)	43	(95.6)	15	(88.2)
	Yes	4	(6.4)	2	(4.4)	2	(11.8)

Abbreviations: GED, high school diploma equivalency; IDU, injection drug use.

[a]Marital status has the sizes 61, 44, and 17 for all, treated, and untreated patients; forensic history has the sizes 59, 44, and 15 for all, treated, and untreated patients; all of the other social function variables have the sizes 62, 45, and 17 for all, treated, and untreated patients.

[b]"Other drugs" includes alcohol, benzodiazepines, and marijuana/hashish.

[c]"Yes" includes cocaine, alcohol, benzodiazepines, marijuana/hashish, and methadone.

[d]"Other" includes benzodiazepine abuse, anxiety, posttraumatic stress disorder, anger, bipolar disorder, and suicide.

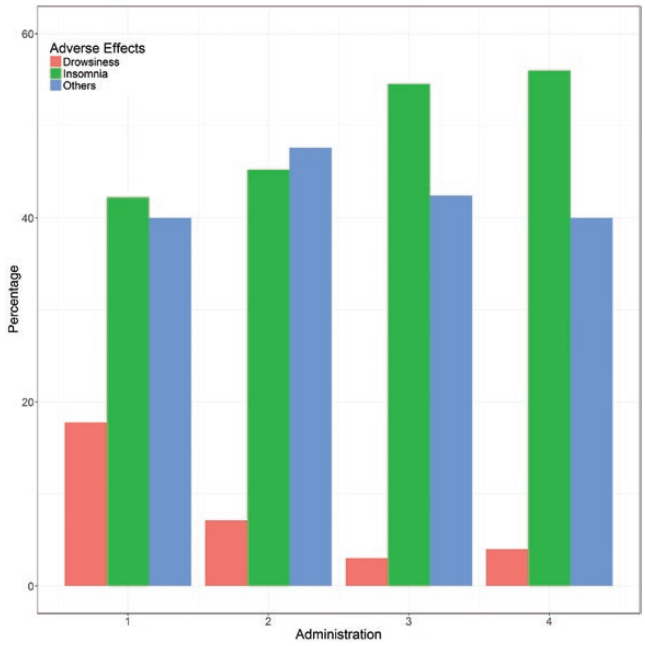

Figure 3. Prevalence of adverse effects over the course of medication administration: drowsiness, insomnia, and "others" (includes nausea, vomiting, diarrhea, constipation, bloating, headache, dizziness, nightmares, rash, changes in mood, numbness/tingling, gas).

disabilities, while they are also more likely to be living alone and to be unemployed and disabled.

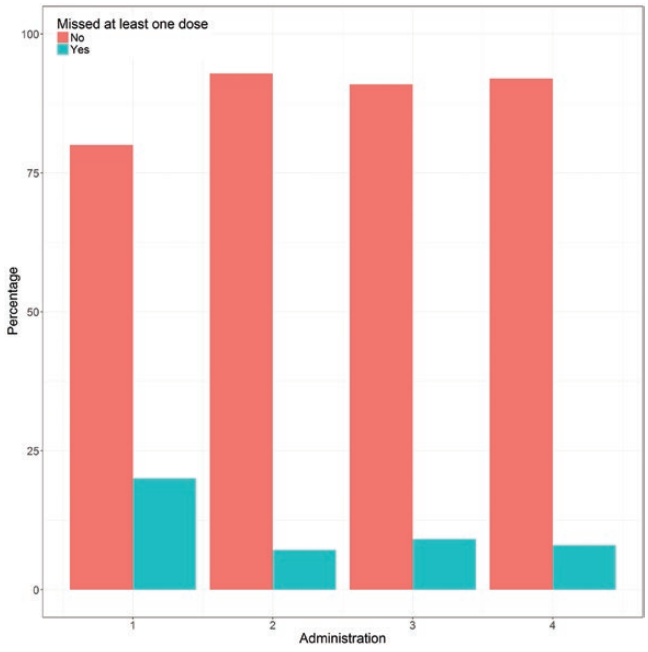

Figure 4. Adherence to direct-acting antivirals. Adherence was determined based upon responses to questions inquiring about at least one dose missed in the preceding 2 weeks at weeks 2, 4, 6, and 8 of medication dosing. Percentage of missed doses and percentage of doses administered are indicated in green and orange, respectively.

Positive and Negative Factors for HCV Treatment Engagement

Only the 11th principal dimension (SFI.Dim11) was selected as significant. Then, logistic regression was used to assess the effect of the 11th principal dimension on treatment status (bias-unadjusted odds ratio, 18.89; $P = .039$). Figure 5 presents the directionality and strength of social variable influence on treatment engagement. Any category with a positive value could increase the probability of receiving treatment and any category with a negative value could decrease the probability of receiving treatment. For example, being married and having a psychiatric diagnosis other than depression contribute the largest increment in the probability of receiving treatment and therefore appear to be the biggest treatment motivators. Conversely, being divorced, separated, or widowed and only attending some high school (without a GED) lead to large reductions in the probability of receiving treatment.

DISCUSSION

In this study, we evaluated the effectiveness of HCV management via telemedicine integrated into an OST program. We leveraged OST requirements for frequent attendance and the repertoire of services available in the OST program to support patients during HCV treatment. Of 62 patients evaluated, 45 (73%) received treatment and 42 (93%) achieved viral eradication. As 34.5% of the patient population had advanced fibrosis or cirrhosis (stage 3 or greater), this population was highly deserving of antiviral therapy. In addition, the population was comprised overwhelmingly of racial and ethnic minorities, populations with large healthcare disparities. The ability to pursue HCV treatment onsite in the OST program bypasses several of the difficulties encountered with the traditional HCV management strategy, offsite referral to a liver specialist. Among PWSUD, principal deterrents to HCV treatment pursuit have included stigmatization, which is frequently encountered in conventional healthcare settings, and a lack of awareness of the consequences of HCV infection [3, 24]. Virtual integration of substance use and HCV treatment may increase OUD patients on methadone HCV treatment engagement. Prior studies have illustrated that these individuals are more likely to adhere to a treatment protocol if it is delivered at convenient locations and in a familiar environment [25, 26]. The supportive environment of an OST program, especially those with on-site professional services including counseling, medical/psychiatric care, employment assistance, and family therapy, has been shown to reduce rates of morbidity and premature mortality among PWSUD and can be leveraged to improve HCV treatment outcomes [27, 28]. Indeed, if telemedicine had not been available, it is highly likely that this medically disenfranchised population with high fibrosis stage would not have received therapy for HCV.

Table 3. Characteristics of Patients in Different Clusters

Social Functioning Information	Cluster 1 (n = 20)	Cluster 2 (n = 17)	Cluster 3 (n = 22)
Marital status	Divorced/separated/widowed	Married	Never married
Employment status	…	Unemployed and not disabled or employed	Unemployed and disabled
Highest level of education	GED or above	…	No GED/some high school
History of injection drug use	No	Yes	…
Other illicit drug #1	Other drugs or no drugs	…	Cocaine
Other illicit drug #2	…	No	Yes
Forensic history	…	No	Yes
Psychiatric history	Depression	Others	No
Development disability	Yes	…	No
Reported living situation	Living with someone	Homeless/shelter	Living alone

Abbreviation: GED, high school diploma equivalency.

Viral eradication occurs in 80%–96% in real-world studies of injection drug users who receive DAAs [29]. In the first phase 3 trial of DDA therapy in OST-maintained individuals, 91% achieved viral eradication [30]. Another recent study reported that 94% achieved viral eradication among people with recent injection drug use who received DAAs; fatigue, headache, and nausea were the most common adverse events [31]. Our eradication rate is equivalent to those obtained in

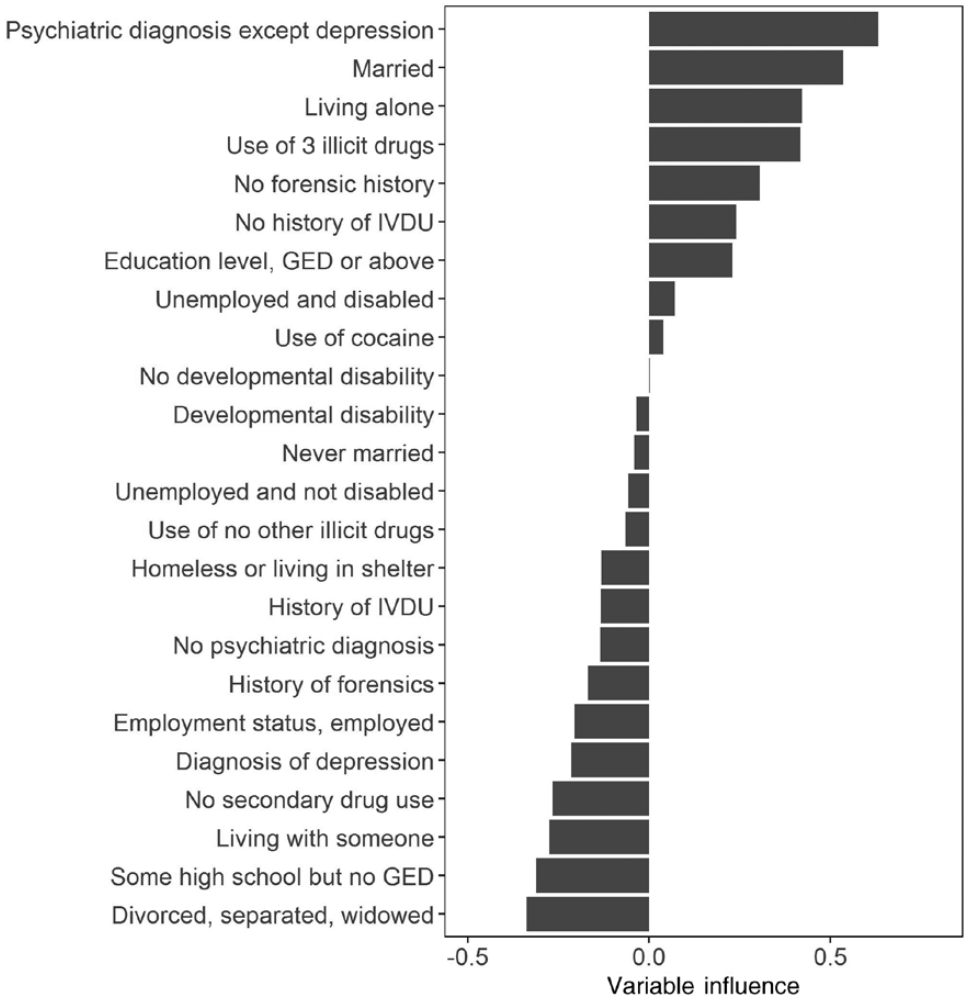

Figure 5. Directionality and strength of social variable influence on treatment engagement. The 11th principal direction provides a continuous variable expressed as a linear combination of the categories illustrated. Categories with positive direction increase the likelihood of treatment uptake, whereas those with negative direction decease the likelihood of obtaining treatment. Abbreviations: GED, high school diploma equivalency; IVDU, intravenous drug use.

registration trials of DAAs in patients with OUD on OST (reviewed in [3]).

Integration of treatment of substance use and co-occurring conditions has been advocated [3, 13]. In an early study, we documented that integrated HCV and substance use treatment improved adherence with HCV evaluation and treatment among OUD patients on methadone [32]. In the United States, physical integration, however, has been difficult to achieve. Virtual integration has been suggested as a potential alternative for management of comorbid conditions in PWSUD [12]. In this patient cohort, we found that patients' preference for telemedicine increased over time with recognition of its convenience and diminished concerns over confidentiality and privacy [33]. Providers also appreciated the convenience of HCV treatment via telemedicine as it provided a vehicle to address a common medical condition that they generally considered outside their scope of practice. Indeed, a recent systematic review underscored the need for additional investigation of telemedicine for integration of treatment of behavioral and medical disorders [34]. Telemedicine can also reduce healthcare costs and increase linkage to care [35]. It has the potential to establish OST programs as central in the treatment of co-occurring medical conditions among PWSUD and has a potential role in addressing medical conditions in medically underserved individuals living in urban and rural areas.

The development of all-oral HCV treatment regimens with substantially reduced treatment duration and minimal side effects can also enhance integration of HCV and substance use therapy. Elimination of interferon-based therapy is especially relevant in the OST-maintained population due to interferon's requirement for administration by injection and, its propensity to exacerbate mental health issues and simulate methadone withdrawal. DAAs can easily be coadministered with methadone as performed in this investigation. Additionally, point-of-care assays to noninvasively assess fibrosis stage, either using multiparameter indices performed on serum or through transient elastography, can also facilitate PWSUD engagement into HCV care.

We found that marriage and an absence of depression were the strongest predictors of treatment pursuit whereas divorced, separated, or widowed social status was the strongest deterrent. Framing HCV infection and addiction as a syndemic, defined as the presence of 2 or more diseases or conditions and the related social and environmental factors that adversely affect each other, could facilitate the identification, understanding, and strategies to overcome obstacles to HCV treatment pursuit by PWSUD [36]. Syndemics are more likely to develop under conditions of disparity and social inequality, such as poverty and stigmatization. Our findings illustrate the importance of interrelationships between psychosocial characteristics and their potential influence on HCV treatment engagement, knowledge that could be useful to increase HCV treatment uptake in PWSUD.

Recently, DAA registration trials that enrolled OST-maintained patients illustrated improvements in fatigue, psychiatric disorders, and quality of life [37, 38]. Similarly, we observed decreases in drowsiness and increases in insomnia as HCV treatment progressed. Both fatigue and insomnia frequently occur in OST-maintained individuals; insomnia is a noted adverse effect of methadone [39], and fatigue occurred in 20% of OST-maintained patients on placebo and in 14% on DAA-based treatment [30]. Thus, not only are DAAs better tolerated in the OST-maintained population than interferon, but viral eradication appears to improve fatigue.

While this study is relatively unique as it reports real-world data on OUD patients on methadone who received DAAs in the United States, study limitations include the relatively small number of patients treated via telemedicine, enrollment from a single site, and lack of a comparison group. Consequently, we are unable to accurately judge the impact of telemedicine in comparison to usual care. Another study limitation includes the presence of missing values in some of the social function variables. Treated participants were also self-selected, which might have affected their motivation to be adherent. While we were able to identify the strongest positive and negative factors associated with treatment pursuit, larger studies are needed to identify less influential factors. To address this issue, we are currently conducting a randomized trial comparing telemedicine to usual care for HCV management at 12 OST programs throughout New York State [40]. Third-party payer restrictions on DAAs or telemedicine reimbursements are additional potential limitations. Fortunately, we did not encounter restrictions based upon fibrosis stage or illicit substance use. However, as this study was initiated prior to enactment of the 2016 New York State telemedicine parity law, some third-party payers did not authorize telemedicine-based DAA prescriptions.

In conclusion, HCV care via telemedicine is a feasible model for HCV treatment delivery in an OST program. Virologic efficacy was similar to trials in PWSUD who received DAAs, and medication-associated side effects were minimal. Participants had excellent DAA adherence when coadministered with methadone. Therefore, telemedicine could become a standard method of HCV management among OST patients on methadone.

Supplementary Data

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

Notes

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