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Developing a Modified Directly Observed Therapy Intervention for Hepatitis C Treatment in a Methadone Maintenance Program: Implications for Program Replication

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Abstract

Background—Hepatitis C virus (HCV) is a prevalent chronic blood-borne infection among opioid-dependent patients on methadone maintenance treatment (MMT). Despite case reports and case–control studies, a randomized controlled trial (RCT) examining HCV treatment adherence in methadone-maintained patients is lacking and was the impetus for this ongoing RCT examining modified directly administered therapy for HCV treatment integrated within a MMT.

Methods—Subjects were randomized 1:1 to receive HCV treatment as modified directly observed therapy (mDOT) into the MMT program or at a liver specialty clinic as self-administered therapy (SAT). Randomization was stratified based on HIV status and HCV genotype.

Results—Twenty-one subjects to date have enrolled in this pilot study. The mDOT subjects have had greater success in starting treatment and 10 of the 12 mDOT subjects achieved early virologic response (EVR) at week 12 and 6 of those 10 achieved sustained virologic response (SVR). Of the nine SAT subjects, only three achieved EVR at week 12 and only one achieved SVR despite not completing the treatment.

Conclusions—Hepatitis C treatment can be successfully integrated into a methadone maintenance clinic, and mDOT can be implemented with a methadone clinic's existing nursing and medical staff. Patients struggling with concurrent substance use and mental illness comorbidity may be successfully addressed in such settings and facilitate access to and completion of treatment through the utilization of on-site clinical services for HCV treatment and adherence support with mDOT. The exact importance of site of services and adherence support remains a significant area for future investigation.

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Keywords

hepatitis C treatment; methadone

Introduction

Nearly 4 million people (1,2), or 1.8% of the US population (3), are infected with Hepatitis C virus (HCV). This is an underestimation because current approximations excluded high-prevalence populations such as medically and socially marginalized drug users and incarcerated persons (4). Injection drug use (IDU) accounts for the overwhelming majority of HCV-infected persons (5,6). It is therefore not surprising that prevalence estimates from methadone maintenance treatment (MMT) programs, where IDU is common, range from 72% to greater than 90% (1,7,8).

Multiple studies confirm that HCV-infected patients with current or past problems with substance use disorders (SUDs) are unlikely to be screened for and/or treated for their HCV (9,10). Among veterans, reasons for withholding treatment include psychiatric comorbidity, history of drug use, concurrent medical problems, nonadherence to medical appointments, advanced liver disease, and patient refusal (11). Indeed, longitudinal cohorts of HCV-infected patients report that approximately one-fifth of those with active alcohol and drug use without sufficient support struggle to adhere to HCV treatment monitoring or are lost to follow-up, and ongoing drug use may increase viral load and reduce virologic response to treatment (5,12). Such difficulties in adherence speak to the need to create effective adherence interventions to provide support to HCV-infected patients to complete the complicated HCV treatment course. One approach is introducing HCV treatment within MMT settings, where retention is high and patients are seen more frequently, which provides not only an ideal environment to enhance adherence to treatment, but also support for this patient population.

Despite the proliferation of case reports and case–control studies on HCV treatment adherence among drug users, a randomized controlled trial (RCT) examining HCV treatment adherence in methadone-maintained patients is lacking (5,13–16). These studies vary in their use of nonpegylated interferon, and coordination and location of substance abuse and HCV treatment services. The lack of an existing RCT to optimize HCV treatment and adherence in an MMT was the impetus for this pilot RCT examining modified directly observed therapy (mDOT) for HCV treatment that is integrated within an MMT. Although this study is ongoing, several important lessons have already been gleaned that provide the foundation for and feasibility of the intervention and have implications for program development in other MMT sites.

Methods

In developing the study protocol, the goal was to create a model of care that would result in the highest likelihood of patients achieving access to and retention in HCV treatment. We therefore reviewed the characteristics of successful directly observed therapy (DOT) programs from the medical literature, including a previously created mDOT program for

antiretroviral therapy created by the authors (17,18). The review of this literature was used to organize services with the goal of creating an intervention that would optimize the highly reinforcing effects of methadone in the setting of providing standard hepatitis C treatment [weight-based ribavirin (RBV) and pegylated interferon alfa-2a (PEG)] to enhance adherence to HCV treatment.

Study Site

Subjects were recruited over a 3-year period (2007–2010) from a single site in New Haven, CT, that is primarily organized for treating SUDs, including methadone maintenance. This clinic was subsequently adapted through provision of additional medical and behavioral health personnel to create a multidisciplinary, integrated healthcare team within New Haven's largest community health center. This licensed site currently provides methadone maintenance for 315 patients. Prior to starting the HCV treatment program, support from the administration was necessary because staff time would be used toward the project. Standard admission procedures to the clinic were designed that included opt-out HIV, HBV, and HCV testing for all new patients. Those with evidence of infection with HCV were subsequently seen by a medical provider to begin the evaluation process for HCV treatment (e.g., obtaining HCV viral load, genotype, and eventually a biopsy for staging if genotype 1 or 4). All percutaneous liver biopsies were done by Yale Interventional Radiology to maximize availability in scheduling. All medical providers, nursing staff, and counselors underwent a standard training by the authors on HCV treatment and side effects. Side effects were managed in a similar fashion between the two arms – both seeking to use adjuvant therapy (e.g., erythropoietin) rather than reduce the dose of study medications.

Selection of Participants

Subjects were eligible for participation if they were prescribed methadone and were opioid negative by urine toxicology in the past 30 days to ensure methadone dosage was appropriate (other drug and alcohol use were not exclusion criteria), age 18 years or older, underwent documented HIV testing, competent to provide informed consent, and met the following criteria for HCV treatment: detectable HCV RNA and genotype testing. Those with genotype 2 or 3 were exempt from liver biopsy staging, whereas genotypes 1 and 4 had to demonstrate a fibrosis score of >1 using Metavir staging. Subjects were screened for mental illness (current and lifetime) using the Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders (SCID) (see Table 1), and the Hamilton Rating Scale for Depression (HAMD) was an additional screening measure utilized for major depression as this was felt to better account for the somatic symptoms of interferon that may skew the Beck Depression Inventory. Subjects who screened in for mental illness were seen by a licensed mental health provider to consider the need for medication and to evaluate the subject's psychiatric stability prior to starting treatment. PEG is well known to result in the development of clinical depression and hence it was necessary to monitor for the development of depression (19). During the course of treatment, subjects in the mDOT were screened for depression prior to each PEG shot with the Patient Health Questionnaire-9. Subjects with a positive screen were referred for immediate psychiatric evaluation. Subjects meeting eligibility criteria, after providing written informed consent, were randomized 1:1, using block randomization to control for genotype (1,4 vs. 2,3) and

HIV status, to receive either the adherence intervention or the self-administered therapy (SAT). To avoid a bias between the SAT and the mDOT arms, subjects had to have completed an evaluation for HCV treatment and be ready to start treatment. Subjects who were ready to start treatment were required to undergo baseline study procedures and randomization to site of treatment.

Study Monitoring

At baseline, each subject underwent a 3-hour structured interview assessing demographic and social circumstances, several domains from the Addiction Severity Index, which include drug use and general psychiatric health status (20), healthcare utilization, quality of life (Short Form-36) (21), and phlebotomy to measure HCV RNA (real-time PCR using COBAS AmpliPrep/COBAS TaqMan HCV Test Kit from Roche Molecular Systems, Inc. Pleasanton, CA). Follow-up interviews were performed on all subjects at baseline, and after weeks 4, 12, 24, and 48 for all subjects and additionally at weeks 36 and 72 weeks for genotypes 1 and 4.

Description of Treatment Intervention Arms

All subjects initiating HCV therapy were initiated on weekly PEG 180 μg subcutaneously and weight-based RBV. Subjects randomized to the SAT arm received their methadone remote from their site of HCV treatment. HCV treatment was provided within the Yale Liver Center, the university-based liver specialty clinic. All subjects in this arm were taught how to self-administer their PEG and RBV at the Liver Center and both were maintained separately in MEMS® (Aardex Group, Sion, Switzerland) capped bottles. Subjects followed a prespecified time period of attending the Liver Center for clinical follow-up and blood work. Neither SAT nor mDOT sites offered case management services to subjects in this study. Both groups were responsible to take nonobserved doses. The research assistant for the study ensured timely referral to the Yale Liver Center so that initiation of treatment was commensurate with completing eligibility criteria. After treatment initiation, the research assistant met with the subject only at prespecified study monitoring visits.

Subjects randomized to the intervention arm received mDOT as part of an adherence intervention. Clinical nurses administered all methadone doses in a private room to minimize breeches of confidentiality. For study subjects, they also coadministered the morning RBV dose. The evening dose of RBV was prepackaged by a pharmacist in a labeled MEMS® container to confirm adherence and also accessible for the subject to self-administer 12 hours later. PEG was administered to mDOT subjects weekly on Thursdays (“shot day”) by either a nurse or other licensed practitioners. All mDOT subjects who earned take-home bottles for methadone also received take-home doses of RBV in a bottle with a MEMS® cap to monitor adherence. The range of take-home bottles varied from no-take homes and attendance at the clinic 7 days a week to 6 take homes (only one subject) and attendance only once a week. All subjects, consistent with clinical practice, attended the clinic at least weekly to receive supervised PEG injections on-site.

Results

Preliminary results are provided in order to inform program replication. Twenty-one subjects to date have enrolled in this pilot. Unlike the SAT subjects, all the mDOT subjects started HCV treatment. Baseline characteristics are provided in Table 1 and virologic outcomes are listed in Table 2. The mDOT subjects appeared to have higher levels of psychiatric comorbidity (including depression, post-traumatic stress disorder, and panic disorder). Cocaine dependence is high in both groups, and this includes both past and current cocaine dependence. Past use is also included because of the high risk of relapse in this group upon starting treatment.

Ten of 12 mDOT subjects achieved early virologic response (EVR) at week 12, with 6 of those 10 achieving sustained virologic response (SVR). Two subjects did not achieve EVR. One subject was a HIV/HCV coinfected patient who achieved viral suppression by week 24 and throughout the rest of treatment. The second subject saw a three log drop in HCV RNA (13,500,000–15,116 IU/mL). One subject with PTSD relapsed to cocaine use and discontinued HCV treatment at week 9 after a physical assault by her partner. After stabilization of her substance use and assault, the patient sought to resume HCV treatment but was incarcerated prior to restarting. After release from incarceration, the patient restarted methadone maintenance, and restarted HCV treatment and has achieved EVR.

Of nine subjects randomized to SAT, four initiated treatment. Three subjects achieved an EVR and one subject achieved SVR despite prematurely discontinuing HCV treatment. One HIV/HCV coinfected patient started treatment but did not achieve EVR (2,821,850–462,190 IU/mL). Five subjects never started treatment due to varying reasons. One subject was homeless and lacked a place to store his medications. Another subject was not able to start due to ongoing depression and missed appointments. One subject refused SAT, preferring the concept of mDOT because he did not want to self-administer PEG shots and felt the additional attendance requirement of an off-site hepatitis C treatment center was inconvenient. Two subjects have yet to start because of ongoing missed appointments at the off-site hepatitis C treatment center. Both consistently attend their scheduled methadone clinic appointments to obtain methadone.

Discussion

Considerable information was learned during the initial phase of developing this mDOT intervention. First, it was feasible but challenging to move beyond colocation of HCV treatment, where clinical services are offered on-site by nonmethadone staff and has been described extensively in the literature (14–16,22), to full integration of HCV treatment protocols into a busy methadone clinic in a community health center where the methadone staff was trained to implement the HCV treatment. Prior to this pilot, no one in the clinic had conducted a baseline evaluation for HCV nor had anyone treated a patient for HCV. The first challenge was to achieve integration without additional staffing resources. To accomplish this, trainings were conducted to inform healthcare providers (nurse practitioners and physician assistants) on how to treat HCV and manage the side effects of HCV therapy. Additionally, cross-training of nursing and counseling staff was done first to improve

awareness and management of treatment side effects and how they might influence substance abuse and mental health outcomes – two highly prevalent comorbidities in this subject population. Logistical changes were also made to achieve integration. Nurses, whose primary job was only to dispense methadone, now had the additional responsibility for administering a morning dose of RBV as well as providing a "take-home" dose of RBV for evening self-administration. During these morning administration sessions, the nurses also Inquired about adverse side effects and other problems and were able to immediately refer subjects to ancillary services if they were needed.

There was initial resistance to accepting additional tasks. Extensive motivational enhancement was used to encourage staff in their work on this project, and patient success in treatment was used as a vehicle to praise the nurses and encourage them in ongoing work on the project. Over time, adherence work for HCV therapy became accepted as a routine service in the clinical setting. Providers and nurses began suggesting mDOT as a way to assist in adherence to other treatments for patients outside of the adherence program (e.g., HIV therapy, psychiatric medications).

Although not a goal of this initial project, the success of administration of the morning dose of RBV has important implications for future mDOT interventions. RBV is pharmacokinetically able to be administered once daily (23), but was administered twice daily in this pilot because the RCTs that demonstrated a benefit of RBV use were dosed twice daily. One recent retrospective study suggests once daily RBV might be an option; however, the study was retrospective and with a small sample size (24). Other studies of mDOT suggest that there is less adherence to the evening dose of twice daily medications (18). Hence, future studies may consider trials of once-daily RBV administration to overcome such adherence issues. As the protease inhibitors telaprevir and boceprevir become part of treatment, such mDOT interventions may obviate once-daily RBV dosing strategies as these agents will require twice-daily and thrice-daily administration, respectively (25).

Two other important logistical issues emerged. First, lessons learned from our earlier work with mDOT for HIV required making either "dispensing" or "observation" of self-administered medications legally compliant with state and federal legislation (18). Specifically, nurses cannot legally dispense medications; therefore, a pharmacist was required to prepour evening doses of the RBV into separate bottles to which the nurse could then affix a MEMS cap and provide to the subject for the evening dose. Second, the logistical set-up of this program was ideal for confidentiality concerns. All MMT patients enter into a private dispensing room where no other patients can observe them taking additional medications. This is not always possible in busy methadone programs where a privacy barrier might need to be constructed to ensure patient confidentiality. Although RBV could be administered with methadone, the PEG injections could not be administered by the dispensing nurse because of the physical barrier between nurse and patient required by federal statute. As a result, the patients had to either have a nursing visit with another nurse in the clinic or had to see their medical provider in order to obtain the injection. Such logistical considerations will need to be addressed in program replication elsewhere.

Comorbid cocaine use did not apparently interfere with HCV treatment in patients who were supported through their methadone and HCV treatment, while it interfered greatly with subjects whose HCV treatment was treated off-site. Two mDOT subjects with problematic cocaine use successfully initiated HCV treatment and discontinued cocaine use during treatment and achieved a SVR, while noncocaine-using subjects randomized to off-site treatment relapsed to cocaine use, missed several appointments at the off-site liver specialty clinic (while successfully remaining on MMT), and, as a consequence, have never started HCV treatment.

There was a high prevalence of psychiatric comorbidity – conditions that negatively contribute to successful HCV treatment outcomes (26,27). Despite the high prevalence of depression, panic disorder, and PTSD (comorbidities that often preclude HCV treatment in other settings), 10 of 12 subjects in the mDOT treatment arm achieved an EVR. The high level of psychiatric comorbidity required an increased level of vigilance and ongoing assessment by nursing and counseling staff to ensure that subjects did not become destabilized either as a consequence of HCV treatment itself or because of unexpected life exigencies that often occur with such socially and medically marginalized patients.

An important lesson was learned through our referral process to a liver specialty clinic. In order to avoid cross-contamination of support for treatment, referred subjects did not receive “additional” counseling and assessment by MMT and other clinical staff members. As a result, the SAT group struggled considerably to make scheduled appointments there, despite excellent adherence to MMT and the liver specialty clinic being located only a few blocks from the MMT program. As a result, these subjects were often not started on HCV treatment. The reasons for these missed appointments are not known, but reasons provided may include stigma related to being a drug user, and comfort and trust in the site they attend daily for their drug treatment and mistrust and/or discomfort in creating trusting relationships in a new site. Future approaches to addressing healthcare organization and its impact on HCV treatment will have to factor time to initiation of treatment that may be different depending on the setting. Alternatively, for sites where integration of services has either not yet happened or is unlikely to happen, development of alternative support services within MMT that enhances referral and retention in HCV treatment within liver specialty settings merits further investigation.

Incarceration, violence, and homelessness are structural issues that led to HCV treatment discontinuation in this study. In addition to the difficulty adhering to a medication regimen with severe side effects, methadone patients must face external pressures that add to the difficulties of adherence.

It is difficult to ascertain if the site of treatment or the mDOT intervention was the most critical factor, but we posit that both are necessary. Specifically, the on-site treatment was clearly more convenient to the patients since they had to come to the clinic for methadone regardless and they already knew and trusted the staff. These important relationships were key to being willing to be evaluated for treatment and also for engaging in treatment. Individuals experiencing adverse events from a difficult treatment, however, can clearly struggle with adherence to treatment. The mDOT intervention and on-site services were

important in helping those who have engaged in treatment to successfully complete their HCV treatment.

Irrespective of the final outcome, it is apparent that there is a great need to optimize HCV treatment outcomes among patients with challenging medical, psychiatric and social comorbidities and with the advent of new, more complex treatment regimens, adherence support will become a critical component of HCV treatment programs. The initial phase of this trial provides considerable insight into mechanisms that are likely to bridge the health disparity gap and ensure optimal outcomes among a population that has traditionally been outside the HCV treatment purview.

Several limitations are apparent in this study. This initial report contains a small sample size of patients with considerable comorbidity and is drawn from one specialized treatment setting. Although the HCV treatment outcomes cannot be conclusive, several logistical and organizational obstacles that were identified during study initiation have important implications for future treatment of HCV-infected drug users. These findings also have important implications for health services delivery strategies where health services issues may more immediately impact access to treatment, while organization of services may impact adherence and retention. Such conclusions will need empiric testing within carefully conducted RCTs.

Conclusion

Hepatitis C treatment can be successfully integrated into a methadone maintenance clinic, and mDOT can be implemented with existing staff. Successful program development requires obtaining support from both the administrators of the program and the frontline medical, nursing, and counseling staff. The utilization of on-site clinical services for HCV treatment and adherence support with mDOT may assist patients with substance use and mental illness to successfully complete HCV treatment. With the advent of new, more complex treatment regimens, adherence support will become a critical component of HCV treatment programs. The exact importance of the location of services and adherence support remains a significant area for future investigation.

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Table 1

Demographics of HCV patients on methadone maintenance.

Demographic	mDOT	SAT
Number of subjects	12	9
Mean age (range) in years	40 (29–51)	43 (36–54)
Gender		
Female	7	3
Male	5	6
Race/ethnicity		
African-American	1	1
Hispanic	0	3
Caucasian	11	5
Mean (range) years of nonconsecutive opioid use	8 (1–25)	15 (3–37)
Mean (range) duration of current methadone maintenance (months)	140 (1–36)	149 (7–29)
Genotype		
1, 4	8	6
2, 3	4	3
Biopsy staging (only GT 1,4)		
2	4	4
3	2	0
4	2	2
HIV coinfection	3	3
Depressive disorders	8	5
Anxiety disorders	8	3
Diagnostic and Statistical Manual of Mental Disorders-IV criteria for alcohol abuse/dependence	4	2
Diagnostic and Statistical Manual of Mental Disorders-IV criteria for cocaine abuse/dependence	9	7
Positive cocaine urine toxicology in 30 days prior to study enrollment	3	4

Note: HCV, hepatitis C virus; GT, genotype; mDOT, modified directly observed therapy; SAT, self-administered therapy.

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Table 2

Virologic outcomes.

Subject	Age	Race	Gender	Arm	GT	Metavir	HIV	Baseline (IU/mL)	EVR viral load (IU/mL)	EoTR viral load (IU/mL)	SVR (IU/mL)
1	31	W	F	DOT	1	3	No	366,000	<43	<43	<43
2	38	W	M	DOT	1	3	No	696,000	<43	<43	<43
3	44	W	F	DOT	1	2	No	409,000	448,000 – Stopped treatment due to assault prior to this lab		
3[3]	47	W	F	DOT	1	2	No	253,541	<43	Pending	Pending
4	38	B	M	DOT	3	N/A	No	244,000	<43	<43	<43
5	41	W	F	DOT	1	2	No	164,000	<43	<43	12,745
6	51	W	F	DOT	2	N/A	Yes	29,501	<43	<43	_[1]
7	46	W	F	DOT	3	N/A	No	17,100	<43	<43	<43
8	46	W	M	DOT	1	1–2	Yes	1,350,000	322	<43	<43
9	29	W	F	DOT	1	3–4	No	859,264	<43	Pending	Pending
10	46	W	M	DOT	1	N/A	Yes	12,900,000	<43	<43	<43
11	41	W	F	DOT	1	2–3/4	No	13,500,000	15,116	Pending	Pending
12	48	W	M	DOT	3	N/A	No	301,904	<43	Pending	Pending
13	49	H	M	SOC	4	4	No	56,900	Never started due to mental health problems and missed appointments		
14	54	W	M	SOC	2	N/A	No	30,100,000	Never started due to homelessness		
15	38	W	F	SOC	1	2	No	521,000	<43	<43[2]	<43[2]
16	48	B	M	SOC	1	3–4	Yes	2,821,850	462,190	NR	NR
17	38	W	M	SOC	1	2	No	7,910,000	<43	<43	349,204
18	42	W	M	SOC	1	2	Yes	7,012,364	Never started due to missed appointments and incarceration		
19	36	H	F	SOC	3	N/A	No	154,000	<43 – Stopped treatment when jailed		
20	37	H	M	SOC	3	N/A	No	24,752	Refused SOC and wanted DOT		
21	48	W	F	SOC	1	1–2	Yes	180,251	Never started due to missed appointments		

Notes: W, white; B, black; H, hispanic; DOT, directly observed therapy; SOC, standard of care; EVR, early virologic response; EoTR, end of treatment response; GT, genotype; SVR, sustained virologic response; NR, nonresponder.

[1] Patient died of lung cancer prior to SVR draw.

[2] Patient completed 24 of 48 weeks of treatment. EoTR viral load was at 35 weeks; SVR was at 55 weeks posttreatment cessation.

[3] Patient retried with HCV treatment 3 years after initial trial and currently doing well.