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Hepatitis C identification and treatment in rural Pennsylvania, USA

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ABSTRACT

The opioid epidemic in the United States has led to increases in hepatitis C virus (HCV) infection especially in rural communities. It is recommended that persons who inject drugs undergo screening and treatment. We initiated HCV screening and treatment within a mostly rural area of Pennsylvania by targeting medicated-assisted treatment (MAT) facilities and community events.

Screening was conducted in 43 rural and 13 urban counties by a clinical team. At MAT facilities, the clinical team performed HCV screening between 4:30AM and 1:00PM using the OraQuick HCV test free of charge. Participants with a positive screen were linked to treatment.

In all, 3,051 screening tests were conducted among 2,995 unique participants, who were mostly white (2821, 94%) and from rural counties (2597, 87%). Participants were most frequently 25-to-34 years old (798, 27%). A total of 730 patients were HCV screen positive, 371 patients received an HCV RNA PCR test, and 272 were HCV RNA positive. Of them, 249 met with a healthcare provider, 102 initiated treatment, and 50 completed SVR testing, with 49 achieving SVR. Anti-HCV positivity was more frequent among MAT facility versus non-MAT patients (41% versus 5%) ($p < .001$). Non-MAT participants were more likely to begin treatment for HCV (91% [21/23] versus 30% [81/272]) and achieve SVR (71% versus 43%).

In HCV screening and treatment among high-risk patients, substantial numbers of participants were lost at every point of care between screening and follow-up testing. Specific screening, treatment, and follow-up strategies for persons in rural communities may be needed.

1. Introduction

Chronic infection with hepatitis C virus (HCV) can cause progression of liver disease leading to cirrhosis, hepatic decompensation, or hepatocellular carcinoma. (Baumert et al., 2017; Westbrook and Dusheiko, 2014) In the United States, the prevalence of adults who are positive for HCV antibodies is approximately 1.3%. (Gower et al., 2014) Baby Boomers (persons born between 1945 and 1965) have the highest prevalence of anti-HCV positivity and are an ongoing priority for screening and treatment initiation. (Smith et al., 2012) However, since the early 2000′s, the opioid epidemic in the U.S. has caused HCV prevalence to rise among young adults, women of childbearing years, and children. (Ly et al., 2017; Koneru et al., 2016; Suryaprasad et al., 2014; Zibbell et al., 2018) Given these changes, in early 2020 the U.S. Preventive Services Task Force (USTFPS) recommended HCV screening be done in all adults as well as in adolescents with risk factors such as injection drug use. (Owens et al., 2020; Chou et al., 2020)

Successful treatment for chronic HCV can halt or reverse fibrosis progression, decrease the risk of hepatocellular carcinoma, and reduce transmission. (Poynard et al., 2002; Morgan et al., 2013) Treatment of high-risk groups such as injection drug users is an important component of achieving the World Health Organization (WHO)'s goal of eliminating global hepatitis by 2030. (World Health Organization. Global Hepatitis Report, 2017) However, HCV screening and treatment efforts face several challenges depending on the local environment. For example, non-urban areas commonly have limited numbers of physicians, treatment facilities, and public transportation options. (Schranz et al., 2018) In the U.S., rural communities have been disproportionately affected by the opioid epidemic, where HCV infection is associated with injection of prescription opioids. (Schranz et al., 2018; Havens et al., 2013) In Pennsylvania, a largely rural state, the number of newly reported HCV infections among persons aged 15–34 years rose by more than 73% from 2003 to 2010. (Boktor et al., 2012)

The American Association for the Study of Liver Diseases (AASLD)

Abbreviations: AASLD, American Association for the Study of Liver Diseases; HCV, hepatitis C virus; IDSA, Infectious Diseases Society of America; LLOQ, lower limit of quantification; SVR, sustained virological response; ULN, upper limit of normal; USPSTF, United States Preventive Services Task Force.

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and Infectious Diseases Society of America (IDSA) recommend HCV screening and treatment in persons who inject drugs. (American Association for the Study of Liver Diseases and Infectious Diseases Society of America, 2020) High rates of sustained virologic responses (SVR) have been shown in individuals undergoing opioid agonist therapy, even in the presence of ongoing drug use. (Dore et al., 2016; Janjua et al., 2019; Grebely et al., 2018; Rosenthal et al., 2020; Macías et al., 2019) We initiated HCV screening and treatment within a mostly rural area of Pennsylvania. This was accomplished by moving screening and treatment options to medicated-assisted treatment (MAT) facilities and community events. The use of telemedicine was implemented and expanded throughout the course of the study. Telemedicine appointments enabled rural patients who lacked transportation to our medical office to access treatment.

2. Methods

2.1. Patients

To participate, individuals were required to be at least $\geq$ 18 years and volunteer for the HCV screening. Participants initiated screening at medicated assisted treatment (MAT) facilities (n = 36) or non-MAT facilities (e.g. community events) (n = 23). The participants in MAT facilities were seeking treatment for previous drug addiction, while most non-MAT participants did not identify with current or past drug addiction. Pregnant persons were excluded from participating. Before initiating any clinical screening, each person reviewed and signed a research consent after receiving education on HCV. Study was IRB approved and individual's safety and privacy were upheld during the study.

2.2. Screening

Between June 2017 and December 2019, screening was conducted in 43 rural and 13 urban counties. Initially, MAT facilities were selected by performing an internet search of advertised facilities within a 120-mile radius of DuBois, Pennsylvania. Facilities were contacted regarding their willingness to be part of an HCV screening and treatment effort. In some cases, the MAT facilities contacted the clinical team to request participation. MAT patients received advertising for HCV screening before facility visits.

The clinical team consisted of a physician, licensed practical nurse, and physician assistant. The licensed practical nurse served as a patient navigator to establish a support mechanism to preserve HCV treatment engagement. At participating MAT facilities, the clinical team performed HCV screening between 4:30AM and 1:00PM approximately 2–4 times per month. The testing times were selected due to dosing at MAT facilities, which started at promptly at 5:00AM. HCV-antibody reactivity was determined using the OraQuick Hepatitis C Test. Screening was provided free of charge.

While screening at MAT facilities, the clinical team set up booths for HCV screening at community events. Community events included YMCA initiatives, mental health fairs, and community festivals. These events were chosen for their availability to community members outside of the targeted population group of MAT patients.

Participants with a positive HCV antibody screen were given a list of providers for obtaining follow-up bloodwork and determination of HCV viral load.

2.3. Treatment

HCV RNA positive participants had the opportunity to seek treatment with TruCare Internal Medicine & Infectious Diseases (TruCare) or an HCV provider of their choice. For MAT patients, treatment was available at their MAT facilities, to which the clinical team would return.

For participants requesting treatment by TruCare, bloodwork (liver function and HCV viral load) was reviewed at the first visit, HCV education was provided, and follow-up bloodwork was ordered with more extensive tests. The follow-up blood work included HCV genotype, HCV-FibroSure, HIV screen, HBV serology, alpha-fetal protein, pro-time with international normalized ratio, complete blood count with differential, and comprehensive metabolic panel. An abdominal ultrasound was also ordered at their radiological location of choice. Once the second bloodwork panel was completed, the provider developed a treatment plan, reviewed the intended medication, ordered medication, and provided additional HCV education. The choice of medication, either Mavyret (glecaprevir/pibrentasvir) or Epclusa (sofosbuvir/velpatasvir), was dependent on patient's insurance preference.

After the patient received medication, the provider again reviewed medication directions. When the patient completed one-month of treatment, effectiveness was assessed via bloodwork for liver function and HCV viral load. The provider reviewed the laboratory findings with the patient, continued to encourage treatment, reviewed education, and answered all questions and concerns. Once treatment was completed, liver function and HCV viral load bloodwork was completed to assess treatment outcomes. Treatment outcomes were discussed with patients. Finally, 3-month post-cure labs were ordered. If patients did not initiate treatment or missed appointments, the patient navigator would follow-up and encourage treatment or continuing treatment regimen. Typically, patients who failed to continue care received three phone calls and a letter.

A TeleHep practice was established to offer online medical visits www.telehep.com Communication and virtual care were provided using the digital care platform known as Spruce, which is HIPAA compliant. The Spruce app was preloaded onto the cell phones and facility computers provided at each screening location. If the patient already had cellular phone access, the staff would assist in helping participants download the Spruce app onto their device.

2.4. Data collection and analysis

Participants provided demographic and risk-factor information. Risk factors assessed at the initial screening visit were drug abuse, high risk sexual behavior, health care worker, tattoo/piercing, and year of birth between 1945 and 1965. Participants who did not fully complete the demographic information were not excluded from the research study. Any participant with a positive screening was moved to the next phase of the data collection process. Persons with HCV negative screens were considered to have completed the research, but those who continued to engage in high-risk behaviors were allowed to undergo rescreening.

For each participant with a reactive screening, bloodwork, treatment, and outcomes were tracked. This data was accumulated for a quantitative quasi-experimental study using categorical variables assessing group correlations. A power analysis was performed on the sample size, and the alpha level of significance was set low ($p < .01$) to minimize Type I and Type II error. The analysis was performed on SPSS v26 software assessing frequencies and distributions via the Chi-Square Test.

3. Results

3.1. Patient population

A total of 3,051 screening tests were conducted among 2,995 unique participants. Most participants were white (2,821, 94%) and from rural counties (2,597, 87%) (Table 1). The age group most frequently represented was 25 to 34 year-olds (798, 27% of participants), followed by 35 to 44 year-olds (636, 21%). Of females who were HCV-antibody positive, 54% (n = 198) were between 18 and 34 years old. More than half (59%) of participants reported having two or more risk factors for HCV infection.

Table 1
Participant Demographics.

	Overall Population (n = 2,995)	HCV-Antibody Positive MAT Facilities (n = 653)	Non-MAT Facilities(n = 77)
Female, n (%)	1,701 (57)	338 (52)	28 (36)
Age, years, n (%)			
18–24	260 (9)	51 (8)	4 (5)
25–34	798 (27)	276 (42)	22 (29)
35–44	636 (21)	215 (33)	16 (21)
45–54	429 (14)	62 (10)	22 (29)
55–64	446 (15)	46 (7)	11 (14)
65+	425 (14)	3 (<1)	2 (3)
Unknown	1 (<1)	0	0
Race, n (%)			
White	2821 (94)	614 (94)	72 (94)
African American or Black	102 (3)	19 (3)	3 (4)
Other	72 (3)	20 (3)	2 (3)
Transportation problems, n (%)			
Yes	417 (14)	153 (23)	12 (16)
No	1949 (65)	288 (44)	49 (64)
Unknown	629 (21)	212 (33)	16 (21)
Pennsylvania counties, n (%)			
Urban	361 (12)	130 (20)	9 (12)
Rural	2597 (87)	516 (79)	68 (88)
Non-PA other	37 (1)	7 (1)	0
Number of risk factors, n (%)			
None	219 (7)	1 (<1)	2 (3)
One	1022 (34)	109 (17)	24 (31)
Two	1110 (37)	279 (43)	30 (39)
Three	505 (17)	198 (30)	15 (20)
Four	130 (4)	62 (10)	5 (7)
Five	9 (<1)	4 (1)	1 (1)

MAT, medication-assisted treatment; PA, Pennsylvania.

3.2. Screening and treatment

Participants in MAT facilities were more likely to be anti-HCV positive than those who were not (41% versus 5%), and the difference was statistically significant ($p < .001$) (Table 2). After screening, participants were lost in every step of the cascade of care, and the loss was more pronounced among MAT participants (Fig. 1). The reasons for this loss is ultimately unclear, as patients were repeatedly called and sent one letter urging them to seek care. Patients could have sought care elsewhere, moved away, changed their contact information, or failed to seek care altogether. The non-MAT participants (69%) were more likely to undergo follow-up blood work versus the MAT participants (48%) (Table 3). Among treated patients, HCV genotype 1 infection was most common (53%), and almost three quarters of patients (73%) had F0-F1 liver disease. Mavyret was more frequently prescribed than Epclusa (94% versus 6%). Non-MAT participants were more likely to begin treatment for HCV (91% versus 30%). In the population of treated patients, 48% achieved SVR12 (Tables 4 and Table 5). Non-MAT participants more frequently underwent SVR analysis (71% versus 43%) and achieved SVR (71% versus 42%) ($p = 0.021$) (Table 4).

One patient achieved viral suppression during treatment but did not reach SVR. The patient was a 66 year-old man with remote history of drug use and currently maintained on methadone. At baseline he was treatment naïve, had F1-F2 fibrosis, and HCV genotype 3a with high viral load (15.5 million IU/ml). Four weeks into treatment, HCV RNA was below the limit of detection. The patient denied missing any medication or recent drug use. At the end of treatment, HCV genotype 3a was confirmed, and viral load was 17 million IU/ml.

Table 2
Chi-square Analysis of HCV-Antibody Positive Rates.

		Facility Type			
HCV Antibody	n	MAT	Non-MAT	X^2	p
Reactive	730	653	77	510.72	<0.001
Non-reactive	2265	939	1326		

HCV, hepatitis C virus; MAT, medication-assisted treatment.

4. Discussion

HCV screening and treatment is recommended in persons who inject drugs. (American Association for the Study of Liver Diseases and Infectious Diseases Society of America, 2020) Prior studies have suggested high rates of SVR (>90%) can be achieved even in HCV patients with ongoing drug use. (Dore et al., 2016; Janjua et al., 2019; Grebely et al., 2018) In the recent ANCHOR study, among 100 patients with HCV and ongoing injection drug use, 82% achieved SVR. (Rosenthal et al., 2020) Response was not associated with opioid agonist therapy, on-treatment drug use, or imperfect daily adherence to HCV medication. In the HEPAVIR-DAA cohort, 79% of ongoing drug users achieved SVR12. (Macías et al., 2019) In the SIMPLIFY Phase 4 study, 100 of 103 (97%) of patients completed treatment. (Grebely et al., 2018) In our study, of 102 patients who initiated treatment, 50 underwent analysis for SVR, and all but 1 of them achieved SVR. Given the success of treatment in patients who returned for SVR analysis, it is likely that at least some patients who were lost to follow-up achieved SVR.

Differences in SVR rates may be due to a number of factors. In the multicenter SIMPLIFY study, countries represented included not only the U.S. but also Australia, Norway, Canada, Switzerland, the United Kingdom, and New Zealand. (Grebely et al., 2018) Outside of the U.S., HCV treatment is commonly linked with MAT, perhaps facilitating uptake and adherence. The ANCHOR study was exclusively in the U.S., but in contrast to our study in urban areas of Baltimore, Maryland and Washington D.C. (Rosenthal et al., 2020)

In our treatment efforts, offering mobile and telemedicine opportunities developed an easier and less time-consuming method for delivery of care. Telemedicine does have barriers to usage such as cost, reimbursement, and comfort with technology, (Zachrison et al., 2020; Scott Kruse et al., 2018) although younger adults frequently engage with mobile devices and may be more likely to be agreeable to mobile platforms. (Heron et al., 2019)

We believe that to screen and treat rural, high-risk individuals for hepatitis C, treatment must be delivered using a bundled approach. The bundle must include treatment of specific drug abuse, harm reduction including needle exchange, pre-exposure prophylaxis, and social and psychological support. In rural areas this is difficult due to transportation issues and financial burdens. Many patients can not afford a car and public transportation is very limited in the rural areas where patients live, which was assessed via demographic questions when HCV screening took place. Telemedicine appointments were offered to provide treatment to those who could not access transportation to the TruCare Office. It is possible bundling could be used to deny HCV treatment for individuals not visiting drug treatment centers. An additional strategy could be to have patient-physician contracts to stress the importance of completing medication and follow-up visits.

In this analysis, MAT patients were more frequently lost to follow-up than non-MAT patients (57% versus 29%). However, the percentage of non-MAT patients lost to follow-up after initiating treatment is relatively high compared with other real-world analyses of pangenotypic regimens. (Berg et al., 2019; Persico et al., 2019; Mangia et al., 2020) All but 2 non-MAT patients were partners of new patients at our infectious disease office who were offered free screening. Therefore, most of the non-MAT patients we treated for HCV likely had similar lifestyles and risk factors as the MAT patients. And they may have had similar challenges in undergoing follow-up treatment and testing visits.

There were some limitations to this study. First, the participant screening locations for the non-MAT facilities were chosen for

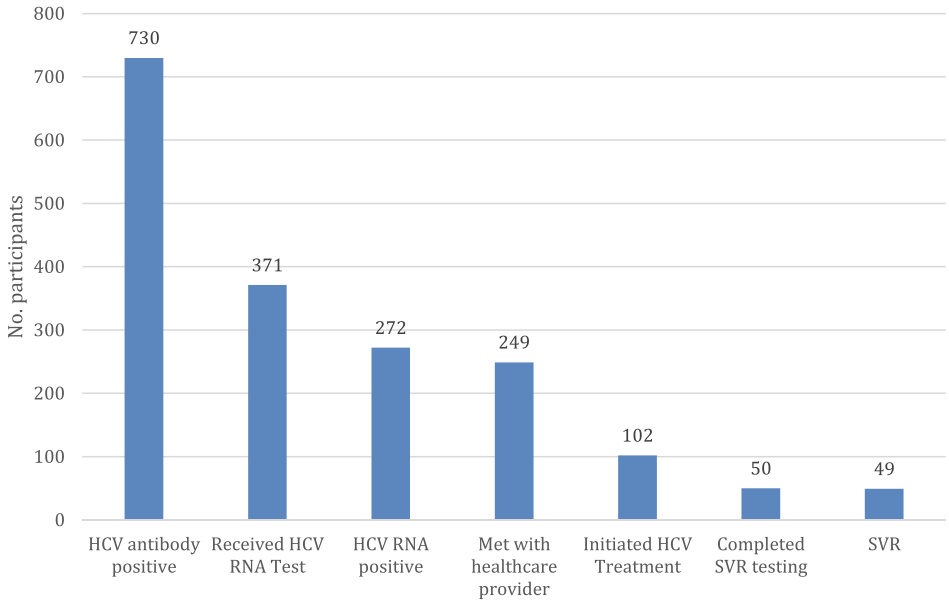

Fig. 1. Cascade of Care. HCV, hepatitis C virus; SVR, sustained virologic response.

Table 3
Total Participant Outcomes.

No. of Participants	Overall Population MAT Facilities(n = 1592)	Overall Population Non-MAT Facilities(n = 1403)	HCV Antibody Positive MAT Facilities(n = 653)	HCV Antibody Positive Non-MAT Facilities(n = 77)
Screened for HCV antibody	1592 (53)	1403 (47)	1592	1403
HCV-antibody positive	653 (22)	77 (2.6)	653 (41)	77 (5.5)
HCV RNA evaluated	318 (11)	53 (1.7)	318 (20)	53 (3.8)
HCV RNA positive	272 (9.1)	23 (<1)	272 (17)	23 (1.6)
Contact with healthcare provider	226 (7.5)	23 (<1)	226 (14)	23 (1.6)
Started HCV treatment	81 (2.7)	21 (<1)	81 (5)	21 (1.5)
SVR	34 (1.1)	15 (<1)	34 (1.5)	15 (1.1)
Lost to follow-up	46 (1.5)	6 (<1)	46 (2.9)	6 (<1)
Relapse	1 (<1)	0	1 (<1)	0

HCV, hepatitis C virus; MAT, medication assisted treatment; PCV, polymerase chain reaction; SVR, sustained virologic response

Table 4
Chi-square Analysis of Outcomes.

Outcome	n	Facility Type MAT	Non-MAT	X^2	p
SVR	48	35	15	5.31	0.021
Received all meds	46	21	6		
Relapse	1	1	0		

MAT, medication-assisted treatment; SVR, sustained virologic response.

convenience and may not have been indicative of the general population or served as an adequate comparator group. Next, the TeleHep platform was not initiated until mid-study. The mobile platform was not measured for increased engagement over the traditional healthcare delivery system.

In conclusion, in this initiative to screen and treat in a largely rural area of Pennsylvania, almost half of patients who initiated HCV treatment had documented SVR. An unknown number likely had SVR but were lost to follow-up. Substantial numbers of patients were lost at every step of the cascade of care, even in patients already engaged with MAT centers. Strategies specific to rural and/or high-risk individuals are needed to improve patient engagement with and continuation through HCV screening, treatment, and follow-up testing.

Table 5
Disease Characteristics and Virologic Outcomes of Participants Treated for Hepatitis C.

	n = 102
Age, mean years (range)	38 (23–69)
Sex, n (%)	
Male	59 (58)
Female	43 (42)
Current OST, n/N (%)	
Methadone	28/59 (47)
Suboxone	18/59 (31)
Subutex	3/59 (5)
Vivitrol	10/59 (17)
HCV genotype, n (%)	
1	54 (53)
2	13 (13)
3	35 (34)
Fibrosis stage, n/N (%)	
F0	61/101 (60)
F1	13/101 (13)
F2	15/101 (15)
F3	6/101 (6)
F4	6/101 (6)
Treatment, n (%)	
Mavyret	96 (94)
Epclusa	6 (6)
SVR, n/N (%)	
PP	49/50 (98)
ITT	49/102 (48)
Failure	1/102 (1)

HCV, hepatitis C virus; ITT, intention-to-treat; OST, opioid substitution therapy;
PP, per protocol; SVR, sustained virologic response.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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