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Integrated Hepatitis C–Opioid Use Disorder Care Through Facilitated Telemedicine
A Randomized Trial

Andrew H. Talal, MD, MPH; Marianthi Markatou, PhD; Anran Liu, MS; Ponni V. Perumalswami, MD, MS; Amreen M. Dinani, MD; Jonathan N. Tobin, PhD; Lawrence S. Brown, MD, MPH

IMPORTANCE Facilitated telemedicine may promote hepatitis C virus elimination by mitigating geographic and temporal barriers.

OBJECTIVE To compare sustained virologic responses for hepatitis C virus among persons with opioid use disorder treated through facilitated telemedicine integrated into opioid treatment programs compared with off-site hepatitis specialist referral.

DESIGN, SETTING, AND PARTICIPANTS Prospective, cluster randomized clinical trial using a stepped wedge design. Twelve programs throughout New York State included hepatitis C–infected participants (n = 602) enrolled between March 1, 2017, and February 29, 2020. Data were analyzed from December 1, 2022, through September 1, 2023.

INTERVENTION Hepatitis C treatment with direct-acting antivirals through comanagement with a hepatitis specialist either through facilitated telemedicine integrated into opioid treatment programs (n = 290) or standard-of-care off-site referral (n = 312).

MAIN OUTCOMES AND MEASURES The primary outcome was hepatitis C virus cure. Twelve programs began with off-site referral, and every 9 months, 4 randomly selected sites transitioned to facilitated telemedicine during 3 steps without participant crossover. Participants completed 2-year follow-up for reinfection assessment. Inclusion criteria required 6-month enrollment in opioid treatment and insurance coverage of hepatitis C medications. Generalized linear mixed-effects models were used to test for the intervention effect, adjusted for time, clustering, and effect modification in individual-based intention-to-treat analysis.

RESULTS Among 602 participants, 369 were male (61.3%); 296 (49.2%) were American Indian or Alaska Native, Asian, Black or African American, multiracial, or other (ie, no race category was selected, with race data collected according to the 5 standard National Institutes of Health categories); and 306 (50.8%) were White. The mean (SD) age of the enrolled participants in the telemedicine group was 47.1 (13.1) years; that of the referral group was 48.9 (12.8) years. In telemedicine, 268 of 290 participants (92.4%) initiated treatment compared with 126 of 312 participants (40.4%) in referral. Intention-to-treat cure percentages were 90.3% (262 of 290) in telemedicine and 39.4% (123 of 312) in referral, with an estimated logarithmic odds ratio of the study group effect of 2.9 (95% CI, 2.0-3.5; $P < .001$) with no effect modification. Observed cure percentages were 246 of 290 participants (84.8%) in telemedicine vs 106 of 312 participants (34.0%) in referral. Subgroup effects were not significant, including fibrosis stage, urban or rural participant residence location, or mental health (anxiety or depression) comorbid conditions. Illicit drug use decreased significantly (referral: 95% CI, 1.2-4.8; $P = .001$; telemedicine: 95% CI, 0.3-1.0; $P < .001$) among cured participants. Minimal reinfections (n = 13) occurred, with hepatitis C virus reinfection incidence of 2.5 per 100 person-years. Participants in both groups rated health care delivery satisfaction as high or very high.

CONCLUSIONS AND RELEVANCE Opioid treatment program–integrated facilitated telemedicine resulted in significantly higher hepatitis C virus cure rates compared with off-site referral, with high participant satisfaction. Illicit drug use declined significantly among cured participants with minimal reinfections.

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Author Affiliations: Author affiliations are listed at the end of this article.

Corresponding Author: Andrew H. Talal, MD, MPH, University at Buffalo, State University of New York, 875 Ellicott St, Ste 6090, Buffalo, NY 14203 (ahtalal@buffalo.edu).

Access to high-quality, convenient health care is a limited resource in the United States, especially for underserved populations.[1,2] Because of telemedicine's ability to transcend geographic and temporal boundaries for health care delivery, it may increase health care access.[3,4] For underserved populations, however, augmenting health care access through telemedicine poses technical and social challenges, such as limited access to digital technology, adequate broadband strength, and trust in technology.[5] Thus, novel approaches, such as facilitated telemedicine, in which a health care staff member facilitates in-person connectivity between a patient and an off-site clinician, are required to increase telemedicine entry points, especially for underserved populations.[6]

People with opioid use disorder are an underserved population largely because of societal stigma. Stigma and shunning frequently encountered in conventional medical settings result in restricted health care access, including for hepatitis C virus (HCV) infection.[7] Pooled HCV incidence is 12.1 per 100 person-years among people who inject drugs,[8] and restricted access to direct-acting antivirals (DAAs) is a leading public health issue. Because of highly efficacious DAAs, many jurisdictions seek HCV elimination by 2030,[9,10] which requires improving DAA access by people with opioid use disorder.[11] Opioid treatment programs (OTPs) are convenient, comfortable, and nonstigmatizing health care delivery sites that successfully integrate medical and behavioral treatment for opioid use disorder.[12-14] In a single-group, single-site study, HCV care through OTP-integrated facilitated telemedicine encounters integrated into OTPs resulted in high cure rates with high patient satisfaction.[15,16]

To assess OTP-integrated facilitated telemedicine's ability to increase HCV access to underserved populations, we evaluated the OTP-integrated facilitated telemedicine model among people with opioid use disorder. We designed a pragmatic clinical trial using the stepped wedge design to compare OTP-integrated facilitated telemedicine with usual care, off-site referral to hepatitis specialists.

Key Points

Question Among people receiving care in opioid treatment programs, does facilitated telemedicine for hepatitis C treatment increase cure rates compared with standard-of-care referral to hepatitis specialists?

Findings Cure percentages were 90.2% in telemedicine and 39.4% in referral, with an estimated logarithmic odds ratio of the study group effect of 2.9. Among cured participants, illicit drug use decreased significantly. We observed minimal reinfections during 2 years of follow-up.

Meaning Facilitated telemedicine integrated into opioid treatment programs resulted in significantly higher cure rates, with significant reductions in illicit drug use and minimal reinfections; facilitated telemedicine increases hepatitis C treatment access for underserved populations.

Methods

Study Description

We conducted a multisite, nonblinded, pragmatic clinical trial at 12 OTPs throughout New York State (study details, including stepped wedge design rationale, are presented elsewhere[17]; Supplements 2, 3, and 4). Study recruitment commenced on March 1, 2017, and concluded on February 29, 2020. Participants with sustained virologic response (SVR) received 2-year follow-up for HCV reinfection assessment.

Study Sites, Site Recruitment, and Regulatory Approval

The New York State Office of Addiction Services and Supports oversees opioid use disorder treatment in New York. The office's collaboration was instrumental in site recruitment and providing cluster-level demographic data for the randomization. For study participation, we required a minimum of 50 HCV-seropositive patients per site. We obtained coordinating and subsite institutional review board approval. Participants provided written informed consent to study case managers before enrollment. This study followed the CONSORT guidelines for reporting stepped wedge cluster randomized trials.

Study Design, Randomization, and Sample Size

In the cross-sectional stepped wedge design, study group assignment was conducted at the cluster level, and we used covariate-constrained randomization (eAppendix 1 in Supplement 1).[17-20] The final randomization was kept confidential, and we notified sites 30 days before commencing OTP-integrated facilitated telemedicine. We conducted the study during 3 separate steps with 4 periods consisting of 9 months each, and each step consisted of 4 clusters (**Figure 1**). Thirteen participants were enrolled per site per period without participant crossover, and we performed the analysis according to the allocated schedule. The projected sample was 624 participants, 312 per group, resulting in 12 clusters.[17] We recruited 602 participants (recruitment rate = 96.5%), 312 in referral and 290 in OTP-integrated facilitated telemedicine. Selection bias is discussed in eAppendix 5 in Supplement 1.

Study Conduct

Consistent with the Office of Addiction Services and Supports recommendations, each site measured HCV antibodies annually. Each site provided lists of HCV-seropositive and, in some cases, HCV RNA–positive individuals. Study case managers had experience working in the health care sector, particularly with people with opioid use disorder. They worked closely with OTP staff, especially counselors, to identify eligible participants and to address potential retention obstacles.[21] Study inclusion criteria required 6-month active OTP enrollment, detectable HCV RNA, aged 18 years or older, and insurance coverage of DAAs. Exclusion criteria were HCV seronegativity, DAA treatment at screening, and HIV-seropositive individuals not receiving stable antiretroviral therapy because of adherence concerns. Decompensated individuals with cirrhosis could participate. During the screening visit, we assessed HCV RNA, HCV genotype, hepatitis panel, complete blood cell count, complete metabolic panel, prothrombin time, and HIV status.

Usual Care and OTP-Integrated Facilitated Telemedicine

Participants in usual care received an off-site hepatitis specialist (ie, hepatologist, infectious diseases physician, or primary care physician) referral following the standard of care at each site. Participants provided permission for study case managers to obtain medical records from the hepatitis specialist to determine referral outcomes, including whether (and when) HCV treatment was initiated, when it was completed, and treatment outcome. After referral, case managers inquired monthly with participants and the referring clinicians' offices to assess referral outcomes. In OTP-integrated facilitated telemedicine, participants had an initial telemedicine encounter facilitated by study case managers on-site in the OTP. Blood for testing was obtained by venipuncture according to local procedures. The telemedicine clinician subsequently evaluated participants, ordering DAAs electronically that were delivered to the OTP monthly (as refills required) and dispensing them with methadone. The OTPs dispensed take-home DAA doses for participant self-medication on days when the participant did not appear in person in the OTP. Telemedicine clinicians consisted of 2 gastroenterologist-hepatologists (A.H.T. and A.M.D.) and a nurse practitioner who had HCV treatment experience. These clinicians individualized treatment of patients with cirrhosis. In both groups, HCV RNA levels were assessed at treatment completion and at weeks 4 and 12 (ie, SVR assessment) posttreatment.

Study Outcomes

The primary outcome was SVR (ie, undetectable HCV RNA 12 weeks after treatment cessation). Predefined secondary outcomes included a comparison of treatment initiation and completion rates, participant satisfaction with health care delivery, and treatment adherence rates between groups. Hepatitis C virus reinfection was an exploratory outcome.

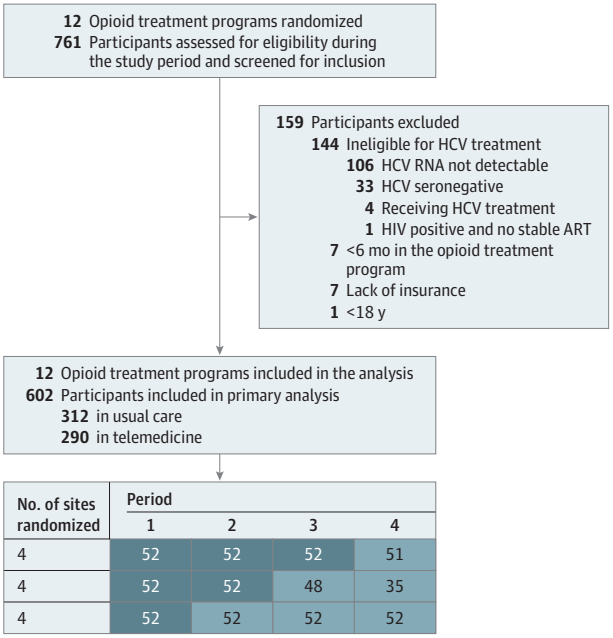
After extensive stakeholder (ie, patients, sponsor, study patient advisory committee, and frontline OTP staff) discussion, we prespecified that participants without an initial hepatitis specialist visit within 5 months of enrollment would cease trial participation.[22-24] A recent study reported that 75% of Medicaid-insured individuals who initiated DAAs did so within 6 months of an initial HCV diagnosis.[25] Furthermore, in chronic HCV infection, spontaneous resolution occurs at 0.36% per person-year of follow-up, an extremely rare event.[26] All other participants initiated treatment.

Missing Data

In designing this study, we implemented strategies[17] to minimize missing data.[27] Despite these strategies, missing data still occurred (eAppendix 2 in Supplement 1). The trial dropout rate was 243 of 602 participants (40.4% overall), 204 of 312 (65.4%) in referral and 39 of 290 (13.4%) in OTP-integrated facilitated telemedicine, calculated with the number of participants without SVR assessments. We illustrate reasons for premature participant discontinuation in eTable 1 in Supplement 1. We assumed that the missing mechanism was missing at random; to handle missing data, we used multivariate imputation by chained equations,[28] which was permitted by a sufficiently low estimated intraclass correlation coefficient of 0.099 obtained through ICCbin (Monte Carlo method) in R version 4.1.1 (R Foundation for Statistical Computing).[29]

We illustrate details and variable justification for construction of the imputation model and variables with missing data in eAppendix 2.1 in Supplement 1. We performed analysis with 20 imputed data sets and summarized the results using Rubin rules for combining estimates and SEs (eTables 2 and 3 and eFigure 2 in Supplement 1). We enumerate participant deaths in eTable 4 in Supplement 1 and associated analytic issues in eAppendix 2.2 in Supplement 1. Deaths were treated as missing at random.[30-33]

Figure 1. Recruitment, Randomization, and Patient Follow-Up in the Stepped Wedge Cluster Randomized Opioid Treatment Program–Integrated Facilitated Telemedicine Trial



No. of sites randomized	Period			
	1	2	3	4
4	52	52	52	51
4	52	52	48	35
4	52	52	52	52

The number of sites randomized and individuals analyzed per period is illustrated at the bottom of the figure. Usual care is shown in dark shading and opioid treatment program–integrated facilitated telemedicine is shown in light shading. ART indicates antiretroviral therapy; HCV, hepatitis C virus.

Statistical Analysis

Analyses were individual-based intention to treat using generalized linear mixed models.[34] They were also cluster level, within period, robust, and nonparametric.[35] Data were analyzed from December 1, 2022, through September 1, 2023.

Factors Associated With SVR

We used covariates such as age, race, sex, and ethnicity in the covariate-constrained randomization.[17] These covariates are no longer SVR predictors because DAAs are highly efficacious.[36] Therefore, although we are expected to adjust the generalized linear mixed models for randomization covariates, given that the covariates themselves are not SVR predictors and may create very small strata, their inclusion in the model is not recommended.[37]

Modeling

The primary outcome was binary; SVR rates between the 2 groups in which SVR = 1 indicated HCV cure and SVR = 0 indicated treatment nonresponse.

We used generalized linear mixed models,[34] adjusted for confounding by calendar time incorporated as a categorical variable. The model accounted for clustering by incorporating a random site effect. This model assumed that the effects of time were common to all clusters, and the correlation between any 2 observations in the same cluster was the same and independent of the time step.

To account for effect modification, we incorporated a time by intervention interaction effect (eAppendix 4 in Supplement 1). eAppendix 3.1 in Supplement 1 presents a nonparametric, cluster-level, robust, within-period analysis to estimate the intervention effect that avoids the generalized linear mixed models assumptions.[35]

Subgroup Analysis

A priori subgroups of interest included comorbid medical and mental health conditions (specifically depression or anxiety), fibrosis stage (binary [F3, F3-F4, or F4] vs all other stages),[38] and participants' residence location (specifically urban or rural classification: US Department of Agriculture Economic Research Service rural-urban commuting area codes). Furthermore, we examined subgroups defined by sex, ethnicity, location, and race.[39,40] These analyses were exploratory, and we used generalized linear mixed models with unadjusted 2-sided $P = .05$.

Adherence Analysis

We defined adherence as the percentage of participants who took greater than or equal to 90% (high) vs less than 90% (low) of prescribed DAAs.[41] We assessed HCV medication adherence through participant self-report of missed DAA doses in the preceding 2 weeks.

Effects of COVID-19

We followed the CONSERVE statement for reporting the impact of COVID-19.[42] COVID-19 restrictions had minimal effects on the study because recruitment had concluded and all sites had already transferred to the OTP-integrated facilitated telemedicine group. The cessation of in-person visits, however, necessitated shifts in data collection methods (ie, through telephone) and intervention delivery. Protocol modifications were approved by the study sponsor. Therefore, no model adjustments were needed, as explained elsewhere.[17]

Exploratory Analysis

We evaluated variable distribution by using graphic analysis and descriptive statistics. Continuous variables are presented by either their means and SDs or medians and IQRs. We present categorical variables as counts and percentages. We performed statistical analyses with SAS 9.4 with add-on analytic products of SAS/STAT 15.2 (SAS Institute) and R version 4.1.1 (R Packages, RStudio; R Foundation for Statistical Computing) as appropriate.

Computing Incidence Density

We followed up cured participants for up to 2 years with HCV RNA determinations every 6 months to assess for reinfection, defined as recurrent viremia after obtaining an SVR. We computed the incidence density (ie, number of reinfections during person-years of follow-up) among SVR participants.

Results

Cluster Recruitment and Randomization

We approached and recruited 12 OTPs. All 12 OTPs began and completed the trial. Further details are provided elsewhere[17] and in eAppendix 5 in Supplement 1.

Baseline Characteristics

We screened 761 individuals for study eligibility, and 159 (20.9%) were excluded (Figure 1) because of lacking insurance, participating fewer than 6 months in the OTP, being younger than 18 years, and having HCV treatment ineligibility. We enrolled 602 individuals, 312 (51.8%) in referral and 290 (48.2%) in OTP-integrated facilitated telemedicine. Baseline characteristics were well balanced between both groups (**Table 1**; eFigures 1, 3, and 4 in Supplement 1). The mean (SD) age of the enrolled participants in the telemedicine group was 47.1 (13.1) years; that of the referral group was 48.9 (12.8) years. A total of 369 participants were male (61.3%) and 233 were female (38.7%), approximately equally balanced between White (306 [50.8%]) and non-White (296 [49.2%]) races. A total of 164 participants (27.2%) were American Indian or Alaska Native, Asian, multiracial, or other (ie, no race category was selected); 132 (21.9%) were Black or African American; and 185 were Hispanic or Latino/a. Race data were collected according to the 5 standard National Institutes of Health categories. A total of 138 participants (22.9%) had cirrhosis.

HCV Treatment Cascade

Of 312 referral participants, 297 (95.2%) obtained an initial visit with the study case manager, and 126 (40.4%) initiated DAAs (**Table 2**). Direct-acting antivirals, as prescribed, are shown in eTable 5 in Supplement 1. Of these participants, 116 completed treatment and 108 had an SVR assessment, of whom 106 (30.4%) achieved an SVR and 2 had detectable virus. Of 290 participants in the OTP-integrated facilitated telemedicine group, 280 (96.6%) completed an initial visit and 268 (92.4%) initiated HCV treatment. Of these participants, 261 completed treatment and 251 had an SVR assessment, 246 (84.8%) with undetectable virus and 5 with detectable virus. The SVR assessments were performed at the appropriate visit in 249 of 251 (99.2%) OTP-integrated facilitated telemedicine visits compared with 66 of 108 (61.1%) referral visits.

Among participants who initiated therapy, the observed SVR rate was similar between the groups (246 of 268 [91.8%] in OTP-integrated facilitated telemedicine vs 106 of 126 [84.1%] in referral). Among participants with SVR determination, detectable HCV RNA occurred at a comparable frequency between the 2 groups (5 of 251 [2.0%] in OTP-integrated facilitated telemedicine vs 2 of 108 [1.9%] in referral).

Table 1. Baseline Characteristics of Study Participants Comparing Opioid Treatment Program–Integrated Facilitated Telemedicine With Off-Site Referral

Demographics	No. (%) Telemedicine (n = 290)	Referral (n = 312)
Age at consent, y		
Mean (SD)	47.1 (13.1)	48.9 (12.8)
Median (IQR)	46.0 (36.3-58.0)	50.0 (37.8-60.0)
Sex		
Female	115 (39.7)	118 (37.8)
Male	175 (60.3)	194 (62.2)
Hispanic or Latino/a	89 (30.7)	96 (30.8)
Race[a]		
Black or African American	49 (16.9)	83 (26.6)
White	155 (53.4)	151 (48.4)
Other	86 (29.7)	78 (25.0)
Geographic location		
Urban	245 (84.5)	267 (85.6)
Comorbid condition		
Anxiety or depression	90 (31.0)	79 (25.3)
Other comorbid conditions besides anxiety or depression[b]	88 (30.3)	91 (29.2)
No comorbid condition or unsure	112 (38.6)	142 (45.5)
HIV	6 (2.1)	18 (5.8)
DAST-10 score at screening visit[c]		
Mean (SD)	4.8 (3.1)	4.5 (3.2)
Median (IQR)	5 (2-8)	4 (1-7)
Virology and fibrosis variables		
HCV RNA (10 log IU/mL)		
Mean (SD)	5.9 (1.0)	5.9 (0.9)
Median (IQR)	6.0 (5.5-6.6)	6.1 (5.4-6.6)
HCV genotype[d]		
1	2 (0.7)	4 (1.3)
1a	172 (59.3)	193 (61.9)
1b	28 (9.7)	38 (12.2)
2	4 (1.4)	0
2a	2 (0.7)	0
2b	18 (6.2)	18 (5.8)
3	27 (9.3)	22 (7.1)
3a	22 (7.6)	17 (5.4)
4	5 (1.7)	1 (0.3)
4a	0	4 (1.3)
HIV	6 (2.1)	18 (5.8)
Fibrosis (APRI category)[e]		
0-1, No fibrosis or mild fibrosis	155 (53.4)	145 (46.5)
2, Moderate fibrosis	44 (15.2)	60 (19.2)
3, Advanced fibrosis	29 (10.0)	31 (9.9)
4, Cirrhosis	62 (21.4)	76 (24.4)
Adherence variables		
No. of months in methadone program[f]		
Mean (SD)	52.2 (72.4)	57.6 (62.1)
Median (IQR)	20 (11-65)	32 (13-83)
NIDA Quick Screen		
Answers per question		
In the past year, how often have you used prescription drugs for nonmedical reasons?		
Daily or almost daily	15 (5.2)	12 (3.8)
Weekly	12 (4.1)	9 (2.9)
Monthly	10 (3.4)	17 (5.4)
Once or twice	53 (18.3)	40 (12.8)
Never	193 (66.6)	220 (70.5)
In the past year, how often have you used illicit drugs?[g]		
Daily or almost daily	46 (15.9)	37 (11.9)
Weekly	45 (15.5)	42 (13.5)
Monthly	51 (17.6)	39 (12.5)
Once or twice	38 (13.1)	57 (18.3)
Never	103 (35.5)	123 (39.4)

Abbreviations: APRI, AST to platelet ratio index; DAST-10, Drug Abuse Screening Test; HCV, hepatitis C virus; NIDA, National Institute on Drug Abuse.

[a] Race data were collected according to the 5 standard National Institutes of Health categories.[43] Other races include American Indian or Alaska Native, Asian, multiracial, and other (ie, no race category was selected).

[b] Other comorbid conditions besides anxiety and depression include cardiac, gastrointestinal and liver, pulmonary, rheumatologic, diabetes and endocrine, kidney, cancer, and psychiatric disorders. Comorbid conditions were assessed by case manager review of the medical record.

[c] The score variable for DAST-10 is calculated as the total number of yes responses (which receive 1 point each), except for 1 question for which no receives 1 point. The DAST-10 score ranges from 0 to 10, and a score from 3 to 5 represents a moderate degree of problems related to drug abuse. The DAST-10 questionnaire covers the use of prescribed or over-the-counter medications and drugs in excess of the directions and any nonmedical use of drugs, including cannabis, solvents, tranquilizers, barbiturates, cocaine, stimulants, hallucinogens, and narcotics.[44]

[d] Hepatitis C virus genotype was assessed with reverse transcriptase–polymerase chain reaction and the INNO-LiPA HCV genotype 2.0 DNA line probe assay (Siemens). Hepatitis C virus genotype analysis is based on the DNA sequence of the core and the 5′ UTR of the HCV genome and categorizes the virus into distinct types (eg, 1-6) and subtypes (ie, a, b, c).

[e] The APRI was assessed as follows according to Raab et al[38]: APRI value stage interpretation: less than 0.5, F0 to F1 indicates no or mild fibrosis; 0.5 to less than 0.7, F2 indicates moderate fibrosis; 0.7 to 1.0, F3 indicates advanced fibrosis; and greater than 1.0, F4 indicates cirrhosis.

[f] A total of 292 of 312 participants in referral (93.6%) and 279 of 290 participants in telemedicine (96.2%) appeared daily in person for methadone dispensing. The remainder of participants adhered to a schedule requiring weekly or monthly in-person appearance in the opioid treatment program to receive methadone.

[g] Illicit drug use was assessed by a question on the NIDA Quick Screen questionnaire.[45]

Models Adjusted for Time, Clustering Effect, and Effect Modification

We analyzed the data according to the intended randomization schedule. The estimated intraclass correlation coefficient was 0.099 (95% CI, 0-0.2). The intention-to-treat analysis used data

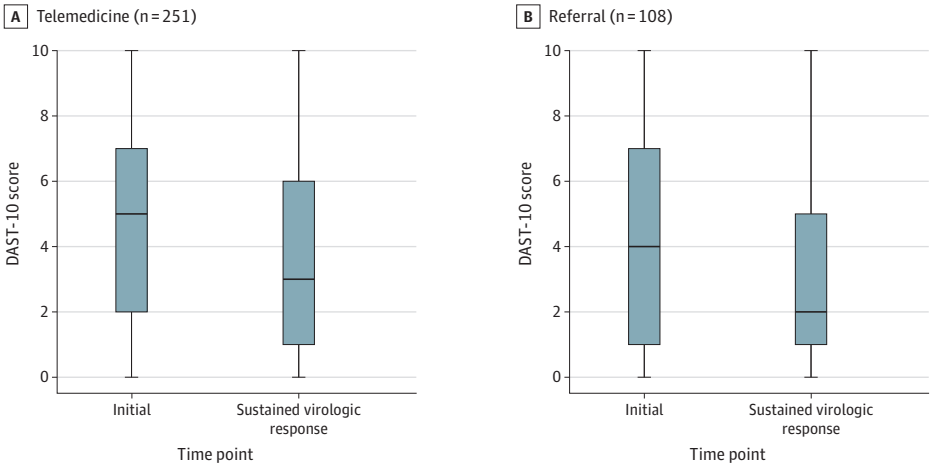
Table 2. Hepatitis C Virus Care Cascade

	No. (%)		
	OTP-integrated facilitated telemedicine (n = 290)	Referral (n = 312)	Log odds estimate (95% CI)
Visit 1[a]	280 (96.6)	297 (95.2)	0.1 (−0.8 to 1.0)
Treatment initiation	268 (92.4)	126 (40.4)	2.8 (2.3 to 3.3)
Treatment completion	261 (90.0)	116 (37.2)	2.7 (2.2 to 3.1)
Sustained virologic response assessed	251 (86.6)	108 (34.6)	2.4 (2.0 to 2.9)
Observed sustained virologic response	246 (84.8)	106 (34.0)	2.3 (1.9 to 2.7)

Abbreviation: OTP, opioid treatment program.

[a] The percentage of study participants in both groups who attended the initial visit with the case manager to provide blood for testing for the initial telemedicine encounter or to obtain a referral to an off-site hepatitis C virus clinician. The log odds estimates and associated 95% CIs for comparing the proportions in the 2 groups were obtained by fitting a linear mixed model incorporating the study group effect and a random effect to account for clustering.

Figure 2. Distributions of Scores Obtained From the Drug Abuse Screening Test (DAST-10) at the Initial and Sustained Virologic Response Visits



The Tukey boxplot illustrates a significant decline in DAST-10 scores in individuals cured of hepatitis C virus infection in facilitated telemedicine ($P < .001$) and referral ($P = .001$). The box extends from the 25th to the 75th percentile, with the line in the middle of the box depicting the median. The lines extending from the top and bottom of the box depict the upper and lower values. For information on the components and scoring of the DAST-10, see the footnote in Table 1.

from 602 participants, with missing values imputed as described. The overall SVR percentages were 262 of 290 (90.3%) in the OTP-integrated facilitated telemedicine group compared with 123 of 312 (39.4%) in the referral group. The estimate of the logarithmic odds ratio of the time-averaged intervention effect, obtained from combining the results of the 20 imputed data sets, was 2.9 (95% CI, 2.0-3.5; $P < .001$) using generalized linear mixed models as described in the Modeling section.

When the model accounted for effect modification using time as a continuous variable, the intervention effect estimate was still significant (2.8; 95% CI, 0.8-4.8; $P = .004$). The interaction coefficient was −0.002 (95% CI, -0.64 to 0.64; $P = 0.5$), indicating no effect modification.

Timing of Treatment Uptake

The time between screening and initial appointments was significantly shorter in OTP-integrated facilitated telemedicine (referral median, 18 days [IQR, 7-35 days]; OTP-integrated facilitated telemedicine median, 14 days [IQR, 7-26 days]; test statistic = 2.1; $P = .04$).[46] Similarly, the duration between the initial visit and DAA initiation was significantly shorter in OTP-integrated facilitated telemedicine (referral mean [SD], 123.5 [92.4] days; OTP-integrated facilitated telemedicine mean [SD], 49.9 [48.1] days; test statistic = 3.85; $P < .001$).[47]

Substance Use

At baseline, the mean (SD) response score for the Drug Abuse Screening Test was 4.45 (3.23) and 4.82 (3.10) in the referral and OTP-integrated facilitated telemedicine groups, respectively, in which a score between 3 and 5 represents moderate problems with drug abuse.[44] At the SVR time point, the Drug Abuse Screening Test score decreased significantly among HCV-cured participants in referral, with a median at the initial time point of 4 (IQR, 1-7) and 2 (IQR, 1-5; $P = .001$ for both) and a median of 5 (IQR, 2-7) and 3 (IQR, 1-6; $P < .001$ for both) in OTP-integrated facilitated telemedicine, respectively (**Figure 2**).[47]

HCV Adherence

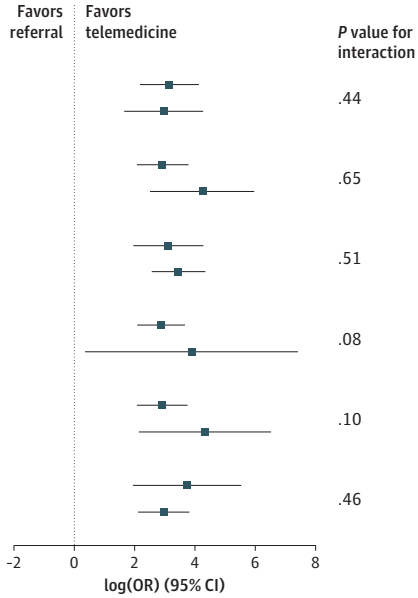
We observed very high DAA adherence. Among participants with non-SVR in the OTP-integrated facilitated telemedicine group, 4 of 5 (80%) had 90% adherence at treatment weeks 6 and 12 (eTable 6 in Supplement 1). We observed no differences in methadone doses between study groups (eFigure 5 in Supplement 1) or when stratified by participants with a treatment start date, treatment end date, or SVR (eFigure 6 in Supplement 1).

Subgroup Analysis

The effects of the intervention on the primary outcome were examined in prespecified subgroups (fibrosis stage, comorbid medical conditions, residence, sex, race, and ethnicity)

Figure 3. Hepatitis C Virus Cure Subgroup Analysis

Subgroup	SVR rate = (No. of participants with SVR = 1)/(No. of participants)		Time-adjusted log(OR) (95% CI)	*P* value for interaction
	Telemedicine (%)	Referral (%)		
Sex				
Male	160/175 (91.4)	77/194 (39.7)	3.16 (2.18-4.13)	.44
Female	103/115 (89.6)	33/118 (28.0)	2.98 (1.66-4.29)	
Ethnicity				
Non-Hispanic or Latino/a	185/201 (92.0)	86/216 (39.8)	2.93 (2.07-3.79)	.65
Hispanic or Latino/a	78/89 (87.6)	24/96 (25.0)	4.25 (2.51-5.98)	
Race				
Other[a]	120/135 (88.9)	57/161 (35.4)	3.12 (1.96-4.29)	.51
White	143/155 (92.3)	53/151 (35.1)	3.46 (2.56-4.35)	
Geographic location				
Urban	219/245 (89.4)	97/267 (36.3)	2.88 (2.09-3.67)	.08
Rural	44/45 (97.8)	13/45 (28.9)	3.89 (0.36-7.43)[b]	
Comorbid conditions				
Other or no comorbid condition	176/200 (88.0)	80/233 (34.3)	2.92 (2.08-3.76)	.10
Anxiety or depression	87/90 (96.7)	30/79 (38.0)	4.34 (2.15-6.54)	
Fibrosis score				
F3-F4 (advanced fibrosis or cirrhosis)	83/91 (91.2)	34/107 (31.8)	3.75 (1.95-5.55)	.46
F0-F2 (no fibrosis, mild or moderate fibrosis)	180/199 (90.5)	76/205 (37.1)	2.98 (2.12-3.83)	



Dot and whisker plot of time-adjusted log(OR) with associated 95% CIs for various subgroups of interest. The level of α = .05 (2-tailed), and no adjustments for multiplicity were made. OR indicates odds ratio; SVR, sustained virologic response.

[a] Race data were collected according to the 5 standard National Institutes of Health categories.[43] Other races include American Indian or Alaska Native, Asian, multiracial, and other (ie, no race category was selected).

[b] A normal distribution prior was used and the results were obtained with the blme R package, which encodes bayesian methods for fitting linear mixed models; priors were used for the model parameters.

(**Figure 3**). We present the time-adjusted effects (log odds) for the subgroups of interest and their 95% CIs. All results favored the intervention. We consider these analyses exploratory owing to lack of adjustment for multiplicity of testing. However, only 2 of 28 Hispanic female participants in referral achieved an SVR compared with 23 of 26 participants in OTP-integrated facilitated telemedicine (eAppendix 6 and eTable 7 in Supplement 1). These findings do not appear to be due to English proficiency (eTable 8 in Supplement 1). Similar results (ie, favoring OTP-integrated facilitated telemedicine) were observed among rural participants (eFigure 7 in Supplement 1).

Follow-Up Data

We observed 3 reinfections in referral, with a total follow-up of 162.0 person-years. In OTP-integrated facilitated telemedicine, we noted 10 reinfections, with a total follow-up of 365.2 person-years. The overall incidence density rate was 2.5 per 100 person-years of follow-up, with rates of 2.7 reinfections per 100 person-years of follow-up in OTP-integrated facilitated telemedicine and 1.9 in referral. No significant differences existed between the 2 study groups in the number of reinfections (eAppendix 7 in Supplement 1).

COVID-19 Effects on the Study

COVID-19 pandemic lockdowns resulted in an increase in methadone and DAA take-home doses. Although no significant DAA interruptions or discontinuations occurred among participants who had initiated treatment before the COVID-19 lockdowns, treatment initiation was delayed for 13 participants, and SVR assessment was also delayed.

Discussion

In this pragmatic trial, 262 of 290 participants (90.3%) in the OTP-integrated facilitated telemedicine group achieved an SVR compared with 123 of 312 participants (39.4%) in referral. These participants also initiated DAAs significantly more expeditiously. Our patient population consisted of similar numbers of White and non-White races, one-third were Hispanic, one-third had anxiety or depression, and a quarter had cirrhosis. Illicit drug use decreased significantly for cured participants in both groups. An SVR was durable, with minimal reinfections occurring during the 2-year follow-up period. No significant differences between groups were identified in terms of anxiety or depression, fibrosis score, urban or rural residence, or demographics.

Our study has several desirous attributes for well-designed pragmatic clinical trials,[48] including intervention implementation in routine clinical settings with usual staff and workflows. Our study sites routinely provide opioid use disorder treatment to a population with high HCV prevalence and incidence. Study case managers were fully integrated into OTP workflows and OTP-integrated facilitated telemedicine encounters, and they educated and communicated with study participants.[21,49] Furthermore, research conduct in comfortable and destigmatizing OTPs facilitated trial performance be-

cause people with opioid use disorder often encounter stigma and shunning in conventional health care settings.[50-52] Additionally, our primary outcome, SVR, is meaningful to patients, clinicians, and payers.[53]

Participants were highly satisfied with health care delivery through OTP-integrated facilitated telemedicine, equivalent to in-person encounters, with clinician empathetic characteristics rated higher than logistic attributes such as accessibility and convenience.[54] Our qualitative data suggest that an HCV cure fosters self-confidence, promoting overall well-being.[52] Our observation of significant decreases in illicit drug use among HCV-cured participants is consistent with prior studies that showed improved HCV and opioid use disorder treatment outcomes with simultaneous treatment of both entities.[55-59] Although desired, physical integration of medical and behavioral therapy has been difficult to achieve[60,61]; OTP-integrated facilitated telemedicine appears to integrate HCV and opioid use disorder care with improved convenience, accessibility, and flexibility. Situating telemedicine encounters in OTPs mitigated potential broadband access issues and introduced new telemedicine access points.[3]

Through OTP-integrated facilitated telemedicine, we observed that a high percentage of Hispanic women achieved an SVR. Hispanic individuals have lower DAA treatment initiation rates owing to mistrust of health care clinicians, incarceration, homelessness, lack of insurance, cultural and linguistic barriers, and fear of deportation.[62-64] Stabilization of opioid use disorder through methadone treatment with HCV care via OTP-integrated facilitated telemedicine may have satisfactorily addressed obstacles encountered by Hispanic women in other health care settings. Similarly, we observed that rural inhabitants achieved a higher SVR percentage than urban individuals. These findings should be interpreted cautiously because of the small sample sizes and noncorrection for multiple comparisons (eg, urban or rural). Sufficiently powered clinical trials are warranted to address the effectiveness of OTP-integrated facilitated telemedicine in these populations.[4,6] The COVID-19 pandemic delayed HCV treatment initiation and SVR assessments for a few participants, although it did not affect recruitment, which was completed 2 weeks before the lockdowns.

Although participating OTPs had minimal prior research experience, they successfully completed a pragmatic clinical trial using a rigorous design. To increase clinical transferability, we required insurance coverage of DAAs. We enrolled 602 of 624 projected participants (96.5%) and fully enrolled the usual care group. We sought to minimize bias by notifying sites only 1 month before telemedicine initiation.

Limitations

In terms of limitations, although our sites represent almost all New York State metropolitan areas, New York methadone reimbursement practices are more generous compared with those of other states, and we had a relatively low number of participating OTPs. Additionally, methadone treatment requires a more frequent in-person appearance than other substance use treatment approaches, including buprenorphine. Our inclusion criteria required 6 months of active OTP enrollment because prior data suggest that approximately 50% of patients admitted to an OTP will discontinue within the first 3 months.[65] Future investigations should address transferability of OTP-integrated facilitated telemedicine, as well as the role of socioeconomic factors, and include more recent entrants to substance use treatment. Future study designs might also not require SVR assessments because DAAs are so efficacious.

Conclusions

In conclusion, OTP-integrated facilitated telemedicine resulted in substantially higher SVR rates than off-site referral. Our intervention successfully builds patient-clinician trust across the screen, and significant decreases in substance use were observed in cured participants with minimal HCV reinfections. Opioid treatment program–integrated facilitated telemedicine promotes increased access and integrates HCV treatment into venues that offer opioid use disorder treatment.[6]

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Author Affiliations: Division of Gastroenterology, Hepatology, and Nutrition, Jacobs School of Medicine and Biomedical Sciences, University at Buffalo, Buffalo, New York (Talal); Department of Biostatistics, University at Buffalo, Buffalo, New York (Markatou, Liu); Division of Liver Diseases, Department of Medicine, Icahn School of Medicine at Mount Sinai, New York, New York (Perumalswami, Dinani); Division of Gastroenterology and Hepatology, University of Michigan, Ann Arbor (Perumalswami); Clinical Directors Network, Inc (CDN), New York, New York (Tobin); The Rockefeller University Center for Clinical and Translational Science, New York, New York (Tobin); START Treatment & Recovery Centers, Brooklyn, New York (Brown); Weill Cornell Medicine, New York, New York (Brown).

Author Contributions: Drs Talal and Markatou had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: Talal, Markatou, Tobin, Brown.
Acquisition, analysis, or interpretation of data: Talal, Markatou, Liu, Perumalswami, Dinani, Tobin.
Drafting of the manuscript: Talal, Markatou, Liu, Perumalswami, Dinani, Tobin.
Critical review of the manuscript for important intellectual content: All authors.
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Supplementary Online Content

Talal AH, Markatou M, Liu A, et al. Integrated Hepatitis C–Opioid Use Disorder Care Through Facilitated Telemedicine. *JAMA*. Published online April 3, 2024. doi:10.1001/jama.2024.2452

eFigure 7. Number of Rural Participants Achieving a Sustained Virologic Response (SVR) Stratified by Study Arm

eAppendix 7. Analysis of Incidence Rates

eReferences.

We provide details associated with randomization, treatment of missing data, and selection bias aspects of the trial. Furthermore, we note some observations on subgroups in our data.

eAppendix 1: Randomization

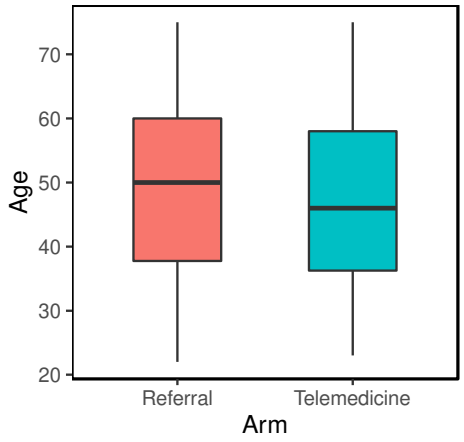
We used covariate-constrained randomization. Details on our randomization scheme are presented in[1] (specifically Sections 3.2 and A.1.2 of Appendix A). Here, we note that the covariates used in the randomization are age, sex, race and ethnicity. All covariates used in the randomization are cluster level covariates. Li et al (2017) have shown that covariate-constrained randomization reduces power loss for redundant analysis-based adjustment for non-prognostic covariates.[2]

To control for differential recruitment and avoid arm contamination, we implemented a variety of procedures. The randomization schedule was kept confidential. Sites were notified 30 days prior to cross-over to the intervention. All other sites were unaware of the randomization schedule. We minimized bias as neither the sites nor the potential participants were aware when the intervention would occur at their sites. Sites strictly adhered to the randomization schedule. Participants who were motivated to be treated were enrolled first and no warehousing of potential participants occurred. Furthermore, we maintained lists of individuals participating in the usual care and opioid treatment program (OTP)-integrated facilitated telemedicine arms to avoid usual care participants entering into the telemedicine arm.

As an example of the effect of randomization on the characteristics associated with the obtained sample, we present eFigure 1.

eFigure 1 presents boxplots associated with the age distribution in referral (i.e., usual care [UC]) and OTP-integrated facilitated telemedicine arms. Differences in medians (means) between the two arms are not statistically significant (p-value = 0.60). Furthermore, Table 1 of the main document illustrates the balance between the two arms in terms of sex, race, and ethnicity. Notice that the variable referring to residence location (i.e., rural versus urban) is also balanced between the arms.

eFigure 1: Age distributions at baseline (N= 602) between referral (red) and opioid treatment program-integrated facilitated telemedicine (blue) in both study arms.



eAppendix 2: Treatment of Missing Data

We define "dropouts" as participants who terminated HCV treatment (in either the referral or OTP-integrated facilitated telemedicine arms) before obtaining a sustained virological response (SVR) determination. In the referral arm, 186 participants and in OTP-integrated facilitated telemedicine, 22 participants, did not have a treatment start date. Furthermore, 18 participants in usual care and 17 in OTP-integrated facilitated telemedicine initiated treatment but dropped out of the study for various reasons. Therefore, the final rate is 243/602=40.36%. Furthermore, individuals in both arms were provided 5 months to undergo an HCV evaluation to initiate treatment. In chronic HCV infection, spontaneous HCV resolution occurs at 0.36% person years.[3]

eTable 1 presents the number of individuals who terminated study participation prematurely and the associated reasons for early termination. There were 18 dropouts in usual care and 17 in OTP-integrated facilitated telemedicine. Since the missing mechanism is assumed to be "missing at random" (MAR), we utilized multiple imputation using the R package "MICE (Version 3.15.0)-Multivariate Imputation by Chained Equations" to generate 20 different imputed data sets per arm.[4]

eTable 1: Reasons for early termination of study participants by study arm among participants with a treatment start date.

Discontinuation Reasons	Referral	Telemedicine	Total
Discharge from MMTP	9	8	17
Incarceration	2	2	4
Loss of insurance	1	0	1
Medication side effects	1	0	1
Other	1	5	6
Death	2	1	3
Relocation	2	1	3
Total	18	17	35

Because SVR is a binary outcome, we use logistic regression to obtain the imputed SVR values. The logistic regression model we constructed includes the following variables: an indicator variable, denoted treatment start date (TSD), that specifies whether the participant had a treatment start date (the value is 1) or not (value is 0), age, sex, race, ethnicity, urban/rural residence location, Drug Abuse Screening Test (DAST10), number of months enrolled in the methadone program, comorbid conditions, alanine aminotransferase to platelet ratio index (APRI), prescription drugs used for non-medical reasons, illicit drugs, arm, period, interaction of DAST10 with number of months in the methadone program, and site (as a fixed effect to account for clustering). We follow the principle that the imputation model is neither intended to provide a parsimonious description of the data nor does it represent structural or causal relationships among the variables. It is merely a device to preserve important features of the joint distributions in the imputed variables.[5] Furthermore, the variables incorporated in the model are thought to influence the rate of missingness.

eAppendix 2.1: Justification of Variables Included in the Model

The justification of incorporating these variables in the imputation model is as follows:

Arm: Chronic HCV infection has spontaneous occurrence rate at < 0.36% person-years.[3]

Pooled HCV incidence is 12.1 per 100 person*years.[6] Younger age, female gender, longer duration of follow-up, longer duration of injection drug use (IDU), and >80% injection in the cohort were associated with increased HCV incidence.

Age: Most substance users in high income countries are older. Younger people only make up 15% of the injecting population.[7]

Sex: Globally, 2.8 million women and 12.1 million males inject drugs. In North America, 2.3 million men compared to 1 million women.[7]

Race: African-Americans are twice as likely to be infected with HCV compared to other races.[8]

HCV-associated death rates among non-Hispanic Black people are 1.8 times higher than among non-Hispanic white people.[8]

Non-Hispanic Black persons involved more with HCV.[9]

Ethnicity HCV treatment rates are lower in Hispanic individuals compared with non-hispanics.[10]

- Compared with Caucasians, Latinx individuals tend to initiate HCV treatment less frequently, discontinue treatment, become infected younger, and have higher reinfection rates.[11]
- An older study from the interferon era also showed that even though Hispanic individuals were more likely to meet criteria for antiviral therapy, they were less likely to initiate treatment, were more likely to discontinue early, and tended to have lower SVR rates.[12]

DAST10: 66% of acute HCV infections occur in injection drug users.[8]

- Opioids are used by 83% of the world's injection drug users.[7]

Comorbid conditions

People with substance use disorders are more likely to have co-existing mental health issues.[8]

A recent systematic review confirms high levels of depression and anxiety in IDUs.[7]

Months in methadone program:

- The number of months in the methadone program has been shown to be related to methadone adherence. [13]

APRI-(as a noninvasive measure of hepatic fibrosis):

- APRI has been shown to have equal performance characteristics for fibrosis assessment compared to Fibrosis-4 index and Fibrosure.[14]

TSD (Treatment start date)

- An indicator variable specifying whether or not a participant initiated HCV treatment

Urban/rural

- Most participants on methadone reside in urban areas and the transportation requirements to obtain methadone may be important determinants of adherence.

Interaction (DAST-10) X months in methadone program

- DAST-10 is a measure of substance use and months in the methadone program is a measure of methadone adherence. The interaction between these two variables provides an indication of the degree to which substance use affects participants' lives and the potential effect of methadone.

Period

- Effect of study time period as a determinant of HCV treatment.

Site

- To account for clustering.

In total, five variables were affected by missing values, of which the outcome variable, SVR has the highest percentage of missing values at 40.6%. The lowest percentage of missing values was 1.99%, median of 3.49% [3.32%, 3.49%]. All missing values were imputed using MICE and for variables on ordinal and/or interval ratio scale, we used the predictive mean matching method. Diagnostics were used to compare agreement between imputed and observed data. eTable 2 presents descriptive statistics associated with the 20 imputed, per arm, datasets.

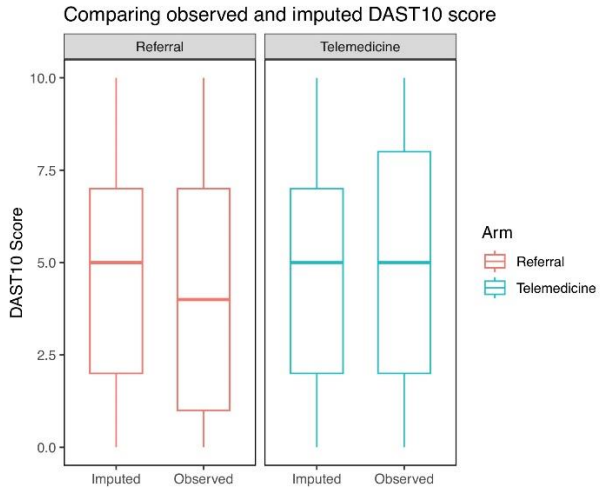
eTable 2: Descriptive statistics of sustained virological response associated with the 20 imputed datasets. The total number of participants is 602.

Arm	Minimum	Median (IQR)	Mean (SD)	Maximum
Usual care	38.5%	39.4% ([39.3%, 39.4%])	39.4% (0.32%)	39.7%
Telemedicine	88.6%	90.2% ([90.0%; 90.7%])	90.2% (0.52%)	91.0%

Abbreviations: IQR, interquartile range; SD, standard deviation

eFigure 2 presents the comparisons, per arm, of observed and imputed data for the DAST10 variable. eTable 3 presents the imputed and observed percentages (per category) for the variable illicit drug use.

eFigure 2: Distribution of imputed and observed Drug Abuse Screening Test (DAST10) levels per arm



eTable 3: Percentages of observed and imputed, per arm, illicit drug use per category as obtained by NIDA Quick Screen.

	Referral		Telemedicine	
Category	Observed	Imputed	Observed	Imputed
1	41.28%	34.64%	36.40%	34.29%
2	19.13%	20.00%	13.43%	20.00%
3	13.09%	16.43%	18.02%	17.86%
4	14.09%	13.57%	15.90%	12.85%
5	12.42%	15.36%	16.25%	15.00%
Total	100.00%	100.00%	100.00%	100.00%

eAppendix 2.2: Deaths

During the course of the study, we observed 13 deaths associated with excessive substance use, ten in the OTP-integrated facilitated telemedicine arm and 3 in referral (i.e., usual care) arm. Out of these 13 participants, ten did

not affect the main study outcome, i.e., SVR, as the HCV treatment outcome had already been obtained with nine participants obtaining an SVR and 1 participant was nonresponsive to therapy. eTable 4 presents data associated with the deceased participants in each category. The outcome of three patients who expired prior to SVR determination were subsequently imputed using the MICE algorithm. Therefore, deaths were handled as missing at random observations. Notice that the missing outcome death rate is 0.5% (3/602), and this event is unrelated to the study outcome. A participant who expires leaves the universe of interest, and the associated SVR outcome can be regarded as missing at random and, hence, imputed.[15]

eTable 4: Deceased participants by relevant demographic and residence location variables. Percentages are calculated using as a denominator the total number of deaths (n=13).

Study arm		SVR status			Age		Gender		Race		Ethnicity		Geographic	
Ref (%)	TM (%)	Yes (%)	No (%)	ND (%)	Mean (SD)	Median (IQR)	M (%)	F (%)	White (%)	Black/AA Other (%)	NH (%)	H (%)	U (%)	R (%)
3	10	9	1	3	55.5	57	8	5	7	6	12	1	11	2
23	77	69	8	23	9.26	[55,62]	61.5	38.5	53.9	46.1	92.3	7.7	84.6	15.4

Abbreviations: Ref, referral; TM, telemedicine; SVR, sustained virological response; ND, not determined; SD, standard deviation; IQR, interquartile range; M, male; F, female; AA, African-American; NH, Non-Hispanic, H, Hispanic; U, urban; r, rural.

eAppendix 3: Nonparametric Analysis

The nonparametric analysis for estimating the intervention (i.e., OTP-integrated facilitated telemedicine) effect is a cluster-level, robust, within-period method proposed by Thompson et al. (2018).[16] This method does not require pre-specification of the correlation structure, which usually is not known in advance and avoids the assumptions that accompany the GLMM approach.

eAppendix 3.1: Cluster-level analysis:

We used the method proposed by Thompson et al.[16] (and the associated R code) to estimate the intervention effect. This method does not use the entire data; it is, however, assumption-free. The estimate of the period-specific intervention effect expressed by the difference between the mean cluster-period percentage of participants who obtain SVR in OTP-integrated facilitated telemedicine and referral, computed by combining (using Rubin's rules) the results obtained from the 20 datasets is 58.6% (p-value <0.0001; 95% CI [44.0%, 74.1%]).

eAppendix 4: Effect modification

When time is treated as a continuous variable and the fitted model accounts for cluster random effect and arm effect, the results obtained using Rubin's combination rule on 20 separate data sets provide the same significant arm effect estimate with that obtained from the model in which time is treated as a discrete variable (*i.e.,* the estimate of arm effect is 2.9, p-value <0.001, 95% confidence interval (2, 3.5). The time effect is nonsignificant. When the interaction term of time x arm is added, the estimate obtained is -0.002 with a 95% confidence interval of (-0.64, 0.64) and p-value = 0.5, indicating nonexistence of effect modification.

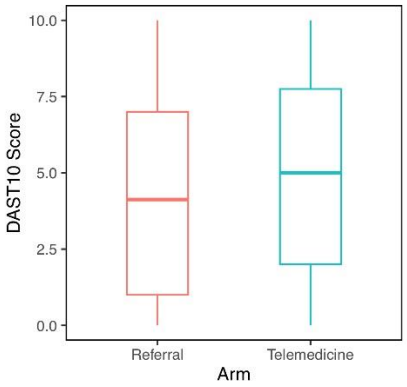
eAppendix 5: Selection Bias

Clustered randomized trials are susceptible to post-randomization selection bias because patient recruitment occurs after randomization.[17] Furthermore, differential recruitment due to non-blinding nature of many clustered randomized trials, including our own, is a real possibility.

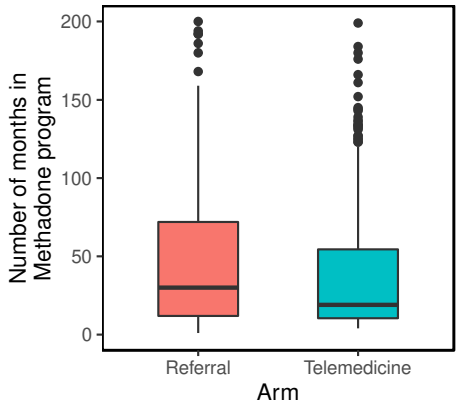
eAppendix 1 provides details on the precautions we took to avoid arm contamination.

We further illustrate below the baseline distribution of DAST10 scores in both referral (UC) and OTP-integrated facilitated telemedicine arms (eFigure 3) as well as similar distributions of the number of months in the methadone program (eFigure 4). These figures illustrate that the two arms are well balanced on both variables, illustrating comparability between the arms. DAST10, as a measure of drug use, is an important variable on which to establish comparability between the two arms since the majority of acute HCV infections occur in injection drug users.[8] Furthermore, more than four fifths of the world's injection drug users use opioids.[7] Similarly, months in the methadone program has been widely accepted as a measure of methadone adherence and stability.[13]

eFigure 3: Distribution of Drug Abuse Screening Test (DAST10) score in the referral (red) and opioid treatment program-integrated telemedicine (blue) arms.



eFigure 4: Distribution of the number of months participants are in the methadone program for the referral (red) and opioid treatment program-integrated telemedicine (blue) arms.



The direct acting antiviral medications prescribed in the study are illustrated in eTable 5. Most patients in both study arms were prescribed glecaprevir/pibrentasvir. Self-reported adherence to direct acting antiviral medication by week of treatment duration is illustrated (eTable 6) Of note, those individuals in the OTP-integrated facilitated telemedicine arm who did not achieve an SVR had <90% adherence during the last two study visits.

eTable 5: Direct acting antiviral medications prescribed to study participants

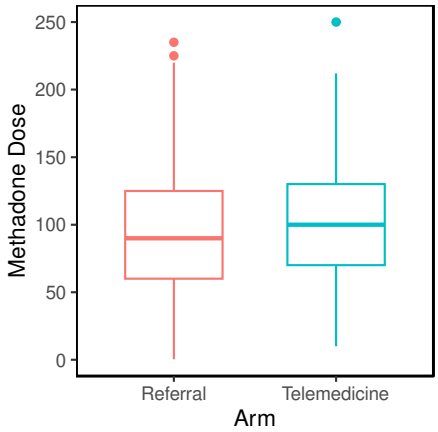
Direct Acting Antiviral	Referral (N=126)	Telemedicine (N=268)	Total (N=394)
Sofosbuvir/ledipasvir	7 (5.6%)	10 (3.7%)	17 (4.3%)
Glecaprevir/pibrentasvir	81 (64.3%)	175 (65.3%)	256 (65.0%)
Sofosbuvir/velpatasvir/voxilaprevir	2 (1.6)	10 (3.7)	12 (3.0%)
Velpatasvir/sofosbuvir	15 (12.0))	73 (27.2%)	88 (22.3%)
Elbasvir/grazoprevir	19 (15.1%)	0 (0.0%)	19 (4.8%)
Missing	2 (1.6%)	0 (0.0%)	2 (0.5%)

eTable 6: Adherence to direct acting antiviral medication by treatment week.

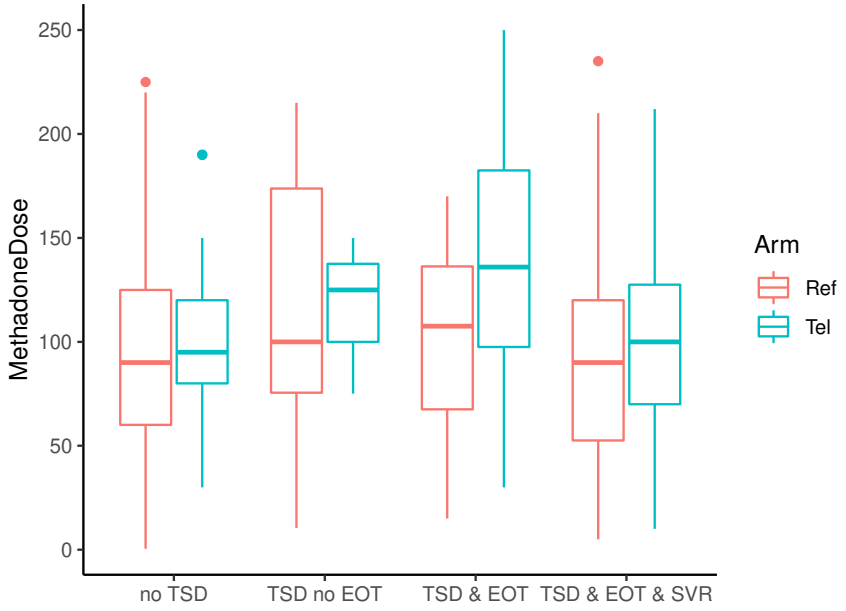
	Usual Care		Telemedicine	
	Percent adherence		Percent adherence	
Visit Week	SVR = Yes	SVR = No	SVR = Yes	SVR = No
Week 2	100	100	95.8	100
Week 6	96.4	100	97.9	80
Week 12	96	100	96.9	80

eFigure 5 presents the boxplots for graphical comparison of distributions of the methadone dose in participants in the referral and OTP-integrated facilitated telemedicine arms illustrating no differences in the doses between the two arms. eFigure 6 illustrates the distribution of methadone dose in participants without a treatment start date (i.e., no TSD), those with a treatment start date but without an end of treatment date (i.e., TSD no EOT), participants with TSD and EOT date, as well as those with TSD and EOT and SVR determination. The figure compared the distribution of the participants' methadone dose between the arms. The two middle groups, i.e., participants with TSD and no EOT and those with TSD and EOT constitute the dropouts in the two arms. The figure indicates that there are no differences in methadone dose between the two arms in the no TSD and TSD and EOT and SVR groups. Retention in treatment with methadone is an acceptable measure of OUD treatment effectiveness, a key component of which is an adequate methadone dose.[18]

eFigure 5: Boxplots comparing the distribution of methadone dose in referral (red) and opioid treatment program-integrated telemedicine (blue) arms.



eFigure 6: Boxplots comparing methadone dose (mg/day) by study outcome in opioid treatment program-integrated telemedicine (blue) and referral (red) arms.



Abbreviations: TSD, treatment start date; EOT, end of treatment; SVR, sustained virological response.

eAppendix 6: Observations related to subgroups.

eTable 7 provides information on Hispanic individuals. Only 7.1% of Hispanic females initiated HCV treatment in referral and achieved SVR. In contrast, 88.56% of Hispanic females in OTP-integrated facilitated telemedicine achieved SVR (eTable 7). Furthermore, our data illustrate (eTable 8) that 100% of Hispanic females and 93.89% of Hispanic males are at least well versed in English.

eTable 7: Sustained virological response rate by period for Hispanic females in referral and opioid treatment program-integrated telemedicine arms

Study period	Referral	Telemedicine
1	1/16	0/0
2	1/11	3/3
3	0/1	10/11
4	0/0	10/12
Total	2 (7.1%)	23/26 (88.56%)

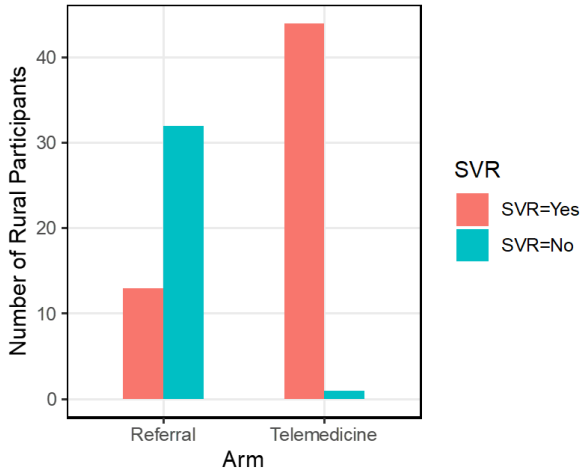
eTable 8: English language ability for Hispanic females and males

English level	Female Hispanics	Male Hispanics	Total
Not at all	0	2	2
Not well	0	6	6
Well	5	47	52
Very well	47	73	120
Missing value	2	3	5
Total	54	131	185

Facilitated telemedicine also favored a successful treatment outcome in participants who reside in rural areas. In the usual care arm, 28.89% of rural participants initiated HCV treatment and obtained an SVR. The remaining 71.11% did not initiate treatment and did not achieve SVR. In the OTP-integrated facilitated telemedicine arm, 100% of the

rural participants initiated HCV treatment and 97.78% obtained SVR (eFigure 7). The difference in response between the two arms necessitated the use of Bayesian methods for obtaining the confidence interval shown in Figure 3.

eFigure 7: Number of rural participants achieving a sustained virologic response stratified by study arm.



Abbreviation: SVR, sustained virologic response

eAppendix 7: Analysis of incidence rates

To assess the effect of the intervention on the outcome reference reinfection rates, we use the methods discussed in Bennett et al. (2002)[19]. Our analysis is unadjusted for covariates. We use RR_M (i.e., gives equal weight to each cluster). The estimate of the rate ratio is 1.24. To obtain the 95% confidence interval, we use 10,000 bootstrap samples of (d_{ij}, y_{ij}), where d_{ij} is the number of reinfection cases in cluster j of reinfection group i and y_{ij} is the number of person-years of observation in cluster j of group i. Further, i = 1, 2; j = 1, 2,…, 12. The 95% confidence interval is (0.4, 5.9) and includes 1. Hence, there is a no difference between the two arms with respect to the reinfection rate.

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