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MAJOR ARTICLE

Care Facilitation Advances Movement Along the Hepatitis C Care Continuum for Persons With Human Immunodeficiency Virus, Hepatitis C, and Substance Use: A Randomized Clinical Trial (CTN-0064)

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Background. Direct-acting antivirals can cure hepatitis C virus (HCV). Persons with HCV/HIV and living with substance use are disadvantaged in benefiting from advances in HCV treatment.

Methods. In this randomized controlled trial, participants with HCV/HIV were randomized between February 2016 and January 2017 to either care facilitation or control. Twelve-month follow-up assessments were completed in January 2018.

Care facilitation group participants received motivation and strengths-based case management addressing retrieval of HCV viral load results, engagement in HCV/HIV care, and medication adherence. Control group participants received referral to HCV evaluation and an offer of assistance in making care appointments. Primary outcome was number of steps achieved along a series of 8 clinical steps (eg, receiving HCV results, initiating treatment, sustained virologic response [SVR]) of the HCV/HIV care continuum over 12 months postrandomization.

Results. Three hundred eighty-one individuals were screened and 113 randomized. Median age was 51 years; 58.4% of participants were male and 72.6% were Black/African American. Median HIV-1 viral load was 27 209 copies/mL, with 69% having a detectable viral load. Mean number of steps completed was statistically significantly higher in the intervention group vs controls (2.44 vs 1.68 steps; χ^2 [1] = 7.36, P = .0067). Men in the intervention group completed a statistically significantly higher number of steps than controls. Eleven participants achieved SVR with no difference by treatment group.

Conclusions. The care facilitation intervention increased progress along the HCV/HIV care continuum, as observed for men and not women. Study findings also highlight continued challenges to achieve individual-patient SVR and population-level HCV elimination.

Clinical Trials Registration. NCT02641158.

Keywords. cascade; hepatitis C; HIV; patient navigation; substance use.

Persons with human immunodeficiency virus (PWH) are at high risk of hepatitis C virus (HCV) infection [1]. Advances in HCV treatment are important for PWH also living with HCV as coinfection is associated with faster progression of liver disease [2–4]. Although HCV treatment with direct-acting antivirals (DAAs) now offers the opportunity for cure, persons who use drugs (PWUD) face disadvantages accessing HCV treatments [5, 6]. Yet, guidelines by the American Association for the Study of Liver Diseases and the Infectious Diseases Society of America

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assert that recent history of (or active) drug use should not contraindicate HCV treatment [7]; research consistently shows that when engaged and treated, PWUD achieve sustained virologic response (SVR) at the same rates as their counterparts who do not use drugs [8–10].

The continuum of care approach was developed to evaluate human immunodeficiency virus (HIV) outcomes across a series of sequential steps of care [11]. Care continuum models can be used to monitor outcomes from HCV antibody screening to SVR, enable quantification of gaps in health services use, and indicate areas where intervention is needed [12]. Progress along the HCV continuum compared with the HIV care continuum has been slow, thus making HCV elimination among historically disadvantaged populations, including PWUD, hard to achieve [13]. Reasons for this delay include lack of knowledge about and awareness of HCV, long wait times for HCV care evaluation (due to treatment prioritization that frequently excludes PWUD as well as state-level restrictions and policies that limit access to care for PWUD), low perceived need for and interest in HCV treatment, provider stigma at the health care system level and internalized stigma at the patient level, cost-related factors due to high drug costs and restrictive payer policies that often lead to absolute denial of DAA regimens by insurers (including commercial insurance and Medicaid/Medicare), and long-standing psychosocial factors, such as unstable housing, lower education level, mental health disorders, and incarceration [14–20]. Efficacious interventions that overcome barriers, incorporate harm reduction, and facilitate movement along an integrated care continuum are needed.

PWUD are at elevated risk of suboptimal outcomes for HIV, HCV, and HIV/HCV coinfection [21]; these individuals are at higher risk of experiencing fragmented care, obtaining health care in emergency departments and hospitals, and may be deterred by providers from receiving life-saving medications [22]. Patient navigation and care facilitation interventions can increase engagement in care for HIV [23, 24] and HCV [25] separately. The CTN-0049 randomized clinical trial (RCT) demonstrated short-term efficacy of a 6-month patient navigation plus financial incentives approach in increasing HIV care engagement and viral load suppression among PWH and substance use [24]. The time-limited nature of HCV treatment and cure (1–3 months) may provide greater opportunity for short-term interventions to move PWUD along the HCV care continuum. The present study (CTN-0064) tested the efficacy of a 6-month care facilitation intervention (vs standard of care [7]) where participants received a care facilitator who used motivational interviewing to build an effective, working relationship with the participant, conducted needs assessments, and used a strengths-based approach to move PWUD with HCV/HIV coinfection along the HCV/HIV care continuum [23, 25–27]. The primary hypothesis was that the average number of steps achieved along the HCV/HIV care continuum would differ between the 2 study groups over the follow-up period.

METHODS

Participants and Baseline Assessment

Participants were recruited from an existing cohort of PWH and substance use who originally participated in CTN-0049 [24]. To enroll in the CTN-0049 cohort, individuals also had to be an inpatient at the time of recruitment; be at least 18 years old; communicate in English; endorse or have medical record evidence of opioid, stimulant, or heavy alcohol use in the prior 12 months; provide informed consent; and have an AIDS-defining illness or CD4 cell count and HIV viral load corresponding to nonsuppression (or likely detectable viral load). To be randomized in the CTN-0064 study, individuals from the existing cohort had to provide informed consent, sign a medical release form, be able to return for follow-up visits, and screen as HCV antibody positive. Study sites were located in Atlanta, Georgia; Baltimore, Maryland; Boston, Massachusetts; Chicago, Illinois; Dallas, Texas; Miami, Florida; New York, New York; and Philadelphia, Pennsylvania. After providing informed consent, recruits completed (1) a computer-assisted personal interview (CAPI) concerning HCV/HIV care, substance use and substance use treatment, demographics, and socioeconomic factors; (2) HCV antibody screening; (3) HCV test information and counseling; (4) blood specimen collection; and (5) urine drug/alcohol screening. Recruits who screened HCV antibody positive were invited to participate in the RCT.

Randomization

Participants were randomly assigned in a 1:1 ratio to a care facilitation intervention or control. A centralized data coordinating center created computer-generated randomization schedules stratified by site, CTN-0049 original treatment assignment, and self-report of both current HIV care status and use of antiretroviral therapy (ART). Research personnel were notified of randomized condition through a web-based system.

Care Facilitation Intervention

Study participants who had tested HCV antibody positive and been randomly assigned to the care facilitation intervention received a reminder card with the date/time of their appointment to receive their HCV RNA results, and an HCV care facilitator (CF) worked individually with participants to motivate them to retrieve the results. CFs delivered the pre-/post-HCV RNA test information using a motivational interviewing approach designed to help them build and maintain an effective working relationship with the participant. CFs also conducted a participant needs assessment and strengths assessment and encouraged the participant to identify and use his/her strengths, abilities, and skills to move participants along the HCV/HIV care continuum. CFs had previous experience in social work,

case management, discharge planning, or delivery of health or prevention services.

When a participant's results were HCV RNA positive, CFs provided a highly active referral to the next step in the HCV/HIV care continuum, that is, they worked with the participant and with the clinical provider(s) to schedule the appropriate clinical appointment (eg, HCV clinical evaluation, HCV care, HIV care) for the participant (or assist the participant in doing this). CFs made multiple attempts to schedule the appointment, as needed. CFs also provided appointment reminder calls, texts, and/or emails prior to the participant's HCV/HIV care or other "next step" visit. Additionally, CFs made follow-up contact for missed appointments and facilitated or provided transportation to/from HCV and HIV care and substance use treatment appointments, as needed. The CF actively coordinated and linked the participant to available community resources (eg, mental health, legal assistance, housing agencies, food banks, support groups) through scheduling appointments, arranging transportation, and assisting the participant with completing any clinic registration, prior authorization (or other) paperwork that the agencies required to access services, tests, or medications as indicated. Finally, the CF accompanied the participant to key visits (eg, HCV clinical evaluation, HIV primary care, substance use treatment visits).

Participants receiving the care facilitation intervention were expected to meet with the CF approximately twice each month either in-person or over the phone during the 6-month intervention period to facilitate and monitor progress along the HCV/HIV continuum of care, and discuss other social service needs as necessary. The CF followed up with participants, providers, and participants' collateral contacts by phone between scheduled visits. Reengagement in HIV care after randomization was also considered progress along the HCV/HIV care continuum as some treating physicians would not consider HCV treatment initiation until participants had stable HIV viral loads.

Control Group

Participants in this group were given a single reminder card with their appointment to receive HCV RNA results. Study personnel delivered the pre–/post–HCV RNA test information and counseling via a manualized instruction approach. At the study visit where HCV RNA–positive results were disclosed, study personnel provided a referral and scheduled the appropriate clinical appointment. If an appointment was not scheduled, study personnel provided a written referral. Study personnel did not provide further appointment reminders.

Follow-up Assessments

At 6 and 12 months postrandomization, participants had HIV RNA load, CD4 cell counts, and HCV RNA measured; completed follow-up CAPIs; and completed urine drug/alcohol screens. Participants received up to $130 for completing nonintervention activities postrandomization. Medical records were abstracted to document HCV testing; HCV clinical evaluation, care, and treatment; and HIV care and treatment before and during the study period.

Intervention Training

CFs received training over 3 phases (prenational training, national training, and postnational training) via conference calls, webinars, written materials, and self-study.

Intervention Fidelity

Intervention sessions were audio recorded with participants' consent. A fidelity monitor rated approximately 14% of randomly chosen intervention sessions for adherence to the intervention manual. The fidelity monitor answered questions on a scale of 0 (not at all) to 3 (completely) on how well the counselors performed; an average fidelity score was created for each session.

Measures

HIV type 1 viral load, CD4 cell count, and HCV RNA were measured by local laboratories. Participants completed urine drug/alcohol screens. HIV medication adherence was measured via self-report as the percentage of pills taken in the last 30 days. HIV and HCV care, HCV evaluation, HCV treatment initiation, and HCV treatment completion were assessed via self-report and medical record abstraction. Final outcome measures were based on medical records. Specific substances used for nonmedical purposes in the prior year and prior 30 days were assessed via the Addiction Severity Index [28]. Substance use severity was measured via the Drug Abuse Screening Test (DAST-10) [29] and the Alcohol Use Disorders Identification Test (AUDIT) [30]. Injection drug use was measured via an adapted Global Appraisal of Individual Needs risk behaviors module [31]. Substance use treatment, housing stability, and psychological distress were assessed with validated measures [32–36].

Safety and Human Subjects Review

Adverse events and deaths were monitored and reported to the medical monitor and the data and safety monitoring board. The institutional review board–approved protocol is available online (eProtocol in Supplementary Data 1).

Outcomes and Analysis

The outcome analysis was performed under intent-to-treat criteria, by assigned group. The primary outcome was number of steps achieved along a series of 8 potentially nonsequential clinical steps of the HCV/HIV care continuum over 12 months postrandomization. Achieved steps were based on medical record abstraction and included (1) receiving HCV viral

load results; (2) HIV care engagement; (3) initiating ART; (4) having an HCV (liver) evaluation; (5) receiving an offer of HCV medications; (6) initiating HCV medications; (7) completing HCV treatment; and (8) achieving SVR at 12 weeks after treatment completion. While a common practice with HCV/HIV-coinfected persons who have untreated or uncontrolled HIV is to focus on HIV care and treatment engagement prior to HCV care and treatment, for analyses achieving HIV or HCV, performing the steps in either order was considered forward movement. Note that participants were only credited with achieving the HIV treatment steps (2 and 3) if they had not achieved that step at baseline. Furthermore, participants who were HCV RNA negative could only achieve step 1 in the continuum. The outcome, number of steps achieved in the HCV/HIV care continuum, is count-distributed. We assessed which count model (Poisson, negative binomial, zero-inflated Poisson, zero-inflated binomial, or beta-binomial) best fit the data by comparing models using Bayesian information criteria; the Poisson distribution was found to fit the data best [37]. The primary model included treatment group with control variables: recruitment site, whether the individual was engaged in HIV care at the baseline assessment, and the treatment assignment in the CTN-0049 study. In sensitivity analyses, we examined whether various subgroups had different treatment effects by adding interaction terms with treatment. Variables examined for treatment interactions included site, whether the individual was in HIV care at the baseline visit, CTN-0049 treatment assignment, gender, race, ethnicity, and stimulant use at baseline. Stimulant use had been independently associated with suboptimal HIV care use in CTN-0049 [24]. Finally, secondary analyses were conducted to assess the CF intervention's impact on HIV care visit attendance, HIV viral suppression (counts ≤200), number of inpatient hospitalizations, substance use (proportion urine drug screen positive and number of days of use), and substance use treatment attendance.

Power analyses were conducted by simulation using SAS version 9.4 software. Data was drawn from a Poisson distribution with the mean rate of the control group set to the Poisson parameter ($\lambda = .4$), which approximated the probability of no HCV assessment ($P = .67$) seen in previous research that tested the CF intervention [22]. The odds ratio for the 2 groups in this previous research for obtaining an HCV evaluation was 4.10. We estimated power for a number of rate ratios between 1.875 and 2.375, all more conservative than 4.10. For sample sizes larger than 100 and rate ratios of 2.13 or higher, the simulations showed statistical power of 80% or higher.

RESULTS

Of the 381 individuals eligible to screen for the RCT, 113 (29.66%) were randomized between February 2016 and January 2017. Of those excluded, 244 (91.0%) were HCV antibody negative. Eighteen (6.7%) tested positive for HCV antibodies but did not return to complete their baseline blood draw, so were ineligible. Other reasons for ineligibility are presented in the Consolidated Standards of Reporting Trials (CONSORT) flowchart (Figure 1). There was no difference in rates of completion between study groups; both groups had 87% completion of the 12-month assessment. The 12-month follow-up assessments were completed in January 2018. Of those randomized, the median time between randomization in CTN-0049 and CTN-0064 was 3.3 years (interquartile range [IQR], 2.9–3.5 years).

The mean age of the randomized sample was 51 years (standard deviation [SD], 8.2 years). Sixteen (14.1%) were Hispanic or Latino, 82 (72.6%) were black or African American, and 14 (12.4%) were white. Sixty-six (58.4%) were male and 102 (90.3%) had insurance, the majority of which (94 [83.2%]) was Medicaid or other government health insurance. Only 7 participants (6.2%) reported income over $20 000. At baseline, 99 of 113 (87.6%) reported substance use in the prior 12 months or had a positive urine drug screen. All participants reported a history of injection drug use and 57 (50.4%) reported having injected drugs in the past 12 months. Seventy-eight (69%) had a detectable HIV viral load (>200 copies/mL) with a median HIV viral load among those detectable of 27 209 copies/mL. The median CD4 count was 251 cells/μL with 47 (41.6%) of participants having CD4 counts <200 cells/μL. Baseline characteristics of study participants by treatment group are detailed in Table 1; there are no important differences between treatment groups.

Primary Outcome Analysis

There were statistically significant effects of treatment (χ^2 [1] = 7.36, $P = .0067$) on the mean number of steps along the HCV/HIV care continuum completed; the intervention vs control group completed a mean number of 2.44 steps (SD, 1.77 [95% confidence interval {CI}, 1.99–2.99]) vs 1.68 steps (SD, 1.32 [95% CI, 1.36–2.08]). Although the distribution of total number of steps completed differed by group (Figure 2), the details of which specific steps were completed indicate some variability in the relative completion of steps by treatment group, with the largest difference being receipt of HCV RNA result (Table 2). The 2 HIV-related steps were only applicable to those who were not in HIV care at baseline (control, n = 21; intervention, n = 15) for step 2 and n = 14 for step 3 and the HCV steps were applicable to those who were HCV RNA positive (control, n = 53; intervention, n = 41). The median time to achieve an HCV evaluation, among those who did achieve this step across treatment groups, was 3.6 months postrandomization (IQR, 1.7–5.8]). The median time to initiate HCV treatment, among those who did achieve this step across treatment groups, was 2.7 months postrandomization (IQR, 1.4–4.1]). A total of 11 individuals achieved SVR at 12

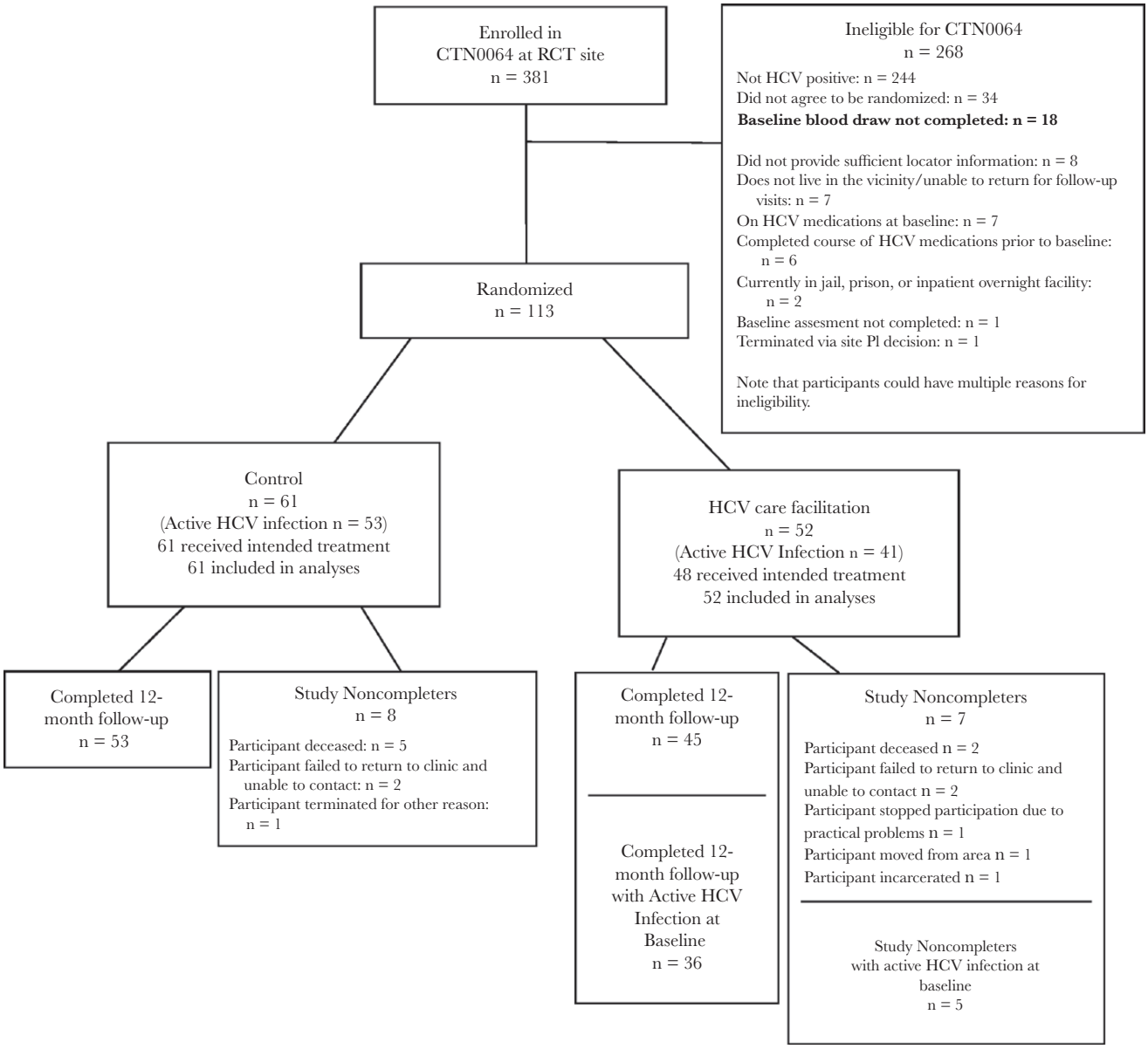

Figure 1. Consolidated Standards of Reporting Trials (CONSORT) flow diagram. Abbreviations: HCV, hepatitis C virus; PI, principal investigator; RCT, randomized controlled trial.

weeks post–HCV treatment completion, 5 (9.4%) in the control group and 6 (14.6%) in the CF intervention group.

Subgroup Analyses

Sites did differ (χ^2 [7] = 16.23, P = .023) on the mean number of steps completed; however, there was no site-by-treatment interaction (χ^2 [7] = 10.11, P = .182). Gender was the only subgroup with a statistically significant impact on the intervention effect (χ^2 [1] = 8.47, P = .004). Men in the intervention group completed a statistically significantly higher number of steps than those randomized to the control group (intervention mean, 3.08 [95% CI, 2.41–3.93] vs control mean, 1.48 [95% CI, 1.12–1.96]; P = .001). There were no statistically significant differences among female participants (intervention mean, 1.74 [95% CI, 1.26–2.41] vs control mean, 1.96 [95% CI, 1.43–2.69]; P = .597). There were no subgroup effects by race, ethnicity, or substance use (any positive urine drug/alcohol screening positive, stimulant use, or opioid use).

Secondary Outcomes

The proportion of participants who had at least 1 HIV care visit across the follow-up period was 52.2% (59/113). HIV viral suppression across groups was 62% (53.2%–71.8%) and 50.5% (40.9%–60.0%) at 6 and 12 months, respectively. The rates of HIV viral suppression (P = .244), HIV care visit attendance (P = .608), and inpatient hospitalizations (P = .546)

Table 1. Baseline Characteristics of Randomized Participants by Treatment Group

Variable	No. (%)	
	Control (n = 61)	HCV Care Facilitation(n = 52)
Age, y, mean (SD)	50.7 (7.8)	51.4 (8.2)
Male/transgender male	38 (62.3)	28 (53.8)
Race/ethnicity		
Hispanic	7 (11.5)	9 (17.3)
Black non-Hispanic	46 (75.4)	36 (69.2)
White non-Hispanic	7 (11.5)	7 (13.5)
Other	1 (1.6)	0 (0.0)
Education		
Less than high school	28 (45.9)	27 (51.9)
High school or equivalent	19 (31.2)	16 (30.8)
More than high school	14 (22.9)	9 (17.3)
Income		
$10 000 or less	40/53 (75.5)	34/45 (75.6)
$10 001–$20 000	8/53 (15.1)	9/45 (20.0)
$20 000 or more	5/53 (9.4)	2/45 (4.4)
Marital status		
Married/partnered	8 (13.1)	10 (19.2)
Divorced/separated/widowed	14 (23.0)	17 (32.7)
Never married	39 (63.9)	25 (48.1)
Health insurance	55/60 (91.7)	47 (90.4)
Medicaid	41/60 (68.3)	38 (73.1)
Other government (state programs)	9/60 (15.0)	5 (9.6)
Rent or own dwelling in prior 6 mo	43 (70.5)	28 (53.8)
Living with family/friends in prior 6 mo	7 (11.5)	17 (32.7)
Severe substance abuse[a]	39 (63.9)	34 (65.4)
Ever injected drugs	61 (100.0)	52 (100.0)
Injected drugs in prior 12 mo	29 (37.5)	28 (53.8)
Any drug use in prior 12 mo	56 (91.8)	43 (82.7)
Any stimulant use	37 (60.7)	31 (59.6)
Any opioid use	28 (45.9)	32 (61.5)
Both stimulant and opioid use	17 (27.9)	23 (44.2)
Urine drug positive at baseline	47/57 (82.5)	40/52 (76.9)
Any stimulant use	29/57 (50.9)	24/52 (46.2)
Any opioid use	22/57 (38.6)	23/52 (44.2)
Both stimulant and opioid use	11/57 (19.3)	11/52 (21.2)
In drug treatment in prior 12 mo	25 (41.0)	22 (42.3)
Professional drug treatment	25 (41.0)	21 (40.4)
Methadone or buprenorphine	11 (18.0)	14 (26.9)
HCV VL (qualitative)		
Unknown	1 (1.6)	0 (0)
Detectable	53 (86.9)	41 (78.8)
Undetectable	7 (11.5)	11 (21.2)
HIV VL, median (IQR) of those detectable	27–603 (3408–108 310)	25 932 (9417–110 420)
Unknown	3 (4.9)	0 (0.0)
Detectable	38 (62.3)	40 (76.9)
Undetectable	20 (32.8)	12 (23.1)
CD4 count, cells/μL, median (IQR)	259 (101–526)	251 (103–392)
Unknown	2 (3.2)	0 (0.0)
≤200	20 (32.8)	27 (51.9)
>200 and ≤350	19 (31.1)	8 (15.4)
>350	20 (32.8)	17 (32.7)

Abbreviations: HCV, hepatitis C virus; HIV, human immunodeficiency virus; IQR, interquartile range; SD, standard deviation; VL, viral load.

[a]Severe substance use includes scores on the Drug Abuse Screening Test (DAST-10) of ≥6 and/or scores on the Alcohol Use Disorders Identification Test (AUDIT) ≥6 for women and ≥7 for men.

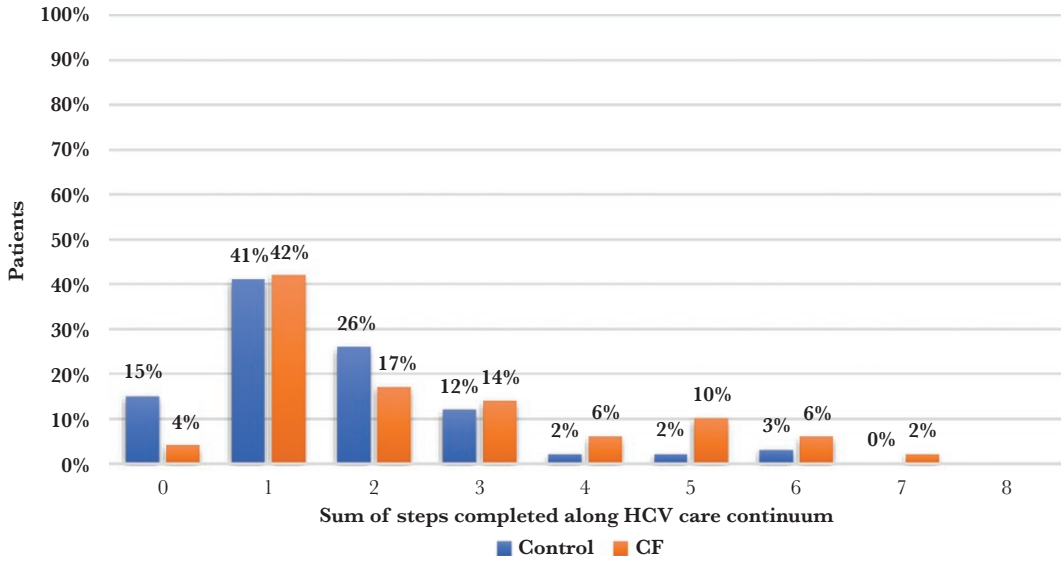

Figure 2. Sum of steps completed on hepatitis C virus care continuum by treatment group. Abbreviations: CF, care facilitator; HCV, hepatitis C virus.

did not differ over time across groups. Similarly, neither self-reported substance use ($P = .194$) nor participation in substance use treatment ($P = .436$) differed over time by treatment group. Positive urine drug screens in the entire sample were 81.9% (77/94) and 87.4% (76/87) at 6 and 12 months, respectively. Substance use treatment attendance in the entire sample was 41.6% (42/101) and 36.1% (35/97) at 6 and 12 months, respectively.

Exposure to Intervention

Among the 11 CF group participants with HCV antibody-positive, RNA-negative status, 3 (27.3%) did not have in-person intervention contact and the remaining 8 (72.7%) had between 1 and 5 contacts. Of the 41 care facilitation participants with active HCV infection, only 1 (2.4%) did not have in-person contact with the CF, 3 (7.3%) had a single session, 3 (7.3%) had between 2 and 5 sessions, 6 (14.6%) had between 6 and 9 sessions, and 28 (68.3%) had 10 or more sessions. There was no statistically significant difference in number of sessions attended by gender (χ^2 [1] = 0.03, $P = .85$). The median number of contacts in which the CF accompanied the participant to a provider visit was 2 (IQR, 1–5).

Fidelity

From audio recordings, a fidelity monitor rated 149 (13.6%) sessions for adherence to the session-specific script. The mean ratings by session type for 12 different types of sessions ranged between 2.31 and 2.92. Median ratings by session type ranged between 2.66 and 3.0. These values indicate that all session types had average or median ratings between "mostly" and "completely" performed. The global median rating was 2.97 (IQR, 2.94–3.0). Sites' fidelity differed (χ^2 [7] = 24.6, $P < .001$).

Table 2. Number Completing Each Step Along the Hepatitis C Virus Care Continuum

	No. (%)		
Step	Control (n = 61)	HCV Care Facilitation (n = 52)	Total (N = 113)
Completion of step 1—receipt of HCV RNA result	33 (54.1)	49 (94.2)	82 (72.6)
HCV RNA positive (denominator for steps 4–8)	53	41	94
Completion of step 2—attendance at HIV primary care visit[a]	14/21 (66.7)	9/15 (60.0)	23/36 (63.9)
Completion of step 3—initiated ART[a]	17/21 (81.0)	14/14 (100.0)	31/35 (88.6)
Completion of step 4—HCV status evaluated	17 (32.1)	22 (53.7)	39 (41.5)
Completion of step 5—HCV treatment offered and declined or prescribed	7 (13.2)	11 (26.8)	18 (19.1)
Completion of step 6—HCV treatment initiated	6 (11.3)	8 (19.5)	14 (14.9)
Completion of step 7—HCV treatment completed[b]	0 (0.0)	4 (9.8)	4 (4.3)
Completion of step 8—SVR achieved after 12 weeks	5 (9.4)	6 (14.6)	11 (11.7)

Abbreviations: ART, antiretroviral therapy; HCV, hepatitis C virus; HIV, human immunodeficiency virus; SVR, sustained virologic response.

[a]Steps 2 and 3 were only applicable to those who were not in HIV care at baseline (control, n = 20; intervention, n = 15).

[b]Step 7 was only achieved if there was a note in medical records that HCV treatment had been completed.

However, the median fidelity score for all sites was between "mostly delivered" and "completely delivered" (mean of the fidelity scores per site ranged from 2.5 to 3.0). A second fidelity monitor co-rated 28 sessions to estimate reliability of the ratings. The intra-class correlation for these co-rated sessions was 0.93 (95% CI, .86–.97).

Adverse Events

Adverse events were specific to blood specimen collection and captured from the time of specimen collection through the remainder of that visit. Only 1 adverse event was reported during the course of the trial. Its severity was mild and it resolved without sequelae. No serious adverse events were reported.

DISCUSSION

In this study, an intensive, short-term CF intervention resulted in a statistically significant, yet modest, intervention effect of increased forward movement among intervention participants. Across both groups, approximately 12% of those RNA positive achieved SVR by the 12-month follow-up period.

The CF intervention sought to provide tailored support to reduce barriers using a motivational interviewing approach, to build on individuals' strengths, and to link them to community services to support them through HCV care evaluation, HCV treatment initiation and completion, and SVR. The CF intervention, built on a foundation of efficacious strategies, recognized the complex needs of PWH, HCV, and substance use disorders. Prior to the availability of DAA for the treatment of HCV, Masson and colleagues [25] demonstrated the efficacy of an HCV CF intervention coupled with screening and education for persons in methadone maintenance treatment who tested positive for HCV antibodies. Findings indicated that the intervention was successful in linking participants to follow-up HCV care evaluation within 6 months of enrollment compared to persons who received only screening and education. The present study sought to extend this research to address the full HCV/HIV care continuum among PWH after learning they were coinfected. The intervention also sought to address key components of effective linkage to care interventions for PWH [23, 26, 38].

Sustained virologic response and virologic cure are the goals of HCV testing, linkage to care, and treatment initiation and completion, and the goal of HCV cure is to reduce morbidity and mortality. In the HIV and HCV care continua, losses through sequential steps of care have been high, both complicating efforts to treat individuals and move toward HCV elimination [39]; furthermore, high rates of losses at each step complicate efforts to detect potential differences in the impact of an intervention designed to facilitate movement through the HCV care continuum. Indeed, while studies have examined interventions to improve outcomes among PWUD at any given HCV care continuum step [40, 41], few have examined the impact of an intervention on the full HCV care continuum, from testing to SVR [42]. Our study makes an important contribution by doing so. Furthermore, while use of care continuum metrics is a standard component of HIV public health surveillance [43] and an increasingly common component of HCV surveillance [44, 45], the use of care continuum metrics, and specifically of net care continuum forward movement, as a study outcome for randomized controlled trial intervention assessment is novel. It provides a potentially valuable and efficient strategy for studying intervention efficacy in situations where event rates (such as SVR) may be low and where the intervention target is a multiplicity of steps.

The positive findings observed in this trial are important given that study participants were recruited from a cohort of PWH and substance users who had experienced significant social disadvantage and had many unmet needs with regard to health and behavioral care services. The intervention tested was successful in promoting a significant increase in forward movement through the HCV care continuum in this population with significant barriers to care; while the study did not identify a significant impact of the intervention on the secondary outcome of SVR rates, it was not specifically a priori powered to do so. As recognized by the World Health Organization [39] with laudable yet ambitious HCV elimination goals, overall access to HCV treatment in the United States (US) has been improving but is still limited. The HCV care infrastructure in the US falls considerably short compared to the HIV care infrastructure, which includes payors of last resort such as the Ryan White Care Act, AIDS Drug Assistance Program, and more robust HIV surveillance; moreover, jurisdictions and payors vary in DAA access, particularly for PWUD. Another point is that in contrast to HIV testing, in which a positive antibody test is sufficient to diagnose active HIV infection, because approximately 25% of those with HCV infections have spontaneous clearance if infected [46], HCV testing requires both antibody and viral load testing to confirm active infection, as was done in our study. However, strategies that use automatic reflex viral load testing of specimens found positive for HCV antibodies may be associated with reduced losses at these testing steps [42]. Other countries have productively addressed HCV care continuum gaps and have tested and implemented more efficient approaches [47, 48]. Similarly, recently studied and implemented interventions for HIV have focused on condensing the steps in the HIV continuum of care and include rapid, same-day initiation of ART [49–53], and bundled HIV/HCV testing [54–56]. For persons who use drugs, there is also the opportunity to test and implement models of integrated HIV/HCV care within substance use disorder treatment, syringe services programs, mobile clinics, telehealth approaches, and long-acting treatment regimens [57–63].

Findings showed a differential intervention effect by gender; increased forward care continuum movement was observed only for men. There are mixed findings from previous observational studies, with some showing that women were less likely than men to progress along the HCV care continuum [64] and others suggesting that men may be less likely than women to seek HCV care [65, 66]. Gender differences in care continuum outcomes are particularly critical as other data have identified a higher HCV incidence, and a shorter time to HCV seroconversion, among females who inject drugs and those who engage in medication-assisted treatment for opioid use disorders [64, 67–69].

Although the current study had good retention and intervention fidelity rates, some limitations should be noted. First, recruitment was limited to individuals who had participated in the CTN-0049 trial [24], potentially limiting generalizability. Second, while statistical power was sufficient to detect a meaningful difference in forward movement along the HCV treatment care continuum, the trial was not powered to detect differences on any particular step within the continuum. Third, the long-observed time to engage in HCV treatment and the study's limited (12-month) follow-up period meant that the study's secondary endpoint of SVR could not be observed for many participants.

In conclusion, the study findings are important for efforts in the US to move toward the World Health Organization's goal to eliminate HCV by 2030 [70–72]. The findings in this study of people who are among the hardest and most vulnerable populations to treat both point to strategies that facilitate movement along the HCV/HIV care continuum and highlight the continued challenges to achieve SVR and ultimately HCV elimination. The study's high retention rates speak positively to participants' adherence to study visits and thus suggest the need to further address structural and systemic issues that are complex and difficult to overcome even with a CF. These factors would include long waiting times, medication costs, social service needs (eg, unstable housing), and policies requiring sobriety that may serve as formidable barriers to forward movement along the HCV and HIV care continua [14, 15, 47].

Supplementary Data

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

Notes

Patient consent statement. The procedures in this work with human subjects were in accordance with the ethical standards of the Helsinki Declaration (1964, amended most recently in 2008) of the World Medical Association. Patients' written consent was obtained and any information, including illustrations, were kept as anonymized as much as possible. The design of the work has been approved by local ethical committees.

Data availability. The dataset will be posted at https://datashare.nida.nih.gov/.

Disclaimer. The authors are solely responsible for the content of this article, which does not necessarily represent the official views of the National Institute on Drug Abuse.

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