

Rapid hepatitis C test and treat with peer support at opioid treatment programs (RAPID HCV): a hybrid effectiveness-implementation type 1 randomized control trial

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Summary

Background People who use drugs (PWUD) face persistent barriers to hepatitis C virus (HCV) treatment, threatening HCV elimination goals. Integrating HCV testing and treatment into opioid treatment programs (OTPs) may increase access and uptake. We evaluated the effectiveness and implementation outcomes of an onsite HCV test and treat model delivered within OTPs.

Methods RAPID HCV was a multicenter, open label randomized controlled trial conducted at five OTPs in the United States and Canada. PWUD with a reactive antibody test were randomized (1:1) to onsite OTP-delivered HCV test and treat with peer support (RAPID HCV) or referral to offsite specialist care. Randomization was computer generated with concealed allocation. Following randomization, participants underwent clinical eligibility assessment for glecaprevir/pibrentasvir. The primary outcome was HCV treatment initiation within 12 weeks among treatment eligible participants (modified intention-to-treat [mITT]). The trial is registered at clinicaltrials.gov (NCT04677153).

Findings Between August 2021, and November 2023, 182 participants were randomized; 58 were ineligible for treatment and two were administratively excluded, yielding 122 in the mITT population. Median age was 49 years (IQR 38–58), 73 (60%) were male, and 85 (70%) had an illicit substance detected in urine at baseline. Treatment initiation occurred in 59 of 66 (89% [95% Confidence Interval 79–95]) RAPID HCV participants compared with 12 of 56 (21% [95% CI 13–34]) referred participants ($p < 0.001$). No serious adverse events related to study procedures or HCV treatment were observed.

Interpretation Onsite HCV test and treat with peer support delivered by OTP staff significantly increased HCV treatment initiation compared with offsite referral. Integrating HCV care into OTPs is an effective strategy to advance HCV elimination among PWUD.

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Research in context**Evidence before this study**

We searched PubMed from January 1, 2014, to September 1, 2025, using the search terms (hepatitis C AND treatment OR direct acting antivirals) AND (opioid treatment program OR methadone program OR opioid substitution therapy) AND (implementation or care integration) AND (treatment initiation). We identified observational studies and pilot projects suggesting that co-locating hepatitis C virus (HCV) testing and treatment within opioid treatment programs (OTPs) improves linkage to care with high HCV cure rates among OTP clients. However, most studies were small, uncontrolled, or non-randomized without a comparison to standard of care offsite referral and few reported implementation outcomes such as acceptability or feasibility. Two randomized controlled trials evaluated specialist HCV care provided in OTPs compared to offsite referral. One from North America evaluated and demonstrated that integration of telemedicine care provided at OTPs by an offsite specialist was associated with higher rates of HCV treatment initiation and cure compared to offsite referral. No randomized controlled trial has previously evaluated integrated HCV test-and-treat delivery by OTP staff compared with standard offsite referral in North America.

Added value of this study

The RAPID HCV randomized controlled trial across five OTPs in the United States and Canada demonstrates that onsite HCV test-and-treat with peer support led to a fourfold increase in treatment initiation within 12 weeks compared with standard offsite referral (89% versus 21%). In addition to clinical outcomes, we assessed implementation outcomes. OTP leadership and staff rated the model as highly acceptable and appropriate, although feasibility ratings highlighted challenges in sustaining integration without additional structural support.

Implications of all the available evidence

Achieving HCV elimination requires reaching people who use drugs, the population most affected by ongoing transmission. This trial provides robust evidence that integrating HCV test-and-treat into OTPs is not only effective but also acceptable to staff and leadership. To realize the potential to upscale HCV treatment integration into OTPs, policymakers must address structural barriers to feasibility, including workforce support, reimbursement, and sustainable infrastructure. Integrating HCV care into OTPs should be prioritized as a strategy to accelerate HCV elimination.

Introduction

Hepatitis C virus (HCV) infection is a leading cause of morbidity and mortality globally.¹ An estimated 6.1 million people with recent injecting drug use have HCV infection with 30.5% of HCV infections in North America among people with recent injecting drug use.² Although the availability of oral, highly effective and well tolerated HCV treatments has made HCV elimination biologically feasible, HCV treatment uptake among people who use drugs (PWUD) in routine care settings remains low.^{3–6} The World Health Organization (WHO) set a target for HCV treatment in 80% of people with HCV infection as part of its HCV elimination strategy.⁷ However, only 11–21% of PWUD have been treated for HCV highlighting a substantial implementation gap.^{8–10} Implementation strategies that address multilevel barriers to HCV care delivery and uptake among PWUD are needed to achieve the WHO goal to eliminate HCV as a public health threat.^{7,11}

Opioid treatment programs (OTPs) provide evidence-based treatment for people with substance use disorders (SUD). As of 2023 there were over 2000 OTPs serving approximately 600,000 PWUD across the US with oversight from the Substance Abuse and Mental Health Services Administration (SAMHSA).¹² OTPs similarly provide specialized OUD care in Canada. OTPs offer medications for opioid use disorder such as methadone and buprenorphine and other services including peer support and care management with community referrals. OTP service availability is largely

influenced by state and federal financing policies including bundle service requirements for receipt of payments for most OTPs.¹² Across OTPs, methadone is dispensed with medication intake directly observed at the OTP as frequently as daily with some OTP clients able to take methadone doses home for unobserved intake.¹² To support comprehensive care for PWUD, SAMHSA guidelines recommend testing for blood borne infections such as HIV and HCV and highlight the suitability of OTPs for HCV testing and treatment.¹²

However, referral to HCV care at specialist centers continues to represent the dominant treatment model across North America. This approach poses significant structural and behavioral barriers for PWUD, including transportation challenges, fragmented care pathways and stigma resulting in suboptimal HCV treatment uptake.^{4–6} Prior evidence suggests that integrating HCV treatment into opioid treatment program (OTP) settings characterized by frequent contact, established trust and longitudinal engagement is a feasible alternative that can overcome these barriers and improve treatment uptake among PWUD.¹³ Integration alone may however be insufficient to address the complex behavioral, social and structural factors that impact engagement in care. Implementation determinants such as stigma, competing priorities, limited patient navigation capacity within OTPs and variable HCV treatment readiness among patients may undermine HCV treatment uptake.^{4–6} Peer support delivered by

individuals with lived experience of substance use and HCV care represents a potentially powerful implementation strategy to address these determinants. Peers may enhance engagement by normalizing HCV treatment, reducing stigma, supporting navigation through treatment initiation and reinforcing adherence within the context of routine OTP care. Other data suggest that social support at OTPs may be an important facilitator of HCV treatment uptake, yet limited data exists for implementation outcomes of peer supported implementation strategies.¹⁴

We conducted an effectiveness-implementation hybrid type 1 trial which utilized a randomized control trial design to primarily evaluate clinical effectiveness of an onsite HCV test-and-treat model delivered within OTPs, while simultaneously assessing implementation outcomes relevant to real world adoption, implementation and sustainability.¹⁵ Using a randomized controlled design, we compared an integrated, peer-supported HCV test-and-treat strategy delivered onsite at five OTPs across four North American cities with referral to offsite specialty HCV care. Consistent with a hybrid type 1 approach, the primary focus was on treatment initiation while secondary aims evaluated implementation outcomes of acceptability, appropriateness, and feasibility to inform future dissemination and sustainability of peer supported HCV treatment integration in OTP settings.¹⁵

Methods

Study design

The study was a randomized controlled trial conducted at five OTPs (2 in Baltimore Maryland and 1 in each of San Francisco, California, and Birmingham Alabama, in the United States and Toronto, Canada). The OTPs were in urban and suburban settings and had a range of client volumes, staffing models and reimbursement structures (Supplementary Table S1). The RAPID HCV intervention strategies (Supplementary Table S2) were implemented at each OTP.

Ethics approval

The study was approved by the Johns Hopkins University School of Medicine Institutional Review Board as the central IRB (IRB00265240) and was initially approved on April 6, 2021 for US sites. The University Health Network Toronto Research Ethics Board CAPCR and Veritas Independent Review Board provided regulatory oversight for the Canadian site. All participants provided written informed consent. The study is registered at (<https://clinicaltrials.gov/study/NCT04677153>) and the protocol is available as Appendix E.

Participants

Inclusion criteria

Participants were eligible for participation in the randomized control trial if they were ≥ 18 to ≤ 70 years old,

HCV antibody positive, direct acting antiviral (DAA) naïve, not pregnant (for females of childbearing potential) and, if living with HIV, ART naïve with CD4 T cell count >500 cells/mm³ or on a stable ART regimen.

Exclusion criteria

Individuals with a history of decompensated liver disease, hepatocellular carcinoma, or positive hepatitis B surface antigen (HBsAg) test were excluded. Participants with platelet count of $<150,000$ /mm³ were excluded to avoid inadvertent inclusion of patients with decompensated liver disease. Individuals on medications for which co-administration with glecaprevir/pibrentasvir was contraindicated or with a history of allergy/sensitivity to any components of glecaprevir/pibrentasvir were excluded (Appendix B).

Study procedures

RAPID HCV intervention

Local HCV treatment specialists contacted regional OTP leadership to assess interest in receiving technical assistance and support for integrating HCV testing and treatment into routine OTP workflows. Participating sites completed a local context and feasibility assessment overseen by the central coordinating center. Each OTP was required to identify a site champion and designate at least one staff member (MD/DO, Nurse practitioner or Physician Assistant) authorized to prescribe oral DAA treatment. After onboarding, local HCV treatment experts provided ongoing technical assistance to support program setup and implementation of the HCV test and treatment model. OTPs received centralized training through a one-and-a-half-hour session offered over zoom simultaneously to OTP leadership and staff designated for HCV care across all participating OTP sites. This session included a didactic on HCV treatment with a focus on the American Association for the Study of Liver Diseases/ Infectious Disease Society of America (AASLD/IDSA) simplified treatment algorithm provided by an HCV specialist and a walkthrough of the HCV treatment determination tool: an electronic guide for participant HCV treatment evaluation, non-invasive liver disease staging, counseling tailored to participant demographics and laboratory data entered by providers (Appendix A). No additional site or study specific credentialing was required beyond this training. Access to the online HCV treatment determination tool and one-page AASLD/IDSA simplified treatment algorithm was provided to OTPs to support local clinicians with HCV treatment. Each OTP site was asked to identify existing OTP clients who had lived experience of HCV testing and treatment, a willingness to share this experience with others, and good communication skills to serve as peer mentors. These individuals were referred to onsite research program coordinators who trained them to provide peer support using a standardized curriculum

that included five 5–20-min videos and a training guide. Peers were expected to contact mentees weekly and provided a peer manual as a reference for completing peer mentor activities and logs to support documentation of attempted and successful contact with mentees. Peer mentors were supported by a site level research program coordinator at weekly check-ins which included a review of peer mentor weekly contact logs and discussions of challenges and progress in their peer mentorship role. Peers were compensated weekly with \$20 for each attempted/successful contact. OTPs were onboarded individually over 21 months based on timing of local regulatory approvals with OTP 1 onboarded in August 2021, OTP 2 December 2021, OTP 3 June 2022, OTP 4 July 2022 and OTP 5 May 2023. Each OTP implemented on-site HCV testing available to all OTP clients.

Recruitment screen. OTPs clients with a documented positive HCV antibody or detectable HCV RNA test (whichever was available) either self-referred or were referred by OTP staff to trained research staff for screening. Individuals who remained study eligible after completing the screening questionnaire were offered preliminary study enrollment, informed that treatment eligibility would be dependent on results of baseline laboratory testing and, if willing, consented in writing and randomized.

Randomization and masking. Randomization for screened and eligible participants occurred separately for each OTP site in a 1:1 ratio without randomization blocks to the RAPID HCV test and treat with peer support (RAPID HCV) arm or offsite specialist referral (referral) arm. Randomization was generated by the study statistician and uploaded into the study electronic REDCap database with the allocation sequence concealed from investigators and study personnel except for the REDCap programmer and statistician from the study data coordinating center. Randomization arm was electronically released in the REDCap database to study staff at the study site upon completion of all baseline study procedures. Participants and research staff who informed participants of randomization arm, and administered surveys to assess outcomes were not blinded.

Procedures. After consent and randomization, participants completed baseline study laboratory testing including HCV RNA, complete blood count, comprehensive metabolic panel and hepatitis B surface antigen testing. Beta human chorionic gonadotropin (HCG) pregnancy testing was also completed in females of childbearing age. Participants who on laboratory testing were found to have an undetectable HCV RNA, positive HBsAg, a platelet count $<150,000/\text{mm}^3$ or a positive B-HCG were considered ineligible for treatment through the study.

All study participants had access to fixed-dose combination tablet glecaprevir (100 mg) with pibrentasvir (40 mg) to be taken as three tablets daily for 8 weeks dispensed as a 28-day supply with 1 refill. Glecaprevir/pibrentasvir was provided at no cost to participants. Participants could however be treated with other direct-acting antivirals (DAAs) at the discretion of the treating provider.

RAPID HCV arm

Participants randomized to the RAPID HCV arm were informed that HCV treatment evaluation and treatment was available on-site and assigned a trained peer mentor. OTP nurses with oversight from a nurse practitioner/physician assistant, MD/DO evaluated patients. HCV treatment was prescribed by OTP clinicians at their discretion. Peer mentors were expected to meet and engage with participants in the RAPID HCV arm weekly from randomization through assessment of sustained virologic response (SVR) at week 12, or 12 weeks after randomization if participants did not initiate HCV treatment. Peer mentors provided information to support HCV treatment uptake, treatment adherence after initiation and reinfection prevention after treatment completion.

Referral arm

Participants randomized to the referral arm were referred to the local offsite specialist HCV treatment center and given a number to schedule an HCV treatment evaluation appointment. Appointments were facilitated by research staff who coordinated with specialist clinic sites to ensure scheduling within 2 weeks if the participant called the appointment scheduling number.

Study assessments

All participants completed surveys with self-report of sociodemographic characteristics including biological sex, medical history and patient reported outcomes (PRO) and provided blood and urine samples at baseline. PROs included depression symptoms (Patient Health Questionnaire-8 [PHQ-8]),¹⁶ anxiety symptoms (General Anxiety Disorder-7 [GAD-7]),¹⁷ food insecurity,¹⁸ drug use and alcohol use ((Alcohol use disorders identification Test –C (AUDIT-C)). Hazardous alcohol use was defined as an AUDIT-C score of >4 for males and >3 for females.¹⁹ Among participants who initiated treatment, research visits including survey data and blood and urine sample collection at the expected end of treatment, as well as 12, 24, and 36 weeks after the end of treatment. For participants who did not initiate treatment within 12 weeks of randomization, subsequent research visits occurred at weeks 12, 24, 36, and 56 after randomization ([Appendix C](#)).

Blood samples were tested at a commercial laboratory. Urine specimens were tested with multi-drug

screen dip cards for amphetamine, methamphetamine, benzodiazepine, cocaine, delta-9-tetrahydrocannabinol or cannabis, opiate, and oxycodone at baseline and during follow-up visits ([Appendix D](#)). Compensation for study visits varied by site. Participants were compensated US \$25 for study surveys and US \$15–20 for laboratory tests at US sites and \$100 for study surveys and laboratory test completion at the Canadian site.

Outcomes

The primary effectiveness outcome was treatment initiation within 12 weeks of randomization, assessed by self-report and confirmed through medical record review. Secondary outcomes were 1) Time to HCV treatment initiation up to 24 weeks after randomization; 2) HCV treatment completion, defined as taking $\geq 90\%$ of prescribed HCV course by expected end of treatment date; and 3) SVR defined as HCV RNA < 15 IU/ml measured 10–36 weeks after end of treatment to maximize outcome ascertainment and accommodate variable follow-up in OTP settings, with results closest to 12 weeks used when available. Participants with missing SVR data were considered treatment failures. Grade 3 or higher and all serious adverse events related to use of DAA therapy up to 30 days after DAA completion were collected.

Implementation outcomes

Organizational acceptability, appropriateness and feasibility of HCV treatment integration into the OTP context were assessed at the implementer level using brief validated scales, including the acceptability of intervention measure (AIM), intervention appropriateness measure (IAM), and feasibility of intervention measure (FIM).²⁰ Organizational readiness for implementing change was assessed using the ORIC tool.²¹ Measures to assess acceptability (the perception that an intervention is agreeable or palatable), appropriateness (the perception of fit or compatibility), feasibility (the extent to which the intervention can be carried out in the setting); and organizational readiness for HCV treatment integration utilized a Likert scale response ranging from 1 strongly disagree to 5 strongly agree. Surveys were completed by OTP leadership in collaboration with core HCV treatment implementation staff at each OTP prior to implementation and 18–24 months into implementation. Each OTP submitted one complete form to the central coordinating center. Higher scores are indicative of implementation success.

Statistical analysis

Effectiveness outcomes

Analyses were conducted using a modified intention-to-treat approach (which excludes randomized participants who did not meet treatment eligibility criteria, i.e., an undetectable HCV RNA or HBsAg positive).

This approach was pre-specified and an intentional pragmatic design decision aligned with the study implementation objective of evaluating real world strategies for integrating HCV testing and treatment into OTPs where individuals with HCV are usually first identified through antibody screening and treatment eligibility determined downstream. Thus, randomization at the antibody positive stage reflects the real-world decision point at which OTPs must determine whether to initiate onsite care pathways or refer offsite. Results of laboratory testing conducted after study consent and randomization including HCV RNA and HBsAg status were required to confirm treatment eligibility. A modified intention-to-treat approach was essential to assess the differential impact of HCV treatment study arm on HCV treatment initiation among only HCV treatment eligible individuals. Planned enrollment was initially for 250 participants with the protocol amended in 2022 to planned enrollment of 124 treatment eligible participants, based on adjusted estimates of treatment initiation through standard of care offsite referral. The final sample size calculation utilized a conservative estimate of HCV treatment initiation of 40% in the referral arm.²² Assuming a minimum difference in HCV treatment uptake of 30% between study arms (RAPID HCV = 70%; Referral arm = 40%), our sample size was sufficient to detect a statistically significant difference between study arms, with 85% power at an alpha level of 0.05. This estimated sample size accounted for a 10% drop out rate.

Comparisons in baseline sociodemographic and clinical characteristics between arms were assessed as frequencies and proportions. For primary analysis, we estimated proportions of patients and their 95% confidence intervals (CI) of HCV treatment initiation within 12 weeks of randomization by study arm, using bootstrapped standard errors. Risk difference (RD) and 95% CI of RAPID HCV versus referral arms were calculated with standard errors computed using the Delta-method. We also estimated the association between study arm and treatment initiation using a logistic regression model that included site as a covariate and calculated robust standard errors.

For secondary outcomes, we conducted a survival (Kaplan Meier) analysis to compare time to HCV treatment initiation between randomization arms and used a log-rank test to assess for statistically significant difference between groups. The proportions of participants (and their 95% CI) who completed HCV treatment and those who achieved SVR, by study arms, were estimated using bootstrapped standard errors based on 100 iterations. RDs and 95% CI were calculated as described above. Lastly, we described the HCV care continuum by study arm. Analysis of adverse event data was primarily descriptive. Stata/BE version 17.0 (Stata Corp LLC, College Station, TX) was used for all analyses.

Implementation outcomes

Acceptability, appropriateness and feasibility scores were calculated by summing the responses for each of the 4 questions for AIM, IAM, FIM and divided by the number of questions with a score range of 1–5 for each measure. Organizational readiness was calculated for each of the questions on the ORIC with a score range of 12–60 and summarized for each site with means and standard deviation and means for each question across sites.

Role of the funding source

AbbVie Inc funded the study including provision of glecaprevir/pibrentasvir. Funders had no role in data collection, data analysis, interpretation, writing of the report or decision to submit.

Results

Overall, 198 participants were screened for eligibility, of which 16 did not meet screening criteria resulting in 182 participants consented, enrolled, and randomized between August 2021 and November 2023. Of the enrolled participants, 124 participants were HCV treatment eligible; among the 58 participants excluded due to treatment ineligibility, 25 participants were in the RAPID HCV arm and 33 were in the referral arm (Fig. 1). Of 124 participants eligible for treatment through the protocol, 2 participants randomized to the referral arm were excluded from analysis due to a randomization error.

Sociodemographic and clinical characteristics

Among 122 participants included in analyses, 66 were randomized to the RAPID HCV arm and 56 to the referral arm. Participant enrollment varied across OTPs with most enrolled in Baltimore Maryland (Table 1). Baseline characteristics were well balanced between groups (Table 1). Most participants were male (73 (60%)) and white (71 (58%)) with a median age of 48.5 years (interquartile range [IQR]; 37.5–57.8). A significant portion had less than a high school diploma (51 (42%)), were unemployed (51 (42%)), food insecure in the past 12 months (75 (62%)) and homeless in the past 6 months (38 (32%)). The majority had a FIB-4 score ≤ 3.25 indicating lack of advanced fibrosis (118 (97%)) and a positive urine drug screen (85 (70%)) with fentanyl as the most detected substance (64 (55%)). The mean (SD) number of days of drug use in the prior 30 days was 6.3 (10.4) days for heroin, 7.5 (11.2) days for cocaine and 7.6 (10.4) days for amphetamines. Injecting drug use in the prior 30 days was reported by 34 (28%) participants. Hazardous alcohol use was reported in 21 (18%) participants. Among participants on medications for opioid use disorder (MOUD), the majority were on methadone (94/101 (93%)).

Treatment initiation

In the RAPID HCV arm, 59/66, 89% (95% CI [79–95]) of participants initiated HCV treatment within 12 weeks compared to 12/56, 21% (95% CI [13–34]) in the referral arm, RD 68% (95% CI; 55%–81%), adjusted odds ratio

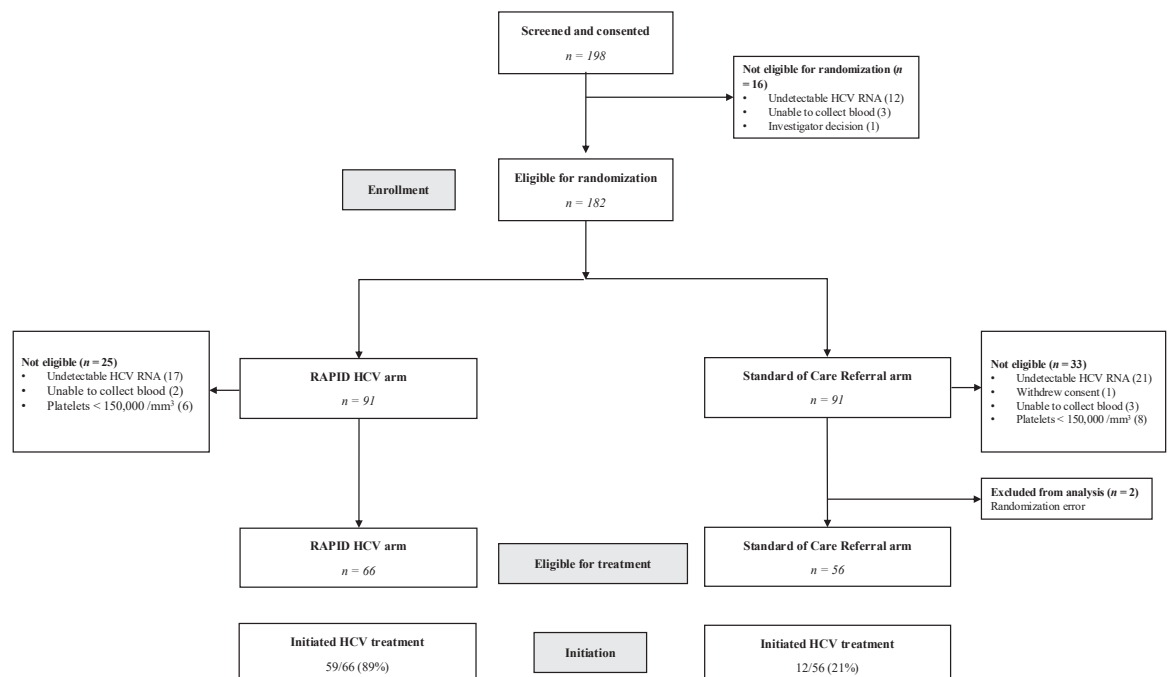


Fig. 1: Trial profile. Flow diagram showing participant screening, randomization, inclusion in analyses, treatment eligibility and treatment initiation.

	Total		Standard of care referral		Rapid HCV	
	(n = 122)		(n = 56)		(n = 66)	
Demographic characteristics						
Age, years						
Mean (SD)	48.0	(11.8)	47.5	(12.3)	48.3	(11.5)
Median (IQR)	48.5	(37.5–57.8)	46.4	(36.4–56.7)	49.5	(37.7–59.2)
Biological sex						
Male	73	(60%)	37	(66%)	36	(55%)
Female	49	(40%)	19	(34%)	30	(45%)
Race						
White/Caucasian only	71	(58%)	34	(61%)	37	(56%)
Black/African only	45	(37%)	20	(36%)	25	(38%)
Others and multiracial	6	(5%)	2	(4%)	4	(6%)
Hispanic	6	(5%)	3	(5%)	3	(5%)
Education level						
Less than HS	51	(42%)	26	(46%)	25	(38%)
HS/GED	41	(34%)	18	(32%)	23	(35%)
Some college or higher	30	(25%)	12	(21%)	18	(27%)
Employment status (Prior 3 years) ^a						
Full time/Part time	29	(24%)	12	(21%)	17	(26%)
Retired/Disability	38	(31%)	14	(25%)	24	(37%)
Unemployed	51	(42%)	28	(50%)	23	(35%)
In a controlled environment (inpatient drug treatment)	3	(2%)	2	(4%)	1	(2%)
Marital status						
Married or committed Relationship	44	(36%)	18	(32%)	26	(39%)
Single, separated, divorced or widowed	77	(63%)	38	(68%)	39	(59%)
Don't know	1	(1%)	0	(0%)	1	(2%)
Homeless in last 6 months	38	(32%)	17	(31%)	21	(32%)
Insurance type ^b						
None	7	(6%)	5	(9%)	2	(3%)
Public	106	(88%)	45	(82%)	61	(92%)
Private	5	(4%)	3	(5%)	2	(3%)
Other/Don't know	3	(2%)	2	(4%)	1	(2%)
Food insecurity in the past 12 months ^g	75	(62%)	34	(62%)	41	(62%)
Hazardous alcohol use ^c	21	(18%)	7	(13%)	14	(22%)
Clinical characteristics						
FIB-4 score						
≤3.25	118	(97%)	55	(98%)	63	(95%)
>3.25	4	(3%)	1	(2%)	3	(5%)
Depression severity (PHQ-8 ≥ 10)	53	(44%)	25	(45%)	28	(43%)
Anxiety severity (GAD-7 ≥ 10)	48	(40%)	24	(45%)	24	(36%)
Treatment for drug use						
Any medication for opioid use disorder (MOUD)	101	(96%)	46	(96%)	55	(97%)
Methadone	94	(93%)	42	(91%)	52	(95%)
Drug use characteristics						
Injection drug use reported in the past 30 days ^f	34	(28%)	13	(24%)	21	(32%)
Mean number of days of drug use in the past 30 days, (SD)						
Heroin	6.3	(10.4)	4.4	(8.3)	7.9	(11.7)
Cocaine	7.5	(11.2)	5.3	(8.9)	9.2	(12.5)
Amphetamine	7.6	(10.4)	6.2	(10.5)	9.1	(10.4)
Other opiates/analgesics	8.1	(11.8)	7.1	(10.8)	9.1	(12.7)
Used shared needle/Syringe						
Never	67	(56%)	28	(52%)	39	(59%)
More than 6 months	46	(38%)	22	(41%)	24	(36%)
Within the past 6 months	7	(6%)	4	(7%)	3	(5%)

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	Total		Standard of care referral		Rapid HCV	
	(n = 122)		(n = 56)		(n = 66)	
(Continued from previous page)						
Urine drug screen results at baseline visit ^d						
Any drug ^e	85	(70%)	43	(77%)	42	(64%)
Fentanyl	64	(55%)	27	(52%)	37	(58%)
Cocaine	56	(49%)	27	(53%)	29	(45%)
Amphetamine	20	(17%)	10	(19%)	10	(16%)
Benzodiazepine	15	(13%)	5	(9%)	10	(16%)
Study site						
Baltimore 1	59	(48%)	25	(45%)	34	(52%)
Baltimore 2	23	(19%)	9	(16%)	14	(21%)
San Francisco	12	(10%)	7	(12%)	5	(8%)
Alabama	12	(10%)	7	(12%)	5	(8%)
Toronto	16	(13%)	8	(14%)	8	(12%)

Variable distributions are reported as n (% of total non-missing responses) unless otherwise specified. Abbreviations: ITT, intention-to-treat; mITT, modified intention-to-treat; PHQ-9, Patient Health Questionnaire-9; OTP, Opioid Treatment Program; MOUD, Medication for Opioid Use Disorder; FIB-4, Fibrosis Index 4. ^aExtent of missing observations varies across the characteristics. Variables with missing values (employment status: 3 (n = 121); homelessness: 2 (n = 120); Insurance type: 1 (n = 121); Hazardous alcohol use: 3 (n = 119); Depression Severity: 2 (n = 120); Anxiety severity: 3 (n = 119); any MAT: 17 (n = 105); IV drug use: 1 (n = 121); used needle/syringe: 2 (n = 120); urine drug screen [fentanyl: 6 (n = 116); cocaine: 7 (n = 115); amphetamine: 7 (n = 115); benzodiazepine: 5 (n = 117)]. Underlying reasons for missing information were mostly unknown. ^bExcept for the "None" and "Don't know" category, all other categories are not mutually exclusive. ^cBased on the Alcohol Use Disorders Identification Test score: Cutoffs are different for male and female participants. ^dPercentages were calculated on the basis of the conducted urine drug screen at baseline visit. ^ePositive for any drug toxicology (including fentanyl, codeine, morphine, hydromorphone, hydrocodone, cocaine, amphetamine, barbiturates, oxycodone, benzodiazepine and phencyclidine). ^fParticipants were asked what their usual route of drug administration was per drug type used in the past 30 days (heroin, cocaine, other opiates/analgesics, amphetamine, sedatives/hypnotics and barbiturates). ^gFood insecurity risk was assessed at baseline using a 2-item validated tool: The Hunger Vital Sign. Patients were considered at risk if they reported a response other than "never" to either question on the tool (worry about running out of food or having insufficient food in the prior 12 months).

Table 1: Baseline characteristics of study participants.

(AOR) 30.79 [95% CI 11.22–84.49], p-value <0.001. An additional 2 participants in the referral arm initiated HCV treatment between 12 and 24 weeks after randomization resulting in HCV treatment initiation in 14/56 (25% [95% CI 15.6–37.5]) of participants overall in the referral arm. The median time to treatment initiation from randomization was 20 days (IQR 12–41) for participants in the RAPID HCV arm and 168 days (IQR 135–168) for participants in the referral arm (p < 0.001) (Table 2, Fig. 2).

Subgroup post-hoc analyses. Across US sites 52/58, 90% (95% CI [80–95]) of participants initiated HCV treatment within 12 weeks compared to 11/48, 23% (95% CI [13–36]) in the referral arm. Similarly, at the Canadian site, 7/8, 88% (95% CI [38–99]) of participants in the RAPID HCV arm compared to 1/8, 13% (95% CI [2–58%]) in the referral arm initiated HCV treatment within 12 weeks (Supplementary Table S3). Proportion of participants initiating HCV treatment in the referral arm varied from 0% in San Francisco to 32% in Baltimore.

	Outcomes in standard of care referral arm, n (% [95% CI]) of N	Outcomes in rapid HCV arm, n (% [95% CI]) of N	Risk difference n (% [95% CI])	p-value
Treatment initiation within 12 weeks	12 (21% [13–34]) of 56 participants	59 (89% [79–95]) of 66 participants	67% (55–81)	<0.001
Time to treatment initiation, median days (IQR)^a	≥168 (134.5–≥168)	20 (12–41)	–	<0.001^c
At least 90% treatment completion				
Total enrolled participants	10 (17% [10–31]) of 56 participants	42 (64% [51–75]) of 66 participants	46% (30–61)	<0.001
Among participants that initiated treatment	10 (71% [40–90]) of 14 participants	42 (71% [59–81]) of 59 participants	–0.2% (–27 to 26)	0.986
Among participants that initiated treatment within 12 weeks	8 (67% [36–88]) of 12 participants	42 (71% [59–81]) of 59 participants	4.5% (–25 to 34)	0.762
Sustained virological response^b				
Total enrolled participants	8 (14% [7–26]) of 56 participants	40 (61% [48–72]) of 66 participants	46% (31–61)	<0.001
Among participants that initiated treatment	8 (57% [35–76]) of 14 participants	40 (68% [55–78]) of 59 participants	11% (–18 to 39)	0.467
Among participants that initiated treatment within 12 weeks	8 (67% [34–89]) of 12 participants	40 (68% [55–78]) of 59 participants	1.1% (–28 to 31)	0.940

Statistically significant p-values highlighted in bold. ^aTime to treatment initiation in days, censored at 24 weeks (168 days). ^bSustained virological response defined as HCV RNA <15 IU/ml post-treatment week 10–36. ^cLog rank test.

Table 2: Comparison of study outcome rates.

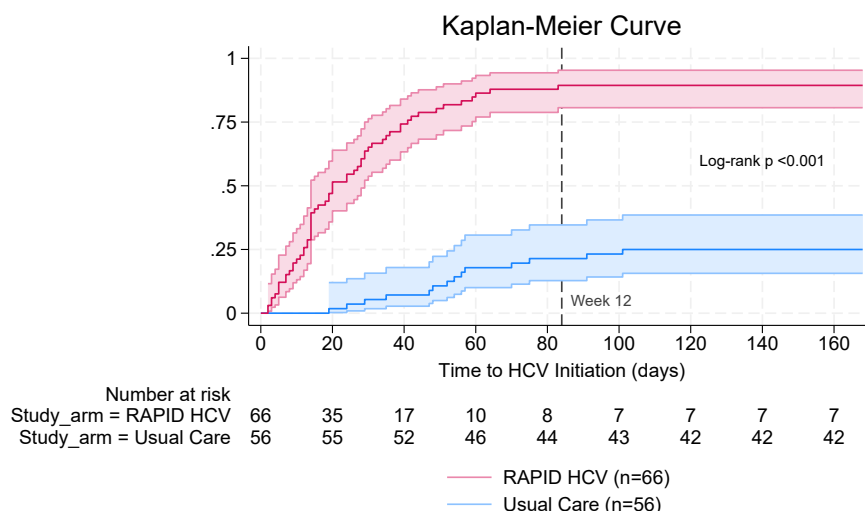


Fig. 2: Time to HCV treatment initiation in days by randomization arm. Kaplan-Meier curves showing the cumulative incidence of hepatitis C virus (HCV) treatment initiation versus time (days) from randomization by treatment arm. Shaded areas represent 95% confidence intervals. The log-rank p-value assesses differences between survival curves.

Treatment completion

Overall, 42/66; 64% (95% CI [51–75]) in the RAPID HCV arm completed treatment compared to 10/56; 17% (95% CI [10–31]) in the referral arm, RD = 46%; 95% CI [30–61] ($p < 0.001$) (Table 2). Among participants that initiated treatment, a similar proportion completed treatment in both RAPID HCV and referral arms (42/59; 71% (95% CI [59–81]) versus 10/14; 71% (95% CI [40–90]), RD = -0.2%; 95% CI [-27 to 26], $p = 0.986$.

Sustained virologic response

Overall, 40/66; 61% (95% CI [48–72]) of participants in the RAPID HCV arm and 8/56; 14% (95% CI [7–26]) in the referral arm achieved SVR, RD = 46%; 95% CI [31%–61%] ($p < 0.001$) (Fig. 3, Table 2). Among participants that initiated treatment, a similar proportion in the RAPID HCV arm 40/59; 68% (95% CI [55–78]) and 8/14; 57% (95% CI [35–76]), RD = 11%; 95% CI [-18 to 39] in the referral arm ($p = 0.467$) achieved SVR (Table 2). Among those that completed treatment, SVR was similar in the RAPID HCV (30/42; 71% 95% CI [56–83]) and referral arms (7/10; 70% 95% CI [30–93]).

Subgroup post-hoc analyses

Among participants who completed treatment and had SVR HCV RNA testing, SVR was documented in 30/35 (86% 95% CI [67–95]) and 7/7 (100%) of participants, and HCV RNA testing for SVR unavailable in 7/42 (17%) and 3/10 (30%) in the RAPID HCV and referral arms respectively. Across all individuals eligible for treatment, the most common reasons for non-SVR in the RAPID HCV arm were recurrent viremia either due to treatment non-response or reinfection in 11/66

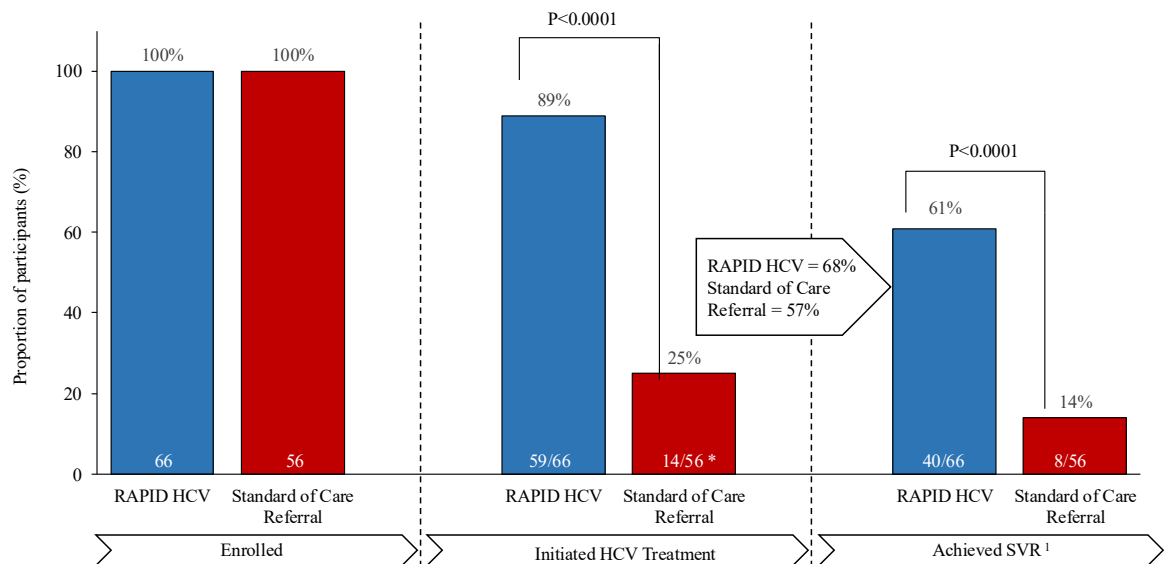
(16.6%), due to lack of SVR HCV RNA testing in 8/66 (12.1%), and non-initiation of DAA in 7/66 (10.6%). Among participants in the referral arm non-initiation of DAA was the most common reason for treatment failure [42/56 (75.0%)] followed by lack of SVR HCV RNA testing [5/56 (8.9%)] and treatment non-response or reinfection [1/56 (1.8%)]. While treatment initiation rates were uniform across sociodemographic characteristics, SVR rates were lower among those in the RAPID HCV arm with less than a high school education (Supplementary Table S3). Majority 19/25 (75%) of participants who did not achieve or have documentation of SVR reported injection drug use in the past 30 days or had a substance detected in urine toxicology at baseline (Supplementary Table S4).

Adverse events

There was no drug related grade 3 or higher or serious adverse events reported.

Implementation outcomes

Integration of HCV treatment into the OTP setting was rated as highly acceptable with a mean score of 5 out of a possible range of 1–5 on the AIM at baseline and mean score of 4.7 at follow up (Supplementary Table S5). Appropriateness measured on the IAM had a mean score of 4.9 at baseline and follow up. Feasibility measured on the FIM was rated lower with a mean score of 4.5 at baseline and 4.2 at follow up. Organizational readiness for implementing HCV treatment assessed by the ORIC was high but reduced in implementation year 2 compared to pre-implementation at all sites, except for 1 site that had integrated components of HCV treatment prior to implementing RAPID HCV (Supplementary



Footnotes: *Two (2) of the 56 patients in the usual care arm initiated treatment more than 12 weeks after randomization.
¹ Participants with missing HCV RNA PCR results were classified as not meeting the SVR outcome.

Fig. 3: Cascade of HCV care by randomization arm. Bar graph illustrating the HCV care cascade by randomization arm. Numbers above bars indicate proportions calculated using the number of treatment-eligible participants within each arm as the fixed denominator. The value shown between "Initiated HCV treatment" and "Achieved SVR" indicates the proportion of participants who achieved sustained virologic response (SVR) among those who initiated treatment.

Figure SA1). Out of a possible score range of 12–60, mean (SD) ORIC scores were 52.7 (7.7) at baseline and 47.5 (8.7) at follow up (Supplementary Figure SA2). The statements which had the lowest levels of agreement on the ORIC were confidence in maintaining momentum in implementing on-site HCV treatment, confidence in handling challenges that might arise in implementing on-site HCV treatment, confidence that people will do whatever it takes to implement on-site HCV treatment and confidence in managing the politics of implementing on-site treatment.

Discussion

This hybrid type 1 study demonstrated that HCV testing and treatment by OTP clinicians with peer support can transform access to curative HCV treatment for PWUD, achieving HCV treatment initiation rates nearly four-fold higher than specialist referral. HCV treatment initiation was also significantly faster, translating to a significantly higher rate of HCV cure in the RAPID HCV arm (61%) versus referral arm (14%) of the HCV treatment eligible population. This shift is not only clinically meaningful but also carries profound public health implications. OTPs provide ongoing contact with large numbers of people at high risk of ongoing HCV transmission, making them a strategic location to accelerate progress towards HCV elimination targets. While other studies have demonstrated high

effectiveness of oral DAAs for achieving HCV cure for PWUD in the OTP setting^{13,23,24} and telemedicine as an effective HCV care integration approach in the OTP setting,²⁵ this study uniquely provides evidence for effectiveness of training, technical assistance and peer support as implementation strategies for HCV treatment integration into OTPs, an existing, trusted, community-based system of care for PWUD.

The HCV cure rate of 68% of participants who initiated treatment in the OTP arm is similar to that reported in other pragmatic studies of HCV treatment among PWUD in the United States for which lack of assessment of post-treatment HCV RNA due to loss to follow-up is defined as non-response.^{26,27} A recent study evaluating peer support with telemedicine linkage to specialist care versus facilitated referral to HCV care in the US demonstrated a significantly higher rate of HCV treatment initiation in the intervention (85%) versus referral arm (13%), translating to higher rates of HCV cure in the intervention arm (63%) compared to referral arm (16%), similar to findings from our study.²⁶ These studies highlight the critical importance of meeting PWUD where they are thus overcoming many of the traditional barriers to HCV treatment initiation for PWUD.

The lower HCV cure rates among PWUD with multiple social vulnerabilities in our study are likely multifactorial, including lack of confirmation of HCV response, lower rates of treatment completion, and

higher rates of HCV reinfection. In our trial, treatment completion was 71%, like the 74% rate observed in the afore mentioned US telemedicine study.²⁶ Among participants in the RAPID HCV arm who took at least 90% of prescribed glecaprevir/pibrentasvir, 7/42 (17%) did not have a sample for HCV RNA testing and were considered HCV treatment failures. Additionally, 14% of treatment completers had detectable HCV RNA at the time of the SVR assessment which is higher than expected for individuals with high treatment completion rates, suggesting HCV reinfection caused post-treatment viremia, not treatment nonresponse. This possibility is further supported by high rates of ongoing substance use including recent injecting drug use in the preceding 30 days (75% of participants without documented SVR). Reinfection rates are estimated to occur at a rate of 6.2 per 100 person years among people who recently injected drugs globally and tends to occur early after treatment completion.²⁸ Additionally, homelessness has been associated with high reinfection risk with data from the US suggesting HCV reinfection rates as high as 18.9/100 person-years (95% CI: 13.3–26.7) among unstably housed individuals.²⁹ Regardless of this reinfection risk, significantly more PWUD achieved HCV cure in the RAPID HCV arm since most (75%) individuals in the referral arm never initiated treatment.

OTPs are uniquely positioned to meet the needs of PWUD, many of whom have multiple social disadvantages that may make it challenging to navigate the complexities of a fragmented health care system. Among participants in the RAPID HCV study, a significant proportion had ongoing drug use, food insecurity, homelessness and less than a high school education. These characteristics have all been associated with lower rates of HCV treatment uptake due to transportation barriers, challenges navigating complex health care settings compounded by limited health literacy and competing priorities.⁶ Integration of HCV treatment into the OTP overcame these barriers resulting in uniformly high rates of HCV treatment initiation across study OTPs. Of note, the specialists involved in this trial all have experience working with marginalized populations of PWUD and still had very low treatment initiation rates with referral to their specialist care settings, highlighting the critical importance of colocation of HCV care with other services. It is reassuring that rates of HCV treatment completion and cure were similar among those who initiated HCV treatment regardless of whether they were treated by clinicians at the OTP or specialists in academic settings. This provides additional data supporting HCV treatment initiation as the most important step of the HCV care continuum for achievement of HCV elimination both at the individual and at the population level.

Given the extensive, existing OTP infrastructure in many countries and demonstrated effectiveness of

HCV treatment integration, routine implementation of HCV treatment into OTP settings has significant potential to advance HCV elimination efforts among PWUD.^{12,13,22,24} OTP leadership and staff rated HCV treatment integration as highly acceptable and appropriate, demonstrating the commitment of OTP providers. Feasibility of implementation was, however, not rated as high. Ongoing barriers to routine integration of HCV treatment into OTP settings include challenges with coordinating tasks such as access to phlebotomy for blood draws and the time needed for HCV counseling and treatment, suggesting that existing personnel may find taking on additional duties required for implementation challenging. This is a critical barrier given lack of reimbursement or compensation for HCV care delivery at OTPs. Similarly, lack of confidence in keeping the momentum of implementing HCV treatment may speak to a need for additional resources including personnel and incentives such as favorable care reimbursement structures for HCV treatment integration into OTPs as an approach to increasing feasibility of sustained implementation. Leveraging mobile phlebotomy or point of care tests may reduce logistical challenges with blood draws. Value based payment models that explicitly include HCV treatment integration within OTPs may provide additional funding to OTPs to overcome feasibility challenges.

Our study has several strengths, including a multi-site trial design which increases generalizability of our study findings. Our study is, however, limited by incomplete outcome data collection due to challenges with blood draws and loss to follow up. The study protocol prespecified collection of Grade 3 or higher SAEs with none reported consistent with the known safety profile of glecaprevir/pibrentasvir. Additionally, since HCV RNA was tested commercially, we could not sequence HCV in persons with recurrent viremia to assess for HCV reinfection. Glecaprevir/pibrentasvir was provided free of charge to study participants; as such challenges with access to DAAs (e.g., prior authorization requirements) outside the study setting cannot be formally assessed and may be a greater barrier in OTPs than referral centers. Additionally, our study sample was predominantly male and white which may limit generalizability of our findings for other sex groups and races. Finally, while our model indicated higher rates of HCV treatment with OTP integration, we are unable to quantify the contribution of peer support in increasing treatment uptake.

In conclusion, HCV test and treat with peer support integrated into OTPs was effective and associated with significantly higher rates of HCV treatment initiation and cure compared to offsite referral to HCV treatment. OTP staff perceived the intervention to be highly acceptable and appropriate with some concerns about the feasibility of implementation. These findings

support policy reform and expanded resources to support HCV treatment integration into OTPs to advance progress towards HCV elimination.

Contributors

OF-N and MS contributed to the study's conceptualization and funding acquisition. OF-N, JCP, JFF, KT, DV, SS and MS contributed to methodology. OF-N, JCP, JFF, EE, RAF, BB, DB, SH, CW, HK-S, KH, CC, STO, and CC contributed to investigation. OF-N, JCP, JFF, EE, RAF, BB, DB, SH, CC, and CC contributed to project administration. BB, SH and TV contributed to data curation. OF-N, TV, BB and SH had access to raw data. BB and SH verified data. OF-N, TV and DV contributed to the formal analysis. OF-N and TV contributed to original draft writing, and visualization. JCP, JFF, EE, RAF, BB, DB, SH, CW, HK-S, KH, CC, SO, CC, KT, DV, SS and MS contributed to writing review and edit of the manuscript. OF-N, JCP, JFF, EE, RAF, DB, and MS contributed to supervision. OF-N and MS have final responsibility for decision to submit for publication. All authors approved the final manuscript.

Data sharing statement

The data supporting this study's findings contain sensitive clinical information from human subjects. Deidentified data and accompanying documentation will be shared with qualified investigators for research purposes upon reasonable request to the corresponding author, contingent on IRB approval and execution of a data use agreement that ensures compliance with institutional and ethical requirements.

Declaration of interests

OF-N, JCP, JFF, EE, and RAF received grant support from AbbVie Inc for the current work. OF-N reports grant support from NIH, SAMHSA, and the Maryland Department of Health, all paid to Johns Hopkins University, and personal payment as consulting fees and honoraria from Gilead Sciences. JCP reports grant support from Gilead Sciences to University of California San Francisco. JFF reports grant support from AbbVie Inc., Gilead Sciences and Atea paid to University of Toronto, and personal payment as consulting fees from AbbVie Inc. and Gilead Sciences. EE reports grant support from NIH, SAMHSA, and the Alabama Department of Mental Health paid to University of Alabama, participation in leadership roles with IAS-USA and HIVMA, and receipt of honoraria from IAS-USA, HIVMA, PRIME CME, and Integrity CME as well as meeting attendance/travel support from IAS-USA and HIVMA. RAF reports grant from AbbVie Inc., paid to University of Alabama. SS received consulting fees from Simpson Healthcare and service as Data Safety Monitoring Board Chair for two HIV-related trials. MS reports grant support from Vir, GSK, Bluejay, and Grifols paid to Johns Hopkins University; consulting fees from AbbVie Inc., Aligos, Bluejay, GSK, Precision Biosciences, Vir, and Virion and participation on DSMB for Gilead Sciences and Immuncore; and serves as Editor-in-Chief of *Journal of Viral Hepatitis*. All other authors declare no competing interests.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at <https://doi.org/10.1016/j.jana.2026.101439>.

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