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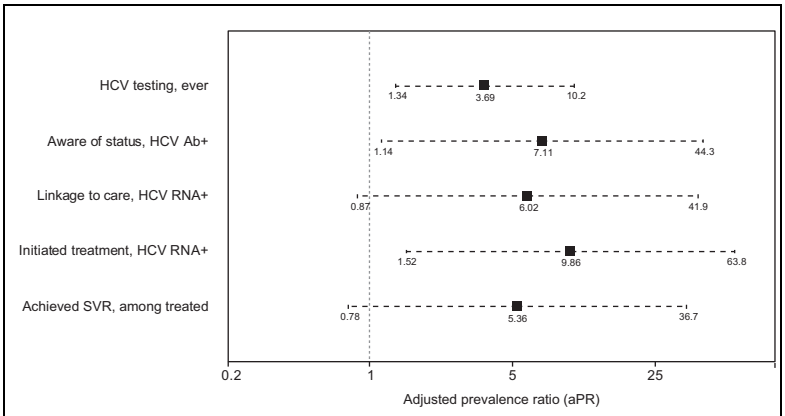
Integrating HCV testing with HIV programs improves hepatitis C outcomes in people who inject drugs: A cluster-randomized trial

Graphical abstract



Impact of of integrating HCV testing with HIV/harm reduction services on HCV care continuum outcomes among PWID in India: Findings from a cluster-randomized trial

Highlights

- Integration of HCV testing with HIV/harm reduction services increased uptake of HCV among PWID.
- PWID in intervention *vs.* usual care sites were more likely to have been tested for HCV.
- PWID in intervention *vs.* usual care sites were more likely to be aware of their HCV status.
- Despite relative increases, absolute numbers aware of HCV status remained low.
- Integration of services is an important early step towards HCV elimination.

Authors

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Lay summary

Delivering hepatitis C virus (HCV) testing to people who inject drugs (PWID) in places where they also have access to HIV prevention and treatment services is an effective way to improve uptake of HCV testing among communities of PWID. To achieve the World Health Organization's ambitious elimination targets, integrated programs will need to be scaled up to deliver comprehensive HCV services.

http://dx.doi.org/10.1016/j.jhep.2019.09.022
 J. Hepatol. 2020, 72, 67–74

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Integrating HCV testing with HIV programs improves hepatitis C outcomes in people who inject drugs: A cluster-randomized trial

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Background & Aims: There have been calls to integrate HCV testing into existing services, including harm reduction and HIV prevention and treatment, but there are few empirical trials to date. We evaluated the impact of integrating HCV testing/education into integrated care centers (ICCs) delivering HIV services to people who inject drugs (PWID) across India, using a cluster-randomized trial.

Methods: We compared ICCs with usual care in the PWID stratum (12 sites) of a 22-site cluster-randomized trial. In 6 sites, ICCs delivering HIV testing, harm reduction, other preventive services and linkage to HIV treatment were scaled from opioid agonist therapy centers and operated for 2 years. On-site rapid HCV antibody testing was integrated after 1 year. To assess impact, we conducted baseline and evaluation surveys using respondent-driven sampling (RDS) across the 12 sites (n = 11,993 recruited at baseline; n = 11,721 recruited at evaluation). The primary outcome was population-level self-reported HCV testing history.

Results: At evaluation, HCV antibody prevalence ranged from 7.2–76.6%. Across 6 ICCs, 5,263 ICC clients underwent HCV testing, of whom 2,278 were newly diagnosed. At evaluation, PWID in ICC clusters were 4-fold more likely to report being tested for HCV than in usual care clusters, adjusting for baseline testing (adjusted prevalence ratio [aPR] 3.69; 95% CI 1.34–10.2). PWID in ICC clusters were also 7-fold more likely to be aware of their HCV status (aPR 7.11; 95% CI 1.14–44.3) and significantly more likely to initiate treatment (aPR 9.86; 95% CI 1.52–63.8).

Conclusions: We provide among the first empirical data supporting the integration of HCV testing into HIV/harm reduction services. To achieve elimination targets, programs will need to scale-up such venues to deliver comprehensive HCV services.

ClinicalTrials.gov identifier: NCT01686750.

Lay summary: Delivering hepatitis C virus (HCV) testing to people who inject drugs (PWID) in places where they also have access to HIV prevention and treatment services is an effective way to improve uptake of HCV testing among communities of PWID. To achieve the World Health Organization's ambitious elimination targets, integrated programs will need to be scaled up to deliver comprehensive HCV services.

Introduction

An estimated 71 million people are chronically infected with HCV.[1] The availability of safe, short duration, curative therapies[2–4] prompted the World Health Organization (WHO) to release targets for HCV elimination – 80% reduction in incidence and 65% reduction in mortality by 2030.[5] Achieving these targets requires 80% of all people with active infection to be treated. Thus, it is essential that major inroads are made in people who inject drugs (PWID) in low- and middle-income countries (LMICs). In these settings, awareness of HCV status is well below 10% and most have not even received the most basic HCV education.[6]

In 2015, it was estimated that there were 15.6 million PWID globally, of whom 8.2 million were exposed to HCV[7] and 6.1 million had active HCV infection requiring treatment.[8] In India, data from a 2013 cross-sectional serosurvey demonstrated that 1 in 3 PWID were infected with HCV.[9] Despite this high burden, at the time fewer than 6% of HCV-infected PWID were aware of their status. Moreover, the majority had not been tested because they had never heard of HCV, highlighting a compelling need for testing and educational programs. Calls have been made to integrate HCV testing into existing services, including harm reduction and HIV prevention and treatment, particularly for drug-using populations, but there are few empirical trials to date.[10–12]

We evaluated the impact of integrating HCV antibody testing and education into community-based centers that deliver integrated HIV prevention (including harm reduction) and

Keywords: HIV; Hepatitis C virus; HCV; People who inject drugs; PWID; India; Cluster-randomised trial; Integrated care.
Received 25 April 2019; received in revised form 18 July 2019; accepted 19 September 2019; available online 8 October 2019

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treatment services to PWID across India, using a cluster-randomized trial.

Materials and methods

Study design of the parent trial

The National Collaboration on AIDS (NCA) study was a cluster-randomized trial (ClinicalTrials.gov identifier: NCT01686750) designed to evaluate the effectiveness of integrated HIV prevention and treatment service delivery on recent HIV testing among men who have sex with men (MSM) and PWID across 22 cities in India. A detailed description of the trial[13] and primary outcomes[14] has been published. Briefly, the intervention, integrated care centers (ICCs), was nested between serial cross-sectional surveys (baseline and evaluation) conducted in 2013 and 2016–17 (Fig. 1). The parent trial was powered to examine improvements in HIV testing among MSM and PWID. A stratified restricted randomization approach was used to assign sites to either intervention (ICC) or usual care.[13] Masking was not feasible. ICCs were established in 2014 at 11 intervention clusters and operated for 2 years prior to evaluation. We present results from an add-on study at the 12 PWID sites, 6 of which were assigned to the ICC intervention and 6 to usual care.

A detailed description of the ICC intervention has been published.[13] Briefly, for PWID, ICCs were stand-alone centers established to provide services for PWID in a single PWID-friendly venue either within a government facility or non-governmental organization. All ICCs provided the following: rapid HIV counseling and testing (HCT); antiretroviral therapy (ART) via a link model; information, education and counseling (IEC) services; screening for tuberculosis (TB) with referrals; condoms; syndromic sexually transmitted infection (STI) management; opioid agonist therapy (OAT); and field-level syringe service programs (SSP). In usual care sites, all services available in the ICC sites were also available free-of-charge but at discrete venues that were not PWID-specific but rather catered to all populations.

There were no eligibility requirements to utilize the PWID ICCs. ICCs were open to all individuals regardless of gender, sexual orientation or drug use history; however, almost all clients self-reported a history of drug use. All services at the ICC were offered free-of-charge and clients could use any service on a voluntary basis. Biometric data were used to track service utilization at ICCs. Clients could refuse to provide biometric data and still utilize services. Participants were not compensated for visiting ICCs.

HCV testing and educational intervention add-on

In September 2015, on-site rapid HCV antibody testing and counseling was integrated into the 6 established PWID ICCs. Existing and new clients visiting ICCs for any purpose (*e.g.*, OAT, SSP, HIV testing, counseling) were offered 1-time free HCV testing with pre- and post-test counseling and delivery of results. In addition, information on availability of HCV testing

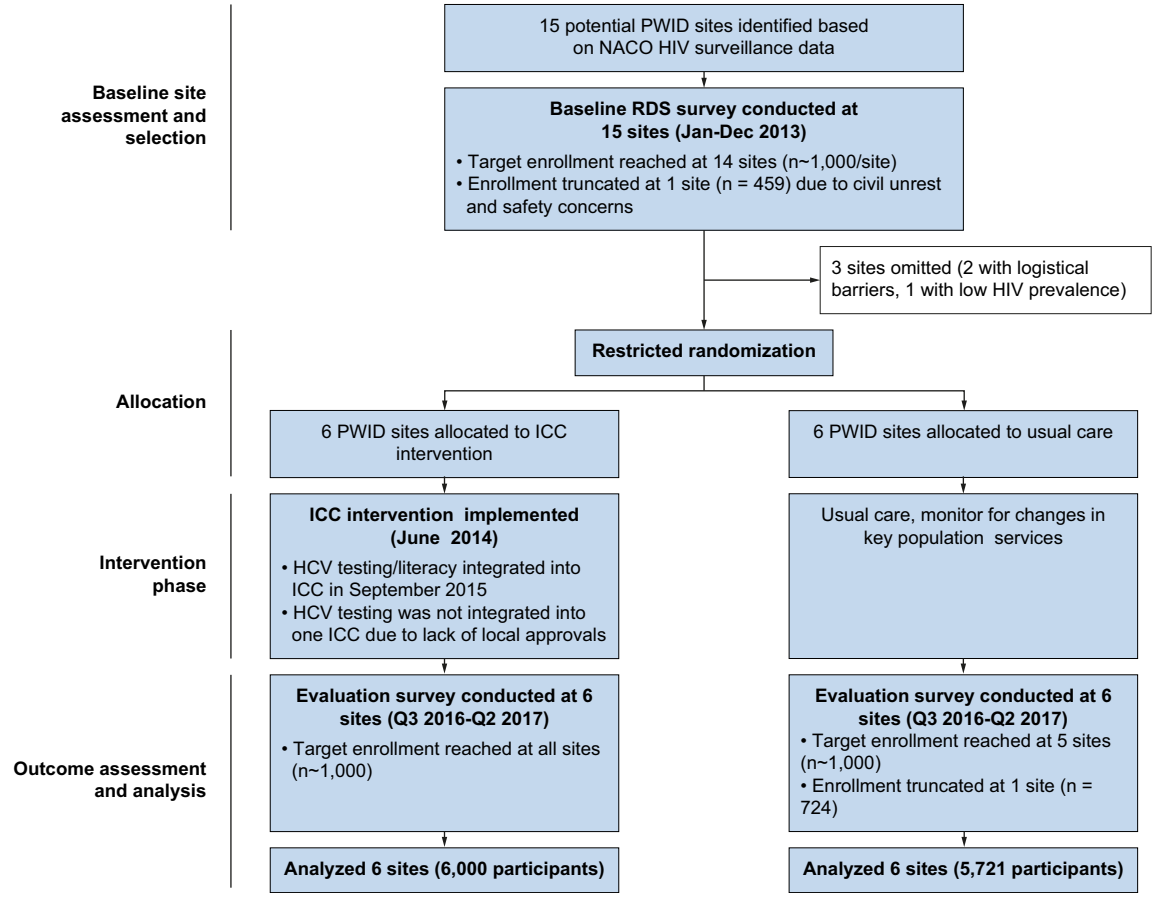

Fig. 1. Cluster-randomized trial design. ICC, integrated care centers; NACO, National AIDS Control Organisation, India; PWID, people who inject drugs; RDS, respondent-driven sampling.

was disseminated to the broader PWID community through outreach workers and existing ICC clients with the goal of engaging new clients in the ICCs. Participants who tested positive for HCV antibodies were counseled on ways to prevent liver disease progression (*e.g.*, reducing alcohol consumption) and were referred to HCV treatment centers where available (Ludhiana) or to the medical gastroenterology departments of government hospitals for further evaluation as is the standard of care in India. In addition to the individual-level testing, ICCs provided group HCV educational sessions which included information on the risk factors for HCV infection, prevention strategies, interpretation of diagnostic tests, clinical course, management and treatment.

In usual care sites, HCV testing availability was variable. Across all sites, antibody testing was available through private labs for a nominal charge (INR 150–300 [USD 2–4.5]). In Punjab, HCV antibody testing was available free-of-charge through government district hospitals as part of an HCV elimination program. Free HCV testing was available via non-governmental organizations in Churachandpur; further, sporadic free HCV antibody testing was conducted in usual care sites by pharmaceutical companies and other organizations. Across all 6 usual care sites, free HCV testing is recommended for all people infected with HIV who visit an ART center.[15]

Baseline and evaluation surveys

The community-level impact of the intervention was assessed via 2 independent cross-sectional surveys. The first survey (baseline) took place prior to when HCV testing was incorporated into the ICCs. The second survey (evaluation) took place approximately 1 year after the integration of HCV testing. Both used identical eligibility criteria and procedures and recruited participants using respondent-driven sampling (RDS) – a chain-referral sampling method that is expected to provide unbiased estimates of the outcome in the community by accounting for recruitment bias.[16,17] RDS was initiated by selecting "seeds" who are considered to be highly connected and influential members of the PWID community in each city. Each seed was given 2 hologram-labeled referral coupons to randomly recruit 2 members of the local PWID community who they knew. When recruits visited the study site and enrolled, they were in turn given 2 coupons to recruit 2 more members. Serial recruitment continued until the desired sample size of 1,000 PWID was achieved per site. The theory of RDS is that the deeper the chains, and the more waves of recruitment achieved, the more the sample becomes independent of the initial seed selection and the less subject to referral bias.[16,17]

Inclusion/exclusion criteria were identical for both surveys. Participants had to: i) be age ≥18 years; ii) self-report on illicit drug injection in the prior 2 years; iii) provide informed consent; iv) possess a valid referral coupon (except seeds). Participants of all genders (male, female and transgender) and sexual orientation (homosexual, heterosexual or bisexual) were eligible. Participants could only participate once in the baseline survey and once in the evaluation survey; however, the same participant could participate in both surveys. Biometric data was used to track participants across surveys and identify duplicate enrollments.

Procedures for each of the surveys were as follows. Following verbal consent, participants underwent biometric capture. No other identifying information was collected. Participants completed an interviewer-administered survey, which captured information on demographics, PWID network characteristics, risk behavior, history of HIV and HCV testing and treatment, and substance use including alcohol. Participants underwent rapid HIV testing with pre- and post-test counseling. Upon completion of study procedures for the baseline and evaluation surveys, all participants were compensated 250 INR (3.5 USD) and provided 2 referral coupons. Participants received an additional monetary incentive of INR 50 (0.7 USD) for each participant referred who completed study procedures.

Samples were shipped to the central laboratory for additional testing and repository storage. HCV antibody and HCV RNA testing were conducted using repository specimens from RDS surveys. As no contact information was collected in RDS surveys, we were not able to provide HCV results from surveys to the participants. The Genedia HCV ELISA 3.0 (Green Cross Medical Science, Chungbuk, Korea) and Murex anti-HCV ELISA 4.0 (Murex Biotech, South Africa) were used to assess exposure to HCV (anti-HCV antibody) in baseline and evaluation surveys, respectively. HCV RNA was quantified in all specimens testing positive for HCV antibodies in both cross-sectional surveys using the RealTime HCV assay (Abbott Molecular, Des Plaines, IL, USA) with a lower limit of quantification (LLOQ) of 30 IU/ml.

Study outcomes

Community-level outcomes were assessed in the evaluation RDS survey. The primary outcome of interest was self-report of prior (ever) HCV testing. Secondary outcomes included recent HCV testing (in the prior 12 months, excluding individuals who report being diagnosed with HCV more than a year prior to the survey) and other HCV care continuum outcomes including awareness of status, linkage to care, treatment initiation and sustained virological response (SVR). Awareness of status was defined as the proportion of HCV antibody-positive individuals who self-reported that they were HCV positive. Linkage to care was defined as the proportion of HCV RNA positive participants (or HCV RNA negative but self-reported that they had been treated for HCV) who reported that they had consulted a clinician for HCV care. Treatment initiation was defined as the proportion of HCV RNA positive persons (or HCV RNA negative but self-reported that they had been treated for HCV) who self-reported that they had initiated HCV treatment. SVR was defined as the proportion of HCV RNA positive participants (or HCV RNA negative but self-reported that they had been treated for HCV) whose HCV RNA was less than the LLOQ at the time of the survey.

Statistical analyses

All statistical analyses excluded the RDS "seeds" and incorporated RDS-II weights as is the standard in RDS analyses.[18] At least 1 author had access to all of the data and can vouch for the integrity of the data analyses. The primary analyses incorporated an intention-to-treat (ITT) approach and estimated community-level prevalence ratios (PR) for ICC *vs.* usual care of each study outcome at the evaluation assessment adjusting for the baseline prevalence of the outcome. Analysis was performed using linear regression, using log-normal transformations of the community prevalence estimates. For some sites, no individuals reported linkage to HCV care or initiation of treatment – therefore, a small prevalence was imputed (0.05%) so that the estimate could be transformed and included in the regression model. Even though only 5 of 6 ICC sites incorporated HCV testing within the ICCs, all 6 sites were used in the

ITT analyses. The study outcomes were also compared between ICC *vs.* usual care clusters in an as-treated analysis that excluded the 1 site (Chandigarh) without HCV testing. Additional sensitivity analyses were conducted: i) we repeated the primary and secondary outcome analyses using unweighted community-level outcomes; ii) we used HCV RNA detection to define the denominator for the testing and awareness outcomes in both RDS-II weighted and unweighted analyses; iii) we used an individual-level approach with multi-level random effects log Poisson regression models with a random intercept for each site to account for the dependence of individual-level responses within a site; iv) we restricted analyses to the ICC sites and compared study outcomes among those who had *vs.* had not visited the ICC, verified by biometric match; and v) we compared people in the ICC sites who did and did not report HCV testing in the prior year, excluding those who had been diagnosed more than 1 year prior. All statistical analyses were performed using Stata Version 15 (StataCorp, College Station, TX).

Ethical clearance

Ethical oversight of the trial was provided by the Johns Hopkins Medicine and the YR Gaitonde Centre for AIDS Research and Education institutional review boards and an independent data safety monitoring board (DSMB).

Results

Participant and cluster characteristics

Across 12 PWID sites, we recruited 11,993 and 11,721 participants at baseline (2013) and evaluation (2016–17), respectively (Table 1). A total of 1,613 (13.7%) participated in both the baseline and evaluation surveys verified via biometric match, and 2,375 (39.5%) intervention site participants surveyed in the evaluation assessment had visited an ICC. One site (Mumbai) did not meet the enrollment target of 1,000 in the evaluation assessment; recruitment was stopped at 724 participants due to slower than expected enrollment. In the evaluation surveys,

Table 1. Demographics and risk behaviors stratified by study arm.

	Usual Care		ICC intervention	
	Baseline	Evaluation	Baseline	Evaluation
Participant-level characteristics*				
Participants, n	5,997	5,721	5,996	6,000
Women, n (site % range)	341 (0–22.7)	272 (0.5–22.0)	346 (0.2–18.7)	221 (0.6–15.4)
Age (years), site median range	24–34	25–35	26–34	26–35
At least secondary school education, n (site % range)	3,331 (30.7–95.1)	3,451 (35.6–97.6)	4,341 (66.1–93.8)	4,652 (60.7–94.3)
Married or living with partner, n (site % range)	2,331 (26.3–48.1)	1,993 (26.5–48.9)	2,999 (33.4–63.9)	2,674 (27.7–62.5)
Monthly household income (USD), site median range	92–306	138–459	107–389	153–459
Recent incarceration, n (site % range)	648 (4.2–27.7)	512 (4.4–24.3)	827 (0.5–30.1)	572 (2.5–12.3)
Lifetime number of sexual partners, site median range	2–4	2–5	1–5	1–5
Unprotected sex in prior 6 months, n (site % range)	2,188 (24.4–51.8)	2,522 (23.2–70.3)	2,894 (37.4–62.9)	2,779 (37.6–61.6)
Hazardous alcohol use[1], n (site % range)	2,127 (11.5–49.3)	2,253 (29.5–51.5)	2,721 (22.2–66.8)	1,926 (8.3–49.2)
Any recent substance use[2], n (site % range)	5,900 (95.8–100)	5,565 (85.8–100)	5,752 (88.7–99.9)	5,432 (81.8 – 98.1)
Ever tested for HIV, n (site % range)	2,728 (7.9–61.5)	2,940 (16.6–68.0)	3,055 (24.3–71.4)	3,702 (44.3–70.2)
Ever tested for HCV, n (site % range)	478 (0.2–11.8)	783 (0.9–28.0)	632 (0.7–27.2)	1,902 (10.9–52.7)
HIV positive[3], n (site % range)	1,220 (8.6–30.8)	1,301 (8.9–38.0)	1,324 (8.9–31.1)	1,216 (5.6–32.2)
HCV Ab + positive, n (site % range)	2,753 (15.3–63.6)	3,099 (16.5–66.8)	2,691 (9.0–64.9)	3,389 (7.2–76.6)
HCV active infection[4], n (site % range)	2,242 (13.2–52.8)	2,420 (10.2–53.9)	2,225 (7.9–54.9)	2,698 (4.1–66.4)
Injection in past 6 months, n (site % range)	5,611 (87.3–99.1)	4,975 (57.7–98.3)	5,211 (68.6–98.2)	4,373 (27.1–89.6)
Age at first injection (years), site median range	18–26	18–25	18–21	20–22
Ever shared needle/syringe, n (site % range)	3,327 (37.0–72.1)	3,113 (24.8–66.7)	2,944 (19.9–80.4)	3,221 (25.7–82.4)
Drugs injected in prior 6 months, n (site % range)				
Heroin	2,875 (2.5–97.0)	2,967 (7.4–96.0)	1,958 (0.6–98.2)	2,699 (0.04–89.5)
Buprenorphine	2,134 (0.3–75.7)	2,066 (0–90.9)	2,289 (0.1–89.9)	1,640 (0–77.2)
Other pharmaceutical opioids	1,634 (0.7–88.7)	844 (1.2–26.2)	1,396 (0.9–62.9)	368 (0–23.6)
Cocaine or other stimulant	54 (0–2.6)	79 (0.1–3.8)	50 (0.2–1.5)	44 (0–1.3)
Sedative/antianxiety	283 (0.1–20.3)	311 (0.1–27.1)	627 (0.4–23.6)	66 (0–2.3)
Antihistamines	2,125 (0.01–90.1)	2,117 (0–96.2)	1,992 (0.04–73.0)	1,418 (0–70.4)
Ever use needle exchange program, n (site % range)	2,703 (6.8–73.8)	2,520 (8.3–63.2)	2,279 (7.7–59.2)	2,083 (6.1–61.1)
Ever use opioid agonist therapy, n (site % range)	1,627 (6.4–48.7)	1,975 (4.7–56.4)	1,296 (0 – 33.0)	2,486 (10.7 – 54.2)
Site recruitment characteristics				
Sites, n	6	6	6	6
Sample size per site, median (range)	1,000 (999–1,000)	1,000 (722–1,000)	1,000 (996–1,000)	1,000 (1,000–1,000)
Number of seeds used per site, median (range)	2 (2–2)	2 (2–2)	2 (2–2)	2 (2–2)
Time to recruit sample (days), median (range)	139 (52–190)	171 (101–269)	136 (89–200)	139 (96–203)
Median network size, site median[5] range	16 (10–20)	12 (7–30)	13 (7–20)	11 (4–20)
Number of recruitment waves reached, median (range)	23 (14–31)	18 (11–27)	32 (14–50)	16 (9–24)
Biometric overlap between evaluation and baseline RDS (%), n (site %[5] range)	–	848 (7.5–23.5)	–	765 (5.8–18.8)
Biometric overlap between evaluation RDS and ICC register (%), n (site %[5] range)	–	–	–	2,375 (16.7–55.5)

*Site percentages and medians weighted using RDS-II weights; [1]Measured using AUDIT, score ≥8; [2]Any alcohol use or illicit drug use; [3]By rapid HIV testing; [4]HCV RNA+ or reported initiating treatment for HCV; [5]Unweighted.
Ab, antibody; ICC, integrated care center; PWID, people who inject drugs; RDS, respondent-driven sampling.

the median number (range) of RDS recruitment waves was 16 (9–27) and the median time (range) for recruitment was 149 days (95–269).

At the evaluation survey, the median age ranged from 26 to 36 years and 493 women were recruited. Forty percent (n = 4,667) of participants at evaluation were married or living with a partner and 69% (n = 8,103) had at least secondary schooling. The median site-level monthly household income ranged from USD 138 to 459. Unweighted data are presented in Table S1. Overall, 9,348 (80%) participants reported injecting in the prior 6 months in the evaluation assessment.

The weighted prevalence of active HCV infection (HCV RNA positive) ranged from 4.1% to 66.4% across the 12 sites in the evaluation assessment. Unweighted estimates are in Table S1.

Uptake of HCV testing services in intervention sites

ICCs were operational in 6 sites for a median 26.3 (range: 25.6–28.7) months prior to the evaluation survey. Across 6 sites, a total of 10,757 unique clients recorded 706,978 ICC visits during the intervention period. HCV antibody testing and counseling was available in 5 of the 6 ICCs for a median 11.4 (range: 11.3–11.5) months prior to the evaluation. Across 5 sites where HCV antibody testing was incorporated, 8,524 visited the ICC after testing became available, of whom 5,263 clients (62%) voluntarily underwent HCV antibody testing with appropriate pre- and post-test counseling and delivery of results, and 2,278 (43.3%) clients were newly diagnosed as HCV antibody positive.

Site-level study outcomes

At evaluation, the weighted mean percentage self-reporting ever having been tested for HCV were 28.6% and 11.6% in the ICC and usual care clusters, respectively (Table S2). Weighted mean percentages tested in the prior 12 months were 22.0% and 7.4%, respectively (Table S3). In the community-level analysis, compared to PWID in the usual care clusters, PWID in ICC clusters were 3.69-fold (95% CI 1.34–10.2) more likely to have ever been tested for HCV and 5.55-fold (95% CI 1.48–20.8) more likely to have been tested in the prior 12 months, adjusting for the baseline levels of HCV testing in the clusters. The weighted absolute mean change in ever having been tested in the ICC and usual care clusters at the evaluation assessment compared to baseline were 19.6% and 5.1%, respectively – the mean difference in absolute percentage point change in the ICC *vs.* usual care clusters was 14.5% (95% CI 1.5–27.5; Fig. 2). These changes were 18.8% and 3.7%, respectively, for testing in the prior 12 months in the ICC and usual care clusters at the evaluation assessment compared to baseline – the mean difference in absolute percentage point change was 15.1% (95% CI 0.9–29.2).

The weighted site-median and range for HCV care continuum outcomes in the baseline and evaluation assessment are listed in Table 2. Individual site outcomes are in Table S4. Adjusting for baseline levels of awareness of HCV status, PWID in the ICC clusters were 7-fold (adjusted prevalence ratio [aPR] 7.11; 95% CI 1.14–44.3) more likely to be aware of their positive HCV antibody status compared to the usual care clusters. PWID in the ICC clusters were also more likely to have linked to care, initiated treatment, and achieved cure compared to PWID in the usual care clusters. Although, after adjusting for baseline levels of each outcome, linkage to care and cure failed to achieve statistical significance (Fig. 3). Inferences remain unchanged in as-treated (excluding Chandigarh) and other sensitivity analyses (Table S5).

Individual-level analysis

In an analysis restricted to the 6 intervention sites, we further compared persons who did and did not report receiving HCV

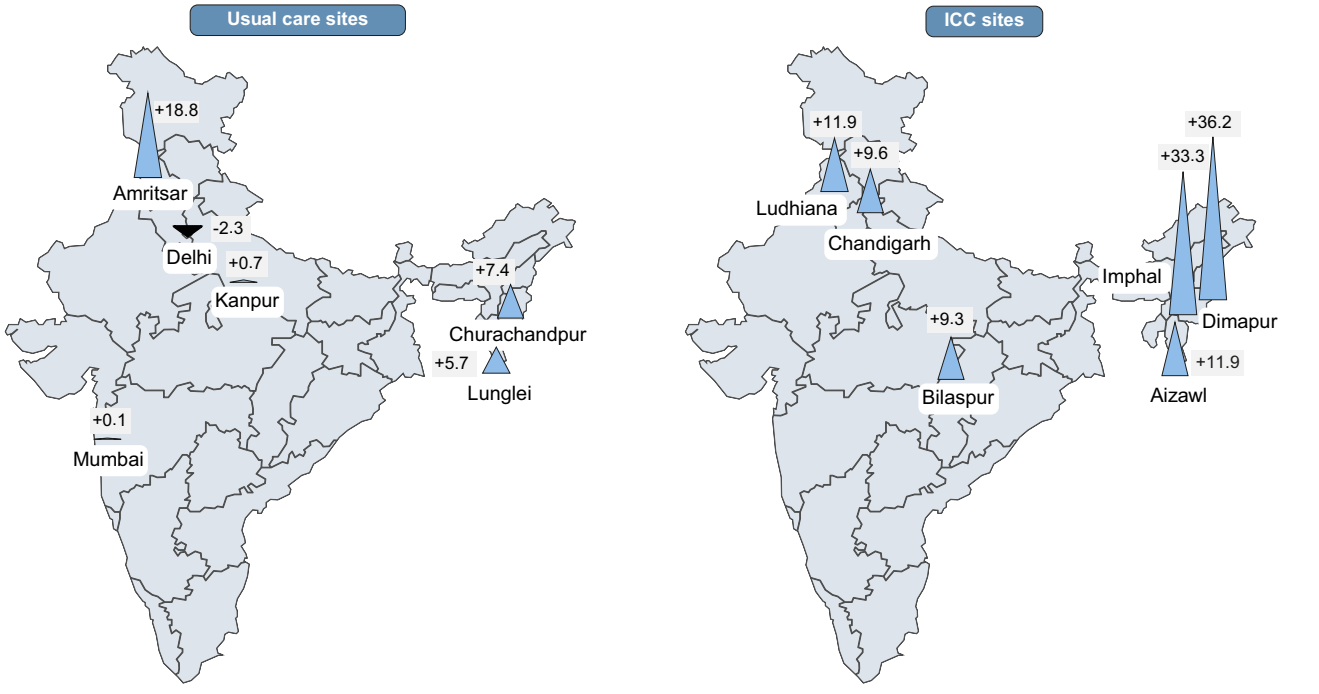

Fig. 2. Indian map depicting the absolute percentage point change in ever being tested for HCV between evaluation and baseline assessment by study arm. Height of triangle is proportionate to the absolute percentage point change at each location. Blue triangle pointing upwards represents a positive change and black triangle pointing downwards represents a negative change.

Table 2. Weighted site-level HCV care continuum outcomes in the ICC *vs.* usual care clusters*.

	Usual care		ICC intervention	
	Baseline	Evaluation	Baseline	Evaluation
Aware of HCV Ab + status, n (site % range)	145 (0.6–7.3)	252 (0.03–14.4)	264 (0.08–17.4)	642 (1.0–37.7)
Linked to care among HCV RNA+, n (site % range)	60 (0.05–5·7)	108 (0–6.0)	122 (0–10.6)	201 (0.4–13.6)
Initiated HCV treatment, n (site % range)	30 (0–6.7)	52 (0–4.9)	42 (0–6.0)	119 (0.5–9.0)
Achieved SVR, n (site % range)	8 (0–1.9)	25 (0–2.8)	9 (0–1.8)	47 (0.1–3.2)

*Weighted using RDS-II weights.
Ab, antibody; ICC, integrated care center; PWID, people who inject drugs; RDS, respondent-driven sampling; SVR, sustained virological response.

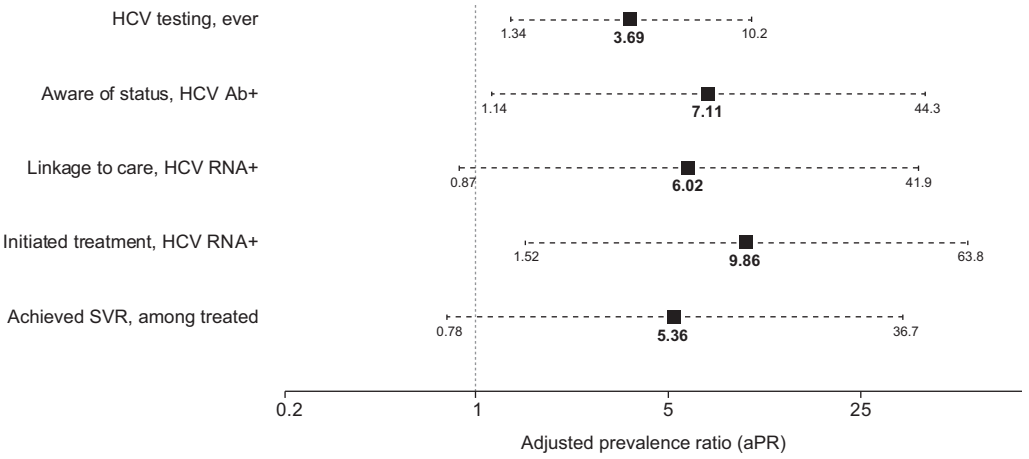

Fig. 3. Community-level impact of ICCs *vs.* usual care on HCV care continuum outcomes among PWID in India. Adjusted prevalence ratios and 95% CIs compare the relative likelihood of outcome in the ICC *vs.* usual care clusters. All data presented were estimated using an intent-to-treat approach incorporating RDS-II weights and adjusted for baseline prevalence of outcome. Ab, antibody; ICC, integrated care center; PWID, people who inject drugs; RDS, respondent-driven sampling; SVR, sustained virological response.

testing in the prior year. In a multivariable age-adjusted model, compared to those who had not been tested in the prior year, those who reported recent testing were significantly more likely to have visited the ICC (aPR 1.74; 95% CI 1.44–2.10), accessed OAT in the prior 6 months (aPR 1.72; 95% CI 1.22–2.43) and been recently tested for HIV (aPR for HIV negative and tested in the prior year *vs.* HIV negative and not tested in the prior year: 5.23; 95% CI 3.10–8.90) or aware of their HIV positive status (aPR 4.35; 95% CI 2.51–7.51).

Discussion

In "Test.Treat.Hepatitis", the WHO recognized the urgent need to improve access to HCV testing and diagnosis if ambitious elimination targets for HCV are to be met.[19] In this trial, we demonstrated a statistically significant population-level impact of integrating HCV testing with HIV/harm reduction services on critical HCV care continuum outcomes including HCV testing, awareness of status and treatment initiation. However, the overall proportion of the target population who were aware of their status after this intervention remained low, and we did not observe statistically significant improvements in SVR. Nonetheless, the simplification of HCV treatment and availability of generic DAAs in over 100 countries further supports task-shifting from tertiary specialty centers to community-based centers, such as the ICCs described in this trial, to potentially further improve HCV testing and downstream outcomes of SVR and consequently, reduce HCV incidence.

HCV testing and counseling was incorporated into integrated HIV/harm reduction centers 1 year prior to the evaluation assessment. Yet, in this brief period, over 5,000 clients were tested across 5 cities, of whom nearly half were newly diagnosed with HCV. Moreover, acceptability of HCV testing was high and comparable among persons on and off OAT. The benefits of integrating HCV testing with OAT have previously been demonstrated,[20] including limited data from LMICs. For example, integration of HCV testing into an OAT program in Tanzania resulted in all 1,350 PWID on OAT undergoing testing.[21] A study from Ukraine further demonstrated a correlation between being engaged in OAT and awareness of HCV status.[22] However, the impact of integration of HCV testing with HIV/harm reduction services at the community-level (regardless of whether the clients were enrolled in OAT or HIV treatment) has not previously been reported to our knowledge. Indeed, recent systematic reviews of HCV interventions,[23,24] which have highlighted successful interventions for PWID including service integration, clearly point to the lack of randomized trials and a dearth of evidence on successful interventions from LMICs, a gap which this trial sought to fill.

In this study, at the community-level, PWID in the ICC cities were more than 3-fold more likely to be tested for HCV compared to PWID in usual care communities. Moreover, this model reached diverse clients including those not engaged in harm reduction or other HIV prevention/treatment strategies who may be most at risk of re-infection.[25] PWID in ICC cities were also 7-fold more likely to be aware of their HCV antibody status. Nonetheless, it is important to note that only 642 out of the 3,389 (19%) HCV antibody positive PWID in the ICC cities were aware of their status. To achieve elimination, awareness levels need to be substantially higher. Moreover, there was important variability in awareness across sites, ranging from 1% in Bilaspur to 37.7% in Imphal. Allowing ICCs to function longer and

consequently reach a larger proportion of the population might have further improved community-level awareness. However, our experience with HIV service integration suggests that additional "demand" creation strategies[14] might be needed to improve population-level HCV awareness to meet elimination targets. We have previously demonstrated the potential role of network-based recruitment in improving case detection rates of HCV among PWID;[26] incorporating network referral strategies could further improve community-level uptake of HCV testing.[26] Additionally, incorporating free HCV treatment into centers like ICCs could further enhance uptake of HCV testing, analogous to what was observed with HIV testing when free antiretroviral therapy programs were introduced. OAT centers represent ideal venues for HCV treatment as many have clinicians on-site who could be trained to deliver treatment, while SVR rates among OAT clients seem to be comparable to those in non-PWID.[20]

The findings presented need to be interpreted with caution. The parent trial was designed in 2012 to evaluate the impact of an integrated care model on HIV testing among MSM and PWID. HCV testing and care continuum outcomes were not originally part of the trial. However, over the course of the study, 2 major developments emerged. First, sofosbuvir was licensed for use in the US in 2013 and negotiations began for generic licensing of sofosbuvir in India. Second, during pre-trial ethnography, HCV testing at the ICCs was raised as a need by PWID in the Northeast. These findings prompted us to seek independent funding to incorporate HCV testing at the ICCs and testing of stored specimens to evaluate population-level impact.

HCV testing increased substantially in 2 usual care cities, both of which had testing available free-of-charge at some point during the study period through either governmental or non-governmental programs, so we cannot rule out the possibility that free rather than integrated testing at least in part drove results. Several of the study outcomes were based on self-report. However, it appears unlikely that there would be differences in social desirability between ICC and usual care clusters. Baseline and evaluation assessment samples were accrued using RDS and RDS weights were utilized to arrive at population-level estimates. There has been criticism of the use of RDS[27,28] but given the inability to randomly sample PWID, RDS is the most widely used method to sample "hidden" populations. Further, all samples satisfied RDS process measures. Finally, HCV testing was integrated only in the PWID sites, which nearly halved the number of clusters used, resulting in large confidence intervals and limited power.

Limitations notwithstanding, these data are among the first to provide empirical evidence of the benefits of integrating HCV testing with HIV prevention and treatment services for PWID. Over a short duration, we observed a significant impact on community-level HCV testing and awareness of HCV status among PWID. While additional strategies might be required to improve population awareness levels, integration of HCV testing with HIV programs for PWID, particularly given the high burden of HIV/HCV coinfection represents a critical first step. To achieve elimination targets, programs will also need to consider delivering HCV treatment from such venues.

Abbreviations

ART, antiretroviral therapy; DSMB, data safety monitoring board; HCT, HIV counseling and testing; ICCs, integrated care centers; IEC, information, education and counseling; ITT, intention-to-treat; LLOQ, lower limit of quantification; MSM, men who have sex with men; NACO, National AIDS Control Organization; OAT, opioid agonist therapy; PR, prevalence ratios; PWID, people who inject drugs; RDS, respondent-driven sampling; SSP, syringe service programs; STI, sexually transmitted infection; SVR, sustained virological response; WHO, World Health Organization.

Financial support

National Institutes of Health and the Elton John AIDS Foundation.

Conflict of interest

SSS and SHM received speaker fees from Gilead Sciences for work outside the study.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

SSS, S Solomon, DDC, GML, and SHM conceptualized the study, designed the trial, and obtained funding. SSS, AKS, SA, and CKV led protocol implementation. VV, MSK, and KSS provided expertise on key populations and HIV/HCV epidemiology in India. DLT and S Saravanan provided technical expertise. S Saravanan and SHI performed all the laboratory testing. TCQ and OL provided material support and technical expertise. SHM and AMM led the statistical analysis. SSS, AMM and SHM drafted the manuscript. All authors contributed to additional drafts and revisions of the manuscript.

Acknowledgements

This research study was supported by the National Institutes of Health (NIH) (R01DA032059, R01MH089266, K24DA035684, R01DA041034, DP2DA040244, F31DA044046, T32AI102623) and the Johns Hopkins University Center for AIDS Research (P30AI094189). Additional support was provided by the Office of AIDS Research, Division of Intramural Research, National Institute of Allergy and Infectious Diseases, NIH, Intramural-to-India program, and the Elton John AIDS Foundation. We thank the National AIDS Control Organisation and the State AIDS Control Societies for their support of this study.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2019.09.022.

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