Published in final edited form as:

Lancet Infect Dis. 2015 January ; 15(1): 36–45. doi:10.1016/S1473-3099(14)71045-X.

High burden of HCV disease and poor access to HCV services among people who inject drugs in India: A cross-sectional study among 14,481 drug users across India

Sunil Suhas Solomon, M.B.B.S.^{1,2,3}, Shruti H Mehta, Ph.D.², Aylur K Srikrishnan, B.A.³, Suniti Solomon, M.D.³, Allison M. McFall, M.H.S.², Oliver Laeyendecker, Ph.D.^{1,4}, David D Celentano, Sc.D.², Syed H Iqbal, Ph.D.³, Santhanam Anand, B.Sc.³, Canjeevaram K Vasudevan, B.Sc.³, Shanmugam Saravanan, Ph.D.³, Gregory M Lucas, M.D.¹, Muniratnam S Kumar, M.D.³, Mark S Sulkowski, M.D.¹, and Thomas C Quinn, M.D.^{1,4}

¹Johns Hopkins School of Medicine, Department of Medicine, Baltimore, Maryland, USA

²Johns Hopkins Bloomberg School of Public Health, Department of Epidemiology, Baltimore, Maryland, USA

³YR Gaitonde Centre for AIDS Research and Education, Chennai, India

⁴National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland, USA

Abstract

Background—Globally, 90% of HCV-infected individuals reside in resource-limited settings (RLS). We characterized the prevalence of HCV, HIV/HCV co-infection, and the HCV care continuum among people who inject drugs (PWID) in India.

Methods—14,481 PWID were sampled from 15 cities throughout India using respondent-driven sampling (RDS) from January–December 2013. HCV prevalence was estimated by the presence of anti-HCV antibodies incorporating RDS weights. HCV care continuum outcomes were self-reported except for viral clearance among treatment-experienced participants.

Findings—Median age was 30 years and 13,608/14,449 (92.4%) were male. Overall weighted HCV prevalence was 37.2% (5,777/14,447); HIV/HCV co-infection prevalence was 13.2%

Corresponding Author: Sunil Solomon, MBBS, PhD, MPH, Assistant Professor, Johns Hopkins University School of Medicine, 615 N. Wolfe Street, Rm. E6608, Baltimore, MD 21205 USA, Phone: +1-410-614-1356, sss@jhmi.edu.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Contributors

Sunil Solomon and Shruti Mehta were responsible for the design of the study, data collection, interpretation of data and drafting the manuscript. Allison McFall was responsible for data analysis. David Celentano, Gregory Lucas, Suniti Solomon and M Suresh Kumar were responsible for the design of the study. Aylur Srikrishnan, Canjeevaram Vasudevan and Santhanam Anand led data collection. Shanmugam Saravanan and Syed Iqbal conducted laboratory testing. Tom Quinn, Oliver Laeyendecker and Mark Sulkowski provided input on the design, interpretation and development of the manuscript. All authors read and approved the final manuscript.

Conflicts of Interest

We declare that we have no conflicts of interest.

(2,085/14,435). Correlates of HCV infection included higher lifetime injection frequency, HIV positivity, and a higher prevalence of persons with HIV RNA > 1000 copies/ml in the community. Of 5,777 HCV antibody positive PWID, 440 (5.5%) were aware of their status, 225 (3.0%) had seen a doctor for their HCV, 79 (1.4%) had taken HCV treatment, and 18 (0.4%) had undetectable HCV RNA. Overall, 6,138/12,128 (50.5%) did not get tested for HCV because they had never heard of HCV. Among the 5,777 HCV antibody positives, 2,086 (34.4%) reported harmful/hazardous alcohol use of whom 1,082 (50.4%) were dependent; 3,007 (52.9%) reported recent needle sharing. Awareness of HCV positive status was significantly associated with higher education, HIV testing history, awareness of HIV positive status, and higher community antiretroviral therapy coverage.

Interpretation—The high burden of HCV and HIV/HCV co-infection coupled with low-access to HCV services highlights an urgent need to include RLS in the global HCV agenda. While newer treatments will become available globally in the near future, programs to improve awareness, and reduce disease progression and transmission need to be scaled-up without further delay. Failure to do so could result in patterns of rising mortality, undermining advances in survival attributed to widespread HIV treatment.

Funding—US National Institutes of Health

INTRODUCTION

Approximately 184 million persons are chronically infected with HCV, of whom 90% reside in resource-limited settings (RLS).¹ People who inject drugs (PWID) bear a disproportionate burden (prevalence 50–90%).² Chronic HCV infection is associated with significant morbidity and mortality.^{3,4} Unfortunately, the majority of HCV-infected individuals are unaware of their infection, because HCV is typically symptom-free for decades.⁵ Treatment for chronic HCV is curative and there have been dramatic advances over the past few years^{6–8} such that interferon-free pan-genotypic short-course non-toxic regimens with cure rates >95% are on the horizon.⁹ Consequently, conversations about HCV eradication have begun.^{10,11} However, such regimens will be expensive (similar to early years of antiretroviral therapy [ART]) and access, particularly among hard-to-reach populations in RLS, will be the major challenge to the global control of HCV.^{12,13}

Little epidemiologic and virtually no data on access to HCV diagnostic and treatment services exist from RLS. While barriers to HCV care have been well-characterized in affluent settings,¹⁴ it remains unknown if these will directly translate to resource-limited settings.¹⁵ Epidemiologic studies to understand disease burden and HCV service uptake are needed if global control of HCV infection is to become a reality.

HCV prevalence in the general population in India is ~1.0–1.9%.¹⁶ India has approximately three million opioid users with as many as 1.1 million PWID.¹⁷ We characterized the burden of HCV infection, HIV/HCV co-infection, the HCV care continuum, and associated factors among a large sample of PWID from 15 cities across India.

METHODS

Study setting

This study was conducted in 15 cities from 11 states in India (Figure 1) as the baseline assessment of a cluster-randomized trial ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study?term=NCT01686750) Identifier: NCT01686750). These cities were selected by study investigators and representatives of the National AIDS Control Organization (NACO), India to represent regions with varying stages of drug use epidemics (established drug use epidemics, large cities, cities with documented emerging drug use epidemics, cities with anecdotal evidence of emerging drug use epidemics) as well as different settings (large metropolitan cities, medium and small cities). In each city, a local partner was identified that maintained a drop-in center for PWID that provided some HIV prevention services (e.g., opioid substitution). Only one study site was established in each city.

Study Population

Eligibility criteria included: (1) age ≥ 18 years; (2) self-report of illicit drug injection in the prior 2 years; (3) informed consent; and (4) possession of a valid referral coupon (*see Study Procedures*). The study population was accrued using respondent-driven sampling (RDS), a chain-referral recruitment strategy that has demonstrated to be effective in recruiting hard-to-reach populations including PWID. RDS uses systematically collected data about the relationships between recruiters and recruits, such that recruitment bias can be adjusted for in the analysis and resulting in estimates that are generalizable to the target population.^{18,19} In each site, ethnography was conducted prior to the RDS with PWID peer leaders and key stakeholders in the local drug-using community to select “seeds” – individuals who were identified during ethnography processes to be well-connected in the PWID community. Recruitment was terminated early in Moreh due to civil unrest.

Study procedures

Following verbal consent, participants provided a fingerprint image to avoid duplicate enrollment. Participants completed an interviewer-administered survey, which captured information on demographics, PWID network characteristics (relationship to recruiter/network size), risk behavior, HIV and HCV testing, and treatment and substance use including alcohol (AUDIT). Participants underwent rapid HIV testing with pre- and post-test counseling. Samples collected for future testing were shipped to the central laboratory in Chennai. “Seeds” and participants were given two hologram-labeled referral coupons to give to any two members of their network. All participants received a monetary incentive of 50 Indian Rupees [INR] (~0.8 US dollars) for each participant referred who completed study procedures.

Laboratory Methods

HIV infection was diagnosed on-site using three rapid tests: Alere™ Determine™ HIV-1/2 (Alere Medical Co., Ltd., Chiba, Japan); First response HIV card test 1–2.0 (PMC Medical India Pvt, Ltd, Daman, India); and Signal Flow Through HIV 1 Spot/Immunodot Test kit, (Span Diagnostics Ltd, Surat, India). HIV-1 RNA was quantified from fresh plasma

specimen using the Real Time HIV-1 assay (Abbott Laboratories, Abbott Park, Illinois, USA). HCV antibody testing was performed on stored specimens using the Genedia HCV ELISA 3.0 (Green Cross Medical Science, Chungbuk, Korea). HCV RNA was quantified in stored specimens from participants who reported receiving HCV treatment in the baseline survey (n=79) using the Real Time HCV assay (Abbott Molecular Inc., Des Plaines, IL, USA); HCV RNA levels <30 copies/ml was considered sustained virologic response.

Statistical Analyses

Data from “seeds” were excluded from analyses. The RDS-II estimator (Volz-Heckathorn), which ‘weights’ for network effects, was used to calculate site-specific estimates.²⁰ All percentages reported in the text incorporate these weights (unweighted estimates can be found in Supplemental Tables). Weights incorporate self-reported network size (number of PWID seen in prior 30 days). Prevalence was estimated incorporating RDS-II weights. Also, a composite weight which accounts for the number of PWID in each city derived from state-level data²¹ was used to estimate overall proportions. Several assumptions are critical when using RDS samples to generalize to the target population such as depth of recruitment (greater than six waves of recruitment), homophily (tendency to recruit others with similar characteristics) and equilibrium (sample characteristics are independent of seeds).¹⁸ Our RDS samples achieved a median depth of 22 waves (Range: 12 – 50) across the 15 sites. Overall, homophily values for HCV status were low (Range: -0.031, 0.134 among HCV-negative persons; and Range: 0.002, 0.444 among HCV-infected persons). All samples achieved equilibrium. Supplementary Table 1 provides site-wise RDS process measures.

Individual and site-level correlates of HCV antibody positivity were identified using multi-level logistic regression with random-intercepts per site (to account for clustering) incorporating scaled RDS-II weights. Individual correlates included demographics and lifetime risk behaviors. Site-level variables included median network size (self-reported by PWID) and prevalence of HIV viremia (number of persons in a community who had HIV RNA > 1000 copies/ml)– we considered this a measure of HIV prevalence and service access in the city. All variables significantly associated with HIV prevalence in univariable analysis (p<0.05) and some variables deemed important *a priori* (age, sex, education, income and region) were considered for inclusion in the multivariable model. With the exception of age, which was included regardless of statistical significance, only those variables associated with the outcome at p<0.05 were retained in the final multivariable model.

HCV care continuum outcomes were based on self-reported data with the exception of sustained virologic response, which was based on HCV RNA testing of specimens from 79 participants who reported ever receiving HCV treatment. Participants were asked if they had ever been to a physician to discuss their HCV to establish linkage to care.

Correlates of awareness of HCV positive status were estimated using methods similar to the HCV prevalence analysis, multi-level logistic regression accounting for clustering by site incorporating RDS-II weights. ART coverage in the community was considered as an additional site-level variable in this analysis as a measure of health services access in the city. Due to strong collinearity between region and the site-level correlates for network size

and proportion of HIV-positives on ART, two different multivariable models were constructed. Model 1 includes the region correlate while Model 2 includes the site-level correlates for network size and proportion of HIV-positives on ART, in addition to individual-level correlates. Years of injection drug use not included in the final multivariate models due to its collinearity with age.

All statistical analyses were performed using RDS Analyst Software Version 0.1 (<http://hpmrg.org>) and STATA Version 12.0 (College Station, Texas, US).

Ethical clearances

This study was approved by the Johns Hopkins Medical Institutions and the YR Gaitonde Centre for AIDS Research and Education institutional review boards.

Role of funding source

The sponsor of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

FINDINGS

Demographics and Risk Behaviors

Median age of the 14,450 PWID was 30 years (interquartile range [IQR]: 24 – 36). Most (13,608/14,449, 92.4%) were male, 40.7% (5,882/14,449) were married and 39.2% (5,018/14,449) had primary school education or less. Median monthly income was US Dollar 82 (IQR:33–115). Median age at 1st injection was 21 years (IQR:18–26). Overall, 47.7% (5,815/14,450) reported sharing injection paraphernalia in the prior 6 months and 42.2% (5,838/14,450) had evidence of harmful/hazardous alcohol use or dependence. HIV prevalence was 21.1% (2,905/14,449).

Considerable variability was observed across sites (Table 1). Median age ranged from 24 to 34 years and proportion female from 0.1% (1/1,000) to 23.3% (200/1,000). Age at first injection ranged from 18 to 26 years. Harmful/hazardous alcohol use ranged from 5.5% (69/999) to 34.5% (297/1,000) and alcohol dependence ranged from 6.0% (33/457) to 51.0% (524/1,000). The proportion who reported ever needle sharing ranged from 19.9% (261/1,000) to 80.4% (804/1,000). HIV prevalence ranged from 5.9% (61/1,000) in Bhubaneswar to 44.9% (198/457) in Moreh. For unweighted estimates, see Supplementary Table 2.

Prevalence of HCV and HIV/HCV co-infection

Overall weighted HCV prevalence was 37.2% (5,777/14,447) (95% confidence interval [CI]: 36.3, 38.0). Site-specific weighted HCV prevalence ranged from 4.9% (41/1,000) in Gangtok to 64.9% (684/1,000) in Imphal (Figure 1A). Weighted HIV/HCV co-infection prevalence was 13.2% (2,085/14,435) (95% CI: 12.7, 13.7)(Figure 1B). Site-specific weighted HIV/HCV co-infection prevalence ranged from 2.0% (18/996) in Dimapur to 28.5% (323/999) in Kanpur (Figure 1B). HCV prevalence among HIV-infected PWID

ranged from 9.3% (18/197) to 96.0% (213/226) - 7 of 15 sites had HCV prevalence >75% among HIV-infected PWID. Unweighted estimates are listed in Table 2.

Correlates of HCV infection

Unadjusted and adjusted weighted correlates of HCV infection are in Table 3. In multivariable analysis, male sex, ever visiting a needle exchange program, ever visiting an OST center, higher number of lifetime injections, younger age at first injection, injecting drugs in combination and a history of sharing needles were significantly associated with HCV infection. HIV-infected PWID were more likely to be infected with HCV (OR: 5.25; 95% CI: 3.41, 8.09). PWID from cities with higher HIV viremia had higher HCV prevalence (OR for site-level HIV viremia >18% vs. ≤6%: 7.11; 95% CI: 6.82, 2.27, 20.5), as did PWID in cities with larger networks (OR for median network size >25 vs. ≤12: 3.45; 95% CI: 2.0, 5.96). Inferences were unchanged in sensitivity analyses that were unweighted (Supplementary Table 3) or used RDS-I weights²² (data not shown).

HCV care continuum

1,272 of 14,450 (7.0% weighted) persons had ever been tested for HCV. The most common reason for not getting tested was never having heard of HCV (6,138/12,128, 50.5%). Of those who had heard of HCV, low perceived risk (4,374/6,047, 73.2%) and not knowing where to get tested (937/6,047, 14.3%) were common reasons for not getting tested. Of those tested, 55.3% (717/1,272) were tested in private and 41% (491/1,272) in government centers; 52.6% (580/1,272) reported being tested because they wanted to learn their status and 24.9% (307/1,272) were referred by a physician. HCV prevalence among those ever tested was 61.6% (869/1,272) compared to 35.3% (4,635/12,340) among those never tested. Among HCV antibody positive persons, 34.4% (2,086/5,777) reported harmful/hazardous alcohol use; of whom 50.4% (1,082/2,086) were alcohol dependent.

Of 5,777 HCV antibody positive PWID, 440 (5.5%) were aware of their status, 225 (3.0%) had been to see a doctor for their HCV (linked to care), 79 (1.4%) had taken HCV treatment and 18 (0.4%) had undetectable HCV RNA at the time of the survey (26.4% of those who reported taking treatment) (Figure 2). Cities with established epidemics had marginally better outcomes along the continuum; cities with anecdotal evidence of emerging drug use fared worst (Supplementary Table 4).

Unadjusted and adjusted weighted correlates of HCV positive awareness are in Table 4 (Supplementary Table 5 lists unweighted estimates). In multivariable analysis (Model 1), awareness of HCV positivity was significantly associated with age (OR per 10 year increase: 1.55; 95% CI: 1.27, 1.90), higher education (OR for high school vs. primary school: 3.75; 95% CI: 2.10, 6.72), ever receiving opioid substitution (OR: 1.87; $p=1.05$, 3.32), and ever being tested for HIV (OR: 3.61; 95% CI: 2.43, 5.36). Compared to HIV-negatives, HIV-positives who were aware of their status were more likely to also be aware of their HCV infection (OR: 3.75; 95% CI: 1.83, 7.67); being HIV-positive but unaware of status did not increase likelihood of knowledge of HCV status. Persons from regions other than those with established epidemics were significantly less likely to be aware of their HCV positive status (OR for emerging epidemics [anecdotal]: 0.11; 95% CI: 0.05, 0.25). In models with site-

level correlates (Model 2), PWID from cities with better ART coverage and larger drug-using networks were more likely to be aware of their HCV positive status.

Seventy-nine participants reported receiving some form of interferon-based treatment for their HCV; sixty-one (77.2%) were from cities with established epidemics. Seventeen (21.6%) reported discontinuing treatment. Fifty-six (70.8%) received treatment in a private setting. Compared to PWID who were not treated, those treated were significantly more likely to be educated, to have been tested for HIV and if positive, on ART ($p < 0.01$ for all).

INTERPRETATION

This study demonstrates a high burden of HCV and HIV/HCV co-infection in one of the largest samples of PWID from a resource-limited setting. Despite this high burden, it was striking that fewer than half of the participants had heard of hepatitis C, and of those found to be HCV-infected only one in twenty were aware of their status. By contrast, in the United States, it is estimated that 50% of HCV-infected persons are aware of their infection.⁵ While the HCV care continuum has been described as a “cascade” in such high-income regions, these data suggest that in this population of PWID in India, the care continuum is more reflective of a “cliff.” In this time of rapidly expanding HCV therapeutic optimism, these data have important implications for global HCV control.

As expected, HCV prevalence among PWID in India was high – 1.5 to 2 times the HIV prevalence in most sites reflecting the high transmissibility and large reservoir of HCV among PWID.²³ There was; however, significant variability across sites likely due to diversity in drug use epidemic stage and socio-demographic and risk behaviors. For the most part correlates of HCV infection were as expected. We did observe a positive association between attending a SNEP or OST program and HCV prevalence, which likely reflects that the heaviest injectors and potentially those with the highest levels of risk behavior tend to be referred for these services. Interestingly, community HIV viremia, a surrogate for access to HIV prevention and treatment services,²⁴ was strongly associated with HCV prevalence, suggesting the need to integrate HCV-related services into existing HIV programs for PWID, a strategy endorsed by the World Health Organization (WHO).²⁵ Integration is further supported by the high co-infection prevalence observed in this study and the strong association between awareness of HIV positive status and awareness of HCV positive status. The Indian national program is currently focused on improving HIV-related service access for PWID. While this will decrease AIDS-related mortality, India may begin to see increased HCV-related mortality if access to HCV services remains unchanged as is currently being seen in high-income settings.²⁶ In a prior study, we identified that liver-related mortality is already a serious concern in North eastern India where drug use has been endemic for decades and PWID have above average access to ART compared to PWID in other regions of India.²⁷

In April 2014, the WHO published its first ever guidelines on HCV management reflecting a changing global perspective towards HCV.²⁵ They recommended that all persons with chronic HCV, including PWID, be assessed for treatment, with prioritization of patients with advanced fibrosis/cirrhosis. Within the guidelines is a call for epidemiologic data in RLS.

Several of the findings from this study will inform successful implementation of these guidelines.

First, over half of the study population where more than one in three was HCV-infected had never even heard of HCV. This poor knowledge translated into low testing rates and consequently, very poor awareness of HCV status among those infected – the first step in the HCV care continuum. This poor knowledge coupled with low HCV treatment access is reminiscent of the HIV epidemic among PWID in India nearly 15 years ago. In HIV, only after treatment costs declined dramatically and programs such as the Presidents Emergency Program for AIDS Relief (PEPFAR) and local governmental programs improved access, was it recognized that the majority of individuals were not accessing treatment due to lack of awareness or lack of engagement in care, prompting still ongoing efforts to improve outcomes along the continuum.²⁸ Our data highlight that we face the same challenges with HCV and that while access to treatment may still be years away, literacy and testing programs especially among vulnerable populations should be implemented immediately.

Second, as outlined by WHO, management of HCV infection is about more than just about antiviral drugs. Alcohol use is a well-recognized driver of HCV disease progression.³ In this population, more than one-third of HCV antibody positive persons reported harmful/hazardous alcohol use. Interventions to reduce alcohol use in this population will help delay disease progression and thereby, prolong survival until new antiviral agents are accessible. Moreover, while newer antivirals are efficacious at clearing HCV infection even among cirrhotics, the management of cirrhosis itself will remain challenging in resource-limited settings, further highlighting the need for interventions to reduce alcohol use and halt progression to cirrhosis.

Third, harm reduction interventions (e.g., opioid substitution therapy, needle syringe exchange programs) among highly vulnerable populations such as PWID will be critical for minimizing onward transmission of HCV. Furthermore, when treatment does become available, harm reduction interventions will play a key role in minimizing re-infection risk. This will be of critical importance to cost-effectiveness of these novel agents whose pricing has already sparked much debate.²⁹ In this study, rates of needle sharing were unacceptably high – for example, in Imphal where the HCV prevalence was 65%, needle sharing was reported by 80% of participants. Additionally, of the 79 persons who reported HCV treatment, only 26% were virus free at the time of the study, which likely reflects some combination of non-response and reinfection, emphasizing the potential benefits of harm-reduction interventions.

Finally, HCV therapeutics are rapidly evolving. Simepravir and Sofosbuvir, recommended for use in current guidelines, have demonstrated higher efficacy in genotype 1 infection vs. genotype 2/3.^{25,30} We have previously demonstrated a preponderance of genotype 3 infection among PWID across India,²⁷ similar to what is seen in other countries in Asia. Moreover, current guidelines call for HCV RNA and HCV genotyping to inform treatment decisions.²⁵ In settings like India, where access to HCV antibody testing itself is challenging as observed here, HCV genotyping and HCV RNA quantification are simply out of reach. For comparison, despite the widespread global availability of antiretroviral therapy since

early 2000s, HIV RNA quantification is seldom performed in RLS due to inadequate infrastructure and cost. Even if newer pan-genotypic regimens become available, HCV RNA testing will remain a critical part of HCV management making low-cost methods for identification of HCV RNA essential. Further, in RLS, continuing medical education is not normative, which can be challenging given the rapid pace at which HCV therapeutics are evolving. Currently, only pegylated interferon and ribavirin (PEG/RBV) are available in India, but the cost of even a 24-week regimen of PEG/RBV is ~INR 140,000 – about 3–5 times the annual income of PWID recruited in this study. Moreover, patients need to pay for HCV treatment out-of-pocket making treatment unaffordable for the vast majority of PWID. However, while treatment cost is and will remain a major barrier to management of HCV infection in RLS, these data collectively highlight several other challenges need to be addressed alongside improving treatment access for global HCV control.

Our analysis had several limitations. All outcomes along the care continuum except for viral clearance among those who received treatment were ascertained via self-report and therefore, bear limitations related to recall bias. The lack of HCV RNA data on all samples precludes our ability to estimate the proportion actually needing treatment and proportion virus-free. However, even if we recalibrated estimates to account for clearance previously observed among PWID in India (~30%),³¹ the proportion requiring treatment that received treatment would still be 2%. RDS requires several assumptions in order to arrive at a truly representative sample, only some of which can be validated (e.g., depth of recruitment, homophily). A key assumption in estimation of RDS weights that cannot be validated is that participants' network size as this information was collected by self-report from the participant – however, we do not foresee any reason for participants to misreport their network size.

In conclusion, these data clearly highlight explosive epidemics of HCV among PWID in India with minimal access to HCV-related services and potentially reflecting scenarios among PWID in other resource-limited settings. While there is heightened optimism on global eradication of HCV given advances in therapeutics, these data highlight several challenges starting with low-levels of awareness and access to HCV testing – the first steps in the pathway to global control of HCV infection. While newer treatments will become available in resource-limited settings in the near future, programs to improve awareness and reduce disease progression and transmission need to be scaled-up without further delay. Failure to do so will result in replication in RLS of mortality patterns currently being observed in high-income settings and will also undermine the survival benefits of ART currently being observed among HIV-infected PWID.

PANEL

Systematic Review

We conducted two independent PubMed searches on August 27, 2014 corresponding to the two major objectives of our paper: epidemiology (prevalence of HCV and HIV/HCV coinfection) and the HCV care continuum. We used terms for Hepatitis C (e.g., “hepatitis C” and “HCV”), “prevalence” or “epidemiology”, people who inject drugs (e.g., “IDU” and “people who inject drugs”), and low-middle income countries (e.g., “less developed

countries" and "India") for the epidemiology search and identified 121 publications. We used the same terms for Hepatitis C and people who inject drugs with additional terms for care continuum (ex: "linkage to care" and "continuity of patient care") for the care continuum search and identified 143 publications. There were reports of epidemiological studies of prevalence of HCV and HIV/HCV co-infection among people who use drugs (PWID) and review articles on the prevalence of HCV among PWID in low- and middle-income countries (LMICs). There were also reports on the management of HCV infection among PWID. Of the 143 publications related to the care continuum, we did not identify any studies that reported the HCV care continuum among PWID from any LMIC. There is an increased sense of optimism in HCV management given recent advances in HCV therapeutics. In fact, editorials have cited the "beginning of the end" of the HCV epidemic. In April 2014, the World Health Organization released their first ever guidelines for the management of HCV infection. In these guidelines, they recognized a gap in knowledge of epidemiology and management of HCV among persons living in LMICs as most data related to the management of HCV and the HCV care continuum came from high-income settings. Review articles in the past have demonstrated that there is a high burden of HCV infection among PWID globally, with PWID in LMICs bearing a higher burden. Beyond data on prevalence, there is little information on challenges that one might face in the global control of HCV infection.

Interpretation

Our study identified at least three important findings that are critical to the global HCV control agenda. First, to achieve global control of HCV infection, hard-to-treat populations such as PWID in LMICs need to be targeted as they bear a significant burden of HCV and HIV/HCV infection. This study, one of the largest epidemiological studies among PWID in a LMIC, identified that about one in three PWID was infected with HCV and more than one in ten were co-infected with HIV/HCV. Failure to address HCV will result in increased mortality due to HCV in LMICs especially among HIV/HCV co-infected PWID – a trend currently being observed in high-income settings. Second, while the majority of the debate surrounding management of HCV in LMICs has been focused on cost of the novel agents, our data clearly show that there are several steps prior to treatment that need to be addressed. Less than 50% of PWID had ever heard of HCV and only about 1 in 20 HCV-infected PWID were aware of their HCV positive status. Until treatment becomes available, interventions need to focus on improving HCV literacy and improving access to HCV testing – both antibody and HCV RNA, which is essential for determining eligibility for HCV therapy. Third, there is a high prevalence of risk behaviors that could jeopardize the impact of the treatment. High rates of needle sharing as observed in our study could result in high rates of re-infection adversely impacting the cost-effectiveness of these novel regimens and high levels of alcohol consumption could result in faster progression to liver cirrhosis – cirrhotics have been shown to respond to therapy less favorably than non-cirrhotics. Therefore, prior to widespread roll-out of HCV therapy, it is essential to scale up harm reduction interventions and introduce programs to reduce alcohol use in these population to maximize effectiveness of HCV therapy.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

This research has been supported by the National Institutes of Health, US Grant# DA 032059 and K24DA034621 and the Office of AIDS Research, NIH, Intramural-to-India program and was facilitated by the Johns Hopkins CFAR (1P30AI094189). We acknowledge Andrew Redd and Joshua Pascual for assistance with manuscript preparation. We thank the National AIDS Control Organization (NACO), India, and all of our partner non-governmental organizations throughout India, and the countless participants, without whom this research would not have been possible.

References

1. Mohd Hanafiah K, Groeger J, Flaxman AD, Wiersma ST. Global epidemiology of hepatitis C virus infection: new estimates of age-specific antibody to HCV seroprevalence. *Hepatology*. 2013; 57(4): 1333–1342. [PubMed: 23172780]
2. Aceijas C, Rhodes T. Global estimates of prevalence of HCV infection among injecting drug users. *Int J Drug Policy*. 2007; 18(5):352–358. [PubMed: 17854722]
3. Thomas DL, Astemborski J, Rai RM, et al. The natural history of hepatitis C virus infection: host, viral, and environmental factors. *JAMA*. 2000; 284(4):450–456. [PubMed: 10904508]
4. Seeff LB, Buskell-Bales Z, Wright EC, et al. Long-term mortality after transfusion-associated non-A, non-B hepatitis. The National Heart, Lung, and Blood Institute Study Group. *N Engl J Med*. 1992; 327(27):1906–1911. [PubMed: 1454085]
5. Volk ML, Tocco R, Saini S, Lok AS. Public health impact of antiviral therapy for hepatitis C in the United States. *Hepatology*. 2009; 50(6):1750–1755. [PubMed: 19824079]
6. Sulkowski MS, Gardiner DF, Rodriguez-Torres M, et al. Daclatasvir plus sofosbuvir for previously treated or untreated chronic HCV infection. *N Engl J Med*. 2014; 370(3):211–221. [PubMed: 24428467]
7. Afdhal N, Zeuzem S, Kwo P, et al. Ledipasvir and Sofosbuvir for Untreated HCV Genotype 1 Infection. *N Engl J Med*. 2014; 370(20):1889–1898. [PubMed: 24725239]
8. Fried MW, Buti M, Dore GJ, et al. Once-daily simeprevir (TMC435) with pegylated interferon and ribavirin in treatment-naïve genotype 1 hepatitis C: the randomized PILLAR study. *Hepatology*. 2013; 58(6):1918–1929. [PubMed: 23907700]
9. Everson, GT.; Tran, TT.; Towner, WJ., et al. Safety and efficacy of treatment with the interferon-free, ribavirin-free combination of sofosbuvir5816 for 12 weeks in treatment naïve patients with genotype 1–6 HCV infection [Abstract O111]. International Liver Conference; London, United Kingdom. 2014.
10. Hagan LM, Wolpe PR, Schinazi RF. Treatment as prevention and cure towards global eradication of hepatitis C virus. *Trends Microbiol*. 2013; 21(12):625–633. [PubMed: 24238778]
11. Alter HJ, Liang TJ. Hepatitis C: the end of the beginning and possibly the beginning of the end. *Ann Intern Med*. 2012; 156(4):317–318. [PubMed: 22351718]
12. Jayasekera CR, Barry M, Roberts LR, Nguyen MH. Treating Hepatitis C in Lower-Income Countries. *N Engl J Med*. 2014; 370(20):1869–1871. [PubMed: 24720680]
13. Only just the beginning of the end of hepatitis C. *Lancet*. 2014; 383(9914):281. [PubMed: 24461110]
14. Oramasionwu CU, Moore HN, Toliver JC. Barriers to Hepatitis C Antiviral Therapy in HIV/HCV Co-Infected Patients in the United States: A Review. *AIDS Patient Care STDS*. 2014; 28(5):228–239. [PubMed: 24738846]
15. McGowan CE, Monis A, Bacon BR, et al. A global view of hepatitis C: physician knowledge, opinions, and perceived barriers to care. *Hepatology*. 2013; 57(4):1325–1332. [PubMed: 23315914]

16. Sievert W, Altraif I, Razavi HA, et al. A systematic review of hepatitis C virus epidemiology in Asia, Australia and Egypt. *Liver Int.* 2011; 31(Suppl 2):61–80. [PubMed: 21651703]
17. United Nations Office on Drugs and Crime. 2008 World Drug Report. 2008
18. Heckathorn D. Respondent-driven sampling: a new approach to the study of hidden populations. *Social Problems.* 1997; 44(2):174–199.
19. Solomon SS, Lucas GM, Celentano DD, Sifakis F, Mehta SH. Beyond Surveillance: A Role for Respondent-driven Sampling in Implementation Science. *Am J Epidemiol.* 2013; 178(2):260–267. [PubMed: 23801014]
20. Volz E, Heckathorn DD. Probability Based Estimation Theory for Respondent Driven Sampling. *Journal of Official Statistics.* 2008; 24(1):79–97.
21. National Institute of Medical Statistics and National Aids Control Organisation. Technical Report: India HIV Estimates. 2010
22. Salganik M, Heckathorn DD. Sampling and estimation in hidden populations using respondent-driven sampling. *Social Problems.* 2004; 49:11–34.
23. Garfein RS, Vlahov D, Galai N, Doherty MC, Nelson KE. Viral infections in short-term injection drug users: the prevalence of the hepatitis C, hepatitis B, human immunodeficiency, and human T-lymphotropic viruses. *Am J Pub Health.* 1996; 86(5):655–661. [PubMed: 8629715]
24. Solomon, SS.; Mehta, SH.; Sri Krishnan, AK., et al. Community Viral Load and HIV Incidence: A Multi-city Study of High-Risk Populations in India. 21st Conference on Retroviruses and Opportunistic Infections; Boston, MA. 2014.
25. World Health Organization. Guidelines for the screening, care and treatment of persons with hepatitis C infection. 2014.
26. Ly KN, Xing J, Kleven RM, Jiles RB, Ward JW, Holmberg SD. The increasing burden of mortality from viral hepatitis in the United States between 1999 and 2007. *Ann Intern Med.* 2012; 156(4):271–278. [PubMed: 22351712]
27. Solomon, SS.; Srikrishnan, A.; Saravanan, S., et al. Diversity of HCV infection among HIV-infected injection drug users in India: Implications for HIV and HCV Treatment. 20th Conference on Retroviruses and Opportunistic Infections; Atlanta, George. 2013.
28. Gardner EM, McLees MP, Steiner JF, Del Rio C, Burman WJ. The spectrum of engagement in HIV care and its relevance to test-and-treat strategies for prevention of HIV infection. *Clin Infect Dis.* 2011; 52(6):793–800. [PubMed: 21367734]
29. Hill A, Khoo S, Fortunak J, Simmons B, Ford N. Minimum costs for producing hepatitis C direct-acting antivirals for use in large-scale treatment access programs in developing countries. *Clin Infect Dis.* 2014; 58(7):928–936. [PubMed: 24399087]
30. Lawitz E, Mangia A, Wyles D, et al. Sofosbuvir for previously untreated chronic hepatitis C infection. *N Engl J Med.* 2013; 368(20):1878–1887. [PubMed: 23607594]
31. Mehta SH, Vogt SL, Srikrishnan AK, et al. Epidemiology of hepatitis C virus infection & liver disease among injection drug users (IDUs) in Chennai, India. *Indian J Med Res.* 2010; 132:706–714. [PubMed: 21245619]

Figure 1. Prevalence of HCV and HIV/HCV co-infection among 14,450 people who inject drugs in India

Panel A: HCV Prevalence. 95% confidence interval: AIZ 59.7–69.0%; AMR 42.8–54.6%; BBE 5.6–10.1%; BIL 16.4–28.2%; CDH 46.1–56.0%; CCP 45.5–55.1%; DEL 37.3–47.5%; DIM 6.9–11.2%; GTK 2.7–7.0%; IMP 60.1–69.7%; KAN 59.2–68.0%; LDH 21.6–29.6%; LGL 11.7–18.9%; MOR 33.0–49.2%; MUM 29.4–38.7%.

Panel B: HIV/HCV Co-infection Prevalence. 95% confidence interval: AIZ 18.1–21.2%; AMR 15.0–25.6%; BBE 1.8–4.4%; BIL 5.1–11.0%; CDH 4.0–13.7%; CCP 10.2–19.5%; DEL 8.9–13.9%; DIM 0.9–3.2%; GTK 0.5–4.4%; IMP 26.3–29.1%; KAN 24.1–32.9%; LDH 6.1–16.2%; LGL 0.9–3.9%; MOR 14.1–25.6%; MUM 2.4–9.3%.

Figure 2. HCV care continuum among 5,777 HCV antibody positive people who inject drugs across 15 cities in India

Lines in the figure represent the range of HCV care continuum outcomes across sites. For site-specific outcomes along the care continuum, please see Supplementary Table 4.

Table 1

Characteristics of people who inject drugs across 15 sites in India (n=14,450) *

	North East India (Established Epidemics)					Large cities			North India (Emerging Epidemics - documented)			Central India (Emerging Epidemics - anecdotal evidence)		
	AIZ	CCP	DIM	GTK	IMP	LGL	MOR	DEL	MUM	AMR	CDH	LUD	BBE	KAN
Sample size (including "seeds")	1002	1002	1002	1003	1002	1002	459	1001	1001	1001	998	1002	1002	1002
Median age in yrs	26	29	30	28	34	24	32	30	30	27	29	27	32	34
Proportion Male (%)	81.3	77.3	85.8	93.3	87.7	87.9	76.7	99.7	96.4	98.8	99.5	99.7	99.9	99.3
Education (%)														
<i>Primary school or less</i>	6.2	26.6	33.7	17.3	28.9	4.9	39.4	69.3	61.4	42.0	33.8	33.9	32.0	30.1
<i>Secondary school</i>	63.0	49.7	51.3	38.7	38.2	68.9	55.6	27.6	33.0	45.1	48.3	40.2	46.6	46.7
<i>High school and above</i>	30.9	23.6	15.0	44.0	32.8	26.2	5.0	3.1	5.7	12.9	17.9	25.9	21.3	23.2
Median monthly income (rupees)	2500	4000	5000	7000	6000	2000	6000	5000	6000	4500	6000	6000	6000	5000
Proportion currently married (%)	26.6	41.3	50.4	40.5	50.7	16.9	55.3	30.4	34.0	44.2	47.0	37.1	59.8	53.0
Median age at 1st injection	18	22	20	18	21	18	25	23	23	21	21	21	23	21
Ever shared needle/syringe (%)	72.8	62.8	36.3	56.8	80.4	52.9	37.2	37.5	37.0	49.0	38.4	24.5	31.0	19.9
Injected drugs in past 6 months (%)	92.0	98.5	68.6	83.2	98.2	91.6	88.2	97.4	89.3	87.3	83.0	80.3	91.1	95.7
Drugs ever injected (%)														
<i>Heroin</i>	86.3	98.7	45.8	53.8	99.9	9.5	99.8	61.8	98.5	45.3	10.0	6.4	37.3	2.1
<i>Buprenorphine</i>	1.5	1.5	3.4	8.6	2.7	2.2	0.5	81.0	1.0	80.0	74.7	89.7	10.5	93.8
<i>Painkillers</i>	76.6	20.7	95.8	99.7	29.0	98.9	1.8	11.2	2.2	11.4	15.6	8.7	48.1	5.0
Alcohol use (AUDIT) (%)														
<i>Low alcohol use</i>	54.5	54.2	33.2	71.0	77.5	72.0	80.8	50.7	88.5	52.5	44.5	77.8	35.8	44.9
<i>Harmful/hazardous use</i>	17.8	22.8	15.8	12.5	13.0	18.4	13.2	23.9	5.5	18.6	16.4	10.6	26.3	34.5
<i>Alcohol dependence</i>	27.7	23.0	51.0	16.5	9.4	9.6	6.0	25.5	6.0	28.9	39.1	11.5	37.9	20.6
Ever sex with a man, male or transgender only (%)	3.5	0.8	2.3	2.7	2.7	1.8	0.7	12.3	7.4	11.7	12.8	2.5	2.8	4.1
Unprotected heterosexual sex in the past 6 months (%)	57.9	35.8	55.8	54.1	40.5	36.3	49.2	26.7	24.2	51.8	37.6	36.9	63.1	62.8
HIV Prevalence (%)	25.4	22.4	21.8	11.2	31.1	11.5	44.9	13.8	8.6	21.1	10.6	18.1	5.9	8.9

* All estimates presented at RDS-II weighted – refer to supplemental material for unweighted estimates;

AIZ – Aizawl, CCP – Churachandpur, DIM – Dimapur, GTK – Gangtok, IMP – Imphal, LGL – Lunglei, MOR – Moreh, DEL – New Delhi, MUM – Mumbai, AMR – Amritsar, BBE – Bhubaneswar, CDH – Chandigarh, KAN – Kanpur, LUD – Ludhiana

Table 2
Hepatitis C and HIV infection prevalence among 14,450 people who inject drugs across 15 sites in India (unweighted estimates)

	North East India (Established Epidemics)					Large cities				North India (Emerging Epidemics - documented)			Central India (Emerging Epidemics – anecdotal evidence)			
	Overall	AIZ	CCP	DIM	GTK	IMP	LGL	MOR	DEL	MUM	AMR	CDH	LUD	BBE	BIL	KAN
Sample size *	14435	1000	1000	996	997	1000	999	457	999	995	997	998	1002	1000	1000	999
HCV and HIV negative, n (%)	7840 (54.3)	259 (25.9)	341 (34.1)	713 (71.3)	871 (87.4)	289 (28.9)	764 (76.5)	151 (33.0)	522 (52.3)	627 (63.0)	460 (46.1)	430 (43.2)	579 (57.9)	887 (88.7)	654 (65.4)	293 (29.3)
HIV mono- infected, n (%)	820 (5.7)	57 (5.7)	69 (6.9)	179 (18.0)	85 (8.5)	27 (2.7)	78 (7.8)	98 (21.4)	21 (2.1)	20 (2.0)	13 (1.3)	21 (2.1)	80 (8.0)	29 (2.9)	13 (1.3)	30 (3.0)
HCV mono- infected, n (%)	3690 (25.6)	435 (43.5)	380 (38.0)	86 (8.6)	24 (2.4)	392 (39.2)	133 (13.3)	108 (23.6)	311 (31.1)	274 (27.5)	311 (31.2)	445 (44.7)	193 (19.3)	52 (5.2)	193 (19.3)	353 (35.3)
HCV/HIV co- infected, n (%)	2085 (14.4)	249 (24.9)	210 (21.0)	18 (1.8)	17 (1.7)	292 (29.2)	24 (2.4)	100 (21.9)	145 (14.5)	74 (7.4)	213 (21.4)	100 (10.0)	148 (14.8)	32 (3.2)	140 (14.0)	323 (32.3)

* Number of recruits with HCV and HIV antibody results. “Seeds” data are excluded.

AIZ – Aizawl, CCP – Churchurchandpur, DIM – Dimapur, GTK – Gangtok, IMP – Imphal, LGL – Lunglei, MOR – Moreh, DEL – New Delhi, MUM – Mumbai, AMR – Amritsar, BBE – Bhubaneswar, CDH – Chandigarh, KAN – Kanpur, LUD – Ludhiana, ALL – All cities

Table 3

Correlates of HCV infection among people who inject drugs across 15 sites in India*

	Number	Unadjusted Odds Ratio (95% confidence interval)	Adjusted Odds Ratio (95% confidence interval)
Age (per 10 year increase)		1.23 (1.02, 1.48)	1.20 (0.97, 1.48)
Marital Status			
<i>Never married</i>	6028	1	-
<i>Currently married living with partner</i>	6498	1.03 (0.89, 1.19)	
<i>Other (widowed/divorced)</i>	1923	1.09 (0.76, 1.55)	
Education			
<i>Primary school or less</i>	2149	1	-
<i>Secondary school</i>	2649	0.99 (0.80, 1.22)	
<i>High School graduate</i>	979	0.83 (0.60, 1.15)	
Sex			
<i>Male</i>	13608	1	1
<i>Female</i>	834	0.47 (0.26, 0.84)	0.32 (0.12, 0.83)
Ever visited a SNEP	6132	3.08 (2.38, 3.99)	2.04 (1.57, 2.65)
Ever visited an OST center	3352	2.30 (1.82, 2.90)	1.67 (1.26, 2.22)
Age at first injection (per 10 year increase)		0.72 (0.64, 0.80)	0.78 (0.66, 0.93)
Number of lifetime injections			
<i>1 – 500</i>	3363	1	1
<i>501 – 15,000</i>	7836	3.12 (2.05, 4.75)	2.15 (1.44, 3.20)
<i>>15,000</i>	1194	5.87 (3.22, 10.7)	2.96 (1.82, 4.82)
Type of drug injected			
<i>Buprenorphine only</i>	546	1	1
<i>Heroin only</i>	3172	0.97 (0.44, 2.15)	1.25 (0.61, 2.55)
<i>Combination</i>	7676	2.30 (1.35, 3.92)	1.80 (1.08, 2.99)
<i>Pharmaceutical only</i>	3044	0.48 (0.29, 0.79)	0.53 (0.35, 0.81)
Ever shared a needle/syringe	7500	2.59 (1.97, 3.39)	1.63 (1.27, 2.08)
Infected with HIV	2906	5.06 (3.02, 8.47)	5.25 (3.41, 8.09)
Region of Residence			
<i>Established epidemics</i>	6457	1	-
<i>Large cities</i>	2995	1.67 (0.51, 5.47)	
<i>Emerging epidemics (documented)</i>	1998	1.48 (0.51, 4.26)	
<i>Emerging epidemics (anecdotal)</i>	3000	0.84 (0.14, 4.98)	
Median network size (site-level)			
<i>Less than or equal to 12</i>	4999	1	1
<i>13 to 25</i>	4994	2.75 (0.75, 10.1)	2.24 (0.92, 5.42)
<i>Greater than 25</i>	4457	3.98 (1.45, 10.9)	3.45 (2.00, 5.96)
Prevalence of HIV viremia (site-level)			
<i><=6%</i>	3000	1	1
<i>>6 to 12%</i>	4995	4.73 (1.74, 12.9)	6.16 (2.21, 17.2)
<i>>12 to 18%</i>	2999	8.42 (3.06, 23.2)	4.79 (1.94, 11.9)

	Number	Unadjusted Odds Ratio (95% confidence interval)	Adjusted Odds Ratio (95% confidence interval)
>18%	3456	13.1 (6.26, 23.3)	6.82 (2.27, 20.5)

SNEP = syringe/needle exchange program; OST = opioid substitution therapy

* Odds ratios from multi-level logistic regression models with random intercepts to account for clustering by site and scaled RDS-II weights among 12,381 persons with complete data on all covariates

Table 4

Correlates of awareness of HCV positive antibody status*

	Number	Unadjusted Odds Ratio (95% CI)	Model 1: Adjusted Odds Ratio (95% CI)	Model 2: Adjusted Odds Ratio [†] (95% CI)
Age (per 10 year increase)		1.77 (1.42, 2.22)	1.55 (1.27, 1.90)	1.57 (1.28, 1.92)
Marital Status				
<i>Never married</i>	2307	1		
<i>Currently married/living with partner</i>	2527	1.30 (0.83, 2.04)	-	-
<i>Other (widowed/divorced)</i>	943	1.37 (0.94, 1.99)		
Education				
<i>Primary school or less</i>	2149	1	1	1
<i>Secondary school</i>	2649	2.05 (1.33, 3.15)	1.96 (1.29, 2.98)	2.01 (1.33, 3.04)
<i>High School graduate</i>	979	4.00 (2.26, 7.09)	3.75 (2.10, 6.72)	3.83 (2.13, 6.89)
Sex				
<i>Male</i>	5517	1		
<i>Female</i>	257	0.54 (0.20, 1.48)	-	-
Monthly income (rupees)				
<i><=5000</i>	3203	1	-	-
<i>>5000 to <=15,000</i>	2234	0.63 (0.41, 0.97)		
<i>>15,000</i>	340	1.79 (0.94, 3.42)		
Ever visited a SNEP	3156	1.36 (0.91, 2.02)	-	-
Ever visited an OST center	1886	2.95 (1.76, 4.93)	1.87 (1.05, 3.32)	1.80 (1.00, 3.25)
Years of injection drug use (per 10 years)		2.06 (1.61, 2.65)	-	-
Number of lifetime injections [†]				
<i>1 – 500</i>	756	1		
<i>501 – 15,000</i>	3718	1.04 (0.66, 1.63)	-	-
<i>>15,000</i>	727	1.92 (1.02, 3.63)		
Ever shared a needle/syringe	3821	2.32 (1.47, 3.65)	1.70 (1.06, 2.75)	1.66 (1.02, 2.72)
Ever tested for HIV	3496	8.08 (5.15, 12.7)	3.52 (2.35, 5.26)	3.61 (2.43, 5.36)
Knowledge of HIV status				
<i>Negative</i>	3692	1	1	1
<i>Positive and unaware</i>	1375	0.67 (0.28, 1.61)	0.77 (0.32, 1.85)	0.73 (0.31, 1.75)
<i>Positive and aware</i>	710	6.11 (2.54, 14.7)	3.83 (1.85, 7.95)	3.75 (1.83, 7.67)
Ever tuberculosis diagnosis [†]	500	2.58 (1.36, 4.91)	-	-
Region of Residence				
<i>Established epidemics</i>	2468	1	1	-
<i>Large cities</i>	1411	0.24 (0.08, 0.73)	0.33 (0.12, 0.89)	
<i>Emerging epidemics (documented)</i>	804	0.18 (0.09, 0.35)	0.28 (0.17, 0.46)	
<i>Emerging epidemics (anecdotal)</i>	1094	0.06 (0.02, 0.21)	0.11 (0.05, 0.25)	
Median network size (site-level)				
<i>Less than or equal to 12</i>	1210	1	-	1

	Number	Unadjusted Odds Ratio (95% CI)	Model 1: Adjusted Odds Ratio (95% CI)	Model 2: Adjusted Odds Ratio ^I (95% CI)
<i>13 to 25</i>	2244	1.85 (0.34, 10.1)		4.60 (2.05, 10.3)
<i>Greater than 25</i>	2323	5.65 (1.95, 16.4)		4.31 (2.67, 6.95)
Proportion of HIV-positives on ART (site-level)				
<i>≤30%</i>	2011	1	-	1
<i>>30 to 60%</i>	2790	9.31 (3.38, 25.6)		5.31 (2.67, 10.5)
<i>>60%</i>	976	10.38 (3.40, 31.7)		4.93 (1.91, 12.7)

SNEP = syringe/needle exchange program; OST = opioid substitution therapy; ART = antiretroviral therapy

* Odds ratios from multi-level logistic regression models with random intercepts to account for clustering by site and scaled RDS-II weights among 5,743 HCV antibody positive participants with complete data on all covariates

^I Neither number of lifetime injections nor TB diagnosis remained significantly associated with HCV awareness after adjustment for other correlates in the multivariable model; therefore, neither was included in final multivariable models presented.