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An intervention to improve HCV testing, linkage to care, and treatment among people who use drugs in Tehran, Iran: The ENHANCE study

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ABSTRACT

Background: Globally, HCV testing, linkage to care and treatment is sub-optimal among people who use drugs (PWUD). This study aimed to evaluate the impact of an innovative intervention to enhance HCV testing, linkage to care, and treatment initiation among PWUD in Tehran, Iran.

Methods: ENHANCE is a non-randomized trial evaluating the effect of on-site rapid HCV antibody testing, venepuncture for HCV RNA testing (HCV antibody positive only), liver fibrosis assessment, and linkage to care to enhance direct-acting antiviral (DAA) therapy (sofosbuvir/daclatasvir) initiation for HCV among people with a history of drug use. Recruitment was from April 2018 and will continue to July 2019, through three opioid substitution treatment (OST) clinics, five community-based drop-in centres, and one homeless reception centre. Participants initiated DAA therapy at a specialist clinic (OST clinics) or on-site (other sites), with monitoring provided on-site or at the specialist clinic (for those with cirrhosis attending OST clinics).

Results: Among 632 participants enrolled (median age, 44 years), 97% were male, 28% had a history of injecting drug use, and 58% had used drugs within the previous year. HCV antibody prevalence was 27%; 62% and 15% among those with and without a history of injecting drug use. Among 170 HCV antibody positive participants, 168 had HCV RNA testing (99%), of whom 134 (80%) were positive. Among HCV RNA positive participants, treatment initiation was 84%: 100% (45/45), 96% (46/48) and 54% (22/41) in OST clinics, drop-in centres, and homeless reception settings, respectively.

Conclusion: Following on-site HCV testing and linkage to care, HCV treatment uptake was extremely high among PWUD, apart from the homeless reception population. This intervention could be explored in other settings globally to enhance HCV scale-up and elimination efforts.

Introduction

In Iran, traditional management of hepatitis C virus (HCV) infection, through referral to tertiary healthcare centres, has failed to provide access to HCV care among the more marginalised populations with HCV, including people who use drugs (PWUD) (Malekinejad et al., 2015; Massah et al., 2017). Sub-optimal HCV diagnosis and treatment uptake among PWUD has contributed to ongoing transmission of infection and rising burden of HCV-related liver disease (Hajarizadeh et al., 2016). Highly effective direct-acting antiviral (DAA) therapies have the potential to lower chronic HCV disease burden and reduce HCV transmission, but PWUD need to be prioritised for treatment (Hajarizadeh, 2017). Development of new models of HCV care, that are tailored to the specific needs of PWUD, is crucial for enhancing HCV diagnosis and treatment uptake in this population.

Approximately 186,500 Iranians are living with chronic HCV infection (Hajarizadeh et al., 2016). However, only 35% are estimated to have been diagnosed and less than 3% were treated with interferon-based therapies per year (Hajarizadeh et al., 2016). Iran is among countries with high prevalence of opioid use and dependence (Amin-

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Esmaeili et al., 2016). Use of opium (raw, usually smoked or ingested) and its residues have a long history in the country. In 2013, 1.6 million of Iranians had used drugs in the previous year; opium, shireh (refined product of opium, usually smoked or ingested), and crystal methamphetamine were the most common types of used drugs, followed by heroin. An estimated 12.5% had injected drugs in the past year (Nikfarjam et al., 2016). Since the late 1990s, given emergence of HIV epidemic among people who inject drugs, Iran has gradually shifted from the "supply-reduction only" policies that criminalised any type of drug use, to establishing an extensive network of drug treatment and harm reduction (Alam-mehrjerdi, Abdollahi, Higgs, & Dolan, 2015; Nissaramanesh, Trace, & Roberts, 2005). By 2014, opioid substitution therapy (OST) and needle exchange programs were available in more than 5000 clinics and nearly 500 centres, respectively (National AIDS Committee Secretariat, Ministry of Health & Medical Education, 2015). This existing harm reduction infrastructure could be used to implement integrated models of HCV care, providing access to testing and treatment where PWUD are already receiving other services. Co-located interventions have been shown to improve linkage to HCV care among PWUD (Bajis et al., 2017); however, in the DAA era, well-designed studies evaluating the impact of integrated interventions in low- and middle- income countries are scarce.

The Enhancing Hepatitis C Linkage to Care (ENHANCE) recruited participants from April 2018, within a network of OST clinic, community-based drop-in-centres, and a homeless reception centre in Tehran, Iran. The aim of this study was to evaluate the impact of an intervention, including on-site HCV rapid antibody testing, venepuncture for HCV RNA testing, and non-invasive liver fibrosis assessment on HCV testing, linkage to care, and treatment initiation among PWUD.

Methods

Study population and design

ENHANCE is a non-randomized trial evaluating the effect of on-site HCV rapid antibody testing, venepuncture for HCV RNA testing, non-invasive liver fibrosis assessment, and linkage to care to increase DAA therapy for HCV among PWUD in Tehran, Iran. Study enrolment started in April 2018 and is on-going through July 2019. Participants were enrolled through nine sites in Tehran, including three OST clinics, five community-based drop-in centres, and one homeless reception centre.

Inclusion criteria were age ≥18 years, written informed consent, and history of drug use. The study protocol was approved by the Human Research Ethics Committee at the Iranian National Institute for Medical Research Development.

Study sites

Opioid substitution therapy clinics

In Tehran, OST is available from public clinics or private prescribers. In addition to OST dispensing, primary healthcare, group therapy, and counselling for individuals and families are available in majority of clinics. Larger clinics offer several other services, including sexual health and alcohol dependency management. All services are subsidised; however, a small out-of-pocket cost remaines, which is lower in public clinics. In public and private clinics, monthly cost of methadone varies between half and triple the single day's income for a person on minimum wage. Three clinics took part in this study, including one public, and two private (Supplementary Table 1). In all OST clinics, general practitioners dispensed and monitored HCV treatment.

Community-based drop-in centres

In Tehran, community-based drop-in centres serve as points of access for sterile injecting equipment, condoms, warm meals, and personal hygiene facilities. Additional services often include HIV screening, management of injecting-related wounds, and HIV, sexual health, viral hepatitis, and safe injecting education. All services are free of charge. Five community-based drop-in centres participated in this study, operated by two non-governmental organisations (Supplementary Table 1). In all centres, peer-support workers dispensed and monitored HCV treatment.

Homeless reception centre

In Tehran, there are two homeless reception centres, operating under Municipality of Tehran. At entrance, individuals receive an assessment by a general practitioner, a psychologist, and a social worker. Hospital transfer is arranged if required; otherwise, reunification with a contactable family member is prioritised, followed by referral to homeless shelters for temporary housing or State Welfare Organization for long-term accommodation. Processing is generally over a few days to few months, depending on severity of co-morbidities and the time required for family counselling and accommodation arrangement. People who are homeless remain in the centres during the processing time. Primary healthcare, individual counselling, and addiction care are among available services at the centres. All services are free of charge. One homeless reception centre participated in this study (Supplementary Table 1). In the homeless reception centre, general practitioners and nurses dispensed and monitored HCV treatment.

Study procedures

In the weeks preceding ENHANCE campaign days, site staff encouraged eligible clients to participate in the study. On campaign days, site staff provided information about the study to the participants while they were accessing services, and eligible participants who consented were then consecutively enrolled. Each site held a minimum of three campaign days.

Enrolment assessment comprised collection of a finger-stick capillary whole-blood sample for on-site rapid HCV antibody testing (SD BIOLINE HCV rapid assay, Abbott), and a self-reported behavioural survey, collecting demographic information, drug use history and behaviours, alcohol consumption, health service utilisation, HCV and liver disease knowledge, and willingness to receive HCV treatment. High risk alcohol consumption was assessed using the Alcohol Use Disorders Identification Test-Consumption (AUDIT-C), derived from the first three questions of the full AUDIT (Bush, Kivlahan, McDonell, Fihn, & Bradley, 1998). Scores equal or greater than three and four indicate hazardous consumption or active alcohol use disorders among women and men, respectively (Bush et al., 1998).

Among participants positive for anti-HCV serology, post-test counselling was provided, and on the same day, a venepuncture blood sample was collected for HCV RNA and routine clinical care testing, including hepatitis B virus (HBV) and HIV serology, liver function tests, and complete blood count. HCV RNA testing results were available between two and ten days.

Among participants attending OST clinics, individuals with HCV infection (positive HCV RNA test) were referred to a liver clinic for specialist assessment, liver disease assessment using transient elastography (FibroScan®), and treatment initiation. Closest and farthest OST clinics were 10 and 27 km away from the liver clinic. Visits were scheduled within a week of the day HCV RNA test results being available and re-scheduled for participants who could not attend their initial appointment. At treatment initiation, all participants received the first four weeks of DAA therapy. Those with advanced liver disease (fibrosis stages F3-F4) had a monthly schedule to return to the liver clinic to visit a specialist and collect tablets for the next four weeks. Participants without advanced liver disease (fibrosis stages F0-F2) were not required to return to the liver clinic; they visited a general practitioner at the OST clinic of their enrolment every month, to receive their subsequent medication (Fig. 1). FibroScan® has a lower and upper detection limit of 2.5 and 75 kPa, respectively, and fibrosis stages were defined by scores 2.5–7.4 (F0/1), 7.5–9.4 (F2), 9.5–12.4 (F3) and ≥12.5 kPa (F4,

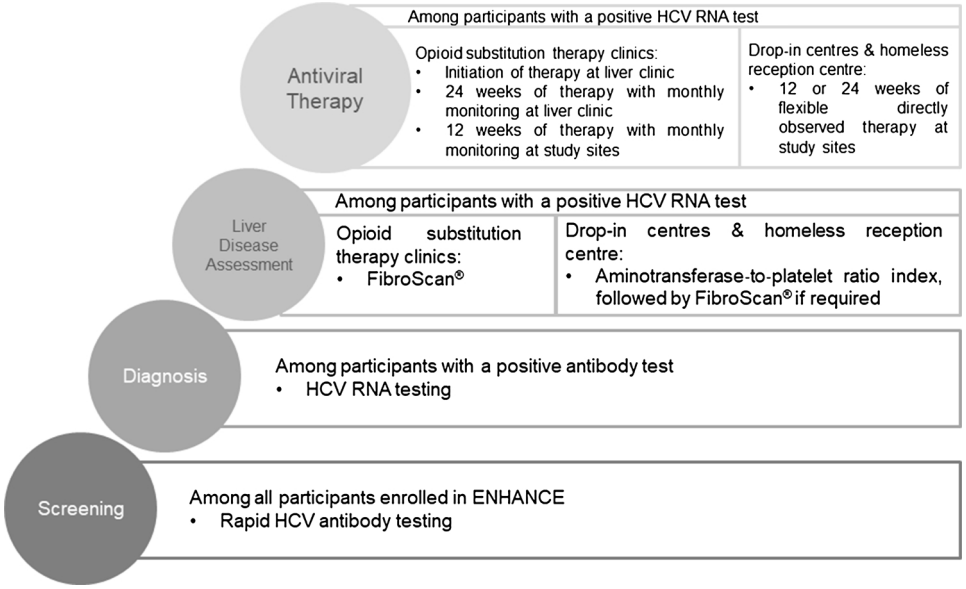

Fig. 1. ENHANCE study design among participants with a history of drug use, attending opioid substitution therapy clinics, community-based drop-in centres, and a homeless reception centre, n = 632.

cirrhosis) (Castéra et al., 2005).

Among participants attending community-based drop-in centres and the homeless reception centre, referral to the liver clinic was not considered feasible. Instead, the aspartate aminotransferase (AST)-to-platelet ratio index (APRI) was used for initial liver disease staging. APRI was calculated using AST and platelet count: [AST (U/l)/upper limit of normal (considered as 40 U/l)/platelet count (10^9/l)] × 100. Given moderate diagnostic utility of APRI for the prediction of HCV-related fibrosis (Shaheen & Myers, 2007), site staff helped to organise transportation for participants with a score greater than 1.0, to attend the liver clinic for a confirmatory liver disease assessment using transient elastography (FibroScan®). Treatment was initiated by a specialist at the liver clinic. Flexible directly observed dispensing of the medications, either weekly or daily at study sites was used to deliver HCV treatment at the community-based drop-in centres and homeless reception centre (Fig. 1). Further, DAA medications were delivered to inpatient drug treatment centres or hospitals if required.

At treatment initiation and subsequent monthly of DAA therapy dispensing, a medication count sheet was provided to participants who took their medication home, or to site staff who were responsible for directly observed dispensing of medication. At scheduled treatment completion date, the Study Coordinator collected the medication count sheets, for review and comparison with each month's medication bottles. In cases of missed doses, treatment completion date was extended until all missed doses were taken. To evaluate response to therapy, venepuncture blood samples were collected for HCV RNA testing at treatment sites, 12 weeks following treatment completion. For patients who did not attend this appointment, a later visit was scheduled.

For additional support during antiviral therapy and follow-up, participants and care providers were encouraged to contact the Study Coordinator for enquires about HCV treatment, phone consultation with a specialist, or booking unscheduled specialist appointments. Contact options included landline and mobile phone numbers and popular messaging applications. During DAA therapy, participants who did not return for their scheduled daily or weekly dispensing for two weeks were considered lost to-follow-up.

HCV treatment

Treatment consisted of a locally-manufactured generic fixed dose combination of sofosbuvir 400 mg/daclatasvir 60 mg (Sovodak®, Rojan Co., Iran). Participants with and without cirrhosis were treated for 24 and 12 weeks, respectively (Alavian et al., 2017). Previous studies have demonstrated safety and efficacy of Sovodak® for treating HCV genotypes 1 and 3 (Merat et al., 2017), which comprise the majority of people with HCV infection in Iran (Keyvani, Alizadeh, Alavian, Ranjbar, & Hatami, 2007).

Study outcomes

Primary outcomes were HCV diagnosis and treatment initiation. Prevalence of HCV antibodies and HCV RNA were evaluated among all participants and those with a positive HCV antibody test result, respectively. HCV treatment initiation was assessed among people with current HCV infection, defined as receipt of one-month supply of medication.

Secondary outcome included response to therapy, measured by sustained virologocial response (SVR). SVR was defined as undetectable HCV RNA 12 weeks post-treatment (SVR12). If HCV RNA had not been assessed at 12 weeks post-treatment, the result of the re-scheduled assessment was used for SVR. SVR12 was calculated by intention to treat (ITT), including participants who initiated a 12- or 24-week course of DAA therapy and were scheduled to have their evaluation by 30 March 2019.

Statistical analysis

The proportion of individuals with positive HCV antibody and positive HCV RNA tests were evaluated, among all participants and by study site (OST clinics, community-based drop-in centres, and homeless reception centre). Treatment initiation and treatment completion were evaluated among individuals with current HCV infection, overall and by study site. Overall and study site-based treatment response was evaluated among individuals who initiated DAA therapy within timeframe to have completed SVR12 assessment.

Results

Study participants

Between April and December 2018, 632 participants were recruited into the ENHACE study, 49% (n = 308) from OST clinics, 26%

Table 1
Demographic characteristics of participants with a history of drug use in the ENHANCE study, n = 632.

Characteristics, n %	Total n = 632	Opioid substitution therapy clinics n = 308	Community-based drop-in centres n = 166	Homeless reception centre n = 158
Age, median (IQR)[a,b]	44 (37, 55)	43 (34, 53)	45 (38, 53)	49 (40, 61)
Male sex[a]	608 (97)	302 (98)	149 (90)	158 (100)
Highest level of education[a]				
Did not finish high school	349 (56)	138 (46)	100 (61)	111 (72)
Finished high school	199 (32)	121 (40)	49 (30)	29 (19)
Higher education	73 (12)	43 (14)	15 (9)	15 (10)
Full- or part-time employment[a]	275 (44)	182 (59)	92 (55)	1 (1)
Monthly income[a]				
Minimum wage or below	396 (65)	133 (45)	107 (67)	156 (99)
Living wage[c]	147 (24)	107 (36)	40 (25)	0 (0)
Above living wage	68 (11)	55 (19)	12 (8)	1 (1)
Owned or rental housing[a]	246 (39)	197 (64)	49 (23)	0 (0)
Imprisonment, ever[a]	271 (43)	88 (29)	108 (65)	75 (48)
Opioid substitution therapy[a]				
Never	188 (30)	58 (19)	54 (33)	76 (49)
History, not current	178 (29)	52 (17)	74 (45)	52 (34)
Current	252 (41)	188 (63)	37 (22)	27 (17)
HCV screening, ever[a,d]	174 (28)	75 (24)	62 (37)	37 (24)
HCV treatment uptake, ever[a,d,e]	21 (4)	12 (4)	8 (5)	1 (1)
Willingness to initiate HCV treatment in the next 12 months, if diagnosed with HCV[a]	596 (97)	283 (96)	160 (97)	152 (97)

[a] Among participants with available information.
[b] Interquartile range.
[c] Living wage sets a socially acceptable minimum above minimum wage, to keep an individual out of poverty.
[d] Self-reported.
[e] 52% (n = 11) had a positive HCV RNA test. All self-reported history of interferon-based therapy that was not completed and were offered DAA therapy.

(n = 166) from community-based drop-in centres, and 25% (n = 158) from the homeless reception centre. Compared to participants enrolled through OST clinics, individuals from drop-in centres and the homeless reception centre were older, had lower levels of education and income, and higher levels of unstable housing and history of imprisonment. History of HCV diagnosis and treatment uptake were low in all groups. However, nearly all participants (97%) were willing to receive HCV treatment in the next 12 months (Table 1).

Median age at first drug use was 20–21 years across the three groups. However, recent (past 12 months) drug use ranged from 41% in participants from OST clinics to 89% in those from the homeless reception centre. The most frequently used drug in the past 12 months was opium in OST clinics and heroin in other settings. Among all participants who had recently used drugs, daily use was predominant (Table 2).

Overall, a history of injecting drug use was reported in 28% (25% in OST clinics; 42% in community-based drop-in centres and 17% in the homeless reception centre) (Table 2). Only 5% (29 of 632) of the total population reported injecting within the last 12 months. Sharing of injecting paraphernalia was most common among participants attending the homeless reception centre, followed by drop-in centres. Among all participants, the vast majority smoked daily. Compared to smoking, current alcohol use was less common; however, in all setting, the majority of those who used alcohol, had hazardous levels of drinking (Table 2).

Hepatitis C and liver disease knowledge

Knowledge of HCV and liver disease was varied and suboptimal. Overall, less than a third (27%, n = 170) were aware of the association between HCV infection and liver cancer, and less than a quarter (21%, n = 132) correctly identified the meaning of having a positive HCV PCR test. Only 2% (n = 15) correctly identified the meaning of a positive HCV antibody test, and 12% (n = 78) knew chances for cure following HCV treatment were high.

Hepatitis C diagnosis

Over a quarter of participants were anti-HCV positive (27%, n = 170) and 21% (n = 134) had HCV infection based on HCV RNA detection. The highest prevalence of anti-HCV and HCV RNA positive results were among participants attending community-based drop-in centres (38%, n = 63 and 29%, n = 48 respectively), followed by the homeless reception centre (32%, n = 51 and 26%, n = 41, respectively), and OST clinics (18%, n = 56 and 14%, n = 45, respectively) (Fig. 2). Among participants with a history of injecting drug use (n = 167), 62% were anti-HCV positive and 47% had HCV infection.

Hepatitis C treatment initiation

Median time between HCV RNA test results being available and treatment initiation was 7 days in OST clinics (interquartile range 5–14 days), 14 days in community-based drop-in centres (interquartile range 7–17 days), and 7 days in the homeless reception centre (interquartile range 4–15 days). Among participants with HCV infection (n = 134), 84% (n = 113) commenced antiviral treatment. HCV treatment initiation was 100%, 96%, and 54% among participants from OST clinics, drop-in centres, and the homeless reception centre, respectively (Fig. 2). Among participants with HCV infection who reported injecting within the last 12 months (n = 13), treatment initiation was 100%.

Response to DAA therapy

Response to DAA therapy was evaluated among participants who initiated treatment and were due to have SVR12 assessment prior to 30 March 2019 (n = 99), including 44, 33, and 22 participants attending OST clinics, community-based drop-in centres, and the homeless reception centre, respectively. The majority (80%) received 12 weeks of therapy. All participants from OST clinics (n = 44) completed DAA therapy. Treatment completion date was extended for 14 people; median number of missed doses was 3 (interquartile range 1–5). The majority (89%, n = 39) achieved SVR12. Five participants have not yet

Table 2
Drug, alcohol, and tobacco use among participants with a history of drug use in the ENHANCE study, n = 632.

Characteristics, n %	Total n = 632	Opioid substitution therapy clinics n = 308	Community drop-in centres n = 166	Homeless reception centre n = 158
Age at first drug use, median (IQR)[a,b]	20 (17, 27)	20 (17, 26)	20 (17, 25)	21 (18, 34)
Drug use, within the last 12 months[a]	348 (58)	117 (41)	98 (60)	133 (89)
Most commonly used drug				
Opium	206 (34)	140 (47)	25 (15)	41 (28)
Heroin	167 (27)	58 (20)	56 (34)	53 (36)
Methamphetamine	77 (13)	33 (11)	34 (21)	10 (7)
Daily use	288 (83)	88 (76)	84 (86)	116 (89)
Injecting drug use, ever[a]	167 (28)	72 (25)	69 (42)	26 (17)
Age at first injecting drug use, median (IQR)[a,b]	25 (20, 30)	26 (21, 30)	26 (20, 30)	23 (20, 30)
Shared needle and syringes, ever	76 (46)	25 (35)	31 (45)	20 (77)
Shared other equipment, ever	89 (53)	35 (49)	39 (57)	15 (58)
Most commonly shared[c]				
Spoon	61 (69)	23 (66)	28 (72)	10 (67)
Filter	52 (58)	16 (46)	27 (69)	9 (60)
Water	51 (57)	17 (49)	24 (62)	10 (67)
Injecting within the last 12 months	29 (17)	7 (10)	14 (20)	8 (31)
Most commonly injected drug				
Heroin	18 (62)	4 (57)	7 (50)	7 (89)
Methamphetamine	4 (14)	0 (0)	4 (29)	0 (0)
Smoking, current daily[a]	513 (82)	238 (79)	134 (81)	141 (90)
Alcohol use[a]				
History, not current	344 (56)	201 (69)	99 (61)	44 (28)
Current	57 (9)	27 (9)	20 (12)	10 (6)
Hazardous drinking	41 (72)	20 (74)	14 (70)	7 (70)

[a] Among participants with available information.
[b] Interquartile range.
[c] Each participant could select more than one option.

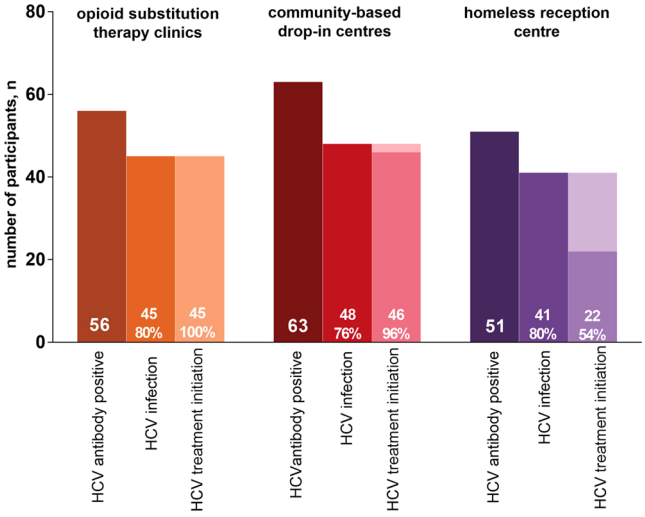

Fig. 2. Hepatitis C virus screening, diagnosis, and treatment initiation among participants with a history of drug use in the ENHANCE study, n = 632.

returned for SVR status assessment. Among participants from drop-in centres (n = 33), 31 (94%) completed DAA therapy. Treatment completion date was extended for 23 people; median number of missed doses was 6 (interquartile range 3–9). The majority (64%, n = 21) achieved SVR12. Two participants (6%) were lost to follow-up during treatment and nine (27%) have not yet returned for SVR12 assessment. One participant had documented virological failure; a history of prior DAA therapy (and failure) was disclosed post-treatment. Among participants from the homeless reception centre (n = 22), all (100%) completed treatment on the scheduled date (no extension of the treatment completion date) and had undetectable HCV RNA at the completion of treatment; however, none could be followed for SVR12 assessment.

Among participants who initiated DAA therapy with expected SVR12 assessment who reported injecting within the last 12 months (n = 13), eight completed treatment and achieved SVR12 (62%); four participants were lost to follow-up following treatment, and one was the participants who had virological failure.

Discussion

This study presents real-world data on the impact of an intervention integrating on-site rapid HCV antibody testing, venepuncture for HCV RNA testing, and non-invasive liver fibrosis assessment, on HCV testing, linkage to care, and treatment uptake among PWUD in Tehran, Iran. Overall, 21% of PWUD and 47% of those with a history injecting drug use had HCV infection, highlighting the significant burden of HCV in this population. Rapid HCV antibody testing enabled low-cost initial screening, with 99% uptake of subsequent HCV RNA testing among the antibody positive population. Although HCV knowledge was poor, there was high (97%) survey-based willingness for treatment which translated to high DAA therapy initiation (84%). High levels of treatment completion (100% among those attending OST clinics and the homeless reception centre and 94% among participants attending community-based drop-in centres) reflected the impact of a flexible monitoring approach that endorsed a trusting patient-provider relationship and removed some of the traditional barriers to HCV care. HCV treatment outcomes among the population due for SVR12 assessment were also extremely encouraging. These outcomes support expansion of these models of HCV screening and linkage to treatment to PWUD populations in Iran.

Evaluation of HCV screening and linkage to care initiatives for PWUD in low- and middle-income settings has been limited, including in Iran (Bajis et al., 2017). In this study, history of HCV diagnosis was lower than previous estimates (28% vs. 35%) (Hajarizadeh et al., 2016); however, self-reported information in our study might be less accurate. HCV prevalence among our PWUD population with a history of injecting drug use (47%) was comparable with previous Iranian findings (45%) (Malekinejad et al., 2015). Markers of socioeconomic marginalisation were common among all participants (Amin-Esmaeili, Rahimi-Movaghar, Gholamrezaei, & Razaghi, 2019; Rahimi-Movaghar, Amin-

Esmaeili, Shadloo, Noroozi, & Malekinejad, 2015). However, compared to those attending OST clinics, participants attending drop-in centres and the homeless reception centre represented a more vulnerable population, highlighting diversity of PWUD. Despite the high levels of marginalisation, and overall drug use within the last 12 months (58%), only 5% reported injecting drug use within the last 12 months, possibly due to current low price and widespread availability of drugs (Rahimi-Movaghar et al., 2015). Further studies are needed to evaluate current patterns of injecting and non-injecting drug use among the broader PWUD population in Iran; however, if this finding is representative, a focused program of engagement of those who continue to inject into DAA therapy could have population-level impact on HCV transmission.

In Iran, models of HCV care that are adapted for specific needs of different PWUD populations are emerging in different settings, including in prisons (Sharafi et al., 2019). However, at the population-level, HCV elimination among PWUD require major policy reform, including provision of unrestricted access to HCV diagnosis and treatment (Dore & Hajarizadeh, 2018). Currently, no publicly funded HCV program exists in Iran; the existing combination of 17 health insurance funds with different bases for membership has created incomplete coverage, specifically for marginalised populations (Mousavi & Sadeghifar, 2016). Recent attempts at creating universal health coverage, including HCV diagnosis and treatment, have not been successful. At present, 85% of the cost of diagnosis and 25%–75% of treatment costs (depending on type of medication) are covered by insurance, respectively. The out-of-pocket cost remain significant for most people with HCV infection; further, the more marginalised PWUD often do not possess identification documents that are required to apply for insurance. Another important component for the success of HCV elimination is high coverage of harm reduction (Dore & Hajarizadeh, 2018), which is currently not considered sufficient to prevent transmission in Iran (Larney et al., 2017). Recent shifts from hard-line drug laws have placed harm reduction in the centre of the public health response to drug use; however, it is possible that further reforms, including decriminalisation of marijuana and opium use are being considered (Nikpour, 2018). The effect of this change could be profound, facilitating increased access to harm reduction and other health services among PWUD. Further, ongoing drug use, high levels of smoking, and hazardous drinking were indicators of considerable co-morbidities among PWUD. Compared to people from higher socioeconomic status, health risk behaviours cause greater health harm in this population, given the lived experiences of poverty and predisposition to poor material circumstances and psychosocial stress (Innes et al., 2018; Katikireddi, Whitley, Lewsey, Gray, & Leyland, 2017). A comprehensive public health response to HCV should include DAA scale-up, as well as improving social equity and action on health risk behaviours.

Treatment initiation in OST clinics and community-based drop-in centres (100% and 96%, respectively) was higher than previous estimates from community-based studies (Pourmarzi et al., 2018). However, unrestricted access to DAA therapy might have motivated those most enthusiastic about treatment to participate in this study. In the homeless reception centre, treatment uptake was limited by the specific site procedures that prioritised family reunification and/or accommodation arrangement over antiviral therapy. Overall, ninety-eight percent of participants completed antiviral therapy. Among treated participants from the homeless reception centre, all were reunited with family members or referred on for temporary or long-term accommodation arrangement prior to SVR12 assessment. SVR12 was achieved by 89% and 64% of those from OST clinic and drop-in centre sub-populations. The findings from the OST clinic population are comparable to other community-based models of HCV care in the DAA era (Hajarizadeh et al., 2018; Mason et al., 2017; Morris et al., 2017; Read et al., 2017). Among participants attending drop-in centres, the proportion of patients who achieved SVR was limited by non-attendance at the SVR12 or later visits. However, among those who completed therapy and attended for SVR testing, 95% were cured. Higher post-treatment loss to follow-up among participants attending drop-in centres could be explained by higher marginalisation of this population (Bastani, Marshall, Rahimi-Movaghar, & Noroozi, 2019). Among clients of drop-in centres, other priorities, including accommodation and food, and frequent encounters with law enforcement compete with nonurgent medical needs. In order to optimise SVR assessment, HCV treatment programs should include robust models of post-treatment care. Specific supportive strategies, including contingency management, could improve retention in the post-treatment components of the HCV care cascade (Bajis et al., 2017; Schulkind et al., 2018). Further, engagement with HCV care has been shown to be associated with an increase in treatment knowledge and awareness of DAA effectiveness (Valerio et al., 2018). In settings with limited HCV knowledge including Iran, educational initiatives during antiviral therapy may encourage PWUD to seek their HCV status post-treatment.

The study has some clear limitations. First, to build a trusting relationship with participants, self-reported drug use behavioural data were collected. Urine drug screening was not routine in the study sites. A history of injecting drug use or ongoing drug use were not an exclusion criterion for treatment; however, these behaviours have been under-reported, potentially due to social desirability bias and stigma of injecting. This was particularly evident in the homeless reception centre, given that 17% of participants had a history of injecting drug use, while 32% were anti-HCV positive. Second, treatment outcomes are preliminary, given that some participants have not reached SVR12 assessment. Treated participants will continue to be followed, both to determine virological cure in those who have not yet returned for SVR assessment, and to monitor for HCV re-infection. Third, women were underrepresented in the study population. Previous studies among people attending harm reduction services have shown lower proportions of female recruitment (Rahnama et al., 2014). Smaller population of female PWUD (four to twelve times smaller than males, depending on the type of drugs used (Nikfarjam et al., 2016)) could be a partial explanation; however, higher stigma of drug use among women means access to harm reduction is more restricted in this population (Dolan et al., 2011). Fourth, non-randomised design of the study might have limited applicability of findings to other populations of PWUD. Finally, findings in this study may not be replicated in standard of care clinical practice unless testing and treatment are free.

In conclusion, in a middle-income country setting, integration of HCV care within drug treatment and harm reduction services provided a unique opportunity to facilitate increased HCV diagnosis and DAA uptake among marginalised PWUD. This study demonstrates that in the context of social marginalization and ongoing drug use, a community-based, supportive model of HCV care can promote high levels of adherence to treatment and virological cure. However, supportive strategies should be developed to improve post-treatment engagement with HCV care. Scaling up appropriate treatment models for different PWUD populations, and optimising treatment outcomes are crucial for battling the HCV epidemic in Iran and elsewhere.

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Author contribution

MA, HP, JG, GD, BH, ARM, and RM contributed to study conception and design, data acquisition and analysis, interpretation of findings, and drafting of the manuscript; and BS, SM, and SK contributed to data acquisition and analysis and interpretation of findings.

Disclaimer

All inferences, opinions, and conclusions drawn in this publication are those of the author(s), and do not necessarily reflect the opinions or policies of the Australian Government Department of Health or the Iranian Government Ministry of Health.

Declaration of interest

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.drugpo.2019.07.002.

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