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Research Paper

Hepatitis C virus treatment in people who inject drugs (PWID) in Bangladesh

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ABSTRACT

Background: Given the considerable social marginalization experienced by people who inject drugs (PWID), treatment of hepatitis C virus (HCV) in this population presents unique challenges. This study assessed the feasibility of treating HCV infection with direct-acting antiviral (DAA) medications among PWID receiving harm reduction services from a Drop-in-Center in Dhaka, Bangladesh.

Methods: In this prospective study conducted between December 2016 and May 2018, 200 PWID with either recent injecting drug use (i.e., within the previous two months) or a history of injecting drug use and are currently receiving opioid substitution therapy were recruited. Blood was collected to conduct relevant laboratory tests. Eligible PWID who tested positive for HCV RNA (n = 55), were provided daily daclatasvir (60 mg) and sofosbuvir (400 mg) for 12 weeks after which adherence level, sustained virologic response (SVR), and reinfection were assessed.

Results: At baseline, 40% (n = 79) of the 200 participants recruited to the study tested positive for antibodies to HCV and 34% (n = 68) had detectable HCV RNA in their blood. Of 55 eligible PWID who initiated treatment, 93% (n = 51) completed treatment while 87% (n = 48) were available for follow-up SVR assessment, all of whom achieved SVR. Thus, intent-to-treat SVR was 87% and the modified intent-to-treat SVR was 100% with one reinfection (4•2 cases per 100 person–years). Further, 75% (i.e., 41 out of the 55 participants) were at least 90% adherent to therapy.

Conclusion: Our findings strongly suggest that HCV treatment using sofosbuvir + daclatasvir for PWID enrolled in existing harm reduction programs in Bangladesh is feasible but may require additional interventions such as Opioid Substitution Therapy, intense follow up by outreach workers, and services and counselling provided by full time clinicians.

Background

Hepatitis C virus (HCV) infection is a major global public health threat affecting an estimated 71 million people in 2015 and killing 400,000 people worldwide each year (Blach et al., 2017). A recent global review suggests that approximately 6.1 million people between the ages of 15 and 64 who inject drugs are living with HCV (Grebely et al., 2019). A high prevalence of HCV infection among PWID has been reported from various countries in South Asia, including India (Solomon et al., 2015), Afghanistan (Chemaitelly, Mahmud, Rahmani & Abu-Raddad, 2015), and Pakistan (Bergenstrom et al., 2015). These studies found that the main HCV transmission route is the sharing of contaminated needles/syringes and drug preparation equipment (e.g., swabs, water, water container drug ampoules, cookers) (Doerrbecker et al., 2013; Thibault, Bara, Nefau & Duplessy-Garson, 2011; Villena, 2006).

Limited data about HCV infections rates in Bangladesh suggest relatively low prevalence (i.e., less than 1%) in the general population

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(Mahtab et al., 2008; Safiullah, Bhuiyan, Miah & Raihan, 2009). This translates into approximately 0.3–1.5 million Bangladeshis chronically infected with HCV. When considering PWID only, high rates of HCV have been documented since the late 1990s (Azim et al., 2008), with rates varying across cities from a high of 96% in a north-western city to 40% in the capital city of Dhaka (NASP, 2011). Within Dhaka city itself, HCV prevalence varied with a higher rate of infection in old-Dhaka (43%) compared to the rest of Dhaka (34%) (NASP, 2011). More recently, an integrated bio-behavioral survey (IBBS) among PWID in old-Dhaka (NASP, 2016a) found that 52% of PWID shared needles/syringes during their last injection while 38% shared other injection paraphernalia in the two months preceding the survey.

Harm reduction programming in Bangladesh follows a multi-pronged approach to injecting drug use intervention developed by WHO, UNAIDS and UNODC (World Health Organization, 2012). The Needle Syringes Program (NSP) is one part of the approach and is operated primarily by outreach workers. The NSP has expanded since 2004 across the country and it now provides services to approximately 71% of the estimated 33,067 PWID in Bangladesh (NASP, 2016b). However, despite a harm reduction programs being available for PWID in Dhaka since 1998, high risk injecting behaviors remains a significant concern (Azim et al., 2009; Azim, Hussein & Kelly, 2005; Sharma, Oppenheimer, Saidel, Loo & Garg, 2009).

In addition to harm reduction programs, there are several Drop-in-Centers within the community run by the not-for-profit organization CARE Bangladesh, through which services are provided for sexually transmitted infections (STI), abscess management, rest and recreational facilities, HIV and AIDS education, HIV testing and counseling, and provision of HIV treatment. Currently, there are 21 Drop-in-Centers across Bangladesh with 15 Centers located in Dhaka city. Each Drop-in-Center has a catchment area site where PWID also have access to prevention and other health and social services provided by outreach workers. All PWID who receive services through a Drop-in-Center or from outreach workers, must be registered under a particular Drop-in-Center where they receive a unique ID. Drop-in-Centers offer opportunities to stay safe, to pass time without harassment from law enforcement agencies, and to receive various harm reduction services. Most PWID are already identified in their community as people who use drugs; therefore, they do not hesitate in coming to the Drop-in-Center. Significantly, there is anecdotal evidence suggesting that some PWID avoid coming to the Drop-in-Center as they fear that they will become identified and stigmatized as a person who uses drugs.

Opioid Substitution Therapy (OST) was introduced in Bangladesh in July 2010 and currently, there are five OST clinics providing services to approximately 950 PWID, representing roughly 3% of PWID in Bangladesh (Azim, Bontell & Strathdee, 2015; Crofts & Azim, 2015). The OST clinics are generally located within the community with the exception of one situated in a government drug rehabilitation center. Clients are either referred by outreach workers, harm reduction service providers, and detoxification and other rehabilitation centers, or they access services directly intending to stop their injecting drug use. The services provided by OST clinics include the dispensing of methadone (free of cost), counseling sessions for families and individuals, general medical treatment including free medications, additional referral services, urine screening test for substance use, and HIV testing services.

Treatment for HCV was revolutionized in 2013 with the approval of interferon-free direct-acting antiviral (DAA) drugs (Falade-Nwulia et al., 2017; Soriano et al., 2011) that have a short duration of treatment (i.e., 8–12 weeks), are highly effective (i.e., cure rates >95%), and have fewer side effects. Recent clinical trials and observational studies have demonstrated that HCV treatment for PWID is safe and effective (Christensen et al., 2018; Grebely et al., 2018; Hajarizadeh et al., 2018; Janjua et al., 2019); however, there is a lack of evidence on the effectiveness of DAAs with PWID in low-income countries. Even in resource rich countries, limited access to HCV treatment and reinfection remain major issues of concern especially if all members of injecting networks are not treated (Hellard et al., 2015; Rossi et al., 2018). Evidence suggests that, in order to treat HCV in populations of PWID, additional health and social services including harm reduction programming such as NSP and OST must be in place to maximize accessibility, adherence and prevention of reinfections (Islam et al., 2017). Currently, the Ministry of Health and Family Welfare in Bangladesh is providing limited DAAs free of cost at a tertiary hospital in Dhaka through Communicable Disease Control of Directorate General of Health Services, thus increasing accessibility to HCV treatment.

In Bangladesh, Dhaka has the highest concentration of PWID (an estimated 6157 out of 33,067 countrywide) with most living in old Dhaka where the prevalence of HCV and HIV are both higher than the national average (NASP, 2016b). This study focused on PWID in old Dhaka to determine the feasibility of treating HCV infection with DAAs in this specific population. Here we describe (i) demographic and risk behavior profile among PWID with recent injecting drug use or history of injecting drug use currently receiving OST; (ii) adherence to DAA, sustained viral response (SVR), and reinfection; and (iii) clinical outcomes of enrolled PWID.

Methods

Study design and setting

This study used a prospective observational design to follow PWID treated for HCV infection using DAAs in order to assess feasibility of treatment by measuring adherence, SVR and reinfection. The study was conducted between December 2016 and May 2018 through a Drop-in-Center located in old Dhaka that currently provides harm reduction programming. Old-Dhaka was chosen as the study setting because the population of PWID accessing that particular Drop-in-Center is particularly vulnerable. For example, the prevalence of both HIV and HCV is higher in PWID in old-Dhaka compared to the rest of Dhaka (NASP, 2011). Further, many PWID in old-Dhaka are homeless (Azim et al., 2008) and, consequently, the likelihood of adhering to treatment is low. Thus, given these vulnerabilities, it is safe to assume that if the proposed intervention is effective in old-Dhaka, it will be feasible in other jurisdictions across Bangladesh as well.

Participants

PWID accessing harm reduction services through the Drop-in-Center located in old-Dhaka were recruited from March 2017 to July 2017 for this study. Individuals were invited to participate in the study if they were 18 years or above and met one of two criteria: (i) injecting drug use in the previous two months; or (ii) history of injecting drug use and currently receiving OST. PWID providing written consent to participate in the study underwent initial screening for HIV status. The study counselor conducted pre-test counseling for HIV using a standard questionnaire and collected oral fluid for HIV testing using the OraQuick Rapid HIV 1/2 Antibody test. PWID testing positive for HIV were excluded from the study because treatment for HIV-HCV coinfections is different from treatment for HCV alone. Individuals testing positive for HIV were referred to the nearest HIV care center. PWID testing negative for HIV underwent a clinical examination and relevant laboratory tests. At this stage, participants meeting any of the following criteria were excluded from the study: (i) cirrhosis; (ii) chronic kidney disease (CKD); (iii) on medication such as anti-tubercular drug, anti-convulsant drugs, anti-arrhythmic drug, which provide contra-indication for use with the study oral DAAs; (iv) known hypersensitivity to drugs used to treat HCV; and (v) severe concurrent medical disease including severe infections.

Procedure

In-person interviews using a semi-structured questionnaire were

conducted with all PWID screening negative for HIV. Blood specimens were collected from all participants and were tested for HCV antibodies using a microparticle enzyme immunoassay (Hepanostika®HCV Ultra, Beijing United Biomedical Co., LTD). Additionally, RNA testing was conducted using RT-PCR. Genotyping was performed through NS5b gene sequencing using the HCV database (Los Alamos National Laboratory; http://lcv.lanl.gov/). Alanine aminotransferase (ALT), aspartate aminotransferase (AST) and complete blood count (CBC) were conducted and aminotransferase/ platelet ratio index (APRI) was calculated to measure hepatic fibrosis as per WHO recommended formula. Cirrhosis was diagnosed based on an assessment of these parameters and clinical examination. If cirrhosis was diagnosed, the patient was excluded from further participation and referred to a hepatologist for advice and treatment. Study-affiliated physicians also examined participants for any significant medical conditions such as tuberculosis, severe infections, kidney function (using a serum creatinine test followed by Estimated Glomerular Filtration Rate (eGFR)), or other conditions that would result in exclusion from the study (as per the exclusion criteria). All study participants were asked to return to the Drop-in-Center one week later to receive their test results.

PWID meeting the eligibility criteria who also tested positive for HCV RNA were provided daily daclatasvir (60 mg) and sofosbuvir (400 mg) for 12 weeks. Weekly doses were provided to participants; however, if an individual's life circumstances (e.g., living on the street) did not permit this, the number of doses dispensed was ascertained depending on what was feasible. Three strategies were used for dispensing DAA: (i) weekly doses were provided to participants with a fixed address and/or family support; a plastic pill box preprinted with weekdays were used for pill count which was returned to the Drop-in-Center every week for refilling the following week; (ii) daily doses were provided to OST clients who visited the Drop-in-Center regularly for methadone; the pill count was recorded in a log sheet; or, (iii) daily doses were provided by outreach workers directly to clients who had no fixed address. Treatment completion was measured by counting 84 pills dispensed.

Outcome variables

The primary outcomes of interest in this study were the following: (i) adherence to HCV treatment; (ii) achievement of SVR; and, (iii) rate of reinfection.

Adherence was defined as taking at least 80% of prescribed doses (67 out of 84 doses) with continuous missing doses not more than 20% (17 doses). The study staff completed a pill count sheet to monitor adherence. Adherence percentage was calculated by subtracting the missed days from the expected total treatment duration of 12 weeks (84 days). All participants receiving DAAs were followed by outreach workers daily at least for the first five days and afterwards, twice per week to ensure adherence to treatment. Adherence levels were categorized as follows: (i) good adherence (>95%), (ii) moderate adherence (90–94%); and (iii) poor adherence (80–89%); (iv) no adherence (<80%).

In order to assess SVR and reinfection, all study participants receiving HCV treatment were asked to return three months after completion of treatment for a second blood test. Intent-to-treat SVR was defined by undetectable serum HCV RNA among all PWID receiving treatment and modified intent-to-treat SVR was among PWID who were available for SVR data (removing the people with missing SVR data). In addition, all individuals who were negative for HCV during enrolment were requested to visit the Drop-in-Center after six months in order to test their HCV status.

Sample size calculation

Based on the availability of funds, we decided to enroll 55 participants for HCV treatment with DAAs. It was estimated that in order to recruit a minimum of 55 PWID testing positive for HCV and negative for HIV (prevalence 38%; Azim et al., 2008), at least 145 participants were required to be screened. In order to incorporate refusal rate, the sample size was inflated by 15%, i.e., 166. However, the number of participants approached in our study were 235 so as to get the desired number of 55 eligible clients.

Statistical analysis

The data files were cleaned in Excel and analysed using SPSS (version 15). Descriptive analyses were conducted by running frequency tables, calculating means and medians. Biochemical profiles of DAA clients before and after treatment were compared using chi-square for categorical variables and a median test for non-parametric numeric variables. Any difference observed between these two visits at a minimum 5% level was considered significant.

Results

Participants

Recruitment occurred between 27 March 2017 and 10 July 2017. The PWID enrolment flowchart is presented in Fig. 1. Of the 253 PWID approached to participate, 224 provided written consent to participate in the study. After an initial HIV screening test, 24 participants were excluded from the study due to their positive HIV test (10%). The remaining 200 PWID were interviewed, underwent clinical examination and were tested for HCV. Forty percent of participants (n = 79) tested positive for HCV antibodies and 34% (n = 68) for HCV RNA. A total of 27 participants were excluded from the study: HCV antibody positive RNA negative (n = 14); cirrhosis (n = 11), CKD (n = 1), lost to follow-up (n = 1), leaving 173 PWID enrolled in the study. Of these, 55 participants tested positive for HCV RNA and were eligible to receive DAA treatment. All but one participant tested positive for HCV subtype 3 (3a, 51% and 3b, 49%) and one tested positive for HCV subtype 1a.

Baseline characteristics

The characteristics of participants undergoing DAA treatment (n = 55) as well as comparisons between participants with recent injecting drug use (n = 41) versus a history of injecting drug use and currently receiving OST (n = 14) are shown in Table 1. All participants were male and their mean age was 41•4 years. Most had little or no education (64%) and the majority (71%) lived with their families and relatives while 27% lived alone. Fifty-eight percent (n = 32) were married and the vast majority (94%) were living with their spouse. Although 76% had a fixed address where they lived, a substantial proportion were transient (18%). All were characterized as low- or middle-income groups. Among the drugs consumed, the most frequently used was cannabis (74%) and orally ingested methamphetamine (72%). Seventy-five percent of participants injected drugs in the last two months and among the injectable drugs taken, buprenorphine and a cocktail of pharmaceuticals (buprenorphine + sedative + antihistamine) were the most commonly reported (69% and 28%, respectively). Among those who injected drugs in the last two months (n = 41), 83% and 85% borrowed and loaned used needle/syringes, respectively. Sharing of injection paraphernalia (other than needles/syringes) among those who injected in the last two months was also common (88%) and all injected from the same ampoule (100%).

Among those who injected drugs in the last two months, they had been injecting drugs for 11 years, on average. The average length of participation in the harm reduction program was 5•7 years. Despite being enrolled in the harm reduction program, only 46% had heard of HCV, route of transmission and treatment before participating in the study.

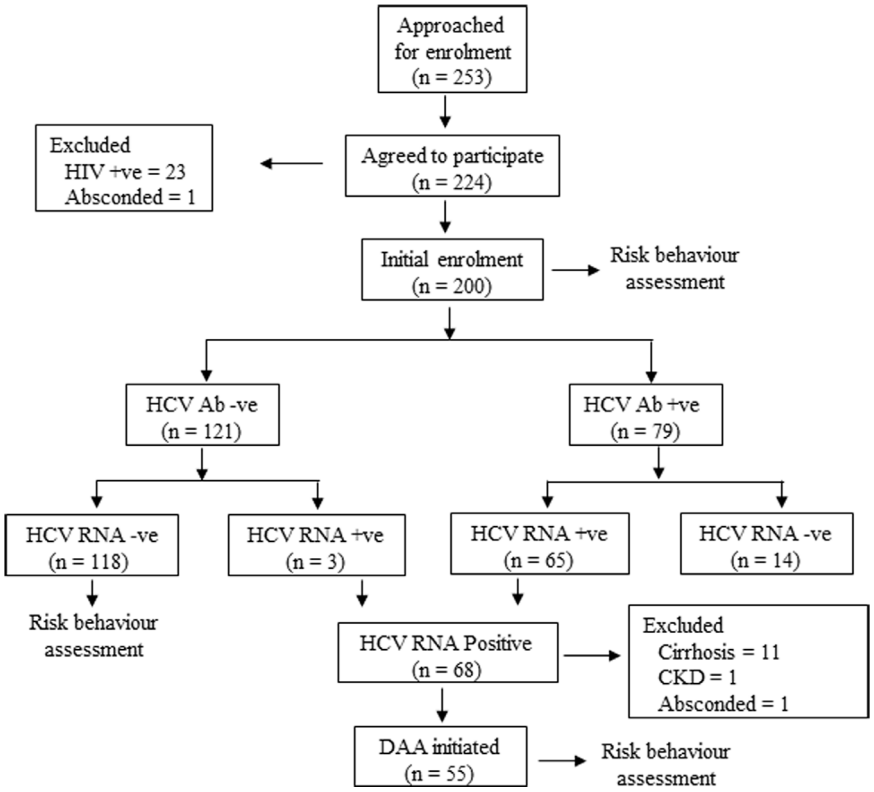

Fig. 1. Recruitment of PWID for HCV DAA treatment.

Clinical and biochemical profile

Complete biochemical profiles are available for 48 participants (Table S1). No severe adverse effects were observed during 12 weeks of the DAA treatment course. The most common side effects reported by participants within the first week included generalized fatigue (13%) and headaches (6%), which gradually improved with over-the-counter medication. Among the 13 participants who were also receiving methadone under OST, 54% (n = 7) reported gastro-intestinal complaints such as vomiting and dyspepsia. Additionally, 11% (6 of 48 participants) were suffering from chronic leg ulcers that were treated with antimicrobial therapy and regular aseptic dressing. Between enrolment and follow up, liver function improved, on average, while kidney function remained unchanged.

Adherence

Among the 55 participants who initiated DAA, 82% (n = 45) adhered with the assistance of intense follow up, motivation and counselling. Good adherence (adhered with DAA >95% time) was achieved by 65% (n = 36), moderate adherence (adhered with DAA 90–94% time) by 9% (n = 5) and poor adherence (adhered with DAA 80–89% time) by 7% (n = 4). OST clients were more likely to achieve good adherence rather than either moderate or poor adherence (64% vs. 37%); although this was not statistically significant (p value 0.057). Eighteen percent (n = 10) failed to achieve adherence (adhered with DAA less than 80%); although among these, six completed treatment through additional interventions such as enrolment in OST, intensive motivation that included home visits and involvement of family members, discussion about consequences of untreated hepatitis C with pictorial demonstrations and videos in computer by the study physician and additional follow up.

SVR

Of the 55 participants who initiated treatment, 93% (n = 51) completed treatment and 87% (n = 48) returned for assessment of SVR after six months. All 48 (100%) achieved SVR. Thus, intent-to-treat SVR was 48/55 (87%) and modified intent-to-treat SVR was 48/48 (100%) among participants who initiated DAA treatment and were available for follow-up assessment. Of the seven who were not available for SVR assessment, three completed treatment but did not return for SVR assessment. Among these, one could not be traced and two died roughly two months after completing the treatment, neither of which were related to the DAAs (i.e., one died from cardio-respiratory failure due to septicemia and one died from opioid drug overdose). Four participants were lost to follow-up after initiating treatment. Two of those moved away from old-Dhaka, one could not be traced, and one withdrew from treatment complaining of vomiting and voicing skepticism about treatment effectiveness.

Reinfection/new infection

One participant who achieved SVR with DAA treatment became reinfected with HCV (4.2 cases per 100 person–years). At baseline, the participant tested positive for HCV subtype 3b and consequently tested positive for HCV subtype 3a after DAA treatment. Among the 118 participants who tested negative for HCV RNA at baseline, 98 returned for a six month follow up visit. Of these, only one tested positive for HCV RNA. This individual was a 40-year-old man who was an OST client, and at baseline, tested positive for HCV antibodies but negative for HCV RNA and reported no injecting behavior during the study period.

Discussion

The main purpose of this study was to assess the feasibility of HCV treatment with DAA among PWID engaged in harm reduction

Table 1
Baseline characteristics of recent injectors and OST clients treated with DAA for HCV infections.

Variables	Recent injectors[a] $N = 41$ n (%)	OST clients[b] $N = 14$ n (%)	Total $N = 55$
Age			
20–30 Years	5 (12)	14 (0)	5 (9)
31–40 Years	15 (37)	7 (50)	22 (40)
40–70 Years	21 (51)	7 (50)	28 (51)
Mean (SD)	4 (9)	41 (6)	41 (8)
Median (IQR)	41 (34–50)	41 (37–44)	41 (35–48)
Sex			
Male	41 (100)	14 (100)	55 (100)
Education			
Primary or less	30 (73)	5 (36)	35 (64)
Secondary	8 (20)	3 (21)	11 (20)
Higher secondary and above	3 (7)	6 (43)	9 (16)
Marital status			
Currently married	24 (59)	8 (57)	32 (58)
Never been married	9 (22)	3 (21)	12 (22)
Separated/divorced/widow/widower	8 (20)	3 (21)	11 (20)
Current living status			
Alone	13 (32)	2 (14)	15 (27)
With family and relative	27 (66)	12 (86)	39 (71)
With friends	1 (2)	0 (0)	1 (2)
Location where PWID live			
Fixed address (public, private building)	29 (71)	13 (93)	42 (76)
Transient (on the street/platform etc.)	9 (22)	1 (7)	10 (18)
Working place (office, hotel etc.)	3 (7)	0 (0)	3 (6)
Occupation[c]			
Transport worker	14 (34)	2 (14)	16 (29)
Service	5 (12)	4 (29)	9 (16)
Business	5 (12)	3 (21)	8 (15)
Rag picker/daily labor/beggar	7 (17)	1 (7)	8 (15)
Drug selling/cheating/stealing/snatching	8 (20)	2 (14)	10 (18)
Unemployed	7 (17)	7 (50)	14 (26)
Yearly income (deduced from last month income)			
Low (<1025 USD)	2 (5)	3 (21)	5 (9)
Middle (1026–12,475 USD)	39 (95)	11 (77)	50 (91)
High (> 12,475 USD)	0 (0)	0 (0)	0 (0)
Sold blood for money in the last 6 months	1 (2)	0 (0)	1 (2)
Drugs used[c]	$N = 41$	$N = 13$	$N = 54$
Cocktail (buprenorphine + sedative + antihistamine)	15 (37)	0 (0)	15 (28)
Buprenorphine	37 (90)	0 (0)	37 (69)
Heroin	5 (12)	2 (15)	7 (13)
Methamphetamine (yaba)	30 (73)	9 (69)	39 (72)
Avil, Easium, Phenergan, B-50	2 (5)	0 (0)	2 (4)
Codeine containing cough syrup (Phensedyl)	2 (5)	0 (0)	2 (4)
Alcohol	1 (2)	1 (8)	2 (4)
Cannabis	32 (78)	8 (62)	40 (74)
% Borrowed used needles/syringes			
Yes	34 (83)	0 (0)	34 (83)
No	7 (17)	0 (0)	7 (17)
% Lent used needles/syringes			
Yes	35 (85)	0 (0)	35 (85)
No	6 (6)	0 (0)	6 (6)
% Shared injection paraphernalia	36 (88)	0 (0)	36 (88)
Duration of receiving harm reduction services			
≤ 3 Years	8 (20)	11 (77)	19 (35)
4–5 Years	9 (22)	0 (0)	9 (16)
>5 Years	24 (59)	3 (21)	27 (49)
Type of harm reduction services received[c]			
Needles/syringe through outreach	38 (93)	1 (7)	39 (71)
Awareness/education	27 (66)	5 (36)	32 (58)
Condoms	9 (22)	2 (14)	11 (20)
Methadone from OST clinic	4 (10)	13 (93)	17 (31)
Treatment for STI	0 (0)	1 (7)	1 (2)
Treatment for abscess/ulcer	4 (10)	1 (7.1)	5 (9)
Treatment for general health	13 (32)	12 (86)	25 (46)
Rest and recreation	17 (42)	9 (64)	26 (47)
HIV testing services(HTS)	12 (29)	3 (21)	15 (27)
HCV counseling	1 (2)	0 (0.0)	1 (2)
Remained in a controlled environment during treatment	$N = 4$	$N = 0$	$N = 4$
Jail	2 (50)	0 (0)	2 (50)
Others (rehabilitation center/clinic)	2 (50)	0 (0)	2 (50)
Knowledge about hepatitis C virus before enrolment	15 (37)	10 (71)	25 (46)
Sources of knowledge (among those who had knowledge about HCV)	$N = 15$	$N = 10$	
Outreach Worker	13 (87)	5 (50)	18 (72)
DIC Doctor	1 (7)	3 (30)	4 (16)
Rehab Center	1 (7)	2 (20)	3 (12)

[a] People who have recently injected drugs (within previous two months).
[b] People with a history of injecting drug use currently receiving opioid substitution therapy.
[c] Multiple responses.

programming in a developing country setting. Our findings confirm that HCV treatment using sofosbuvir + daclatasvir delivered in conjunction with interventions such as OST, intense follow up by outreach workers, and additional support services provided by full time clinical staff to PWID is feasible in developing country settings.

This study, although small scale, demonstrated treatment success as there were no virological failures among participants who were followed up at six months. These findings add to the growing body of literature reporting that a high rate of SVR in PWID can be achieved in a real-world setting. It should be noted that our study provided more intense drug use intervention compared to regular harm reduction services available in the country (i.e., OST, NSP only). However, even with an enhanced intervention through close follow-up and support, seven of the 55 participants initiating DAA treatment did not return for SVR assessment, resulting in intention-to-treat SVR of 87%. These findings are comparable to other real-world studies that reported SVR rates of 85–95% among people with recent injection drug use and who are under OST (Christensen et al., 2018; Grebely et al., 2018; Hajarizadeh et al., 2018; Janjua et al., 2019).

The HCV prevalence found in our study population (40%) is comparable to rates reported in previous studies using the same population. Although the HCV prevalence rate among the general population in Bangladesh is low (<1%; Mahtab, 2016), the HCV prevalence rates among PWID specifically is very high (NASP, 2011). The latest nationwide HCV prevalence data in PWID is available from the ninth round of HIV serological surveillance conducted with PWID between December 2010 and June 2011. A total of 7529 individuals were sampled from 30 different geographical areas of Bangladesh and were tested for HCV antibodies using enzyme linked immunosorbent assays and confirmed by line immunoassay. The overall prevalence of HCV was 40% in the capital city Dhaka a shockingly high prevalence of 96% recorded in the Northwestern region of the country (NASP, 2011).

In our study, 75% (41 of 55) participants were at least 90% adherent to DAA therapy which is slightly higher than those (66%) in the recent SIMPLIFY study (Cunningham et al., 2018; Grebely et al., 2018). The extent of adherence to DAA varied in this small group of PWID so that those with more stable living conditions demonstrated better adherence compared to those with less stable living conditions who required intense follow-up and in some cases constant motivation. It is noteworthy that even among the ten non-adherent participants, six completed DAA treatment with additional support measures, as described above.

This study also revealed that the existing harm reduction program offered in old-Dhaka was entirely concentrated on HIV care and, to a lesser extent, on STIs. Thus, additional services were required and

provided through this study for the clients with an HCV infection. A full time clinician provided services and although this was targeted to HCV but he did address all concerns of the PWID participating in this study and close monitoring of outreach workers was conducted by a study supervisor. Since there was very little awareness of HCV both among the staff and among PWID accessing services through the Drop-in-Center, it was necessary to provide in-depth information about HCV prior to starting DAA therapy in order to convince PWID that HCV can be a problem and that it can and should be treated. Additionally, counselling of families was also required to convince them of the benefits of treatment. As a result, considerable preparatory work was required before treatment could be initiated. However, once started, this study demonstrated that HCV treatment with DAA for this highly vulnerable group of PWID is feasible and SVR can be achieved with additional interventions.

In this study only one participant receiving treatment (OST client) was re-infected after six months (4·2 cases per 100 person–years). Such a rate of reinfection is comparable to other studies conducted elsewhere where reinfection rate was 5·4 per 100 person–years among people with recent injecting drug use and 2·7 per 100 person–years among people receiving OST (Hajarizadeh et al., 2019). This suggests that a comprehensive approach to treatment includes education and counselling in addition to DAA therapy.

Enrolment was restricted to PWID who were accessing services from the existing harm reduction program in old-Dhaka because that harm reduction services have been found to be related to HCV treatment engagement and adherence and to prevent reinfection (Ford et al., 2015; Grebely, Matthews, Lloyd & Dore, 2013). In Dhaka, the NSP has been in place for more than two decades with a history of success in providing adequate numbers of needles/syringes to a large number of PWID (NASP, 2016a). In an effort to curb the sharing of needles, the number of syringes distributed per PWID per year in Bangladesh is roughly 205 (personal communication with NGO providing HR services). As of 2016, only 12 countries provided at least 200 clean needles per PWID per year as recommended by WHO. Despite distributing such a significant number of needles and syringes, sharing of contaminated needle and syringes remains quite high (NASP, 2016a). The recent IBBS data show a sharp rise in HIV in male PWID in old Dhaka from 7% in 2011 to 27% in 2016 and in females from 1% to 5% (NASP, 2011, 2016a). One of the explanations for high levels of sharing could be the high drug price during periods of crises when there is a shortage in drug supply. To mitigate the shortage in supply, PWID usually buy one ampoule of drug and prefer to expand their network size by including more partners, which eventually leads to more sharing of injection equipment (i.e., needles and syringes. It is noteworthy that methamphetamine commonly known as 'yaba' (orally ingested) has gained immense popularity recently all over the country but its impact on injectable opioid drugs is yet to be evaluated.

The study had several limitations. First, participants screening positive for HIV ($n = 23$) and for cirrhosis ($n = 11$) were excluded from the study. Thus, many of the PWID with HIV in our study may have been co-infected with HCV and would have required treatment. Further, participants with cirrhosis who were also excluded should have receive DAA treatment as well. The reason for not including HIV and cirrhotic patients is that concurrent conditions would require a different intervention and this study was focused solely on exploring the feasibility of providing daily doses of DAAs effectively for 12 weeks to PWID many of whom have chaotic lifestyles and may not be living in a stable home with a fixed address. In such a situation, we first need to understand whether this can be done in PWID who do not have other complications that require regular treatment and follow up. Treatment duration for cirrhotic patients is longer (24 weeks) compared to patients with HCV without cirrhosis (12 weeks) and treatment for HIV-HCV coinfections is different from treatment for single infection. Given the differences in treatment durations and regimens, a more complex study design would have been necessary and additional participants would have needed to be recruited to conduct the appropriate data analyses. We therefore used the simplest situation in this study by selecting PWID who were HCV positive but had no other complications and concurrent illnesses. Moreover, as there was no previous experience with treating PWID with DAAs in Bangladesh, this study was designed to help gain an understanding on how best to treat HCV in PWID. The findings from this study can be used to develop a larger, more complex study in the future. Second, the spouse of PWID infected with HCV were not included in the study. Importantly, spouses were not tested for HCV although they were at-risk and could transmit HCV to PWID leading to reinfection. Third, many of the PWID in the Drop-in-Center area were not enrolled in the harm reduction program and were excluded from this study. Thus, reliance on the reach of the harm reduction program may have resulted in the biased selection of PWID amenable to treatment and to a limited selection of PWID within a network. Importantly, to keep the number of new infections and reinfection low, it is recommended to treat everyone in a network, where people may share needles and syringes.

Fourth, adherence among our study populations was measured based on pill count by different study staff using a pre-structured form depending on patient's statement which could result in an overestimation of adherence. Several studies indicated that when prompted to report adherence rates, patients overestimated their adherence and underestimated their number of missed doses (Cunningham et al., 2018; Wagner & Rabkin, 2000). However, adherence as studied here may be different from other settings depending on differences in the study populations. Considering low numbers of clients under treatment, our outreach workers often checked the pill box, gave reminders via phone and took family members support to monitor adherence of all participants who received take-away doses. Moreover, a substantial proportion of participants (18 of 55 or 33%) were given directly observed therapy daily at Drop-in-Center where adherence was monitored by the study physician. Finally, the sample size of this pilot study was small since only one Drop-in-Center with ~350 enlisted PWID was targeted. Future studies should consider expansion to include PWID from all over the city, regardless of participation in a harm reduction program.

Conclusion

In conclusion, this study has shown that HCV treatment using sofosbuvir+ daclatasvir for PWID is feasible when administered within existing harm reduction services but additional interventions are required to maintain good adherence. These findings will help with the development of strategies for effectively treating PWID for HCV with DAAs in Bangladesh and other developing country settings. We suggest strongly that Drop-in-Center-based interventions should be considered as treatment access points for PWID all over the country and that they should be treated as early as possible to reduce the burden of liver disease and the rate of new and re-infections.

CRediT authorship contribution statement

Mustafizur Rahman: Conceptualization, Formal analysis, Writing - original draft. **Naveed Zafar Janjua:** Conceptualization, Writing - review & editing. **Tanveer Khan Ibne Shafiq:** Data curation. **Ezazul Islam Chowdhury:** Data curation. **Md. Safiullah Sarker:** Methodology. **Sharful Islam Khan:** Methodology, Writing - review & editing. **Masud Reza:** Formal analysis. **Mohammad Omar Faruque:** Data curation. **Ahmedul Kabir:** Data curation. **Aslam H. Anis:** Conceptualization, Writing - review & editing. **Tasnim Azim:** Conceptualization, Formal analysis, Writing - original draft.

Declaration of Competing Interest

All authors declare no competing interests.

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Role of the funding source

The funder 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.

Ethics committee approval

International Center for Diarrhoeal Disease Research, Bangladesh (icddr,b) has approved this study (PR-16033) after receiving the approval from institutional Research Review Committee (RRC) and Ethical Review Committee (ERC). The participants provided the written consent prior to enrolment. The summary of the consent form was read out for those who could not read and the left thumb impression was obtained from those who could not sign. They were assured about the non-disclosure of information and the use of data for analysis and for improving patient care activities such as publication without disclosure of their names or identity. ERC has approved the consent procedure after carefully scrutinizing the subject voluntary participation, preservation of their right and confidential administers of personal information by the project physicians.

Data sharing

In accordance with the icddr,b policy, the principal investigator and those authorized by the principal investigator shall have an exclusive right to analyze and publish such data from the onset of the data collection and until three years after the protocol or study completion date. Thereafter, the data will be made accessible.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.drugpo.2019.09.002.

References

Azim, T., Bontell, I., & Strathdee, S. A. (2015). Women, drugs and HIV. *International Journal of Drug Policy, 26*, S16–S21.

Azim, T., Chowdhury, E. I., Reza, M., Faruque, M. O., Ahmed, G., Khan, R., et al. (2008). Prevalence of infections, HIV risk behaviors and factors associated with HIV infection among male injecting drug users attending a needle/syringe exchange program in Dhaka, Bangladesh. *Substance Use & Misuse, 43*(14), 2124–2144.

Azim, T., Hussein, N., & Kelly, R. (2005). Effectiveness of harm reduction programmes for injecting drug users in Dhaka city. *Harm Reduction Journal, 2*, 22.

Azim, T., Khan, S.I., Nahar, Q., Reza, M., Alam, N., Saifi, R. et al. (2009). 20 years of HIV in Bangladesh: Experiences and way forward. In: World Bank.

Bergenstrom, A., Achakzai, B., Furqan, S., Ul Haq, M., Khan, R., & Saba, M. (2015). Drug-related HIV epidemic in Pakistan: A review of current situation and response and the way forward beyond 2015. *Harm Reduction Journal, 12*(1), 43.

Blach, S., Zeuzem, S., Manns, M., Altraif, I., Duberg, A. S., Muljono, D. H., et al. (2017). Global prevalence and genotype distribution of hepatitis C virus infection in 2015: A modelling study. *The Lancet Gastroenterology & Hepatology, 2*(3), 161–176.

Chemaitelly, H., Mahmud, S., Rahmani, A. M., & Abu-Raddad, L. J. (2015). The epidemiology of hepatitis C virus in Afghanistan: Systematic review and meta-analysis. *International Journal of Infectious Diseases, 40*, 54–63.

Christensen, S., Buggisch, P., Mauss, S., Boker, K. H. W., Schott, E., Klinker, H., et al. (2018). Direct-acting antiviral treatment of chronic HCV-infected patients on opioid substitution therapy: Still a concern in clinical practice? *Addiction (Abingdon, England), 113*(5), 868–882.

Crofts, N., & Azim, T. (2015). Harm reduction in Asia and the Pacific: An evolving public health response. In: BioMed Central.

Cunningham, E. B., Amin, J., Feld, J. J., Bruneau, J., Dalgard, O., Powis, J., et al. (2018). Adherence to sofosbuvir and velpatasvir among people with chronic HCV infection and recent injection drug use: The simplify study. *International Journal of Drug Policy, 62*, 14–23.

Doerrbecker, J., Meuleman, P., Kang, J., Riebesehl, N., Wilhelm, C., Friesland, M., et al. (2013). Thermostability of seven hepatitis C virus genotypes in vitro and in vivo. *Journal of Viral Hepatitis, 20*, 478–485.

Falade-Nwulia, O., Suarez-Cuervo, C., Nelson, D. R., Fried, M. W., Segal, J. B., & Sulkowski, M. S. (2017). Oral direct-acting agent therapy for hepatitis C virus infection: A systematic review. *Annals of Internal Medicine, 166*, 637–648.

Ford, N., Wiktor, S., Kaplan, K., Andrieux-Meyer, I., Hill, A., Radhakrishnan, P., et al. (2015). Ten priorities for expanding access to HCV treatment for people who inject drugs in low-and middle-income countries. *International Journal of Drug Policy, 26*, 1088–1093.

Grebely, J., Dalgard, O., Conway, B., Cunningham, E. B., Bruggmann, P., Hajarizadeh, B., et al. (2018). Sofosbuvir and velpatasvir for hepatitis C virus infection in people with recent injection drug use (SIMPLIFY): An open-label, single-arm, phase 4, multicentre trial. *Lancet Gastroenterology & Hepatology, 3*, 153–161.

Grebely, J., Larney, S., Peacock, A., Colledge, S., Leung, J., Hickman, M., et al. (2019). Global, regional, and country-level estimates of hepatitis C infection among people who have recently injected drugs. *Addiction (Abingdon, England), 114*(1), 150–166.

Grebely, J., Matthews, G. V., Lloyd, A. R., & Dore, G. J. (2013). Elimination of hepatitis C virus infection among people who inject drugs through treatment as prevention: Feasibility and future requirements. *Clinical Infectious Diseases, 57*, 1014–1020.

Hajarizadeh, B., Cunningham, E. B., Reid, H., Law, M., Dore, G. J., & Grebely, J. (2018). Direct-acting antiviral treatment for hepatitis C among people who use or inject drugs: A systematic review and meta-analysis. *Lancet Gastroenterology & Hepatology, 3*(11), 754–767.

Hajarizadeh, B., Cunningham, E. B., Valerio, H., Martinello, M., Reid, H., Law, M., et al. (2019). Hepatitis C virus reinfection following antiviral treatment among people who inject drugs: A systematic review, meta-analysis, and meta-regression (SAT-233). *Journal of Hepatology, 70*(S1), e733.

Hellard, M., McBryde, E., Davis, R. S., Rolls, D. A., Higgs, P., Aitken, C., et al. (2015). Hepatitis C transmission and treatment as prevention – the role of the injecting network. *International Journal of Drug Policy, 26*, 958–962.

Islam, N., Krajden, M., Shoveller, J., Gustafson, P., Gilbert, M., & Buxton, J. A. (2017). Incidence, risk factors, and prevention of hepatitis c reinfection: A population-based cohort study. *Lancet Gastroenterology Hepatology, 2*, 200–210.

Janjua, N. Z., Darvishian, M., Wong, S., Yu, A., Rossi, C., Ramji, A., et al. (2019). Effectiveness of ledipasvir/sofosbuvir and sofosbuvir/velpatasvir in people who inject drugs and/or those in opioid agonist therapy. *Hepatology Communications, 3*(4), 478–492.

Mahtab, M. A. (2016). Past, present, and future of viral hepatitis in bangladesh. *Euroasian Journal of Hepato-Gastroenterology, 6*(1), 43–44.

Mahtab, M. A., Rahman, S., Karim, M. F., Khan, M., Foster, G., Solaiman, S., et al. (2008). Epidemiology of hepatitis B virus in Bangladeshi general population. *Hepatobiliary & Pancreatic Diseases International, 7*, 595–600.

NASP. (2011). National HIV serological surveillance, 2011 Bangladesh – 9th Round Technical Report. IEDCR and ICDDR, B (2011) Retrieved February 06, 2013 fromhttp://aidsdatahub.org/dmdocuments/HSS_9th_round_2011.pdf.

NASP. (2016a). Behavioural and serological surveillance amongst key populations at risk of HIV in selected areas of Bangladesh, 2016. In: National AIDS/STD Program, Directorate General of Health Services, Ministry of Health and Family Welfare, Govt. of Bangladesh. (unpublished).

NASP. (2016b). Mapping study and size estimations of key populations in Bangladesh for HIV programs 2015-2016. In: National AIDS/STD Program (NASP), Directorate General of Health Services (DGHS), Ministry of Health and Family Welfare, Govt. of the People's Republic of Bangladesh.

Rossi, C., Butt, Z. A., Wong, S., Buxton, J. A., Islam, N., Yu, A., et al. (2018). Hepatitis C virus reinfection after successful treatment with direct-acting antiviral therapy in a large population-based cohort. *Journal of Hepatology, 69*, 1007–1014.

Safiullah, A. B., Bhuiyan, M. R., Miah, M. A., & Raihan, A. S. (2009). Prevalence of hepatitis C virus infection in rural adult population of Bangladesh. *Bangladesh Medical Research Council Bulletin, 35*, 30–32.

Sharma, M., Oppenheimer, E., Saidel, T., Loo, V., & Garg, R. (2009). A situation update on HIV epidemics among people who inject drugs and national responses in South-East Asia region. *AIDS (London, England), 23*, 1405–1413.

Solomon, S. S., Mehta, S. H., Srikrishnan, A. K., Solomon, S., McFall, A. M., Laeyendecker, O., et al. (2015). Burden of hepatitis C virus disease and access to hepatitis C virus services in people who inject drugs in India: A cross-sectional study. *Lancet Infectious Diseases, 15*, 36–45.

Soriano, V., Vispo, E., Poveda, E., Labarga, P., Martin-Carbonero, L., Fernandez-Montero, J. V., et al. (2011). Directly acting antivirals against hepatitis C virus. *Journal of Antimicrobial Chemotherapy, 66*, 1673–1686.

Thibault, V., Bara, J. L., Nefau, T., & Duplessy-Garson, C. (2011). Hepatitis C transmission in injection drug users: Could swabs be the main culprit? *Journal of Infectious Diseases, 204*, 1839–1842.

Villena, E. Z. (2006). Module l transmission routes of hepatitis C virus infection. *Annals of Hepatology, 5*, 12–14.

Wagner, G. J., & Rabkin, J. G. (2000). Measuring medication adherence: Are missed doses reported more accurately then perfect adherence? *AIDS Care, 12*, 405–408.

World Health Organization. (2012). WHO, UNODC, unaids technical guide for countries to set targets for universal access to HIV prevention, treatment and care for injecting drug users–2012 revision.