EClinicalMedicine 41 (2021) 101148

Contents lists available at ScienceDirect

EClinicalMedicine

journal homepage: https://www.journals.elsevier.com/eclinicalmedicine

Research Paper

Outcomes of Real-World Integrated HCV Microelimination for People Who Inject Drugs: An expansion of the Punjab Model.

Radha K. Dhiman, MD, DM, FAMS, FACG, FRCP, FAASLD, Technical Consultant; Chairman[a,c,d,e,*], Gagandeep S. Grover, MD, Program Officer[b], Madhumita Premkumar, MD, DM[a], Akash Roy, MD, DM[a], Sunil Taneja, MD, DM[a], Ajay Duseja, MD, DM, FAMS, FACG, FAASLD[a], Sanjeev Arora, MD[f], MMPHCRF Investigators [†]

[a] Department of Hepatology, Postgraduate Institute of Medical Education and Research, Chandigarh 160012, India
[b] Hepatitis C Virus Infection, Punjab, India
[c] Mukh-Mantri Punjab Hepatitis C Relief Fund (MMPHCRF), Punjab Government, Punjab, India
[d] Technical Resource Group - National Viral Hepatitis Control Program (NVHCP), Government of India, India
[e] Injection Safety Project, Punjab Government, Punjab, India
[f] ECHO Institute University of New Mexico, USA, New Mexico, United States

ARTICLE INFO

Article History:
Received 30 May 2021
Revised 3 September 2021
Accepted 15 September 2021
Available online xxx

Keywords:
hepatitis C virus
HCV
people who inject drugs
injection drug use
microelimination
India

ABSTRACT

Background: The prevalence of chronic hepatitis C (CHC) in People Who Inject Drugs (PWID) is 8-10% as compared to 3·6% in the general population in Punjab, India. We assessed the real-world efficacy and safety of free-of-charge generic direct-acting antivirals (DAAs), sofosbuvir with an NS5A inhibitor (ledipasvir, daclatasvir or velpatasvir)±ribavirin in the microelimination of CHC in PWID in a public health setting.

Methods: An integrated care team at 25 sites provided algorithm based DAAs treatment to PWID supervised by telemedicine clinics between 18th June 2016 and 31st July 2019. The primary endpoint was sustained virological response at 12 weeks (SVR-12); the secondary endpoints were treatment completion, adherence, safety, and adverse events. ClinicalTrials.gov number: NCT01110447.

Findings: We enrolled 3477 PWID (87·2% men; mean age 33·6±12·5 years; 83·8% rural; 6·8% compensated cirrhosis). While 2280 (65·5%) patients completed treatment, 1978 patients completed 12 weeks of follow up for SVR-12. SVR-12 was achieved in 91·1% of patients per protocol, 49.5% as per intention to treat (ITT) and 90·1% in a modified ITT analysis. Of 546 (15·7%) patients with treatment interruptions, 99 (19·7%) could be traced to test for SVR-12 with a cure rate of 77·8%. There were no major adverse events or consequent treatment discontinuation.

Interpretation: Integrated care of PWID with CHC with DAAs is safe and effective. Measures for reducing treatment interruptions will further improve outcomes.

Funding: The Government of the state of Punjab, India under the Mukh Mantri Punjab Hepatitis C Relief Fund (MMPHCRF) project, funds the project.

1. Introduction

Injection drug use (IDU) is fast becoming the primary cause of new hepatitis C virus (HCV) infection in most developed and developing countries [1]. The number of People Who Inject Drugs (PWID) has increased from 185 million in 2004 to 250 million in 2015 globally [2], with an estimated 177,000 persons in India [3]. The prevalence of chronic hepatitis C (CHC) in PWID is 8-10% as compared to 3·6% in the general population in Punjab, India. IDU contributes significantly to the HCV epidemic in India, particularly in certain pockets as in the northern region of Punjab [4]. The sharing of injection paraphernalia

Abbreviations: ALT, alanine aminotransferase; CHC, chronic hepatitis C; CI, confidence interval; DAAs, direct-acting antiviral agents; DH, District Hospital; ECHO, Extension for Community healthcare Outcome; G, Genotype; IDU, injection drug use; INASL, Indian National Association for study of the Liver; HCC, hepatocellular carcinoma; HBV, hepatitis B virus; HCV, hepatitis C virus; MMPHCRF, Mukh Mantri Punjab Hepatitis C Relief Fund; NVHCP, National Viral Hepatitis Control Programme; DCV, Daclatasvir; LDV, ledipasvir; OST, opioid substitution therapy peg-interferon; PWID, People Who Inject Drugs; RBV, ribavirin; SOF, sofosbuvir; VEL, Velpatasvir; SVR, sustained virologic response

* Corresponding Author: Dr. Radha K. Dhiman, MD, DM, FAMS, FACG, FRCP (Edin), FRCP (London), FAASLD, Professor, Department of Hepatology, Postgraduate Institute of Medical Education and Research, Chandigarh 160012, India

† MMPHCRF Investigators

https://doi.org/10.1016/j.eclinm.2021.101148

Research in context

Evidence before this study

With the changing epidemiology, injection drug use is projected to be the leading cause of HCV. However, the linkage to care of people who inject drugs (PWID) has remained a challenge. We reviewed available literature from MEDLINE, Embase, and the Cochrane Central Register of Controlled Trial. We searched for randomized controlled trials, cohort studies, cross-sectional studies, and real-world outcomes using the search terms "hepatitis C or HCV," "integrated care," "decentralized care," "primary care," and "PWID". Our review concluded that the literature is mainly confined to centralized supervised treatment, especially in opioid substitution programs. Moreover, literature from Low-Middle-Income countries (LMIC)s where OSTs are not routine is scarce in this crucial population.

Added-value of this study

To our knowledge, our study provides the largest body of evidence of 3477 individuals to demonstrate that a simplified decentralized public health approach for micro elimination of HCV in PWID is feasible and effective with a cure rate >90%. Additionally, our study, a first from India, revealed patterns and practices of injection drug use in an LMIC setting where IDU is rapidly emerging as the most common cause of HCV infection.

Implications of all the available evidence

Decentralized care in HCV with integration into primary health systems has been established as an effective strategy in HCV. However, access of PWID to such systems has been regulated due to fear of dropouts and re-infection. Given the cumulative evidence of the safety of DAAs and both feasibility and efficacy shown in our study, future recommendations should focus on the expansion of decentralized integrated HCV to PWID in consonance with the global theme of universal access to HCV care.

among drug users embodies one of the highest risks of HCV and human immunodeficiency virus (HIV) transmission in PWID than other groups, resulting in increased prevalence with lesser linkage to care [5]. In India, most epidemiological data on the PWID population is reported from high HIV prevalence states from the south or north-eastern regions with a higher point prevalence of HIV (25·4 -59·6 %), hepatitis B virus (HBV,10.0 %), and HCV (54.5-90·4 %) infections. Of 3748 PWID in Delhi, positive HCV serology was reported in 70·9 %; of whom 75·7 % were viremic with an overall prevalence of 53.7 % in this high transmission reservoir [6,7].

A lack of good epidemiological data about PWID in India also impairs the formulation of appropriate and effective HCV care policies. A recent meta analysis reported that pooled data from 46 studies from 14 states in India, anti-HCV seroprevalence rate in PWID was 44.71% [95% confidence interval (CI) 37.50-52.03] [8]. Most data records only anti-HCV antibody prevalence, a marker of exposure, but true estimates of viremia are not available [9].

The introduction of pan-genotypic highly effective, direct-acting antivirals (DAAs) has transformed the therapeutic strategy in HCV elimination. Innovative policies involving decentralization and community-based approaches are becoming an integral part of HCV care globally and in India [10].

Despite expanding access to affordable HCV care, PWID population has had limited access in comparison to the general population. The reasons for this disparity include concerns over poor adherence, reduced tolerability, risk of circulation of strains with resistance associated substitutions (RAS), HCV reinfection and lack of linkage of deaddiction services and HCV therapy[11]. Since DAAs are equally effective in this population irrespective of their drug use status, we have changed the approach to PWID to enable micro-elimination [12,13].

The PWID populations in India show wide variation in socio-demographic characteristics, awareness of HIV and viral hepatitis, social acceptance of therapy and deaddiction services, type of drug use or injection patterns and social stigma [14]. A combined approach, task shifting, decentralized approach with linked services is essential to improve adherence [15]. To this end, the Mukh Mantri Punjab Hepatitis C Relief Fund (MMPHCRF) program provides algorithm-based, free- of-charge generic, all-oral DAAs therapy in the state of Punjab, a model that was replicated across the country under the National Viral Hepatitis Elimination Programme (NVHCP) [4,16]. The microelimination-integrated care model to target PWID was devised specifically to reduce new transmission of HCV infection in the state of Punjab.

Additionally, the model has integrated deaddiction support, counseling and rehabilitation services to PWIDs . This collaborative model employs the use of a central specialist service at the hub and peripheral sites as spokes, including Opioid Substitution Treatment (OST) centers, anti-retroviral therapy (ART) clinics (under the National AIDS Control Organization), de-addiction centers and primary health care units. One of the main strategies of the HCV elimination campaign in India is the strategic microelimination in populations of interest like adolescent HCV, persons on dialysis, incarcerated individuals and PWID. We have used mathematical models to modify the therapeutic algorithm in a dynamic and iterative manner to tailor health resources to these special populations with the aim to achieve elimination by 2030. Multiple stakeholders are involved to achieve this goal including primary physicians, specialists, psychiatrists, deaddiction specialists, ART centres, civil society, and administrative units to provide integrated services. A second focus group for micro elimination of HCV in the state is the prison population in Punjab, and we are actively screening incarcerated individuals and starting treatment at these sites. A third group of interest requiring microelimination is patients on hemodialysis.

The efficacy of this model in the general population with CHC has already been established with SVR rates of greater than 90% [4]. In this study, we assessed the real-world efficacy decentralized care of combined deaddiction services and DAAs based therapy (12 or 24 weeks with drug regimens, i.e., sofosbuvir (SOF) with ledipasvir (LDV) or SOF with daclatasvir (DCV) or SOF with velpatasvir (VEL) with or without ribavirin (RBV) for managing CHC in PWID in a public health care setting in the Punjab state, India.

2. Methods

2.1. Patients

Eligible persons were enrolled from 25 sites (22 district hospitals and 3 university hospitals) during the period between 18th June 2016 and 31st July 2019. As per the algorithm, the recruited individuals were followed up till 12 weeks post-treatment to ascertain the sustained viral response (SVR-12). Patients who were eligible for the study were recruited with informed consent. This study had the approval of the Institutional Ethical Committee and was conducted following the Declaration of Helsinki. The trial is accessible at NCT03488485 available from https://clinicaltrials.gov/ct2/show/NCT03488485. This prospective cohort study adhered to Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement.

2.2. Monitoring and Evaluation at the Peripheral Sites

We have already described the Punjab Model programme with the innovative decentralized care services offered at 25 sites [4,16].

Training and community deaddiction services were provided to psychiatrists posted at the 25 sites. These included screening and referral of all PWID for associated alcohol intake, virological testing, and enrolment. The primary care providers (PCPs), including physicians, psychiatrists and deaddiction personnel, were trained to prescribe DAAs to persons without cirrhosis or compensated cirrhosis as per the algorithm [17]. The allied staff at the OST and ART centres were also trained to treat patients without cirrhosis. Integrated care was given at each of the 25 sites in the form of OST, needle or syringe exchange programmes, HIV testing, counselling and treatment, behavioural interventions, mental health and tuberculosis care, sexual and reproductive health interventions and overdose care programmes.

2.3. HCV Therapy and Study Design

An algorithm was designed (by RKD) using SOF-based regimens, and consequent patients were enrolled in this prospective interventional trial [4,15]. Genotype testing was not routinely recommended for patients without cirrhosis, and they were prescribed SOF/DCV for 12-weeks. (Supplementary Figure 1a) All patients with cirrhosis required genotyping. Subsequently, the drug velpatasvir (VEL) was introduced in the programme, and based on our reported results on 48,088 subjects, we had excellent cure rates with SOF/DCV as a pangenotypic regimen. Thereafter, we modified the algorithm to offer SOF/DCV to all persons without cirrhosis and SOF/VEL for 12 weeks to persons with compensated cirrhosis. (Supplementary Figure 1b) Persons with decompensated cirrhosis also received RBV, if tolerated, as in the previous algorithm. Hence our results show a mixed group reflecting a change in the prescribed regimen over time. End-treatment estimation of viral load was optional, but SVR-12 was mandatory in all patients. Eligibility for SVR-12 analysis implies that 12 weeks had elapsed after the patient had taken the last dose of the drug. The SVR-12 was calculated in patients who had completed treatment as per protocol and in patients who had interrupted therapy and had taken DAAs $\geq$4 weeks in the 12 or 24-week regimens. [17] Drug regimens used in the Punjab Model are given in Supplementary Table 1. The regimens were modified periodically with the availability of data that daclatasvir is pangenotypic, and introduction of velpatasvir in India. After performing mathematical modeling assessment of the best screening methods, and treatment protocol, the management algorithm has been adjusted to make the programme cost effective without compromising on SVR-12 rates [18,19]. All adult persons aged $\geq$ 18 years with viremic hepatitis C infection, all genotypes, treatment-naive or experienced, with current or past history of IDU were eligible for inclusion in the study.

2.4. Exclusion Criteria

Patients aged $<$18 years, pregnancy, hepatocellular carcinoma, chronic kidney disease, and thalassemia, were excluded. Under the program, persons with advanced cardiopulmonary disease or short life expectancy were not enrolled. PWID were regarded as individuals who have used any psychoactive drug through injections in a non-medical context within the previous six months [20]. A protocol deviation was defined as any change or departure from the study design or procedures. Important protocol deviations were defined as subset of protocol deviations that may significantly impact the completeness and reliability of the study data or that may significantly affect a subject's rights, safety, or well-being.[21]Treatment interruptions and compliance strategies have been described by us previously and provided in the supplementary information [4,16]. Treatment interruption was defined if drug therapy was interrupted by $>$7 days or the therapy was discontinued. If treatment interruption was $\leq$7 days, the drugs were resumed as prescribed, and SVR-12 tested 12-weeks after the last dose of drug therapy. An essential component of our compliance monitoring system in PWID was a designated family caregiver's involvement to ensure there were no interruptions. Every PWID patient was issued medications for 28 days, and the prescription was refilled 5 days before the next drug cycle. Drug therapy was coordinated with the regional deaddiction center or OST site to ensure holistic services and rehabilitation. The diagnosis of cirrhosis, non-invasive scores, and public health HCV algorithms are reported in the supplementary information [4,16,17].

Adherence was defined if there was no interruption in therapy and the patient completed the DAAs course on schedule. During visits, residual pill counts of the medication were done. All patients necessarily underwent registration at the district deaddiction center with a link to the treating psychiatrist for starting the deaddiction process. Ongoing drug use was not a contraindication to initiating therapy, but pre-treatment linkage to psychiatric care was encouraged strongly. However, in patients who had cirrhosis or had elevated liver enzymes, treatment was started immediately, with the tandem approach of both the deaddiction and HCV treatment centers.

2.5. Study End Points

Achievement of SVR-12 was the primary end-point. The secondary endpoints were completion of therapy, SVR-12 capture rate, compliance, and all adverse events. We allowed a window period of 4-8 weeks for the SVR-12 test in patients who reported late for the test. Our health care workers contacted the patient, who was due for SVR-12, (both treatment adherent and treatment interruptions) by means of telephonic messages, phone calls using a toll-free number 104 or even visited the residence to ensure data was collected effectively. The health care workers involved in this exercise included the designated Multipurpose Healthcare Worker (MHW), Multipurpose Healthcare Supervisor (MHS) and Accredited Social Health Activist (ASHA) who are all existing cadre under India's National Rural Health Mission. Reinfections were suspected if the person restarted injection use, and confirmed if the genotypes were different. However, genotype testing was not performed in the first instance if the person did not have cirrhosis.

2.6. Statistical Analysis

Continuous variables are expressed as the means $\pm$ standard deviation (SD) or 95% confidence intervals, and categorical data are expressed as numbers (percentages). The primary end-point (SVR-12) was calculated by three analyses which included all participants who initiated at least one dose of therapy. Firstly, the per-protocol analysis was computed as SVR-12 for those who completed treatment as per schedule. Secondly, the intention-to-treat (ITT) was done with the assumption that all treatment interruptions were protocol failures. Lastly a modified ITT analysis was done which determined the actual success rate, i.e. included as 'cures'all those who achieved SVR-12 per protocol or even in treatment interruptions [21]. ANOVA test analyzed differences between groups, and the $\chi 2$ test or Fisher's exact test was applied for the comparison of categorical data. Cox logistic regression was done to identify variables independently associated with treatment failures. P values less than .05 were considered significant. Statistical analysis was performed with SPSS software for Windows, version 22.0 (SPSS, Inc, Chicago, IL).

2.7. Role of funding sources

The Government of the state of Punjab, India under the Mukh Mantri Punjab Hepatitis C Relief Fund (MMPHCRF) project, funded the project. The sponsors did not have any role in the study design, analysis, interpretation of data, report writing and the decision to submit for publication.

Table 1
Baseline Characteristics as per Treatment Regimen

Parameter	SOF/LDV	SOF/LDV/RBV	SOF/DCV	SOF/DCV/RBV	SOF/VEL	SOF/VEL/RBV	Total (all regimens)
N (row %)	94 (2·7%)	61 (1·7%)	3023 (86·9%)	139 (3·9%)	120 (3·4%)	40 (1·1%)	3477 (100%)
DEMOGRAPHIC DATA							
Age (Mean ± SD) in years	40·0± 14·5	35·7± 14·1	32·7 ± 11·9	43·7 ± 15·3	39·7 ± 14·6	31·6 ± 10·7	33·6 ± 12·5
Gender							
Male (%)	22 (23·4%)	10 (16·3%)	375 (12·4%)	19 (13·6%)	16 (13·3%)	1 (2·5%)	443 (12·7%)
Female (%)	72 (76·5%)	51 (83·6%)	2646 (87·5%)	120 (86·3%)	104 (86·6%)	39 (97·5%)	3032 (87·2%)
Transgender (%)	0 (0%)	0 (0%)	2 (0·06%)	0 (0%)	0 (0%)	0 (0%)	2 (0·05%)
Rural (%)	66 (70·2%)	49 (80·3%)	2561 (84·7%)	106 (76·2%)	105 (87·5%)	29 (72·5%)	2916 (83·8%)
Urban (%)	28 (29·7%)	12 (19·6%)	462 (15·2%)	33 (23·7%)	15 (12·5%)	11 (27·5%)	561 (16·1%)
Cirrhosis*	24 (25·5%)	18 (29·5%)†	15 (0·4%)	101 (72·6%)†	54 (45%)	25 (62·5%)	237 (6·8%)
No-Cirrhosis	70 (74·4%)	43 (70·4%)	3008 (99·5%)	38 (27·3%)	66 (55%)	15 (37·5%)†	3240 (93·1%)
Duration 4 weeks	0	0	5	0	0	0	5
Duration 8 weeks	0	0	11	0	0	0	11
Treatment Experienced (n, %)	0·0%	0·0%	16 (0·5%)	0·0%	0·0%	0·0%	16 (0·4%)

Abbreviations for the Table: SD, standard deviation; SOF, sofosbuvir; DCV, daclatasvir; LDV, ledipasvir; RBV, ribavirin; VEL, velpatasvir; CI, Confidence Interval; PWID, Person Who Injects Drugs; SVR-12, Sustained Virological Response at 12 weeks post treatment completion·
‡significant at P<0·005
* Value expressed as % of regimen,
† significant at P<0·05 compared to other regimens,

3. Results

In the first 37·5-months (18 June 2016 to 31 July 2019), we enrolled 3477 PWID (87·2% male; mean age 33·6 ± 12.5 years; 83·8% rural; 6·8 % compensated cirrhotic). Notably 443 (12·7%) female and two transgender persons were also treated in the programme. Besides IDU additional confounding factors like HCV positive partner (5%), unsafe medical practices (14·5%) or prior surgery (3·5%) were observed. While 2280 (65·5%) patients completed treatment, 1978 (56·9%) patients completed 12 weeks of follow up for SVR-12. Table 1 shows the baseline characteristics of the 3477 patients in the whole cohort.

3.1. Response Rates in the PWID Cohort

Of the 2280 patients who have completed therapy, 1978 (86·7 %) were SVR eligible, SVR-12 was done in 1444 (73·8%) patients and 651 (18.7%) patients were on therapy or ineligible for SVR-12 at the time of the analysis. The SVR-12 assessment rate was 73·0% in the per protocol analysis and 1552 (54·9%) of all enrolled patients who were initiated on treatment reported for the SVR-12 test. SVR-12 was achieved in 91·0% of patients per protocol, 49.5% (1398/2,826) in the ITT analysis where all interruptions were treated as failures, and 91.1% (1398/1,552;) in a modified ITT analysis where all those who achieved SVR-12 were treated as cured, regardless of adherence (Figures 1A, B,C). 46 (15·7%) patients had treatment interruptions; of whom 99 (21%) reported for SVR-12 with a cure rate of 77·0%. Overall SVR-12 was achieved in 91·1 % of patients per protocol. Table 2 shows the drug adherence, and treatment outcomes in the patient cohort.

3.2. Adverse Events and Deaths

Adverse events reported by PCPs were weakness, anemia, headache and diarrhoea. However, none required treatment discontinuation of treatment. The 19 deaths were mainly due to injection use related complications, with all aged above 42 years, 2 had advanced liver disease with decompensation (Child C), six deaths (31·5%) were noted in those who interrupted therapy and relapsed on drug use.

3.3. Treatment Interruptions

Table 3 shows that 546 (15·7%) patients interrupted treatment with 259 and 247 persons without cirrhosis discontinuing therapy after 4 and 8 weeks, respectively. The cure rates in these patients were 73% and 80% respectively. In the 24-week regimens, there were 40 dropouts with cure rate of 85·7%. However, the SVR capture rate was only 21% so these may not reflect actual results.

3.4. Predictors of Treatment Failure

Cox proportional hazards analysis was performed to ascertain risk factors for treatment failure in this PWID cohort. On univariate analysis, age (P=0.2), gender (P=0.9), residence (urban vs rural,P=0.7), genotype (P=0.1), baseline viral load (P=0.6), and ongoing abuse (0,7) did not affect response rates. Only prior treatment failure [HR 1·2; 95% CI 1·1-7·3 (p=0·042)] predicted nonresponse. On multivariable analysis, none of these parameters were significant. Male gender, co-infection with HIV or HBV, high fibrosis (APRI or Fib 4), low platelet count, genotype, or classification as cirrhosis, use of OST, alcohol abuse or multiple substance abuse did not affect achievement of SVR-12.

3.5. Patients treated at the Hub

Of the 3477 patients treated in total, 320 patients (were referred for treatment at the hub, of whom 95·3% did not have cirrhosis, 13 (4·1%) had compensated cirrhosis and only 2 (0·6%) had decompensated cirrhosis. This all-male referred group's mean age was 26·6 ± 5·9 years, which is a younger group as compared to persons treated at the peripheral sites (*P*=0·043), and also a referral bias in favour of men. Additional risk factors for referral to the hub included prior treatment failure (176, 55%), concomitant alcohol use (42, 13·1%), recent IDU with last injection <2 weeks ago (99, 30·9%), HIV coinfection (30, 9·3%), HBV coinfection (12, 3·7%) or treatment defaulters (32, 10%). Of the cohort treated at the hub, 284 (88·7%) completed treatment and 221 (77·9%) reported for SVR -12, with 172 (78%) achieving SVR-12.

3.6. Nature of Drugs Used and Injecting Practices

Details of drug use were available in the 320 persons who were treated at the hub. The most common drug used was heroin (180, 56·2%), usually injected daily (22%), weekly (45%) or infrequently (36%). Multiple drug use was reported in 237 (74·0%) patients including use of cannabis (25, 7·8%), opium (49, 15·3%) and diphenhydramine (40, 12·5%). Only 5 (1·5%) persons reported use of chewing tobacco, areca nut and cigarettes but this was rare due to existing cultural practices in the Punjab. PWID often added additional agents like

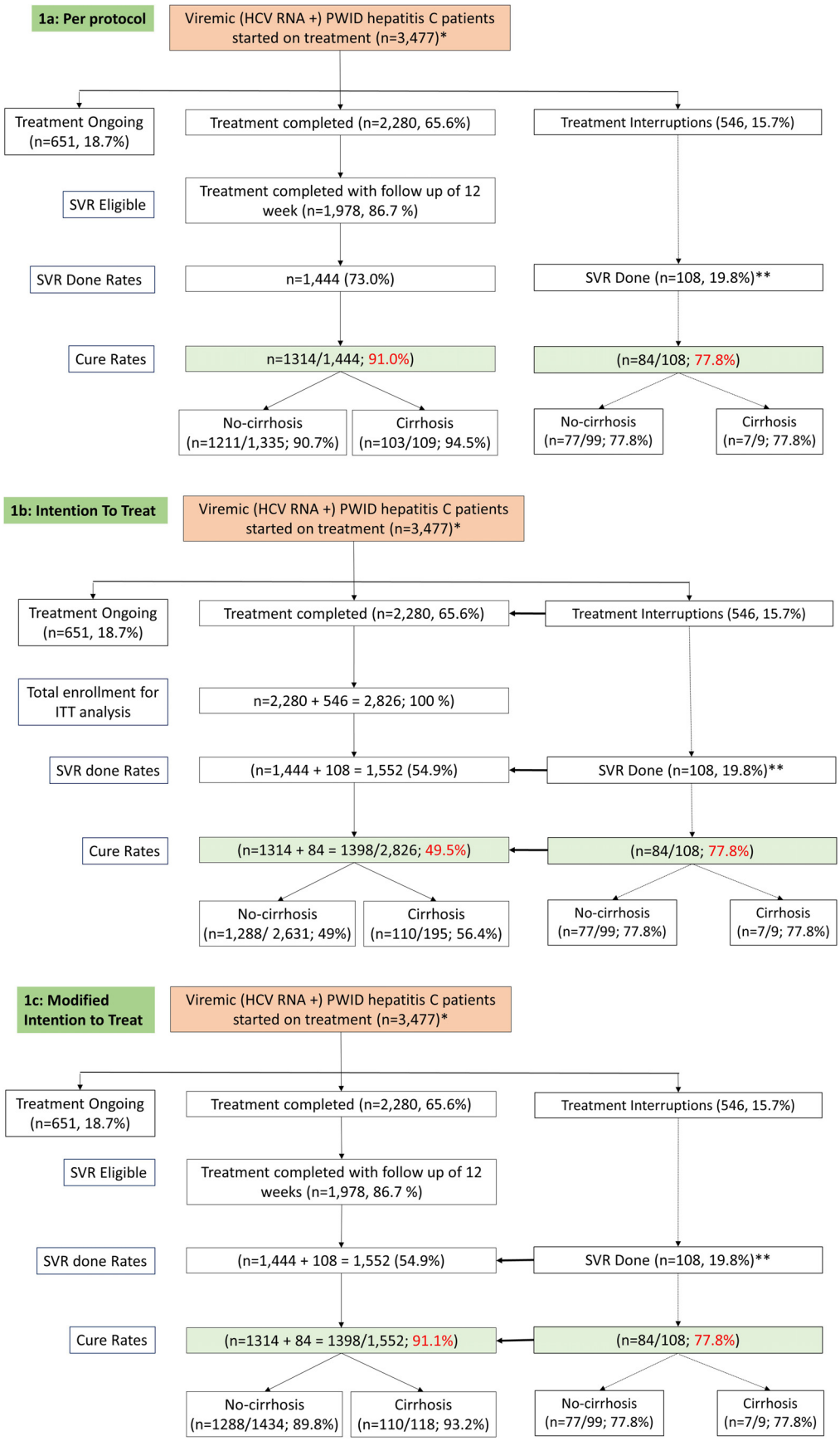

Figure 1. Patient enrolment and outcomes analysis. (a) per protocol (PP) analysis (Cure Rate = 91.0%) (b) Intention to treat (ITT) analysis where all interruptions were treated as failures (Cure Rate = 49.5%) and (c) a modified ITT analysis where all patients with successful sustained virological response (SVR-12) in the interruptions arm were included as cured. (Cure Rate= 91.1%) *Received at least 1-dose of treatment. ** Completed at least 4 weeks of treatment and 12 weeks of follow up.

Table 2
Treatment Outcomes in the Patients as Per Treatment Regimen as Per Protocol

Parameter	SOF/LDV	SOF/LDV/RBV	SOF/DCV	SOF/DCV/RBV	SOF/VEL	SOF/VEL/RBV	Total (all regimens)
N (row %)	94 (2·7%)	61 (1·7%)	3023 (86·9%)	139 (3·9%)	120 (3·4%)	40 (1·1%)	**3477 (100%)**
TREATMENT OUTCOMES							
Treatment completed (n, %)	79 (84·0%)	26 (42·6%)	2000 (66·1%)	107 (76·9%)	64 (53·3%)	4 (10%)	**2280 (65·57%)**
SVR-12 Eligible (n, %)	78 (98·7%)	23 (88·4%)	1737 (86·8%)	106 (99·0%)	31 (48·4%)	3 (75%)	**1978 (86·75%)**
SVR-12 done (n, %)	62 (79·4%)	19 (82·6%)	1249 (71·9%)	96 (90·5%)	16 (51·6%)	2 (66·6%)	**1444 (73%)**
Treatment Responder (SVR-12 attained; n, Cure %)	59 (95·1%)	17 (89·4%)*	1131 (90·5%)	90 (93·7%)	15 (93·7%)	2 (100%)	**1314 (90·99%)**
Treatment failure (SVR-12 not attained; n, %)	3 (4·8%)	2 (10·5%)*	118 (9·4%)	6 (6·2%)	1 (6·25%)	0 (0%)	**130 (9%)**
Interrupted treatment (n, %)	12 (12·7%)	4 (6·5%)	470 (15·5%)	29 (20·8%)	23 (19·1%)	8 (20%)	**546 (15·7%)**
Death in interrupted	0	0	6	1	2	0	**9**
Death in Treatment Complete	0	0	9	1	0	0	**10**
Total Death cases	0	0	15	2	2	0	**19**
Adherence Rate (%)	86·8%	86·6%	80·9%	78·6%	73·5%	33·3%	**80·6%**

Abbreviations for the Table: SOF, sofosbuvir; DCV, daclatasvir; LDV, ledipasvir; RBV, ribavirin; CI, Confidence Interval; PWID, Person Who Injects Drugs; SVR-12, Sustained Virological Response at 12 weeks post treatment completion
* P value <0·005·

Table 3
Cure Rates in Treatment Interruptions

	Number	SVR-12 Eligible	SVR-12 Done	Cure Rate
24-week Regimen				
>4 - ≤8 weeks	14	14	0 (0%)	0 (0%)
>8 - ≤12 weeks	8	8	2 (25%)	2 (100%)
>12 - ≤16 weeks	7	6	2 (33%)	2 (100%)
>16 - ≤20 weeks	3	3	2 (66%)	1 (50%)
>20 - ≤ 24 weeks	8	8	1 (12%)	1 (100%)
12- week Regimen				
>4 - ≤ 8 weeks	259	228	41 (17%)	30 (73%)
>8 - ≤ 12 weeks	247	196	51 (26%)	41 (80%)
Lost to follow-up before the completion of 4 weeks of treatment*				
Overall	**546**	**463**	99 (21%)	77 (77%)

diphenhydramine or morphine (20%) to alter the potency of "low quality" heroin. About 180 (56·2%) participants reported peer groups who prepared and consumed drugs, predisposing to microtransmission and reinfection in social groups. Social stigma and sharing drug costs with peers resulted in resusing paraphernalia, using non-sterile water, with no filtering of the drug solution before injection. 15% of the participants denied sharing needles but admitted to sharing paraphernalia.

3.7. Duration of Drug Use

The median duration of IDU was around 2·5 (1·5-3·6) years in 320 patients reporting to the hub. The median duration of abstinence was 12·1 weeks (range 0-60 weeks), although we did treat patients with ongoing abuse if they were sufficiently motivated, had good family support and were linked to the local deaddiction centre. Another observed cause for treatment default was when persons admitted to private deaddiction centres failed to show up in time to peripheral units to refill their DAA prescription.

4. Discussion

The advent of evidence-based, simplified all-inclusive treatment strategies using pan-genotypic regimens has revolutionized HCV treatment in India. However, until recently, PWID were not offered linked therapy and rehabilitation. Our study provides the largest body of evidence till date to demonstrate the effectiveness of integrated locally available, socially acceptable public healthcare to treat HCV in PWID. Our data corroborates the findings of a recent meta-analysis of smaller studies that suggest complete decentralization of HCV testing and treatment for PWID is associated with improved access to care and high cure rates [22]. It is the first study from the Indian subcontinent that uses microelimination as a model for targeting PWID to expand the successful public health campaign to eliminate HCV.One of the main challenges is to train and counsel medical workers to create an environment conducive to the attitudes and needs of PWID. Since we already had experienced deaddiction personnel, social workers, and counselors at these sites, we could recruit and complete treatment for 86.7% as per the modified intention to treat analysis.

This PWID cohort was aged 18-39 years, which is a decade younger than individuals enrolled under the MMPHCRF [4]. Notably 443 (12·7%) female and two transgender persons were also treated in the programme. Prior studies from this region failed to record female PWID deeming it a male phenomenon as they were based on respondent surveys [23-26]. This gender bias is multifactorial. Firstly, these patients may have admitted to the practice of IDU to seek the free-of-charge HCV treatment available under the programme. Secondly, female PWID reported narcotic misuse like tramadol or morphine rather than synthetic drugs like heroin. It is a cultural practice to seek injection therapy for evepn minor ailments in Punjab, which has contributed to the spread of HCV [4]. Many also had additional confounding factors like HCV positive partner (5%), unsafe medical practices (14·5%) or prior surgery (3·5%). Prior epidemiological data has focussed on synthetic drug users who also had concomitant substance abuse like alcohol, opioids etc which has missed the iceberg phenomenon of IDU and gender disparity in the Punjab [26].

We observed that heroin was the most frequent abused drug, and almost two-thirds of the population resorted to multiple drug use. Global estimates show 82·9% (76·6–88·9) of PWID predominantly inject opioids and 33·0% (24·3–42·0) inject stimulants [27]. In a New York city study, heroin (97%), cocaine (44%), and crack cocaine (47%) were the substances used. About 66% who reported oral non-medical use of prescription opioids [28].

Furthermore, incarceration of PWID due to falling in with the stringent laws of the land or the converse situation of new IDU in persons serving time, is another source of micro-transmission [29]. To this end, our model has evolved to screen and treat all incarcerated individuals free of charge with expanded access to care to meet the HCV Elimination Target by 2030 as mandated by the WHO.

Saraswati et al reported point prevalence rates of HIV, HBV, and HCV as 25·9 %, 9.7 % and 53·7 %, respectively among 2,292 PWID from Delhi [8]. In the Australian CEASE study, use of point-of-care dried blood spot screening in people living with HIV, with subsequent linkage to care resulted in an 86% DAA completion rate. This strategy is a key focus of microelimination, i.e. screening and treating high risk groups [30]. Our relatively low rate of HIV-HCV co infection of 9·3% is explained by the young age of our cohort or viral and host genetics. It is possible that not enough time had elapsed for persons to have acquired multiple infections. The low co-infection rate is also explained as ours is a real world population cohort from Punjab as

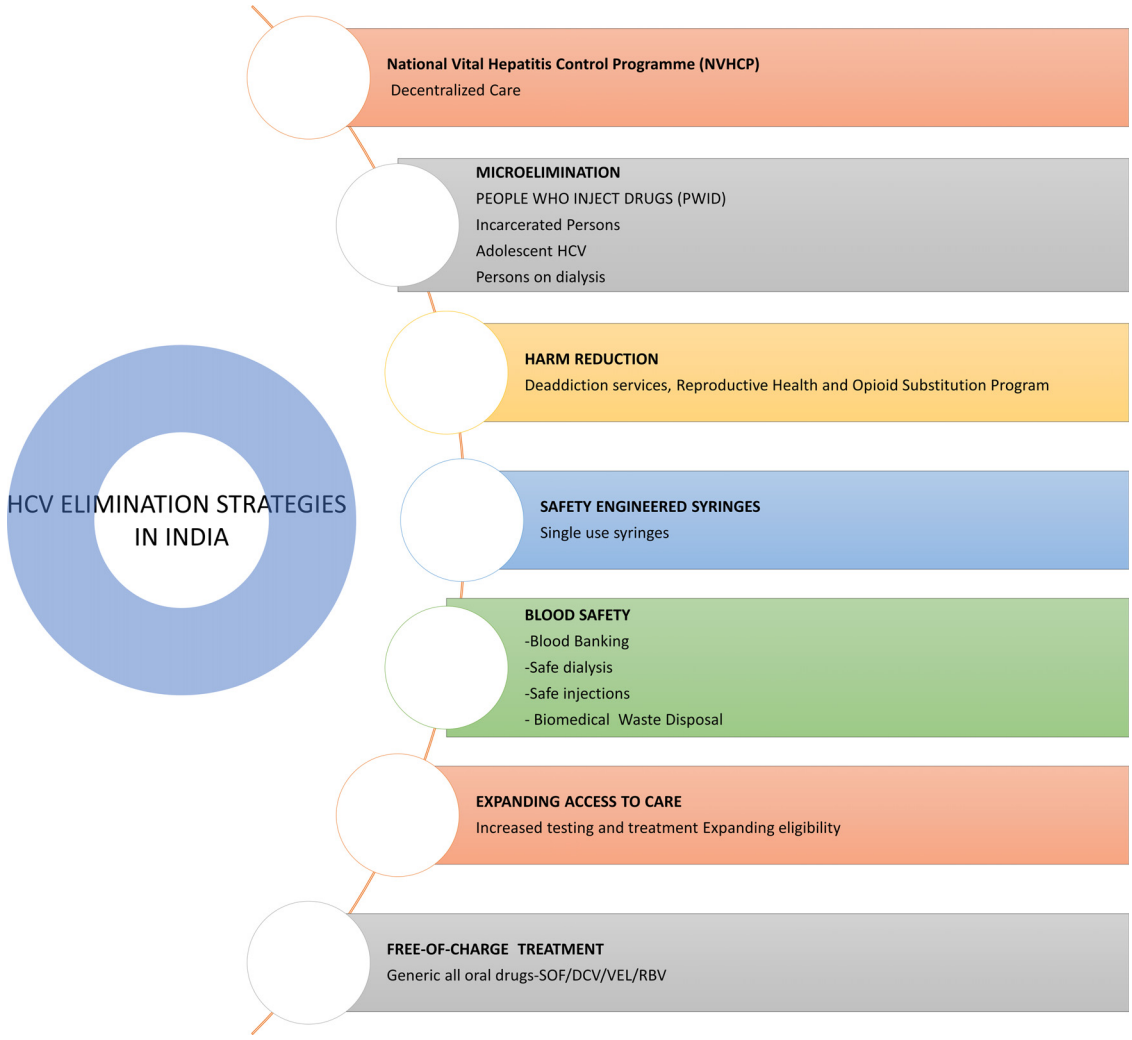

Figure 2. Chronic Hepatitis C Elimination Strategy in India.

The National Viral Hepatitis Control Programme was launched in 2018 to meet the 2030 target for viral hepatitis elimination in India using public health infrastructure with expansion of access to care, vaccination for hepatitis B, delivery of free-of-charge antiviral therapy for chronic hepatitis C and B, use of telemedicine tools to ensure specialist supervision, microelimination in subgroups like people who inject drugs (PWID), dialysis patients etc, improved biomedical waste disposal, blood banking safety, safety engineered syringes and collaboration with other health services.

Abbreviations: DCV, daclatasvir; HCV, hepatitis C virus; PWID, people who inject drugs; NVHCP, National Viral Hepatitis Control Programme; RBV, ribavirin; SOF, sofosbuvir; VEL, velpatasvir.

opposed to hospital PWID or deaddiction registries where high co infection rates are reported [31].

Under the NVHCP, it is cost-saving to tackle PWID as a source of new HCV transmission regardless of current drug use once they are linked to harm reduction, deaddiction and OST services [32]. In the ENHANCE study from Iran, the on site rapid HCV test, confirmatory HCV RNA estimation, liver fibrosis assessment, provision of DAAs and follow up for treatment completion was assessed with a cure rate of 89% in PWID. This study also highlights the need for integrated care [33]. Our drug adherence rate was robust with 80·1% adhering to the protocol overall with cure rates of 90% which is comparable to our data on non PWID groups. Therefore withholding DAA therapy in fear of treatment interruption is not a rational approach for HCV management in PWID [34,35]. Furthermore, even in the difficult-to-treat population reporting to the hub, with 56% treatment-experienced cases, 2 (0.63%) with decompensated cirrhosis, 284 (88·7%) completed treatment,221 (77·9%) reported for SVR -12, with 172 (78%) attained SVR-12.Recently the SIMPLIFY trial reported an SVR-12 rate of 94% with SOF/VEL in 103 currently injecting PWID [12], irrespective of IDU before or during therapy. Median adherence was 94% as compared to our real world cohort of 3477 individuals with 80·1% adherance.

Treatment interruptions are more common in PWID compared to those who do not inject drugs in our published cohort of 48,088 persons (15·7 % versus 12·1%; P=0·043); however, SVR-12 rates were similar (91·1% versus 92·6% P=0·053) [4]. Our data may can be used to formulate policies to reduce HCV transmission in India, such as expansion of the blood banking protocols, biomedical waste disposal, safety engineered syringes, upscaling of OST, microelimination campaigns in incarcerated individuals and 'treatment as prevention' in high-risk groups. (Figure 2) DAAs alone are the most cost-effective intervention. However, with criminal justice system-related costs, DAA and OST/syringe exchange programmes implemented together become the most cost-effective intervention [36]. Supplementary Table 2 shows comparable studies in the PWID population which have used microelimination as a means to control HCV infection.

Although on univariate analysis prior treatment failure predicted non-response, no independent predictor of therapy failure was identified on multivariate analysis. Macías et al. found that the primary reasons for non-response are continued drug abuse and treatment dropouts [37]. Microelimination strategies should tailor therapy based on modelling analysis and involve all stakeholders to ensure

that the treatment strategy can be modified in a dynamic and iterative manner to correct the course and improve outcomes [38].

Our team analysed the barriers to the microelimination strategy in the PWID cohort and we report treatment adherence of 80·5%. However, our SVR-12 assessment rate was 73·0% in the per protocol analysis and only 1552 (54·9%) of all enrolled patients who were initiated on treatment reported for the SVR-12 test. This means a large number of patients did not return for SVR-12 testing despite completing therapy, which is the main limitation. This can be compared with the SVR-12 capture rates of other PWID programmes (Supplementary Table 2). The Australian multicentric trial by Morris et al with 476 patients had cure rate of 98% but offered therapy to only those likely to complete treatment [39]. The Iranian study by Alavi et al had an SVR12 capture rate of 73% and cure rate of 82.8% [33].

Our data remains invaluable in either scenario, as this is a real-world analysis from a public health perspective, involving multiple sites, with integrated healthcare interventions. Young PWID may not have been motivated enough to report for the SVR-12 test even though they completed treatment. This issue of attrition and data loss is due to interruption in the completion of data uploads at the peripheral sites. Due to the COVID-19 related interruptions, we have been unable to capture complete SVR-12 data, which is a major limitation. The missing data, including drug use patterns, needs to be updated once our healthcare personnel are redirected from the pressing duties of the COVID-19 related patient care, testing and vaccination drives. Since this real world cohort has evolved over time, and treatment protocols modiefied in a dynamic way based on efficacy and modelling data, it is not possible to perform efficacy studies or subgroup analyses due to the population heterogeneity.

We noted higher number of treatment interruptions in our PWID subset as compared with our main population (18·5 vs 12·1%).[4] Many cases of interruptions were due to patients missing their monthly prescription refill. Some interrupted therapy as they were enrolled in unregulated private deaddiction centres which did not allow them to report for the prescription on time. Lastly, some patients were less motivated and continued IDU or relapsed soon after treatment initiation. These factors drive home another, important aspect that needs to be considered while interpreting our results which show that although, more than 90% of the population under study achieved SVR-12 in the per protocol and modified ITT analysis, specifically on ITT analysis the SVR-12 rates was only 49.5%. These observations are driven by consideration of all treatment interruptions as failures which should be acknowledged in a real world setting and forms the major challenge in the PWID population. Strategies to reduce treatment interruptions include better education strategies for patients and caregivers, involvement of the family to monitor therapy, and regular audits of the treatment sites [10]. Social support from the family and the project linked deaddiction centres and needle exchange programmes can motivate the patients to be compliant to therapy.[36-39] Therefore, assessment and integration of OST, needle and syringe exchange services, rehabilitation centres, and peer outreach programs need to be upscaled in India to optimize HCV care in PWID [10-12].

In conclusion, our microelimination campaign strategy demonstrates the real world feasiblity to treat CHC in PWID with excellent cure rates using a cost effective integrated public health approach with all oral DAA regimens,. Although, treatment interruptions still remain a major challenge in the PWID population, our model using a telemonitored integrated PWID microelimination approach combining public health services, speciality HCV therapy and deaddiction treatment adds to the growing evidence of feasibility of optimization of care to the PWID population.

5. Contributors

RKD devised the treatment algorithm and is the Chief Consultant for the HCV Elimination Programme in Punjab. GSG is the State Administrative Officer for the MMPHCRF. RKD, GSG and MP were involved in the manuscript preparation and editing. ST, AD, and AR are the consulting physicians involved in patient recruitment and primary care provider training. SA was the chief collaborator for the Extension for Community Healthcare Outcomes (ECHO) clinics and provided technical inputs. All the authors have approved the final version of the manuscript. The MMPHCRF team consisting of Primary Care Providers (PCP) including all medical specialists, civil surgeons, epidemiologists, pharmacists, data entry operators, and data management team from Clinton Health Access Initiative (CHAI) were involved with this multicentric state health programme. The corresponding author had full access to the database, and the final responsibility to submit for publication. The lead authors, RKD, GSG, MP, AR, ST, AD and SA had access to the analysed database and the co-investigators of the MMPHCRF study group could access site specific raw data and were responsible for the raw data associated with the study.

Declaration of Competing Interest

None of the authors has any conflict of interest to declare.

Funding

The Government of the state of Punjab, India under the Mukh Mantri Punjab Hepatitis C Relief Fund (MMPHCRF) project, funded the project.

Data sharing statement

The analysis is part of a central database of patient related information and social security (Aadhar Number) collected by the Punjab Government. Limited access to data can be provided, on request to the corresponding author.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.eclinm.2021.101148.

References

[1] World Health Organization. Guidelines for the screening, care, and treatment of persons with chronic hepatitis C infection Updated version April 2016 available from http://apps.who.int/iris/bitstream/10665/111747/1/9789241548755_eng.pdf?ua=1&ua=1 Last accessed 1st January 2021.
[2] Zibbell JE, Iqbal K, Patel RC, Suryaprasad A, Sanders KJ, Moore-Moravian L, et al. Centers for Disease Control and Prevention (CDC). Increases in hepatitis C virus infection related to injection drug use among persons aged ≤30 years - Kentucky, Tennessee, Virginia, and West Virginia, 2006-2012. MMWR Morb Mortal Wkly Rep 2015;64(17):453–8.
[3] Basu D, Kumar V, Sharma AK, Barnwal PK, Mattoo SK. Seroprevalence of anti-hepatitis C virus (anti-HCV) antibody and HCV-related risk in injecting drug users in northern India: Comparison with non-injecting drug users. Asian Journal of Psychiatry 2013;6(1):52–5. doi: 10.1016/j.ajp.2012.08.008.
[4] Dhiman RK, Grover GS, Premkumar M, Taneja S, Duseja A, Arora S, et al. MMPHCRF Investigators. Decentralized care with generic direct-acting antivirals in the management of chronic hepatitis C in a public health care setting. J Hepatol. 2019;71(6):1076–85. doi: 10.1016/j.jhep.2019.07.006.
[5] Solomon SS, Mehta SH, Srikrishnan AK, Solomon S, McFall AM, Laeyendecker O, et al. 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 Infect Dis 2015;15(1):36–45. doi: 10.1016/S1473-3099(14)71045-X.
[6] Ray Saraswati L, Sarna A, Sebastian MP, Sharma V, Madan I, Thior I, Pulerwitz J, Tun W. HIV, Hepatitis B and C among people who inject drugs: high prevalence of HIV and Hepatitis C RNA positive infections observed in Delhi, India. BMC Public Health 2015;15:726. PMID: 26223866; PMCID: PMC4520270. doi: 10.1186/s12889-015-2003-z.
[7] Saha MK, Chakrabarti S, Panda S, Naik TN, Manna B, Chatterjee A, et al. Prevalence of HCV & HBV infection amongst HIV seropositive intravenous drug users & their non-injecting wives in Manipur. India. Indian J Med Res. 2000;111:37–9.
[8] Goel A, Seguy N, Aggarwal R. Burden of hepatitis C virus infection in India: A systematic review and meta-analysis. J Gastroenterol Hepatol 2019;34(2):321–9 Epub 2018 Sep 26. PMID: 30176181. doi: 10.1111/jgh.14466.

[9] Medhi GK, Mahanta J, Akoijam BS, Adhikary R. Size estimation of injecting drug users (IDU) using multiplier method in five districts of India. Subst Abuse Treat Prev Policy 2012;7:9.

[10] Dhiman RK, Grover GS, Premkumar M. Hepatitis C elimination: a Public Health Perspective. Curr Treat Options Gastroenterol 2019;17(3):367–77. doi: 10.1007/s11938-019-00240-7.

[11] Asher AK, Portillo CJ, Cooper BA, Dawson-Rose C, Vlahov D, Page KA. Clinicians' views of hepatitis C virus treatment candidacy with direct-acting antiviral regimens for people who inject drugs. Subst Use Misuse 2016;51:1218–23.

[12] Grebely J, Dalgard O, Conway B, Cunningham EB, Bruggmann P, Hajarizadeh B. . 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. The Lancet Gastroenterology & Hepatology, 3(3), 153−161.

[13] Akiyama MJ, Cleland CM, Lizcano JA, Cherutich P, Kurth AE. Prevalence, estimated incidence, risk behaviours, and genotypic distribution of hepatitis C virus among people who inject drugs accessing harm-reduction services in Kenya: a retrospective cohort study. Lancet Infect Dis 2019 Sep 17:pii. S1473-3099(19)30264-6. doi: 10.1016/S1473-3099(19)30264-6.

[14] Panda S, Roy T, Pahari S, Mehraa J, Sharma N, Singh G, et al. Alarming epidemics of human immunodeficiency virus and hepatitis C virus among injection drug users in the northwestern bordering state of Punjab, India: prevalence and correlates. Int J STD AIDS 2013;25(8):596–606.

[15] Brooks KM, Castillo-Mancilla JR, Morrow M, MaWhinney S, Rowan SE, Wyles D, Blum J, Huntley R, Salah LM, Tehrani A, Bushman LR. Adherence to Direct-Acting Antiviral Therapy in People Actively Using Drugs and Alcohol: The INCLUD Study. InOpen Forum Infectious Diseases 2021 doi.org/. doi: 10.1093/ofid/ofaa564.

[16] Dhiman RK, Grover GS, Premkumar M, Taneja S, Duseja A, Rathi S, et al. Direct-acting antiviral therapy is safe and effective in pediatric chronic hepatitis C: The public health perspective. J Pediatr Gastroenterol Nutr 2019;68:74–80.

[17] National Viral Hepatitis Control Program- Operational guidelines, 2018 by Ministry of Health and Family Welfare, Government of India January 2021 Available from https://www.nhp.gov.in/national-viral-hepatitis-control-program-(nvhcp)_pg Last accessed 1st.

[18] Chugh Y, Dhiman RK, Premkumar M, Prinja S, Singh Grover G, Bahuguna P. Real-world cost-effectiveness of pan-genotypic Sofosbuvir-Velpatasvir combination versus genotype dependent directly acting anti-viral drugs for treatment of hepatitis C patients in the universal coverage scheme of Punjab state in India. PLoS One 2019;14(8):e0221769. doi: 10.1371/journal.pone.0221769.

[19] Chugh Y, Premkumar M, Grover GS, Dhiman RK, Teerawattananon Y, Prinja S. Cost-effectiveness and budget impact analysis of facility-based screening and treatment of hepatitis C in Punjab state of India. BMJ Open 2021;11(2):e042280. doi: 10.1136/bmjopen-2020-042280.

[20] Rahimi-Movaghar A, Razaghi EM, Sahimi-Izadian E, Amin-Esmaeili M. HIV, hepatitis C virus, and hepatitis B virus co-infections among injecting drug users in Tehran, Iran. Int J Infect Dis 2010;14(1):e28–33.

[21] Abraha I, Cherubini A, Cozzolino F, et al. Deviation from intention to treat analysis in randomized trials and treatment effect estimates: metaepidemiological study. BMJ 2015;27:h2445.

[22] Oru E, Trickey A, Shirali R, Kanters S, Easterbrook P. Decentralisation, integration, and task-shifting in hepatitis C virus infection testing and treatment: a global systematic review and meta-analysis. The Lancet Global Health. 2021;9(4):e431-e445. doi: 10.1016/S2214-109X(20)30505-2.

[23] McFall AM, Solomon SS, Lucas GM, Celentano DD, Srikrishnan AK, Kumar MS, et al. Epidemiology of HIV and hepatitis C infection among women who inject drugs in Northeast India: a respondent-driven sampling study. Addiction 2017;112(8):1480–7. doi: 10.1111/add.13821.

[24] Iversen J, Page K, Madden A, Maher L. HIV, HCV, and Health-Related Harms Among Women Who Inject Drugs: Implications for Prevention and Treatment. JAIDS 2015;69:S176–S81.

[25] Kumar MS, Sharma M. Women and Substance Use in India and Bangladesh. Substance Use & Misuse 2008;43(8/9):1062–77.

[26] Ambekar A, Tripathi BM. Size Estimation of Injection Drug Use in Punjab and Haryana. report submitted to SPYM under the Peer led intervention – supported by DFID. Resource Centre, New Delhi. UNAIDS.

[27] Degenhardt L, Peacock A, Colledge S, Leung J, Grebely J, Vickerman P, et al. Global prevalence of injecting drug use and sociodemographic characteristics and prevalence of HIV, HBV, and HCV in people who inject drugs: a multistage systematic review. The Lancet Global Health 2017;5(12):1192–e1207.

[28] Des Jarlais DC, Arasteh K, McKnight C, Feelemyer J, Perlman DC, Tross S. Prescription opiate analgesics, heroin, HIV and HCV among persons who inject drugs in New York City, 2016-2018. Drug Alcohol Depend 2019;204:107459. doi: 10.1016/j.drugalcdep.2019.04.030.

[29] Larney S, Kopinski H, Beckwith CG. The incidence and prevalence of hepatitis C in prisons and other closed settings: results of a systematic review and meta-analysis. Hepatology 2013;58:1215–24.

[30] Martinello M, Yee J, Bartlett S, et al. Moving Towards Hepatitis C Microelimination Among People Living With Human Immunodeficiency Virus in Australia: The CEASE Study. Clin Infect Dis 2020;71(6):1502–10.

[31] Vickerman P, Hickman M, May M, Kretzschmar M, Wiessing L. Can hepatitis C virus prevalence be used as a measure of injection-related human immunodeficiency virus risk in populations of injecting drug users? An ecological analysis. Addiction 2010;105(2):311–8.

[32] Dhiman RK, Premkumar M. Hepatitis C Virus Elimination by 2030: Conquering Mount Improbable. Clin Liver Dis (Hoboken) 2021;16(6):254–61. doi: 10.1002/cld.978.

[33] Alavi M, Poustchi H, Merat S, et al. An intervention to improve HCV testing, linkage to care, and treatment among people who use drugs in Tehran, Iran: The ENHANCE study. Int J Drug Pol 2019;72:99–105.

[34] Suohu K, Humtsoe C, Saggurti N, Sabarwal S, Mahapatra B, Kermode M. Understanding the association between injecting and sexual risk behaviors of injecting drug users in Manipur and Nagaland, India. Harm Reduction Journal 2012;9(1):40.

[35] Hagan H, Pouget ER, Des Jarlais DC. A systematic review and meta-analysis of interventions to prevent hepatitis C virus infection in people who inject drugs. J Infect Dis 2011;204(1):74–83.

[36] Graf C, Mücke MM, Dultz G, Peiffer KH, Kubesch A, Ingiliz P, Zeuzem S, Herrmann E, Vermehren J. Efficacy of direct-acting antivirals for chronic hepatitis C virus infection in people who inject drugs or receive opioid substitution therapy: a systematic review and meta-analysis. Clinical Infectious Diseases 2020;70(11):2355–65.

[37] Macías J, Morano LE, Téllez F, Granados R, Rivero-Juárez A, Palacios R, et al. Response to direct-acting antiviral therapy among ongoing drug users and people receiving opioid substitution therapy. Journal of hepatology 2019;71(1):45–51.

[38] Lazarus JV, Safreed-Harmon K, Thursz MR, et al. The micro-elimination approach to eliminating hepatitis C: strategic and operational considerations. Semin Liver Dis 2018;38(3):181–92.

[39] Morris L, Smirnov A, Kvassay A, et al. Initial outcomes of integrated community-based hepatitis C treatment for people who inject drugs: findings from the Queensland Injectors health network. Int J Drug Policy 2017 Sep;47:216–20 doi: 10.1016.