Research Article
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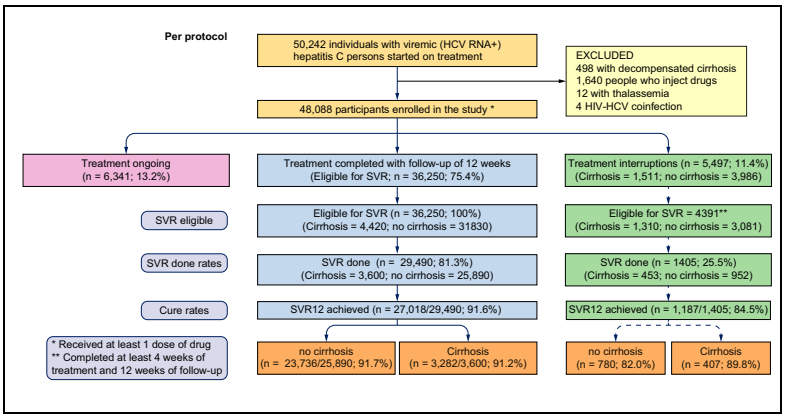
Decentralized care with generic direct-acting antivirals in the management of chronic hepatitis C in a public health care setting

Graphical abstract



Highlights

- The goal of the 'Punjab Model' is HCV Elimination by 2030, using primary care providers and remote treatment monitoring.
- We enrolled 48,088 people (14.8% with compensated cirrhosis; 69.9% with genotype 3).
- SVR12 was achieved in 91.6%, 67.6% and 91.2%, per protocol, intention-to-treat (ITT) and a modified ITT, respectively.
- Decentralized care of hepatitis C with direct-acting antiviral - regimens is safe and effective, regardless of genotype or presence of cirrhosis.

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Lay summary

We assessed the safety and efficacy of public health care using no-cost all-oral generic direct-acting antiviral drugs against hepatitis C in the state of Punjab, India. The goal is elimination of chronic hepatitis C (CHC) by 2030 and involves primary care providers at 25 sites in the state. We enrolled 48,088 individuals (63.8% male; mean age 42.1 years; 80.5% rural; 14.8% compensated cirrhotic; 69.9% genotype 3) between 18th June 2016 to 31st July 2018. Cure was achieved in 91.6% of patients, demonstrating that decentralized care of CHC with generic all-oral regimens is safe and effective.

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Decentralized care with generic direct-acting antivirals in the management of chronic hepatitis C in a public health care setting

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Background & Aims: The prevalence of anti-hepatitis C virus antibody in Punjab, India is 3.6%, with 728,000 people estimated to have viremic chronic hepatitis C (CHC). The Mukh-Mantri Punjab Hepatitis C Relief Fund, launched on 18th June 2016, provides no-cost generic direct-acting antivirals (DAAs) with sofosbuvir + ledipasvir ± ribavirin or sofosbuvir + daclatasvir ± ribavirin with the goal of eliminating CHC from Punjab. We assessed the safety and efficacy of decentralized treatment of CHC in a public health care setting.

Methods: Primary care providers from 3 university and 22 district hospitals were trained to provide algorithm-based DAA treatment and supervised by telehealth clinics conducted fortnightly. The diagnosis of cirrhosis was based on clinical and radiological evidence, including aspartate aminotransferase-to-platelet ratio index (APRI ≥2.0) and FIB-4 score (>3.25), or on liver stiffness measurement ≥12.5 kPa on Fibroscan®.

Results: We enrolled 48,088 individuals with CHC (63.8% male; mean age 42.1 years; 80.5% rural; 14.8% compensated cirrhosis; 69.9% genotype [GT] 3) between 18th June 2016 to 31st July 2018. While 36,250 (75.4%) patients completed treatment, 5,497 (11.4%) had treatment interruptions and 6,341 (13.2%) patients are currently ongoing treatment. Sustained virological response at 12 weeks after treatment completion (SVR12) was achieved in 91.6% of patients per protocol, 67.6% in intention-to-treat (ITT) analysis, where all interruptions were treated as failures, and 91.2% in a modified ITT analysis where all patients with successful SVR12 in the interruptions arm were included as cured. SVR12 rates in patients with and without cirrhosis and GT3 versus non-GT3 were comparable. The SVR12 rate was 84.4% in patients who had treatment interruptions.

Conclusion: Decentralized care of patients with CHC using generic all-oral DAA regimens is safe and effective regardless of genotype or presence of cirrhosis.

ClinicalTrials.gov number: NCT01110447.

Lay summary: We assessed the safety and efficacy of public health care using no-cost all-oral generic direct-acting antiviral drugs against hepatitis C in the state of Punjab, India. The goal is elimination of chronic hepatitis C (CHC) by 2030 and involves primary care providers at 25 sites in the state. We enrolled 48,088 individuals (63.8% male; mean age 42.1 years; 80.5% rural; 14.8% compensated cirrhotic; 69.9% genotype 3) between 18th June 2016 to 31st July 2018. Cure was achieved in 91.6% of patients, demonstrating that decentralized care of CHC with generic all-oral regimens is safe and effective.

Introduction

Of the 28 million people living in Punjab (2011 Census), 3.6% are estimated to be positive for anti-HCV antibody and 2.6% (728,000) are estimated to test positive for HCV RNA.[1,2] A majority of these people may progress to cirrhosis and its complications including variceal bleeding, liver failure and hepatocellular carcinoma (HCC), or death.[3,4] Successful treatment of chronic hepatitis C (CHC) is associated with 62–84% reduction in all-cause mortality, 68–79% reduction in risk of HCC and 90% reduction in need for liver transplantation. Treating CHC saves lives, is cost-effective and cost-saving in the long-term by reducing the overall cost of public health expenditure for treatment of liver disease.[5] With the advent of generic direct-acting antivirals (DAAs), the treatment is less expensive and equally effective (cure rates >90%).[6–8] The Mukh-Mantri Punjab Hepatitis C Relief Fund program, provides free medical treatment for people with CHC with the goal of eliminating hepatitis C from Punjab.[9] The Punjab Model is an innovative interactive model of decentralized services that uses telementoring and algorithm-based treatment with generic drugs. The Punjab Model trains and supports primary care providers (PCPs) to learn about emerging treatment options, adverse effects and treatment adherence, so that they can manage CHC using the existing health care infrastructure.[10,11]

Decentralized services were used to treat patients with CHC through the involvement of PCPs, pharmacists and other team members in district hospitals. The primary hub in this model is the Postgraduate Institute of Medical Education and Research,

Keywords: Mukh-Mantri Punjab Hepatitis C Relief Fund; MMPHCRF; Direct-acting antivirals; DAAs; Chronic hepatitis C; Real-life efficacy study; ECHO Project.
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Chandigarh, India, and 22 district hospitals and 3 university hospitals serve as spokes.[12]

We aimed to assess the feasibility, safety and efficacy of decentralized care for treatment of CHC, including cirrhosis with 12 or 24 weeks of sofosbuvir (SOF) + ledipasvir (LDV) or SOF + daclatasvir (DCV), with or without ribavirin (RBV), in a public health care setting.

Patients and methods

All patients with CHC were enrolled at 25 sites (22 district hospitals and 3 university hospitals) and the study had the approval of the Ethical Committee of Postgraduate Institute of Medical Education and Research, Chandigarh, India and was conducted in accordance with the Declaration of Helsinki. The trial is accessible at NCT03488485 available from https://clinicaltrials.gov/ct2/show/NCT03488485.

Patients with CHC

A total of 48,088 individuals with CHC were enrolled after meeting the study criteria during the period between 18th June 2016 and 31st July 2018 and followed for at least 12 weeks post treatment to evaluate for sustained virological response (SVR12) (Fig. S1). Patients with CHC of any genotype were eligible, whether treatment-naive or treatment-experienced.

Exclusion criteria

Individuals aged <18 years, intravenous drug users, and those with decompensated cirrhosis, HIV-HCV coinfection, HCC, renal impairment, and thallasemia, were excluded from the analysis. People with disseminated malignancy, advanced cardiovascular, pulmonary, or neurological disease with short life expectancy were not enrolled.

Decentralized care: the Punjab Model

Treatment teams

Ninety-four PCPs which included a cadre of medical specialists (internists) and civil surgeons (medical graduates) were trained in a 4-hour long workshop with a predefined curriculum (Table S1) followed by regular telehealth Postgraduate Institute of Medical Education and Research - Indian National Association for the Study of Liver - Punjab Government - Extension for Community Healthcare Outcomes Clinics conducted fortnightly, which included 3 basic components – (i) case presentation from hub (ii) case discussions by the PCPs from the spokes and (iii) didactic lecture by a hepatologist from the hub. A WhatsApp group for the PCPs was also created to solve the case-based queries raised for timely individual care decisions to cover the period between the Extension for Community Healthcare Outcomes (ECHO) clinics.

Each of the 25 spoke teams consisted of PCPs, civil surgeons, epidemiologists, pharmacists and data entry operators and was responsible for recruitment, registration, management, assessment of adherence, follow-up, adverse effect monitoring and record keeping of all individuals with CHC.

Data management

Twenty-two district *epidemiologists* helped medical specialists in managing patients with CHC starting from registration, management, to follow-up. Twenty-five *pharmacists* under the Integrated Disease Surveillance Program, were trained to dispense medicine as per prescription, medical record keeping, and assessment of adherence. Twenty-five trained *data entry operators* uploaded real-time data to the project servers. Management of data was done by Clinton Health Access Initiative to identify administrative and logistic issues, disease hotspots, vulnerability factors among the high-risk groups, service providers in the vicinity, *etc.* The data entered in the master register and drug stocks at each center were verified by the medical team and epidemiologist from time-to-time with weekly online data updates.

Pharmaceutical quality control

Generic drugs were supplied by Indian pharmaceutical companies Natco Pharma Limited, (Hyderabad, India) and Zydus Cadila (Ahmedabad, India), licensed by the originator company Gilead Sciences, Inc. The drugs DCV (60 mg), SOF (400 mg), RBV (200 mg) and a fixed dose combination of SOF (400 mg) + LDV (90 mg) were manufactured at FDA approved facilities.[13,14] The Central Drugs Standard Control Organization, Directorate General of Health Sciences, New Delhi granted permission to manufacture these new drugs formulations for the treatment of patients with CHC.[7]

Strategy to enhance adherence to treatment

All patients with CHC were issued a 4-week supply of medicine at each visit and were requested to return 5 days before the next refill. A district Medical Alert, a compliance monitoring system, was generated if the person failed to return in time and a pharmacist contacted them.[12] In the event personal contact was not established, community health workers visited patients' homes to enhance adherence.

Referral to tertiary care nodal center

The following categories of patients with CHC required referral to the nodal treatment center: (i) patients with compensated cirrhosis were referred for evaluation, regimen selection and tests including endoscopy, transient elastography, triple-phase contrast enhanced computed tomographic scan and for long-term follow-up after achieving SVR12, (ii) patients with decompensated cirrhosis, injection drug use, renal failure, HCC, and thalassemia were treated at the hub, but were excluded from analysis.

Study design

The design of the study was a prospective interventional trial. An algorithm was developed using SOF-based regimens to treat all patients (Fig. S1). Patients without cirrhosis were treated with SOF/DCV for 12-weeks.[9,12] Genotype (GT) testing was not recommended for patients without cirrhosis, but was available based on individual preference. All patients with cirrhosis required genotyping. Patients with GT3 were treated with SOF/DCV/RBV for 24 weeks, while patients without GT3 were treated with SOF/LDV/RBV for 12-weeks or with SOF/LDV for 24-weeks (in RBV intolerant individuals) (Table 1). There were 4 treatment regimens to allow PCPs to define treatment allocation (Table S2). SOF/DCV for 12 weeks was the most commonly prescribed, as most individuals had CHC without cirrhosis. SOF/LDV for 12 weeks was used in patients with GT1,4,5 or 6. SOF/DCV/weight-based RBV for 12 weeks and SOF/LDV/weight-based RBV for 12 weeks were prescribed in case of cirrhosis with GT2/3 and GT1,4,5 or 6, respectively. RBV was prescribed

Table 1. Baseline characteristics as per treatment regimen.

Parameter	SOF/LDV	SOF/LDV/RBV	SOF/DCV	SOF/DCV/RBV	Total (all regimens)
N (row %)	3,538 (7.4 %)	1,371 (2.8 %)	37,033 (77.0 %)	6,146 (12.8 %)	48,088
Demographic data					
Age (Mean ± SD) in years	42.6 ± 13.9	49.9 ± 13.1‡	40.4 ± 13.5	50.3 ± 11.9‡	42.1 ± 13.9
Gender					
Male (%)	2,267 (64.0%)	938 (68.4%)	23,522 (63.5%)	3,978 (64.7 %)	30,705 (63.9%)
Female (%)	1,271 (35.9%)	433 (31.6%)	13,506 (36.4%)	2,166 (35.3%)	17,376 (36.1%)
Transgender (%)	0	0	5(0.01%)	2 (0.01%)	7 (0.01%)
Rural (%)	2,763 (78.1%)	996 (72.6%)	30,248 (81.7%) †	4,697 (76.4%)	38,704 (80.5%)
Urban (%)	775 (21.9%)	375 (27.4%)	6,785 (18.3%)	1,449 (23.6%)	9,384 (19.5%)
Risk Factor for transmission (n = 20,113)	1072	784	15,149	3108	20,113
Dental	31 (2.9%)	26 (3.3%)	697(4.6%)	194 (6.2%)	948 (4.7%)
Unsafe injection use	564 (52.6%)	434 (55.3%)	8,997 (59.3%)	1,882 (60.5%)	11,877 (59.1%)
Surgery	97 (9.1%)	36 (4.6%)	1,083 (7.1%)	204 (6.6%)	1,420 (7.1%)
Unprotected sexual practice	4 (0.3%)	0	95 (0.6%)	13 (0.4%)	112 (0.6%)
Others (tattoo/barber/shared razor)	376 (35.1%)	288 (36.7%)	4,277 (28.2%)	815 (26.2%)	5,756 (28.6%)
Cirrhosis (n, %)*	257 (3.6 %)	1,118 (81.5%)‡	373 (5.2 %)	5,369 (75.4 %)‡	7,117 (14.8 %)
Treatment experienced (n, %)	12 (0.33%)	9 (0.65%)‡	124 (0.33%)	65(1.0%)‡	210 (0.43%)

DCV, daclatasvir; LDV, ledipasvir; RBV, ribavirin; SOF, sofosbuvir; SVR12, sustained virological response at 12 weeks post treatment completion.*value expressed as % of regimen, †significant at p <0.05 compared to other regimens, ‡significant at p <0.005 compared to non-cirrhotics.

at a dose of 1,000 mg/day if the body weight was <75 kg and 1,200 mg/day if the body weight was ≥75 kg. Patients who were intolerant to RBV received 24 weeks of treatment.

End-treatment assessment of viral load was optional but SVR12 was mandatory in all individuals.[8,9,12] While all patients with liver cirrhosis underwent genotyping per protocol, this was not mandatory in those without cirrhosis, and they were tested for genotype only on the individual's request. Adherence was defined as no interruption in the treatment and the patient completing the prescribed duration of treatment. During visits, pill counts of the remaining medicine were carried out.

Study endpoints

The primary endpoint was achieving SVR12, which was defined as an absence of detectable HCV RNA 12 weeks after the completion of treatment. The secondary endpoints were treatment completion, safety and all adverse events. We allowed a window period of 4–8 weeks to complete the SVR12 data in people who did not report for the test. Our health care workers contact the individual, who is due for SVR12, (both treatment adherent and treatment interruptions) by means of phone messaging, phone calls using a toll-free number 104 or house visits to ensure data is collected effectively. A treatment interruption was defined as treatment interruption for >7 days or treatment discontinuation. If the interruption of treatment was for ≤7 days, treatment was continued for the remaining duration as prescribed and SVR12 was assessed 12-weeks after the completion of treatment. If interruption of treatment was >7 days and the patient had taken treatment for <4 weeks, then the treatment was started afresh. If interruption of treatment was >7 days and the patient had taken treatment for ≥4 weeks or more, then HCV RNA was measured after 12-weeks of cessation of drug to assess for SVR12. The SVR12 was calculated in patients who had completed treatment as per protocol and in those who had interrupted therapy and had taken DAAs ≥4 weeks or more in the 12 or 24-week regimens.[15] A significant adverse event was defined as any event that required a diagnostic or therapeutic intervention.[16]

A protocol deviation was defined as any change, divergence, or departure from the study design or procedures defined in the protocol. Important protocol deviations were defined as a subset of protocol deviations that may significantly impact the completeness, accuracy, and/or reliability of the study data or that may significantly affect a subject's rights, safety, or well-being.[16]

Study cohorts

Among patients who received at least 1 dose of DAAs, 3 cohorts could be identified, i) patients with ongoing treatment who had not yet completed allocated therapy or mandatory follow-up of 12 weeks for SVR12, ii) patients who completed desired treatment and completed 12 weeks of follow-up and were eligible for SVR12 and iii) patients who had treatment interruptions, including deaths. Patients with ongoing treatment were not analyzed further as they had not completed treatment. Three different types of analyses were performed in patients who were eligible for SVR12 and those with treatment interruptions, i) per protocol analysis, which only provides the SVR12 for those who completed treatment, ii) the intention-to-treat (ITT) analysis included all participants who initiated at least 1 dose of therapy, except ongoing treatment and iii) a modified ITT, which included the data among people without missing SVR12 values but included those who interrupted drug therapy.

Clinical and laboratory assessments

Clinical and radiological diagnosis

The diagnosis of cirrhosis was based on the presence of stigmata of chronic liver disease, splenomegaly, ascites, history of hepatic encephalopathy or variceal bleeding. Findings of a shrunken liver, irregular surface, altered echotexture, evidence of portal hypertension (portal vein >13 mm and presence of collaterals) on imaging and presence of varices on endoscopy also established the diagnosis of cirrhosis. All enrolled participants underwent an ultrasound of the abdomen to look for evidence of cirrhosis and for the presence of HCC.

Non-invasive markers

The aspartate aminotransferase (AST)-to-Platelet Ratio Index (APRI ≥2.0) or FIB-4 score (>3.25) were used to make a diagnosis of cirrhosis.[17] Liver stiffness measurement (LSM) was performed in participants where there was a clinical suspicion of cirrhosis

and APRI or FIB-4 was inconclusive. An LSM ≥12.5 kPa with Fibroscan® was taken as the cut-off for the diagnosis of cirrhosis (Metavir F4).

Molecular tests

Quantitative HCV RNA measurement was performed by reverse transcription PCR (RT-PCR) using a commercially available assay COBAS AmpliPrep/COBAS TaqMan™ HCV Test. HCV RNA extraction and genotyping were carried out with the QIAamp Viral RNA Kit (QIAGEN, Valencia, CA, USA), using a 1-step RT-PCR kit (AgPath ID, Thermofisher). Sequencing was performed using BDT 3.1 (Thermofisher).[12]

Statistical analysis

Continuous variables were expressed as the means ± SD or 95% CIs, and categorical data were expressed as numbers (percentages). The primary endpoint (SVR12) was calculated. The ANOVA test was used to analyze differences between groups, and the χ^2 test or Fisher's exact test was applied for the comparison of categorical data. We applied univariate logistic regression to identify variables independently associated with treatment response, and then multivariate logistic regression was performed on variables that were significantly different up to 20% in the univariate analysis. Given the differences in disease stage in patients with and without cirrhosis, the analysis of factors influencing treatment failure was undertaken separately, according to the allocated regimen and depending on the presence of cirrhosis.

P values less than 0.05 were considered significant. Statistical analysis was performed with SPSS software for Windows, version 17.0 (SPSS, Inc, Chicago, IL).

Results

Demographic profile

Between 18th June 2016 and 31st July 2018, 50,242 participants were diagnosed with viremic chronic hepatitis C, of whom 498 individuals had decompensated cirrhosis, 1,640 injection drug users, 4 with HIV-HCV coinfection, and 12 with thallasemia were treated exclusively at the hub and were excluded from analysis. Finally, 48,088 individuals (63.8% male; mean age 42.1 ± 13.9 years) were enrolled in the study after meeting criteria.

Cut-off for inclusion of participants in the analysis for patients who received 24-week treatment was November 21st, 2017 and for people who received 12-week treatment was February 13th, 2018, so that they would be eligible for an SVR12 measurement on 31st July 2018. About 80.5% of patients treated lived in rural communities, reflecting Punjab state in which ~85% of the population lives in rural communities. The largest participant subgroup were 18–39 years old (43.7%); people with liver cirrhosis were older (mean 50.1 years) than people without cirrhosis (mean 42.1 years). Table 1 describes the baseline characteristics of people according to the treatment regimen they received. While 7 sites recruited ≤1,000 participants (range 92–874), 10 sites recruited between 1,001–2,000 (range 1,036–1,921), 3 sites recruited 2,001 to 3,000 (range 2,061–2,704) and 5 sites recruited >3,000 participants (range 3,491–6,605) (Fig. 1). Amongst 20,113 individuals who were interviewed for risk-factors, unsafe medical practices (11,877; 59.1%), unsafe dental practice (948; 4.7%), prior surgery (1,420; 7.1%) and unprotected sex (112; 0.6%) were the main suspected modes of viral transmission.

Response rates

Of the 48,088 patients enrolled with CHC who initiated treatment, 38,748 (80.6%) completed treatment, 36,250 (93.5%) were eligible for SVR12, which could be measured in 29,490 (81.3%) patients, with an overall SVR12 rate of 91.6% (Fig. 2). In addition, 5,497 (11.4%) participants had treatment interruptions, including 270 who died during the study period. Treatment was completed in 36,250 (86.8%) patients with CHC. Among those in the interrupted group, 4,391 individuals had taken treatment for at least 4 weeks and completed 12 weeks after the last dose, so were eligible for SVR12 (Fig. 2).

The analysis for SVR12 in this real world cohort was done by 3 methods, (a) per protocol analysis (n = 36,250; cure rate = 91.6%) (Table 2; Fig. 2) (b) ITT analysis where all interruptions were treated as failures (n = 41,747; cure rate = 67.6%) (Fig. 3) and (c) a modified ITT analysis where all patients with successful SVR12 in the interruptions arm were included as cured (n = 30,895; cure rate = 91.2%) (Fig. 4).

The per protocol SVR12 rates were 91.6%; 91.2% in males and 91.7% in females ($p = 0.058$). The results were comparable across all age groups and rural (n = 23,983; 91.9%) versus urban backgrounds (n = 5,507; 91.1 (Table S3). The HCV genotype testing was performed in 20,106 (41.8%) of 48,088 participants. While all patients with liver cirrhosis underwent genotyping per protocol, this was not mandatory in those without cirrhosis. Overall, the predominant genotype was GT3 (69.9%). Of the 3,600 eligible patients with cirrhosis for SVR12, the SVR12 rate was (n = 3,282; 91.1%) which was comparable to patients without cirrhosis (n = 23,736; 91.7%).

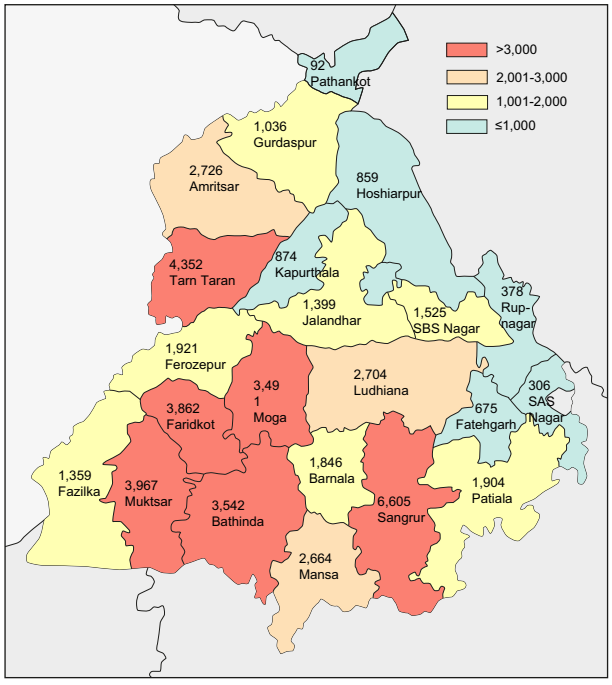

Fig. 1. Disease burden and cure rates across the 25 treatment sites in Punjab (This figure appears in colour on the web.)

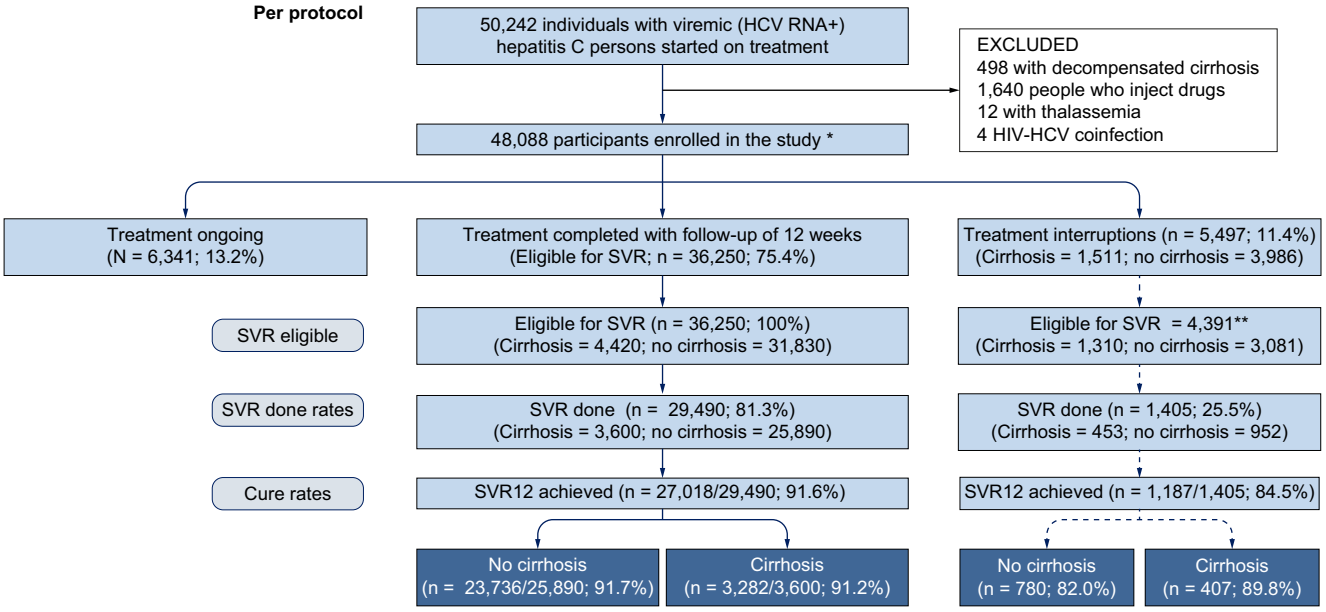

Fig. 2. Participant recruitment flowchart in the program, per protocol analysis. (Cure rate = 91.6%). *Received at least 1-dose of treatment. **Completed at least 4 weeks of treatment and 12 weeks of follow-up. SVR12, sustained virological response at 12 weeks post treatment completion.

Table 2. Treatment outcomes in the study allocated regimen as per protocol.

Parameter	SOF/LDV	SOF/LDV/RBV	SOF/DCV	SOF/DCV/RBV	Total (all regimens)
N (row %)	3,538 (7.4%)	1,371 (2.8%)	37,033 (77.0%)	6,146 (12.8%)	48,088
Treatment outcomes					
Treatment completed (n, %)	3,032 (85.6%)	1,069 (77.9%)	30,762 (83.0%)	3,885 (63.2%)	38,748 (80.5%)
SVR12 eligible (n, %)	2,877 (94.8%)	1,004 (93.9%)	28,752 (93.4%)	3,617 (93.1%)	36,250 (93.5%)
SVR12 assessed (n, %)	2,342 (81.4%)	803 (79.9%)	23,381 (81.3%)	2,964 (81.9%)	29,490 (81.3%)
Treatment responder (SVR12 attained; n, cure %)	2,201 (93.9%)	715 (89.1%)*	21,378 (91.5%)	2,724 (91.9%)	27,018 (91.6%)
Treatment failure (SVR12 not attained; n, %)	141 (6.1%)	88 (10.9%)*	2,003 (8.5%)	240 (8.1%)	2,472 (8.3%)
Interrupted treatment (n, %)	20 (0.6%)	0	130 (0.4%)	5 (0.1%)	155 (0.4%)
Lost to follow-up (n, %)	1 (0.03%)	0	22 (0.07%)	3 (0.08%)	26 (0.07%)
Death (n, %)	16 (0.5%)	3 (0.3%)	242 (0.8%)	9 (0.2%)	270 (0.7%)
Adherence Rate (%)	99.3%	100.0%	99.5%	99.7%	99.5%

DCV, daclatasvir; LDV, ledipasvir; RBV, ribavirin; SOF, sofosbuvir; SVR12, sustained virological response at 12 weeks post treatment completion. *p value <0.005.

Table 3 shows the allocation of the enrolled patients to the treatment regimens and the cure rates in those with and without cirrhosis. Due to the inclusion criteria, most patients with cirrhosis, those with higher APRI/FIB-4 values and those with high liver stiffness values were enrolled in the triple therapy arms (with RBV). The overall adherence rate was 88.6%. Death due to any cause occurred in 270 (0.56%) patients. We found that 18 (0.006%) patients with cirrhosis and 79 (0.003%) without cirrhosis, with GT3 HCV infection, were given SOF/LDV based regimens. The cure rates in these misallocation cases were 87.5% and 92.0% in patients with and without cirrhosis, respectively. The second type of error was when a patient with cirrhosis was misclassified as one without cirrhosis and received only 12 weeks of therapy or a non-RBV-containing regimen. There were 241 (0.006%) such cases in the per protocol analysis which amounted to a minor protocol deviation as the cure rate in these cases was 91.5%. The reverse situation was when a patient without cirrhosis was prescribed an RBV-containing regimen. Only 98 (0.003%) of patients without cirrhosis were allocated to an RBV-containing regimen with SVR12 of 91.1%, which is like our overall cure rate. None of them required treatment discontinuation due to anemia or other adverse events.

Treatment interruptions

Table 4 shows the outcomes of patients who interrupted treatment with complete data available on treatment duration. 5,497 (11.4%) participants had treatment interruptions; 4,391 had taken at least 4 weeks of therapy and completed 12 weeks of follow-up after the last dose, thus deeming them SVR12 eligible. Of these 1,405 could be traced to test for SVR12 with a cure rate of 84.4%. Patients with cirrhosis were twofold more likely to experience treatment interruptions. They comprised 27.4% of all participants who interrupted treatment and 12.2% of those who adhered to the protocol. The Table 4 shows that patients who completed at least 8 weeks of therapy had cure rates >92%, even those who received at least 4 weeks of therapy in the 12-week or 24-week regimens had cure rates of 77.8%.

Adverse events and participant referral

All regimens were well tolerated in patients without cirrhosis and there was no treatment discontinuation. There were no grade 3 or 4 adverse events (severe or life-threatening) reported. In the 3,600 people with compensated cirrhosis, 614 (20.5%) patients had anemia. Most responded to iron, cobalamin and folate supplementation, and erythropoietin was prescribed

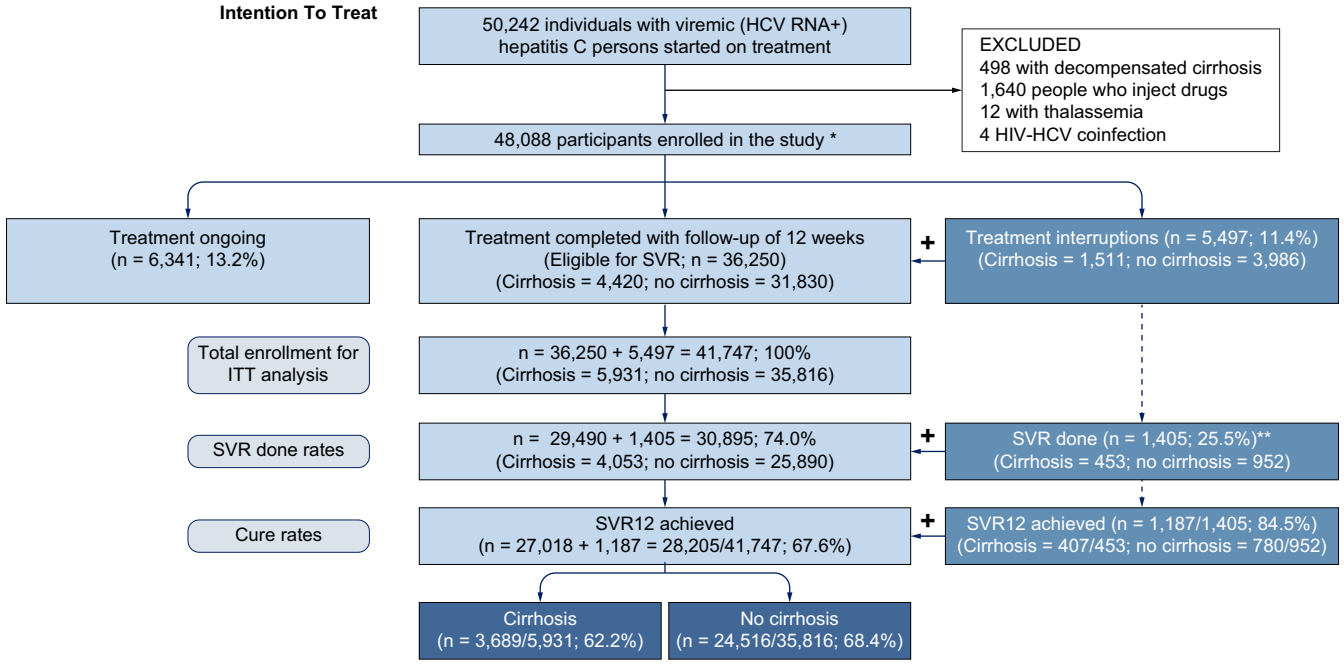

Fig. 3. Participant recruitment flowchart in the program, intention-to-treat analysis where all interruptions were treated as failures. (Cure rate = 67.6%). *Received at least 1-dose of treatment. **Completed at least 4 weeks of treatment and 12 weeks of follow-up. ITT, intention-to-treat; SVR12, sustained virological response at 12 weeks post treatment completion.

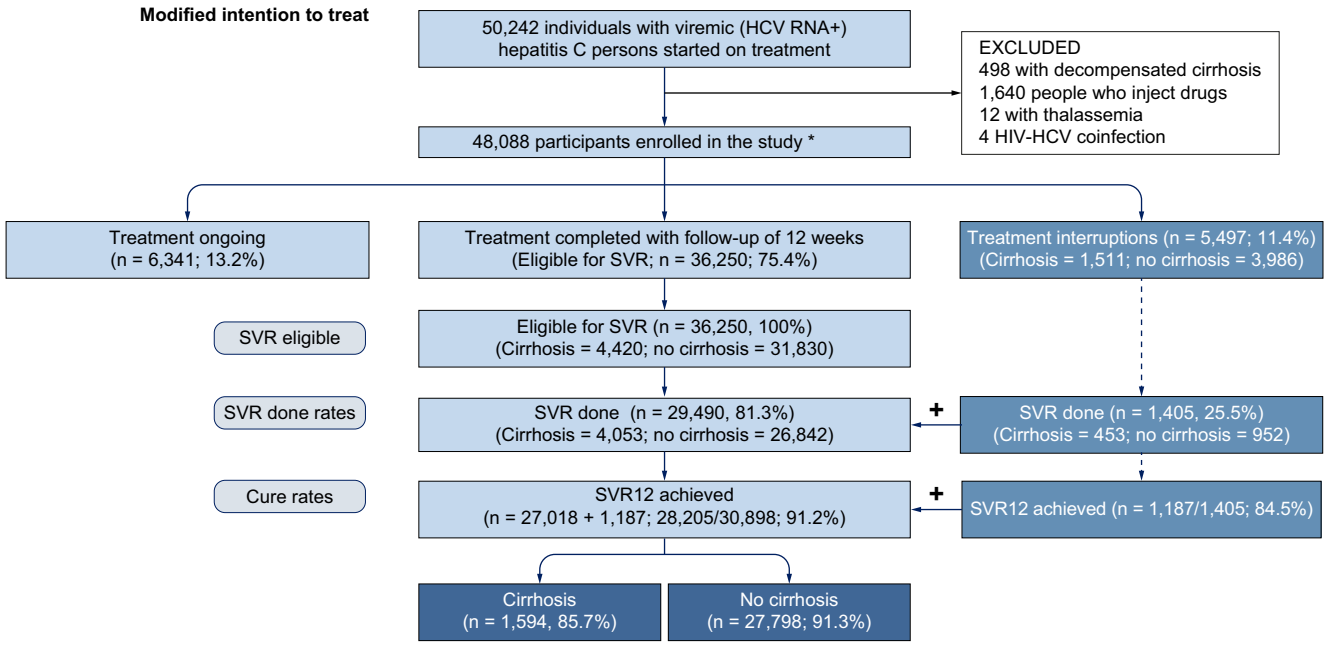

Fig. 4. Participant recruitment flowchart in the program, a modified intention-to-treat analysis where all patients with successful SVR12 in the interruptions arm were included as cured. (Cure rate = 91.2%). *Received at least 1-dose of treatment. **Completed at least 4 weeks of treatment and 12 weeks of follow-up. SVR12, sustained virological response at 12 weeks post treatment completion.

in few cases. Subsequently, 110 (3.1%) participants with persistent anemia, attributable to RBV, were allocated to RBV free regimens and were treated at the hub. Other infrequent events were diarrhea and asymptomatic aminotransferase elevation. A few cases of headache, nausea and fatigue were reported by the PCP, none of which required treatment interruption.

Predictors of response

Table S3 shows the cure rates in specific participant subgroups, which may have affected response. On univariate logistic regression, we assessed the effect of gender, age, residence (urban *vs.* rural), genotype, baseline viral load, presence of cirrhosis, and prior treatment status on response rates. Only the

Table 3. Regimen wise allocation and cure rates in people with compensated cirrhosis and those without cirrhosis as per protocol.

	Cirrhosis				No cirrhosis			
	Treatment failure	Cure	Total	SVR12	Treatment failure	Cure	Total	SVR12
Sofosbuvir + ledipasvir								
Genotype								
NT	0	2	2	100%	8	150	158	95%
1	8	71	79	90%	84	1,197	1,281	93%
2	0	0	0	0%	0	1	1	100%
3	1	1	2	50%	6	66	72	92%
4	1	51	52	98%	24	526	550	96%
5	1	10	11	91%	8	125	133	94%
6	0	0	0	0%	0	1	1	100%
Total	11	135	146	92.47%	130	2,066	2,196	94%
Sofosbuvir + ledipasvir + ribavirin								
Genotype								
NT	1	13	14	93%	3	26	29	90%
1	55	498	553	90%	0	0	0	0%
2	0	3	3	100%	0	0	0	0%
3	3	13	16	81%	0	7	7	100%
4	21	133	154	86%	0	0	0	0%
5	5	17	22	77%	0	3	3	100%
6	0	2	2	100%	0	0	0	0%
Total	84	661	745	88.72%	3	36	39	92%
Sofosbuvir + daclatasvir								
Genotype								
NT	1	31	32	97%	1,561	14,838	16,399	90%
1	0	14	14	100%	29	473	502	94%
2	1	0	1	0%	0	14	14	100%
3	7	130	137	95%	381	5,584	5,965	94%
4	1	7	8	88%	22	266	288	92%
5	0	1	1	100%	0	19	19	100%
6	0	0	0	0%	0	1	1	100%
Total	10	183	193	95%	1,993	21,195	23,188	91%
Sofosbuvir + daclatasvir + ribavirin								
Genotype								
NT	9	47	56	84%	4	46	50	92%
1	2	70	72	97%	0	3	3	100%
2	0	3	3	100%	0	0	0	0%
3	219	2,504	2,723	92%	0	0	0	0%
4	6	41	47	87%	0	6	6	100%
5	0	4	4	100%	0	0	0	0%
6	0	0	0	0%	0	0	0	0%
Total	236	2,669	2,905	92%	4	55	59	93%

NT, not tested.

Table 4. Cure rates in treatment interruptions.

	Number	SVR12 eligible	SVR12 assessed	Cure rate
24-week regimen				
>4–≤8 weeks	302	256 (84.8%)	36 (14.3%)	28 (77.8%)
>8–≤12 weeks	237	216 (91.1.3%)	53 (24.5%)	50 (94.3%)
>12–≤16 weeks	461	419 (90.9%)	180 (42.9%)	161 (89.4%)
>16–≤20 weeks	252	219 (86.9%)	102 (46.6%)	94 (92.1%)
>20–≤24 weeks	322	255 (79.2%)	123 (48.2%)	114 (92.6%)
12-week regimen				
>4–≤8 weeks	1,999	1,489 (74.5%)	380 (25.5%)	294 (77.4%)
>8–≤12 weeks	1,924	1,537 (79.9%)	531 (34.5%)	446 (83.9%)
Lost to follow-up before the completion of 4 weeks of treatment*	1,106	0 (0%)	0 (0%)	0 (0%)
Overall	**5,497**	**4391**	**1,405 (25.5%)**	**1,187 (84.5%)**

SVR12, sustained virological response at 12 weeks post treatment completion.

presence of prior treatment failure (OR 1.4; 95% CI 1.2–9.3; $p = 0.034$) predicted non-response. On multivariable analysis, using differences of up to 20% on univariable analysis, none of these parameters were significant. Male gender, high APRI or FIB-4, low platelet count, presence of genotype 3, or classification as cirrhosis had no bearing on the achievement of SVR12.

Discussion

This prospective community-based study demonstrated that the decentralized care of HCV in Punjab, India with generic all-oral DAA regimens is safe and effective regardless of genotype or presence of cirrhosis. The SVR12 rate of 91.6% in this cohort of individuals with CHC is comparable with studies from

academic medical centers. The Punjab Model is unique as it is entirely state sponsored, offering free treatment to all without discrimination, using the existing public health infrastructure without any industry sponsorship.[1,9,12]

Global public health initiatives to eliminate HCV

The performance of the Punjab Model is comparable to the programs in other countries.[18–26] In Egypt, by September 2017, a cumulative total of 1.5 million people had received HCV treatment. SOF/RBV therapy for 24 weeks had the lowest SVR12 rate (82.7%); while other therapies were associated with SVR12 rates between 94% and 98%.[18] Under this program, dual therapy (Group 1), with SOF/RBV for 6 months or triple therapy (Group 2) with SOF/peg-IFN-alfa-2a/RBV for 3 months, was prescribed in participants with CHC genotype 4. SVR12 was 94% and in group 2 the SVR12 was 78.7%.[19] The HCV treatment program in Georgia provided free of charge DAA therapy through a partnership with Gilead Sciences Inc. By 31st August 2018, a total of 61, 666 HCV-infected individuals were diagnosed, 48,871 started treatment, 41,734 were SVR12 eligible and SVR12 was assessed in 32,880. In per protocol analysis, the SVR12 rate achieved was 98.2% (32,297/32,880) while 77.4% (32,297/41,734) of patients achieved SVR12 in ITT analysis.[23,24] In Mongolia, more than 6,500 people were treated within 20 months of setting up its HCV treatment program.[19] Similar programs have been announced in Portugal, Rwanda, China, Laos, Ukraine, Brazil, Nigeria, South Africa and Uganda.[19–26] Table S4 shows some of the large scale HCV elimination programs active globally.[7,19,26]

Burden of hepatitis C in Punjab, India

CHC is a public health problem in India[4] and causes an annual mortality of 96,000 people.[6] Out of a total population of 1.2 billion, the population prevalence of HCV infection in India is less than 1%. However, Punjab is a high prevalence state with an estimated prevalence of 3.6%.[2] It is estimated that of 728,000 viremic people with CHC in Punjab, we can avert morbidity and mortality in 240,000 people by means of treating all individuals in the state.[7]

Our strategy in Punjab is aligned with the WHO strategy on viral hepatitis elimination defined as 'a 90% reduction in incidence and a 65% reduction in mortality from existing levels'.[8] In addition to expanding prevention services, achieving these targets requires scaling up of hepatitis treatment, such that 80% of people with chronic HBV and HCV infection are treated.[18,19]

Validation of the treatment algorithm and cure rates

The first stratagem of our algorithm was to minimize testing costs by making genotype and end-treatment response testing optional in patients without cirrhosis. Our results validate this strategy as we have reported high cure rates regardless of the genotype in individuals without cirrhosis. Secondly, decentralized care with low cost generic drugs are both cost-effective for treatment of CHC, and cost-saving from the public health perspective.[5,6,10,27] Thirdly, SOF/LDV is also effective in genotype 3 as has been reported in the Georgia program.[23,24] Finally, an important component of the program was to make treatment accessible at all 25 treatment sites and to involve participant families in combined education programs. The simplified treatment algorithm was core to achieving high cure rates in a decentralized public health setting.

Our analyses demonstrated a cure rate of 91.6%, 67.6% and 91.2%, per protocol, ITT and a modified ITT, respectively. Applying the ITT principles yields an unbiased estimate of the efficacy of the intervention on the primary study outcome but will underestimate the magnitude of the treatment effect that will occur in adherent participants.[28,29] In the case of a modified ITT analysis, a more relevant estimate of the treatment success rate is made.[30,31] Since our interrupted cases had cure rates of 84.5%, it is our estimate that the actual success rate in our program is >90% as it will be grossly inaccurate to assume all interruptions are failures. Therefore, we propose that a real-life study should be analyzed very differently from a randomized controlled trial.

Decentralized services of the Punjab Model

The project ECHO first implemented by Arora *et al.* in the University of New Mexico's ECHO operation for CHC enables PCPs to provide specialized care.[11] More data is available from the Project ECHO Ireland HCV pilot[32] and Show Me ECHO in Missouri.[33,34] The Punjab Model treated 48,088 people with CHC until 31st July 2018 of whom a majority (80.7%) were from rural areas. The Punjab ECHO teleclinic has proven to be lifeline of the MMPHCRF Project, which enabled PCPs to deliver specialized care to people with CHC in a largely underserved rural population of the Punjab.

Treatment interruption and strategies to reduce it

Our data on people who interrupted treatment provided interesting results. In both the 12-week and 24-week regimens, we achieved cure rates of about 78% in participants who received at least 4 weeks of therapy (Table 4). We identified a few barriers to treatment completion. Firstly, our SVR12 capture rate was about 81.3%, which implies approximately 19% of patients did not return for SVR12 testing despite completing therapy as many of them deemed it unnecessary. Secondly, many cases of interruptions were because people reported late for the prescription refill due to social reasons (attending a marriage, funeral, *etc.*). Lastly, some people had lower motivation levels and might have assumed that a treatment delay did not impair response. Strategies to reduce treatment interruptions are better public education strategies, involvement of the family to monitor therapy, and regular audits of the treatment sites to ensure timely reporting.

We had few protocol deviations in the implementation of the algorithm, which did not amount to a major shift in our results.

Limitations of the program

We have faced several hurdles, which might have affected our results. Firstly, with the limited resources at our disposal in the public health infrastructure, the data entry in the initial phase was not a focus of the program and missing data impaired our audit in the first 6 months. The SVR12 capture rate also improved with time. We did not collect data on the cause of death in our participants, either liver- related or non-liver related. The SVR12 data loss to the tune of 19% might have biased our results, as there may be differences in the success of people who reported for the test and those who did not.

National viral hepatitis control programme: the way forward

The Punjab Model has demonstrated the efficacy of decentralized care in CHC and has paved the way for the National Viral Hepatitis Programme (NVHCP), which also include hepatitis A,

B and E in addition to hepatitis C.[35] Three protocols devised by the Technical Resource Group, were launched on 28th July 2018 by the NVHCP – i) The standard National Guidelines for the Diagnosis and Management of Viral hepatitis aid PCPs on participant assessment, treatment, and quality service delivery, ii) The Operational Guidelines provide a framework of the organizational structure of the NVHCP and the National Laboratory Guidelines for Viral Hepatitis Testing provide practical guidance and algorithms for viral hepatitis testing. The ECHO model will be used to mentor and support PCPs as part of the national program.[11,34] The launch of NVHCP in India will ultimately achieve the WHO target of viral hepatitits elimination, *i.e.*, a 90% reduction in incidence and a 65% reduction in mortality from existing levels.[8] Under the NVHCP, SOF/DCV has been retained as the treatment for all patients without cirrhosis and SOF/VEL for those with compensated cirrhosis, with additional RBV recommended in patients with decompensated cirrhosis. Using a cost effectiveness predictive Markov model, we have shown that at current prices, the use of SOF/VEL only for those with cirrhosis is a dominant intervention as it does not only increase the health gains but significantly decreases the costs as well. For patients without cirrhosis the use of the pan-genotypic SOF/DCV is cost-effective.[27]

Conclusions

This study highlights the effectiveness of a public health strategy using decentralized care to empower primary healthcare providers to combat and eliminate HCV from the state of Punjab in India. The results demonstrated cure rates of nearly 92% *regardless of* genotypes, degree of liver fibrosis or high-risk subgroups. The feasibility, safety and efficacy of decentralized care and treatment of CHC demonstrated in the Punjab Model, have led to the beginning of the NVHCP in India.

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Conflict of interest

None of the authors has any conflict of interest or financial disclosure to declare.

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

Authors' contributions

RKD devised the treatment algorithm and is the Technical Adviser for the HCV Elimination Program in Punjab. GSG is the State Administrative Officer for the MMPHCRF. RKD, GSG and MP were involved in the analysis of data, manuscript preparation and editing. RKD, GSG, MP, ST, AD, SR, SS and AR are involved in the Extension for Community Healthcare Outcomes (ECHO) clinics and primary care provider training. SA was the chief collaborator for the 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.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2019.07.006.

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