Directly observed therapy of sofosbuvir/ribavirin +/- peginterferon with minimal monitoring for the treatment of chronic hepatitis C in people with a history of drug use in Chennai, India (C-DOT)

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Summary
We assessed the feasibility of field-based directly observed therapy (DOT) with minimal monitoring to deliver HCV treatment to people with a history of drug use in Chennai, India. Fifty participants were randomized 1:1 to sofosbuvir+peginterferon alfa 2a+ribavirin (SOF+PR) for 12 weeks (Arm 1) vs sofosbuvir+ribavirin (SOF+R) for 24 weeks (Arm 2). SOF+R was delivered daily at participant chosen venues and weekly peginterferon injections at the study clinic. HCV RNA testing was performed to confirm active HCV infection and sustained virologic response 12 weeks after treatment completion (SVR12). No baseline genotyping or on-treatment viral loads were performed. Median age was 46 years. All were male and 20% had significant fibrosis/cirrhosis. All self-reported history of injection drug use, 18% recent non-injection drug use and 38% alcohol dependence. Six discontinued treatment (88% completed treatment in each arm). Of 22 who completed SOF+PR, all achieved SVR12 (22/25=88%); 15 of 22 who completed SOF+R achieved SVR12 (15/25=60%; P=.05). Among those completing SOF+R, SVR12 was significantly less common in participants reporting ongoing substance use (36% vs 100%) and missed doses. Active substance use and missed doses did not impact SVR with SOF+PR. Field-based DOT of HCV therapy without real-time HCV RNA monitoring was feasible; however, achieving 100% adherence was challenging. SOF+PR appeared superior to SOF+R in achieving SVR12, even when doses were missed with no discontinuations due to side effects. Further exploration of short duration treatment with peginterferon plus direct-acting antivirals is warranted.
1 | INTRODUCTION

Of the approximately 70 million persons chronically infected with hepatitis C virus (HCV) globally, approximately 90% reside in low- and middle-income countries (LMICs). With the advent of direct-acting antivirals (DAA), HCV infection is curable within 12 weeks of all-oral, nontoxic agents. With these remarkable developments, the World Health Organization released the first HCV global elimination targets for 2030. The goal is to achieve 90% reduction in new cases and 65% reduction in HCV-associated mortality. Achieving these ambitious goals will require massive treatment scale-up in most countries where only about 5% of persons with chronic HCV have been diagnosed and fewer than 2% treated. Elimination programmes in some settings have been facilitated by licensing and preferential pricing agreements and production of generic versions of new DAA, which have brought costs down to <500 USD/treatment course.

However, as elimination programmes shift towards HCV treatment delivery, they must take into consideration factors other than provision of free medications. First, while costs associated with medications have decreased substantially in some places, monitoring costs remain unchanged (for example, in India it costs ~80 USD for HCV RNA and ~90 USD for HCV genotype testing). Moreover, infrastructure for viral load and genotyping is not available in many LMICs. Second, elimination strategies will need to target all persons infected including drug users and populations who bear a disproportionate HCV burden and may have adherence challenges.

Directly observed therapy (DOT), the standard of care for TB, has been demonstrated to improve treatment completion and response rates for TB. Using modified DOT, HCV treatment has been successfully delivered in opioid treatment programmes and prison settings consistently demonstrating improvements in adherence and cure rates. These trials, however, were conducted in the pre-DAA era when regimens were more complicated (twice daily dosing and weekly injections). Further, none were conducted in an LMIC. Key barriers to DOT consistently identified are transportation and patient-level inconvenience, which can lead to missed doses and dropouts, barriers which may be amplified in LMICs, where many patients are daily wage earners.

In India, it is estimated that there are approximately 6.3 million viremic HCV-infected persons. India is also home to the largest number of opioid users globally (~3 million) with HCV prevalence of ~37% among people who inject drugs (PWID). Generic sofosbuvir was licensed in India in 2015, and 11 generic forms are available at a maximum retail price of 300 USD/28 tablets. However, delivery challenges remain. The goal of this trial was to leverage a rich history of DOT in India (cornerstone of the Indian National Tuberculosis Programme) and the dearth of molecular testing to assess the feasibility of field-based DOT with minimal monitoring to deliver HCV therapy to people who use drugs in Chennai, India. We directly compared the safety and efficacy of the only two pan-genotypic HCV regimens available in India in 2015.

2 | MATERIALS AND METHODS

2.1 Study setting and population

This study operated from the YR Gaitonde Centre for Substance Abuse Related Research (YRGCSAR) in North Chennai, India. YRGCSAR was established in 2004 to explore the natural history of drug abuse and incidence and prevalence of associated blood-borne pathogens among PWID in Chennai. Via this centre, we have previously demonstrated high HCV burden (primarily genotype 3) and liver disease among PWID in Chennai. The site, which is approximately 1000 square feet, is staffed by one full-time clinician, one part-time clinician, two nurses, a site manager, a phlebotomist and three outreach workers, has provided testing and/or clinical services to >2000 PWID in Chennai since inception and is currently following a cohort of ~1000. Blood specimens are drawn at the centre and transported to a central laboratory for testing.

Participants were recruited for this trial between September 2015 and March 2016 from an ongoing cohort of PWID. The Chennai HIV, HCV and Eeral Study (CHHEERS) included 1042 persons recruited through community outreach to characterize the epidemiology of liver disease among HCV-infected PWID in Chennai. Participants had to be ≥18 years old, provide written informed consent, report a history of drug injection in the prior 5 years and no intention of migrating for 2 years. At enrolment, 355 participants (34.1%) were HCV antibody positive: (280) 78.9% were chronically infected and 11 (3.9%) reported prior HCV treatment.

In order to be eligible for the trial, subjects had to meet the following criteria, most of which are related to eligibility for peginterferon/ribavirin-based therapy: (i) willing/able to provide written informed consent, (ii) age ≥18 years, (iii) documented evidence of active HCV infection (HCV RNA positive), (iv) resident of Chennai, (v) HCV treatment naïve; and (vi) if co-infected with HIV, have a CD4>350 cells/mm³ and either ART naïve; or if on ART, participant had to be on a tenofovir-containing regimen. Subjects also had to have the following laboratory parameters at screening: (i) alanine aminotransferase (ALT) ≤10×the upper limit of normal (ULN), (ii) aspartate aminotransferase (AST) ≤10×ULN, (iii) haemoglobin ≥12 g/dL for male and 11 g/dL for female subjects, (iv) international normalized ratio (INR) ≤1.5×ULN.
unless subject has known haemophilia or was stable on an antioco-
gulant regimen affecting INR, (v) albumin ≥3 g/dL, (vi) direct bilirubin
≤1.5×ULN, (vii) creatinine clearance ≥60 mL/min as calculated by the
Cockroft-Gault Equation, (viii) alpha fetoprotein < 50 ng/mL, (ix) abso-
lute neutrophil count (ANC) ≥1500/μL, (x) platelets ≥90 000/μL, and
(xi) thyroid stimulating hormone (TSH) ≤ULN.

Participants were excluded if they satisfied any of the following
criteria: (i) women who were pregnant or nursing, (ii) male participants
with pregnant female partners, (iii) hepatic decompensation (Childs
Pugh Class B and C), (iv) co-infection with hepatitis B (HBsAg posi-
tive), (v) using medications contraindicated with peginterferon/ribavi-
rin therapy, and (vi) known contraindication to either peginterferon or
ribavirin. All participants of reproductive potential were counselled to
use at least two forms of contraception for 6 months after the com-
pletion of treatment.

2.2 | Study design

C-DOT was a randomized, open-label trial of sofosbuvir+peginterferon
alfa 2a+ ribavirin (SOF+PR) for 12 weeks (Arm 1) vs sofosbuvir+ riba-
virin (SOF+R) for 24 weeks (Arm 2). Participants were randomized
at a 1:1 allocation ratio using blocked randomization with varying
block sizes. Sofosbuvir (Spegra, Emcure Pharmaceuticals Ltd., Pune,
Maharashtra, India) was administered at 400 mg by mouth once
daily. Ribavirin was sourced from Unison Pharmaceuticals (Univirin,
Ahmedabad, Gujarat, India); based on low body weight, all partici-
pants took ribavirin 800 mg (four 200 mg tablets) by mouth once
daily. Peginterferon alfa-2a (Taspiance, Emcure Pharmaceuticals Ltd.)
was dosed at 180 μg by subcutaneous injection once weekly. All so-
osbuvir and ribavirin doses were delivered daily to participants at
venues of their choosing by three outreach workers. Participants in the
SOF+PR arm were also required to visit the study clinic once
weekly to receive their peginterferon injection. Prior to delivering
medication in the field, outreach workers had to record participant
biometric data (fingerprint) daily, providing confirmation that the cor-
rect participant received treatment. Additionally, outreach workers
provided a small meal.

HCV RNA testing was performed at screening (to document active
HCV infection) and 12 weeks after the end of treatment to determine
sustained virologic response (SVR12) status. As the treatment regime
was pan-genotypic, HCV genotype was not determined prior to treat-
ment, and as HCV resistance was not expected, HCV RNA was not
monitored during treatment. While on treatment, participants were
asked to visit the clinic every 4 weeks and then 12 weeks after end
of treatment to assess SVR12. At each visit, there was a physical ex-
amination including an assessment for adverse events and concomi-
tant medications, and a survey collecting information on quality of life,
depressive symptoms, alcohol and drug use, and adherence barriers.
Safety monitoring comprising a complete blood count was performed
every 4 weeks in both arms; additionally, a hepatic function panel was
performed at week 12 for participants in the SOF+R arm. HCV geno-
typing and end-of-treatment HCV RNA testing were conducted retro-
spectively on stored specimens.

2.3 | Study endpoints and statistical analysis

The primary endpoint was treatment completion defined as com-
pleting 12 (Arm 1) or 24 (Arm 2) weeks of therapy and attending the
SVR12 visit. Secondary endpoints included (i) SVR12 defined as HCV
RNA < lower limit of quantification (LLOQ) 12 weeks after the end of
therapy, (ii) incidence of serious adverse events related to therapy
defined as either Grade 3, 4 or 5 events as per the Division of AIDS
Table for Grading the Severity of Adult and Pediatric Adverse Events,
Version 2.028, and (iii) change in insulin resistance measured by
HOMA-IR. Changes in HOMA-IR were based on fasting laboratory as-
sessments at baseline and SVR12 visit. We also captured information
on quality of life using the EQ-5D which includes a visual analogue
scale (VAS) of self-rated health quality from 0 (worst health state) to
100 (best health state).29

An intent-to-treat (ITT) (missing=failure) approach was used for
the primary analysis. Fisher’s exact tests were used to compare cat-
egorical outcomes and Mann-Whitney tests to compare continuous
outcomes. Secondary analyses considered a per-protocol (PP) ap-
proach and explored factors within each arm associated with SVR12
in the subset that completed treatment (n=44). Factors of interest
included age, pretreatment HCV RNA level, HCV genotype, BMI, liver
stiffness and ongoing substance use (drug and alcohol use). All anal-
yses were conducted using Stata Version 13.1 (College Station, TX,
USA).

2.4 | Ethical clearances

This study was approved by the Johns Hopkins Medicine and
YRG CARE institutional review boards, and all participants provided
written informed consent.

3 | RESULTS

We screened 98 participants, of whom, 61 were eligible and 50 en-
rolled (Figure 1); Common reasons for exclusion were no active HCV
infection (n=24), HIV-positive status with CD4<350 or not on a
tenofovir-containing regimen (n=4) and creatinine clearance<60 mL/
min (n=4). The median age was 46 (interquartile range, 42-49). All
were male and the majority (54%) had less than high school educa-
tion, with a median monthly income of 90 USD/month (Table 1); 24
(48%) were daily wage earners. Two participants were co-infected
with HIV; one was on ART. All participants self-reported that they had
injected drugs in the past—one participant self-reported that he was
actively injecting at entry into the trial. Eighteen per cent reported
active noninjection drug use, and 38% had an AUDIT score consist-
ent with dependence. Based on elastography (Fibroscan), the majority
(58%) had no/mild liver stiffness (<8.5 kPa), 22% had moderate stiff-
ness (8.5-12.3 kPa) and 20% severe stiffness/cirrhosis (>12.3 kPa).
The median AST, ALT and FIB-4 measurements were 49 U/L, 42 U/L
and 2.2, respectively. The median HCV RNA level was 6.4 log₁₀ IU/mL.
Post-treatment testing revealed that the majority of participants were
infected with genotype 3 (n=42, 84%) followed by genotype 1 (n=7, 14%).

3.1 | Outcomes

3.1.1 | Primary outcome

Among the 50 participants, six discontinued treatment (three per arm) for a treatment completion rate of 88% in each arm (Table 2). Of the six participants who discontinued treatment, three discontinued in the first week, and one each in weeks 4, 5 and 6 (Table 3). Despite these discontinuations, we obtained a specimen to examine SVR12 in one participant who received 23 days of SOF+PR before stopping. Reasons for discontinuation are in Figure 1.

3.1.2 | Secondary outcomes

Of the 22 who completed SOF+PR, all achieved SVR12 (ITT: 22/25=88% [PP: 22/22=100%]) but only 15 of the 22 who completed SOF+R achieved SVR (15/25=60% [PP: 15/22=68%]; P-value for ITT=0.05). Of the treatment failures with SOF+R, three had genotype 1a and four had genotype 3a infection; five of the seven had HCV RNA<LLOQ at the end of treatment. The Core/E1 regions were sequenced on the 12-week post-treatment specimens, and the genotype was identical to the baseline in all specimens; however, more detailed phylogenetic analyses were not conducted to distinguish relapse and re-infection. There were no treatment failures on SOF+PR, but of those that did not complete SOF+PR, two had genotype 1a and one had genotype 3a infection. For the one participant treated with SOF+PR from which we obtained a postdiscontinuation sample, HCV RNA was 6.5 IU/mL. No serious adverse events occurred; the frequency of adverse events was comparable across arms (Table S1). The median change in HOMA-IR in the SOF+PR arm and SOF+R arms were 1.2 and 0.2, respectively (P=.30).

3.1.3 | Exploratory outcomes

Of the 44 who completed treatment, the median number of missed doses of oral medication was two in SOF+PR (range: 0-18) and six in SOF+R (range: 0-39). No peginterferon injections were missed for those who completed treatment.

3.2 | Factors associated with treatment completion and SVR12

We further assessed whether treatment completion and SVR12 among those who completed treatment varied within arm by pretreatment characteristics. Among those who completed treatment in the SOF+R arm, SVR12 was significantly lower among those with missed doses, ongoing substance use (drugs or alcohol; Figure 2) genotype 1a, lower HCV RNA and lower BMI. None of these factors including missed doses or active substance use affected SVR12 in the SOF+PR arm—all subsets achieved SVR12.

4 | DISCUSSION

This study is among the first to evaluate directly observed delivery of DAA-based therapy in populations with a history of substance use in an LMIC setting. Our findings provide some insight into the realization of the global HCV elimination goals. First, these data support that substance use populations in a LMIC setting can be cured of HCV using a field-based DOT approach. Second, the data support that therapeutic monitoring before and during can be dramatically simplified including the removal of genotype determination. Third, HCV therapy...
can be delivered in LMICs with minimal infrastructure and staffing. Treatment delivery and monitoring can potentially be even further simplified with newer ribavirin-free pan-genotypic regimens and advances in diagnostics (e.g, Cepheid GeneXpert HCV RNA testing).

Fourth, there may be a benefit of retaining peginterferon in treatment of populations where injections are perceived favourably and adherence may be challenging because: (i) it can shorten the duration of

**TABLE 1** Description of study population at baseline by treatment arm

<table>
<thead>
<tr>
<th></th>
<th>Arm 1 (N=25)</th>
<th>Arm 2 (N=25)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Median age (years), IQR</strong></td>
<td>46 41-50</td>
<td>46 44-47</td>
</tr>
<tr>
<td><strong>Male sex, n(%)</strong></td>
<td>25 100</td>
<td>25 100</td>
</tr>
<tr>
<td><strong>Educational attainment, n(%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None or primary</td>
<td>11 44.0</td>
<td>12 48.0</td>
</tr>
<tr>
<td>Secondary</td>
<td>3 12.0</td>
<td>1 4.0</td>
</tr>
<tr>
<td>High school or greater</td>
<td>11 44.0</td>
<td>12 48.0</td>
</tr>
<tr>
<td><strong>Median monthly income (US dollars), IQR</strong></td>
<td>90 68–120</td>
<td>90 72–150</td>
</tr>
<tr>
<td><strong>Employment status, n(%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Daily wages</td>
<td>13 52.0</td>
<td>11 44.0</td>
</tr>
<tr>
<td>Weekly/monthly wages</td>
<td>10 40.0</td>
<td>13 52.0</td>
</tr>
<tr>
<td>Unemployed</td>
<td>2 8.0</td>
<td>1 4.0</td>
</tr>
<tr>
<td><strong>Median age at initiation of drug injection (years), IQR</strong></td>
<td>21 18-30</td>
<td>24 20-30</td>
</tr>
<tr>
<td><strong>Lifetime injection drug use, n(%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heroin</td>
<td>24 96.0</td>
<td>25 100.0</td>
</tr>
<tr>
<td>Sedatives</td>
<td>19 76.0</td>
<td>16 64.0</td>
</tr>
<tr>
<td>Other opioids including buprenorphine</td>
<td>24 76.0</td>
<td>23 64.0</td>
</tr>
<tr>
<td><strong>Injection drug use in prior 6 months, n(%)</strong></td>
<td>1 4.0</td>
<td>0 0</td>
</tr>
<tr>
<td>Noninjection drug use in prior 6 months, n(%)</td>
<td>7 28.0</td>
<td>2 8.0</td>
</tr>
<tr>
<td>Marijuana use in prior 6 months, n(%)</td>
<td>4 16.0</td>
<td>1 4.0</td>
</tr>
<tr>
<td><strong>Alcohol use in prior 6 months (drinks/day), n(%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>14 56.0</td>
<td>13 52.0</td>
</tr>
<tr>
<td>1-4 drinks/day</td>
<td>9 36.0</td>
<td>9 36.0</td>
</tr>
<tr>
<td>&gt;5 drinks per day</td>
<td>2 8.0</td>
<td>3 12.0</td>
</tr>
<tr>
<td><strong>AUDIT category, n(%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No/mild alcohol use</td>
<td>14 56.0</td>
<td>14 56.0</td>
</tr>
<tr>
<td>Harmful/hazardous alcohol use</td>
<td>1 4.0</td>
<td>2 8.0</td>
</tr>
<tr>
<td>Alcohol dependence</td>
<td>10 40.0</td>
<td>9 36.0</td>
</tr>
<tr>
<td>HIV status, n(%)</td>
<td>0 0</td>
<td>2 8.0</td>
</tr>
<tr>
<td><strong>HCV genotype, n(%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3a</td>
<td>22 88.0</td>
<td>20 80.0</td>
</tr>
<tr>
<td>1a</td>
<td>2 8.0</td>
<td>5 20.0</td>
</tr>
<tr>
<td>6n</td>
<td>1 4.0</td>
<td>0 0</td>
</tr>
<tr>
<td><strong>Median log_{10} HCV RNA (IU/mL), IQR</strong></td>
<td>6.5 6.1-6.6</td>
<td>6.1 5.5-6.7</td>
</tr>
<tr>
<td><strong>Liver stiffness category, n(%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;8.5 kPa</td>
<td>15 60.0</td>
<td>14 56.0</td>
</tr>
<tr>
<td>8.5-12.3 kPa</td>
<td>5 20.0</td>
<td>6 24.0</td>
</tr>
<tr>
<td>&gt;12.3 kPa</td>
<td>5 20.0</td>
<td>5 20.0</td>
</tr>
</tbody>
</table>

Data are presented as n (column %) or median (interquartile range [IQR]).

**TABLE 1** (Continued)

<table>
<thead>
<tr>
<th></th>
<th>Arm 1 (N=25)</th>
<th>Arm 2 (N=25)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Median total bilirubin (mg/dL), IQR</strong></td>
<td>0.8 0.7-0.9</td>
<td>0.7 0.6-1.0</td>
</tr>
<tr>
<td><strong>Median glucose (mg/dL), IQR</strong></td>
<td>84 81-104</td>
<td>90 85-107</td>
</tr>
<tr>
<td><strong>Median insulin (μU/mL), IQR</strong></td>
<td>7 3-13</td>
<td>10 6-22</td>
</tr>
<tr>
<td><strong>Median HOMA-IR, IQR</strong></td>
<td>1.3 0.7-3.4</td>
<td>2.4 1.1-5.6</td>
</tr>
<tr>
<td><strong>Median weight (kg), IQR</strong></td>
<td>55 49-62</td>
<td>65 54-70</td>
</tr>
<tr>
<td><strong>Depressive symptoms, n(%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>21 84.0</td>
<td>19 76.0</td>
</tr>
<tr>
<td>Mild</td>
<td>3 12.0</td>
<td>4 16.0</td>
</tr>
<tr>
<td>Moderate/severe</td>
<td>1 4.0</td>
<td>2 8.0</td>
</tr>
<tr>
<td><strong>Quality of life index, n(%)</strong></td>
<td>1.0 0.82-1.0</td>
<td>1.0 0.83-1.0</td>
</tr>
<tr>
<td><strong>Mobility problems</strong></td>
<td>3 12.0</td>
<td>1 4.0</td>
</tr>
<tr>
<td><strong>Self-care problems</strong></td>
<td>4 16.0</td>
<td>1 4.0</td>
</tr>
<tr>
<td><strong>Usual activities problems</strong></td>
<td>3 12.0</td>
<td>2 8.0</td>
</tr>
<tr>
<td><strong>Pain</strong></td>
<td>10 40.0</td>
<td>7 28.0</td>
</tr>
<tr>
<td><strong>Anxiety or depression</strong></td>
<td>4 16.0</td>
<td>5 20.0</td>
</tr>
<tr>
<td><strong>Median self-rated health state VAS, n(%)</strong></td>
<td>85 80-90</td>
<td>90 80-90</td>
</tr>
</tbody>
</table>

Data are presented as n (column %) or median (interquartile range [IQR]).

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treatment and (ii) the long half-life of peginterferon can be forgiving of occasional missed doses.

Treatment completion rates were high and comparable in both groups in this trial, but SOF+R among those who completed treatment was significantly higher in those who received SOF+PR (100%) compared to those that received SOF+R (68%). Both SVR12 rates are within the range of what has been observed in prior studies of these combinations among genotype 3 populations. For example, in BOSON, a large randomized trial that compared SOF+R for 24 weeks vs SOF+PR for 12 weeks in genotype 3 patients, SVR12 rates were 84% and 93%, respectively.\(^3\) In VALENCE, an SVR12 of 85% was observed with 24 weeks of SOF+R.\(^2\) SVR12 rates were lower in HCV-\(^3\)TARGET, a real-world clinical cohort, which reported SVR12 of 60% and 84%, for SOF+R and SOF+PR, respectively.\(^2\) There have also been several reports evaluating sofosbuvir in India, both clinical trials and observational studies among patients with predominantly genotype 3 infection, with SVR12 rates upwards of 90%.\(^34\) None of these studies in or outside India focused on persons with a history of substance use.

Interestingly and in contrast what has been observed previously,\(^3\) we found low SVR12 among those with genotype 1 infection; only one of four genotype 1 patients who completed treatment with SOF+R achieved SVR12. However, the three patients who failed had characteristics previously associated with poor treatment response. One was actively using drugs and missed 32 doses and two had high pretreatment viral loads and cirrhosis (liver stiffness>30 kPa). These lower response rates are consistent with the NIH SPARE trial, which included genotype 1 infected patients with unfavourable treatment predictors, and observed efficacy of 24 weeks of SOF+R to be 68% in those receiving weight-based ribavirin and 48% in those receiving low-dose ribavirin.\(^3\)

Collectively, these data speak to the possibility of achieving cure in substance users using populations using DOT, but also highlight challenges. On the one hand, the field-based DOT strategy that we used may be particularly suited for LMIC settings where human resources are abundant and salaries relatively low (the monthly salary of an outreach worker is ~250 USD). For example, if one field worker could provide DOT to 20 patients at a time for ~12 weeks, the additional treatment cost would only be 38 USD/individual. On the other hand, we did encounter challenges with this approach. In December 2015, Chennai experienced the worst flooding in over a century, receiving 16 inches of rain in 2 days making it impossible to reach participants for 2-3 days. The floods impacted 31 participants who were already on treatment, explaining 36% of all missed doses experienced. Additional

<table>
<thead>
<tr>
<th>Arm 1 (N=25)</th>
<th>Arm 2 (N=25)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment completion, n(%)</td>
<td>22 88.0</td>
<td>22 88.0</td>
</tr>
<tr>
<td>Secondary outcomes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sustained virologic response(^a), n(%)</td>
<td>22 88.0</td>
<td>15 60.0</td>
</tr>
<tr>
<td>Median number of serious adverse events, IQR</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Median change in insulin resistance (HOMA-IR), IQR</td>
<td>1.2, -0.1, 9.1</td>
<td>0.2, -1.3, 6.0</td>
</tr>
<tr>
<td>Exploratory outcomes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Percentage completed doses, n(%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-30%</td>
<td>3 12.0</td>
<td>3 12.0</td>
</tr>
<tr>
<td>75-90%</td>
<td>3 12.0</td>
<td>2 8.0</td>
</tr>
<tr>
<td>&gt;90-95%</td>
<td>2 8.0</td>
<td>4 16.0</td>
</tr>
<tr>
<td>&gt;95%-100%</td>
<td>17 68.0</td>
<td>16 64.0</td>
</tr>
<tr>
<td>Percentage observed doses received(^b), n(%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>70-90%</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>&gt;90-95%</td>
<td>4 16.0</td>
<td>3 12.0</td>
</tr>
<tr>
<td>&gt;95-100%</td>
<td>21 84.0</td>
<td>19 76.0</td>
</tr>
<tr>
<td>Median change in self-rated health state VAS(^c), IQR</td>
<td>0, -5, 10</td>
<td>5, -10, 8</td>
</tr>
</tbody>
</table>

\(\text{VAS, visual analogue scale with range from 0 (worst health state) to 100 (best health state).}\)
\(\text{\(^a\)Intent-to-treat approach (missing=no sustained virologic response).}\)
\(\text{\(^b\)Out of completed doses.}\)
\(\text{\(^c\)Measured using the EQ 5D-3L instrument.}\)
### Table 3  Characteristics of participants who either discontinued or failed treatment

<table>
<thead>
<tr>
<th>Arm</th>
<th>Week stopped</th>
<th>Age</th>
<th>Liver stiffness (kPa)</th>
<th>HIV status</th>
<th>Substance use in prior month</th>
<th>AUDIT score</th>
<th>Missed doses</th>
<th>Entry genotype</th>
<th>Entry HCV RNA in IU/mL</th>
<th>EOT HCV RNA in c/mL</th>
<th>Genotype at 12-week post-treatment visit</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Discontinued</td>
</tr>
<tr>
<td>Discontinued</td>
<td>1</td>
<td>SOF+PR</td>
<td>1</td>
<td>44</td>
<td>6.8</td>
<td>Negative</td>
<td>Yes</td>
<td>18</td>
<td>82</td>
<td>1a</td>
<td>1 457 217</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>SOF+PR</td>
<td>4</td>
<td>45</td>
<td>20.9</td>
<td>Negative</td>
<td>No</td>
<td>0</td>
<td>60</td>
<td>1a</td>
<td>2 866 567</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>SOF+PR</td>
<td>1</td>
<td>47</td>
<td>28</td>
<td>Negative</td>
<td>No</td>
<td>0</td>
<td>81</td>
<td>3a</td>
<td>3 069 335</td>
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<tr>
<td></td>
<td>4</td>
<td>SOF+R</td>
<td>1</td>
<td>41</td>
<td>4.4</td>
<td>Negative</td>
<td>No</td>
<td>0</td>
<td>167</td>
<td>1a</td>
<td>8 422 551</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>SOF+R</td>
<td>6</td>
<td>54</td>
<td>14.1</td>
<td>Negative</td>
<td>No</td>
<td>0</td>
<td>136</td>
<td>3a</td>
<td>1 321 974</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>SOF+R</td>
<td>5</td>
<td>44</td>
<td>6.7</td>
<td>Negative</td>
<td>Yes</td>
<td>18</td>
<td>151</td>
<td>3a</td>
<td>7 503 580</td>
</tr>
<tr>
<td>Failed treatment</td>
<td>1</td>
<td>SOF+R</td>
<td>27</td>
<td>6.8</td>
<td>Negative</td>
<td>Yes</td>
<td>20</td>
<td>39</td>
<td>1a</td>
<td>199 896</td>
<td>35</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>SOF+R</td>
<td>59</td>
<td>35.8</td>
<td>Negative</td>
<td>Yes</td>
<td>8</td>
<td>4</td>
<td>1a</td>
<td>6 398 338</td>
<td>Undetectable</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>SOF+R</td>
<td>53</td>
<td>36.8</td>
<td>Negative</td>
<td>Yes</td>
<td>29</td>
<td>3</td>
<td>1a</td>
<td>2 257 839</td>
<td>5458</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>SOF+R</td>
<td>41</td>
<td>8.4</td>
<td>Negative</td>
<td>Yes</td>
<td>34</td>
<td>16</td>
<td>3a</td>
<td>1 194 654</td>
<td>Undetectable</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>SOF+R</td>
<td>45</td>
<td>4</td>
<td>Negative</td>
<td>Yes</td>
<td>15</td>
<td>2</td>
<td>3a</td>
<td>193 013</td>
<td>Undetectable</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>SOF+R</td>
<td>45</td>
<td>7.8</td>
<td>Negative</td>
<td>Yes</td>
<td>21</td>
<td>12</td>
<td>3a</td>
<td>68 966</td>
<td>Undetectable</td>
</tr>
<tr>
<td></td>
<td>7</td>
<td>SOF+R</td>
<td>46</td>
<td>11.3</td>
<td>Positive</td>
<td>Yes</td>
<td>5</td>
<td>1</td>
<td>3a</td>
<td>383 733</td>
<td>Undetectable</td>
</tr>
</tbody>
</table>

<sup>a</sup>Measured 8 weeks after last dose.
challenges ensued in April and May for the 16 participants who were still receiving treatment. Extreme heat (temperatures >106 degrees Fahrenheit/42 degrees Celsius) impacted the ease with which contact could be made between participants and field workers. Beyond these weather-related challenges, the primary reasons for missing meetings with DOT field workers were family emergencies and unanticipated travel. A limitation of our study is that we did not have a comparison group that did not receive DOT and it is possible that such intensive intervention was not necessary for all. Subsequent studies among persons with a history of substance use should consider alternatives such as mobile phone-based DOT, clinic-based DOT (with/without opioid agonist treatment) or should compare DOT with standard 4-week prescriptions to determine the optimal strategy.

In this study, as we used pan-genotypic regimens with demonstrated efficacy and no stopping rules, we opted for a minimal number of monitoring tests. No genotyping was performed prior to treatment initiation and neither on-treatment nor end-of-treatment HCV RNA testing was performed. The only safety monitoring included a monthly complete blood count. Despite this, our treatment outcomes were comparable to other reports and, even using agents historically considered to be "highly toxic," no participant experienced an SAE. It can be argued that some on-treatment monitoring, in particular, the 4-week HCV RNA level, may be an important adherence intervention in and of itself. In our study, the absence of this measurement likely had little impact because we maintained daily contact with participants. While we cannot rule out the value of the 4-week HCV RNA level in populations not receiving DOT, we feel these data support WHO guidance that substantial reductions in cost can be achieved by reducing monitoring tests. Further reductions (e.g. less frequent complete blood count) may be possible with newer pan-genotypic ribavirin-free combinations.

Beyond molecular monitoring, we delivered treatment out of a community clinic, chosen because of its convenient location for participants, with minimal infrastructure including a small phlebotomy unit, clinical examination room and liver elastography (available through research funds). Clinicians were trained to treat hepatitis C with oversight from clinicians at the Johns Hopkins Viral Hepatitis Center. Support staff included two nurses and three outreach workers (who were also tracking patients in an ongoing cohort); all were also trained to provide counselling. As LMICs begin to implement elimination programmes, scaling up these types of community clinics to provide HCV treatment may prove critical. Global experience with delivering HIV treatment in similar settings has demonstrated that accessibility is a key facilitator. For HCV, infrastructure required is even more minimal than what is needed for HIV and would include linkage to laboratory that can perform simple tests (e.g. FIB-4), a rapid HCV RNA measure (e.g. Cepheid GenXpert), a clinician (nurse or doctor) and support staff (e.g. outreach workers).

We were concerned about the acceptability of peginterferon particularly because prior observational studies in India have suggested patient preference for SOF+R for 24 weeks over SOF+PR for 12 weeks due to inaccessibility of facilities providing peginterferon, financial constraints (peginterferon is expensive) and fear of side effects. However, in this trial, no participants refused participation because of the potential of being randomized to receive peginterferon. In fact, some participants were disappointed not to have been randomized to receive “injections”. In India, particularly in lower-income groups, there is widespread belief that injections are more potent than pills. The annual per capita number of injections ranges from 3 to 6, one of the highest in the world.

Moreover, all those who completed therapy with SOF+PR achieved SVR12. Contrastingly, the efficacy of SOF+R appeared to have been affected by ongoing substance use and nonadherence. While few
persons in our sample reported ongoing drug injection, 50% reported some substance use in the 30 days prior to initiating treatment of whom 76% had evidence of alcohol dependence. Active substance use was associated with significantly lower response to SOF+R among those who completed treatment (36% vs 100%, P=0.03). Moreover, SVR12 for SOF+R was 75% in those who missed fewer than 5% of doses and it was only 50% in those who missed >10% of doses. No such differences were observed in the SOF+PR arm. Interestingly, a recent study among PWID reported SVR12 of 92% among 32 patients randomized to 4 weeks of Ledipasvir+SOF+PR vs 77% in 32 patients randomized to 4 weeks of Ledipasvir+SOF+R in patients infected with genotype 1, 2 or 3.43 These data lend further support to a DOT-based approach and provide rationale for further investigation into the utility of combining PR with pan-genotypic regimens such as SOF+daclatasvir (SOF+DAC) or SOF+velpatasvir (SOF+VEL) for short durations (e.g. 4 or 6 weeks) in substance using populations (both alcohol and drug use) and others with potentially poor adherence.

Several limitations must be acknowledged. The sample size is small and precluded additional subgroup comparisons. Even those that were conducted should be considered exploratory. We conducted this trial prior to the availability of daclatasvir and velpatasvir in India—these combinations (SOF+DAC or SOF+VEL) are superior to SOF+R with respect to SVR and it possible that these regimens could also be more forgiving of missed doses. However, the potential to shorten duration dramatically (4 weeks) by including PEG with newer combinations such as SOF+DAC or SOF+VEL as demonstrated in the 4WIDU-C study greatly enhances the feasibility of DOT-based therapy and warrants further investigation especially as short durations of PEG are associated with minimal side effects. Further if a 4-week regimen is found efficacious, DOT staff could treat three times as many patients in a 12-week period.43

In conclusion, these data demonstrate the feasibility of curing HCV in persons with a history of substance use in an LMIC setting with minimal use of molecular tests and limited infrastructure using a field-based DOT approach. Simplification of regimens will further facilitate delivery of these medications in such settings. Important challenges remain particularly related to ongoing substance use and nonadherence; there may still be a role for peginterferon in these sub-populations.

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CONFLICT OF INTEREST
The authors have no conflict of interests.

AUTHOR CONTRIBUTIONS
Sunil Solomon, Mark Sulkowski and Shruti Mehta designed the trial. Aylur Srikrishnan, Pradeep Ambrose, Balakrishnan Ramasamy and Santhanam Anand implemented the trial and data collection procedures. Allison McFall and Shruti Mehta analysed the data. David Thomas and Muniratnam Kumar provided critical input into trial design and implementation. All authors reviewed and approved the final manuscript.

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**SUPPORTING INFORMATION**

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