Assessing the impact of simplified HCV care on linkage to care amongst high-risk patients at primary healthcare clinics in Malaysia: a prospective observational study


INTRODUCTION

Hepatitis C virus (HCV) is a major cause of chronic liver disease globally, with an estimated 58 million individuals chronically infected and 290,000 HCV-related deaths each year.1,3 In 2016, the WHO launched the Global Health Sector Strategy on Hepatitis 2016–2021, with the goal of eliminating viral hepatitis as a public health threat by 2030. However, as of 2019, just 21% of individuals with HCV infection worldwide had been...
tested and approximately one-quarter of diagnosed individuals had been treated.3

The global response for the elimination of HCV infection have been transformed by recent advances in treatment and diagnostics, as well as reductions in costs. These advances include direct-acting antiviral (DAA) therapy and the availability of point-of-care serological and nucleic acid testing for HCV. The development of evidence-based WHO guidelines on who and how to test has provided further support for the scale-up of testing and treatment.25

Malaysia is an upper middle-income country of more than 32 million people and an estimated HCV seroprevalence in the general population between 0.3% and 2.5%.5,8 People who inject drugs (PWID) represent just 0.24% (75 000) of the adult population; however, they have an HCV prevalence of 67.5%–89.9%.7 Other key populations in Malaysia at higher risk of HCV include 77 903 people living with HIV (PLHIV) (0.24% of the population),22 000 female sex workers (FSWs) (0.069%) and 15 000 transgender sex workers (TGSWs) (0.047%).9

In 2017, it was estimated that only 6.1% (23 258) of people infected with HCV were diagnosed.10–12 A likely cause of this low rate of diagnosis was the highly complex and centralised testing model used. Prior to the commencement of this project in Malaysia, to screen for HCV antibodies, staff at primary healthcare clinics (PHCs) send samples to a central laboratory leading to long turnaround times and loss to follow-up. An overall goal of the national programme is to expand HCV services to the 1027 PHCs nationally.13,14

The objective of this study was to demonstrate the feasibility and effectiveness of decentralisation of HCV testing using rapid diagnostic tests (RDTs) at PHCs among high-risk populations, with referral of seropositive patients for confirmatory viral load testing and treatment. Effectiveness was evaluated through retention across the HCV care cascade. A further objective was to derive lessons learnt and to inform scale-up of HCV national and regional strategies.

METHODS

Study design and settings

This was an observational, prospective cohort study (figure 1 and online supplemental figure 1), with enrolment conducted between December 2018 and October 2019 in three regions of Malaysia: (a) the state of Kedah, (b) the state of Kelantan and (c) the region of Kuala Lumpur/Putrajaya/state of Selangor. This observational study was designed to evolve with the national HCV programme and therefore included several protocol changes during the study duration outlined below. This enabled the possibility to carry out several subanalyses within the study that were not initially part of the study outcomes. This study was also designed to feed eligible RNA positive participants into a clinical trial entitled ‘Open label phase II/III, multicentre trial to assess the efficacy, safety, tolerance and pharmacokinetics of sofosbuvir plus ritavudavir in HCV (+/-HIV) chronically infected adults with no or compensated cirrhosis in Thailand and Malaysia’ (Malaysian Medical Research Ethics Committee, approval number NMRR-16-747-29183, coordinated by DNDi, hereafter called the DNDi trial).15,16

Study outcomes

The outcomes of the study were the proportion of patients with a positive anti-HCV RDT who have a confirmatory HCV RNA test done, the proportion of patients with a positive HCV RNA test result who initiate hepatitis C treatment. Additional outcomes included; the proportion of patients who tested positive when screened for anti-HCV using RDT, the time required to progress from anti-HCV screening to in the HCV care cascade and the primary cost and resource use of the HCV care cascade services including screening, confirmatory test, pretreatment assessment, monitoring and treatment.

Site selection

Twenty-five PHCs were selected for enrolment and screening of participants (online supplemental figure 1). Site feasibility assessments were conducted for 31 PHCs recommended by the Ministry of Health (MOH), based on the existence of a methadone maintenance therapy programme, presence of a family medicine specialist, sufficient staffing and proximity to the catchment area of five selected hospitals (<100 km) (online supplemental table 1). Sites were selected using a points-based system coupled with a laboratory assessment. Each PHC was linked to one or more hospitals for referral of seropositive participants (Hospital Sultanah Bahiyah in the state of Kedah, Hospital Raja Perempuan Zainab II in the state of Kelantan, and Hospital Selayang, Hospital Ampang, and Hospital Sungai Buloh in the region of Kuala Lumpur/Putrajaya/state of Selangor). The median distance from selected PHCs to the selected hospitals was 29.6 km.

Study participants

Adult participants were enrolled consecutively at the 25 PHCs, based on routine clinical indications for an HCV test as per the Malaysian national guidelines and according to one of the following HCV risk factors (obtained either based on routine triage and/or clinical indications as per national guidelines, self-reported or obtained from medical records): a history of invasive medical procedures (eg, surgery, biopsy, endoscopy, solid organ donation); long-term haemodialysis; received blood/blood products/clotting factor concentrates/organ transplant prior to 1994; a needle-stick injury or mucosal exposure to HCV-infected blood; chronic liver disease and/or hepatitis; tattoos; body piercing; born to an HCV-infected mother; has an HCV-infected partner; is an MSM; is transgender; is an SW; was previously in prison; is HIV-positive; injects drugs; uses illicit intranasal drugs; has any other or undisclosed risk of HCV. Patients

already diagnosed as HCV RNA-positive or already initiated on treatment for the management of HCV infection were excluded from the study.

**Study procedures**

**HCV screening**

Eligible study participants were enrolled at PHCs and following pretest counselling, offered anti-HCV screening using finger-stick capillary or venous blood and tested with an SD Bioline HCV RDT (Standard Diagnostic, Korea). If the result was positive, participants were referred to one of the five selected hospitals for confirmatory testing by appointment (2–4 weeks after screening).

**Confirmatory testing and pre-treatment evaluations**

At the selected hospital, a 10 mL venous blood sample was drawn into EDTA-containing tubes and plasma was prepared within 72 hours, then referred to a reference laboratory in Kuala Lumpur (Institute of Medical Research, IMR) for HCV RNA testing using the Roche cobas 4800 HCV assay. The HCV RNA results were returned to the hospital and, at a subsequent patient visit. A second venous blood sample (5 mL) was obtained from patients who were HCV RNA-positive, for pretreatment evaluations. This sample was tested at the hospital laboratory and included a full blood evaluation and liver function tests measuring alanine aminotransferase, aspartate aminotransferase, bilirubin (direct/indirect), alkaline phosphatase and serum creatinine. At the selected hospitals, patients also received a FibroScan to assess the presence of cirrhosis (cirrhosis: >12.5 kPA with an M probe or >10 kPA with an XL probe, absence of cirrhosis: ≤12.5 kPA with an M probe or ≤10 kPA with an XL probe). Venous blood (10 mL) was obtained for genotyping which was carried out at IMR using the Roche cobas 4800 HCV GT assay.

**Treatment and evaluation of cure**

Following a clinical evaluation, participants were referred for enrolment into the DNDi trial.15 16 If patients were eligible and gave their written informed consent to take part in the DNDi trial, they were also initiated on treatment and managed as per the DNDi trial. Patients who were not eligible or who did not give consent to participate in the DNDi trial were referred to the standard of
care, the MOH national programme under which. Participants were treated for 12 weeks or 24 weeks depending on cirrhotic status.

At 12–24 weeks after the end of treatment, patients were requested to return to the treatment centre for a final venous blood sample to be collected (5 mL) for sustained virological response (SVR) HCV viral load testing, with plasma referral for testing at a designated MOH hospital or central laboratory. Patients with treatment failure were referred for further management by the gastroenterology or hepatology specialist, in accordance to the consensus of the 2019 National Clinical Practice Guidelines Development Group. Treatment outcomes for the 67 RNA-positive DNDi trial enrolees were embargoed until published separately and therefore have been excluded from the treatment outcomes of this publication. The screened population however could not be identified for exclusion from the final analysis.

Protocol changes during the study
At the commencement of the study, HCV treatment in Malaysia was delivered through the MOH national programme in hospitals. However, during the study duration (quarter 3, 2019), the national guidelines were changed to recommend treatment of non-cirrhotic patients (including those coinfected with HIV) at PHCs under the care of family medicine specialists. This enabled a subanalysis of treatment outcomes for patients that received treatment at hospitals versus those that received treatment at PHCs. Cirrhotic patients continued to be treated at hospitals; however, a subgroup of compensated cirrhotic patients (n=59) were treated (using sofosbuvir/daclatasvir without ribavirin) at six PHCs (in the state of Kedah).

Patient and public involvement
Public involvement, via civil society groups, included sharing the protocol design for review and input during the conception phase as well as active participation of civil society groups in results dissemination activities.

Data collection and analysis
Data were collected from primary source documents (screening registers, patient medical records, laboratory registers and laboratory reports) using paper case report forms (pCRFs) at PHCs by PHC study staff. These pCRFs were then manually transcribed into electronic case report forms (eCRFs) by research assistants using OpenClinica enterprise version 3.14 open-source software. At the hospitals, data were directly collected using eCRFs.

To ensure data quality, regular site monitoring visits were carried out (one visit per month), with every CRF checked for completeness and general errors. In addition, both manual and automated data cleaning were carried out on completed database exports.

Data were analysed using R V.3.6.1 to provide descriptive and inferential statistics. Characteristics of HCV antibody-positive and HCV antibody-negative individuals were summarised according to demographic, clinical, laboratory and treatment categories, with median and IQRs for quantitative data and frequencies and percentages for qualitative data. Associations between demographic characteristics and the frequency of HCV-positive patients were assessed using simple and multiple logistic regression (S/MLR). With MLR, all other demographic factors were accounted for by including them in the model as covariates. Variables examined included age, sex, ethnicity, antenatal status, reported risk factors and the total number of confirmed risk factors for each patient. Resulting p values were adjusted for multiple hypotheses using the Benjamini-Hochberg method.

Outcomes across the cascade of care were reported as numbers and percentages for each step for total populations and separately for cirrhotic/non-cirrhotic, hospital/PHC and key population (PWID/non-PWID, PLHIV/non-PLHIV) subgroups. Similarly, the times between HCV care cascade steps were reported as median and IQR values. Subgroup outputs at each step of the care cascade and turnaround time analyses were compared using Pearson’s $\chi^2$ test. Multiple hypothesis adjustment for subgroup comparison was performed using the Bonferroni correction.

Associations between SVR output and demographic characteristics of treated patients were assessed using Pearson’s $\chi^2$ test.

Assessment of costs
Estimates of the costs associated with testing were collected from the study sites. An ingredients-based approach was used to estimate the average cost per person of an antibody test and an RNA test. Unit costs included the costs of diagnostics tests and other consumables used; staff time, recorded as minutes of healthcare worker, administrative staff and laboratory technician time (with costs assigned by multiplying average minutes spent by salary); and overheads, including a proportion of the costs of utilities, phones, computers and other equipment (with costs assigned by dividing the annual or one-off cost of each item by the estimated number of appointments in a year or its estimated lifetime). Estimates of costs associated with treatment and auxiliary tests, such as liver function tests, were provided by the MOH. To assess the relative cost-effectiveness of the testing and care pathways, we used a state-transition model, MATCH (Markov-based Analyses of Treatments for Chronic Hepatitis C), which simulates HCV disease progression. Natural history outcomes from this model have been validated previously.

We adapted this model to simulate the epidemiology of HCV in Malaysia (MATCH-Malaysia) and extended the model to evaluate the cost-effectiveness of the three different care pathways: the total cohort, the treatment pathway at the PHCs and the treatment pathway at the hospitals. The model was developed following the principles of economic analyses with respect to viral hepatitis recommended by WHO.
RESULTS

Study population characteristics

A total of 15,366 adults from 25 PHCs in three regions (3933 (25.6%) in the state of Kedah, 3717 (24.2%) in the state of Kelantan and 7716 (50.2%) in the region of Kuala Lumpur/Putrajaya/state of Selangor) were screened using HCV antibody RDTs between December 2018 and October 2019 (table 1). The median (IQR) age was 38 (30–50) years, 9122 (59.4%) were male and 12,315 (80.1%) were of Malay ethnicity. In terms of self-reported risk factors for HCV exposure, a significant proportion (38.2%) did not disclose any specific risk factors. The most common risk factors reported were body piercings (21.1%), a history of invasive medical procedures (18.2%), injection drug use (13.0%), intranasal illicit drug use (14.7%) and previous imprisonment (12.4%).

Factors associated with HCV antibody positivity

Overall, 2087 were HCV RDT positive (13.6%), and this was similar across the three regions (15.6%, 12.2% and 13.3% HCV RDT positivity in the state of Kedah, the state of Kelantan and the region of Kuala Lumpur/Putrajaya/state of Selangor, respectively) (table 1). RDT-positive participants were on average 7 years older than RDT-negative patients (44 (39–52) vs 37 (29–49) years, respectively, p<0.001) and were more likely to be male (21.6% vs 1.8%, p<0.001). In the MLR analysis, after adjustment for age and sex, the reported risk factors for exposure that were most strongly associated with RDT positivity, compared with their absence, were injecting drug use (OR=28.3, 95% CI 24.3 to 33.0, p<0.001), history of haemodialysis (OR=5.2, 95% CI 2.7 to 10.0, p<0.001) and blood transfusion (OR=4.9, 95% CI 3.3 to 7.4, p<0.001), followed by history of illicit intranasal drug use (OR=2.0, 95% CI 1.8 to 2.3, p<0.001), history of incarceration (OR=2.4, 95% CI 2.0 to 2.8, p<0.001) and HIV infection (OR=2.3, 95% CI 1.8 to 2.9, p<0.001). A history of chronic liver disease was also strongly associated with HCV antibody positivity (OR=6.0, 95% CI 4.7 to 7.7, p<0.001). 4473 (29.1%) participants had 2–4 risk factors and 208 (1.4%) participants had more than four risk factors, having two of more risk factors was strongly associated with HCV antibody positivity, compared with participants with one risk factor (p<0.001).

Outcomes across the HCV care cascade

Overall, of the 2020 HCV antibody positive participants, 1481/2020 (73.3%) had a confirmatory viral load test performed, 1241/1481 (83.8%) were HCV RNA positive, 991/1241 (79.9%) had pretreatment assessments completed, 632/991 (63.8%) initiated treatment, 518/632 (82%) completed treatment, 352/518 (68.0%) were eligible for SVR cure assessment at the time of study completion, 209/352 (59.4%) had an SVR cure assessment and 202/209 (96.7%) patients achieved SVR (figure 2).

Among those who initiated treatment, the majority (452/632, 71.5%) were non-cirrhotic and received a 12-week regimen of sofosbuvir/daclatasvir (figure 3), while 180/632, 28.5% were cirrhotic (of whom, 21/632 (3.3%) were decompensated) (data not shown) and received 12-week or 24-week (depending on genotype) treatment regimen of sofosbuvir/daclatasvir. Of the 991 patients who were HCV RNA positive and completed the pretreatment assessments, 660 (66.6%) were non-cirrhotic and 331 (33.4%) were cirrhotic. Of the 660 non-cirrhotic patients, 596 (90.3%) were referred to a PHC for treatment and 64 (9.7%) were referred to a hospital for treatment. Of those referred, 416/596 (69.8%) initiated treatment at a PHC and 36/64 (56.3%) initiated treatment at a hospital, with both groups receiving a 12-week treatment regimen of sofosbuvir/daclatasvir. During the study period, a total of 208/660 (31.5%) non-cirrhotic patients were not initiated on treatment. Of the 331 cirrhotic patients (of which 23 (7.4%) had decompensated cirrhosis), 73 (22.1%) were referred to a PHC for treatment and 258 (77.9%) were referred to a hospital for treatment. Of those referred, 59/73 (80.8%) initiated treatment at a PHC and 121/258 (46.9%) initiated treatment at a hospital, with both groups receiving a 12-week or 24-week (depending on genotype) treatment regimen of sofosbuvir/daclatasvir. During the study period, a total of 151/331 (45.6%) cirrhotic patients were not initiated on treatment. Of the 359/1241 (36.2%) patients that did not initiate treatment: 197/359 (54.9%) were LTFU; reason was not available for 81/359 (22.6%); 55/359 (15.2%) had other underlying comorbidities and paused HCV treatment; 10/359 (2.8%) were incarcerated; 8/359 (2.2%) patients died (6: unknown reasons, 2: hepatoma/advanced retroviral disease); 6/359 (1.7%) patients did not want to start treatment and 2/359 (0.6%) patients were ineligible for free treatment through the MOH.

Seven serious adverse events were reported during the study period, none were assessed to be caused by the study procedures/interventions. Two participants were hospitalised due to injuries associated with accidents, five participants died (one accident, one stroke, one heart failure, one pneumonia and one chronic liver disease (death was prior to HCV confirmatory testing)).

Cascade outcomes for non-cirrhotic and cirrhotic patients referred to PHCs or hospitals for treatment were similar except for the following: the treatment initiation rate among cirrhotic patients referred to PHCs was significantly higher (80.8%) than those referred to hospitals (46.9%, p<0.001); the treatment completion rate among non-cirrhotic patients referred to PHCs was also significantly higher (94.0%) than those referred to hospitals (69.4%, p<0.001).

Overall, there were 47/632 (7.4%, data not shown) participants lost to follow-up after treatment initiation, of whom similar proportions of participants were cirrhotic (25/47 (53.2%)) versus non-cirrhotic (22/47 (46.8%)). Of those lost to follow-up, 20 (42.6%) initiated treatment at a PHC and 27 (57.4%) initiated treatment at a hospital.
Table 1  Characteristics of participants, those identified as HCV antibody positive and factors associated with HCV antibody positivity

<table>
<thead>
<tr>
<th>Factor</th>
<th>Patient statistics</th>
<th>Simple logistic regression</th>
<th>Multiple logistic regression</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td># Total (% total)</td>
<td># RDT positive (% RDT positive)</td>
<td>OR (95% CI)</td>
</tr>
<tr>
<td>Overall</td>
<td>15366 (100)</td>
<td>2087 (13.6)</td>
<td>13279 (86.4)</td>
</tr>
<tr>
<td>State of Kedah</td>
<td>3933 (25.6)</td>
<td>611 (15.6)</td>
<td>3322 (84.4)</td>
</tr>
<tr>
<td>State of Kelantan</td>
<td>3717 (24.2)</td>
<td>453 (12.2)</td>
<td>3264 (87.8)</td>
</tr>
<tr>
<td>Region of Kuala Lumpur/Putrajaya/state of Selangor</td>
<td>7716 (50.2)</td>
<td>1023 (13.3)</td>
<td>6693 (86.7)</td>
</tr>
</tbody>
</table>

**Median**

| Age                                           | 38 | 44 | 37 |

| IQR (25%–75%)                                 | 30–50 | 39–52 | 29–49 |

| ≤30                                           | 4182 (27.2) | 110 (2.6) | 4072 (97.4)       | Reference |
| 31–40                                         | 4394 (28.6) | 552 (12.6) | 3842 (87.4)       | 5.3 (4.3 to 6.6) | <0.001 |
| 41–50                                         | 3134 (20.4) | 832 (26.6) | 2302 (73.4)       | 13.4 (10.9 to 16.4) | <0.001 |
| 51–60                                         | 2324 (15.1) | 443 (19.1) | 1881 (80.9)       | 8.7 (7.0 to 10.8) | <0.001 |
| >60                                           | 1332 (8.7)  | 150 (11.3) | 1182 (88.7)       | 4.7 (3.6 to 6.1) | <0.001 |

**Sex**

| Female                                        | 6244 (40.6) | 115 (1.8) | 6129 (98.2)       | 0.1 (0.06 to 0.08) | <0.001 |
| Male                                          | 9122 (59.4) | 1972 (21.6) | 7150 (78.4)       | Reference |

**Ethnicity**

| Chinese                                       | 1794 (11.7) | 198 (11.0) | 1596 (89.0)       | 0.7 (0.6 to 0.9) | <0.001 |
| Indian                                       | 1004 (6.5)  | 90 (9.0)    | 914 (91.0)        | 0.6 (0.5 to 0.7) | <0.001 |
| Malay                                        | 12315 (80.1) | 1776 (14.4) | 10539 (85.6)       | Reference |
| Other                                        | 253 (1.7)   | 23 (9.1)    | 230 (90.9)        | 0.6 (0.4 to 0.9) | 0.02 |

**Risk factor**

| People who inject drugs (PWID)               | 2004 (13.0) | 1483 (74.0) | 521 (26.0)        | 60.1 (52.9 to 68.4) | <0.001 |
| Chronic liver disease and/or hepatitis       | 711 (4.6)   | 347 (48.8)  | 364 (51.2)        | 7.1 (6.1 to 8.3) | <0.001 |
| Previously in jail/prison                    | 1903 (12.4) | 894 (47.0)  | 1009 (53.0)       | 9.1 (8.2 to 10.2) | <0.001 |
| Intranasal illicit drug use                  | 2253 (14.7) | 767 (34.0)  | 1486 (66.0)       | 4.6 (4.2 to 5.1) | <0.001 |
| Tattooing                                    | 820 (5.3)   | 263 (32.1)  | 557 (67.9)        | 3.3 (2.8 to 3.8) | <0.001 |
| HIV infection                                | 952 (6.2)   | 290 (30.5)  | 662 (69.5)        | 3.1 (2.7 to 3.6) | <0.001 |
| Long-term haemodialysis                      | 66 (0.4)    | 16 (24.2)   | 50 (75.8)         | 2 (1.2 to 3.6) | 0.02 |
| Recipients of blood/blood products/clotting factor concentrates/organ transplant before 1994 | 267 (1.7)  | 61 (22.9)   | 206 (77.1)        | 1.9 (1.4 to 2.6) | <0.001 |
| Needle stick injury or mucosal exposure to HCV-infected blood | 204 (1.3)   | 34 (16.7)   | 170 (83.3)        | 1.3 (0.9 to 1.9) | 0.24 |
| Sex worker (SW)                              | 137 (0.9)   | 21 (15.3)   | 116 (84.7)        | 1.2 (0.7 to 1.8) | 0.62 |

Continued...
During the study period, 67/632 (10.6%) participants were still undergoing treatment, of which 11/67 (16.4%) were non-cirrhotic and were 56/67 (83.6%) cirrhotic. No patient reported discontinuing treatment due to serious treatment-related adverse events or death.

Among those who returned for SVR testing, there were 7/209 (3.3%) participants who experienced treatment failure, all of whom were non-cirrhotic.

Cascade outcomes among key populations

Of the enrolled participants, 1944/15 299 (12.7%) were PWID, of whom 1464/1944 (75.3%) were HCV sero-positive, compared with 556/13 355 (4.2%) in the non-PWID population (p<0.001) (online supplemental table 2). There was no significant difference in the uptake of HCV confirmatory RNA testing according to PWID status. However, slightly lower proportions of PWID were RNA positive compared with the non-PWID group: 877/1063 (82.5%) and 364/418 (87.1%), respectively (p=0.04). Similar proportions of RNA-positive PWID completed pretreatment assessment, initiated treatment, completed treatment, received SVR testing and achieved SVR compared with non-PWID. There was also no difference in the outcomes between PWID and non-PWID when stratified by treatment site (PHC vs hospital).

There were 983/15 299 (6.4%) participants who were PLHIV and, of these, 298/983 (30.3%) were HCV sero-positive compared with 1722/14 316 (12.0%) in the non-PLHIV group (p<0.001). There was no significant difference in the uptake of positive HCV confirmatory RNA testing according to HIV status. Slightly lower proportions of RNA-positive PLHIV completed pretreatment assessment, received SVR testing and achieved SVR compared with non-PLHIV. However, slightly lower proportions of PLHIV were RNA positive compared with the non-PLHIV group: 82.5% and 87.1%, respectively (p=0.02). Similar proportions of RNA-positive PLHIV completed pretreatment assessment, received SVR testing and achieved SVR compared with non-PLHIV.

There was also no difference in the outcomes between PLHIV and non-PLHIV when stratified by treatment site (PHC vs hospital).

<table>
<thead>
<tr>
<th>Turnaround time between HCV care cascade steps</th>
<th>Patient statistics</th>
<th>Simple logistic regression</th>
<th>Multiple logistic regression</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td># Total (% total)</td>
<td># RDT positive (% RDT positive)</td>
<td># RDT negative (% RDT negative)</td>
</tr>
<tr>
<td>Partner who is HCV-infected</td>
<td>189 (1.2)</td>
<td>27 (14.3)</td>
<td>162 (85.7)</td>
</tr>
<tr>
<td>Children born to HCV-infected women</td>
<td>32 (0.2)</td>
<td>4 (12.5)</td>
<td>28 (87.5)</td>
</tr>
<tr>
<td>History of invasive medical procedures (eg, surgery, biopsy, endoscopy, solid organ donation)</td>
<td>2798 (18.2)</td>
<td>200 (7.1)</td>
<td>2598 (92.9)</td>
</tr>
<tr>
<td>Body piercing</td>
<td>3236 (21.1)</td>
<td>182 (5.6)</td>
<td>3054 (94.4)</td>
</tr>
<tr>
<td>Transgender</td>
<td>201 (1.3)</td>
<td>11 (5.5)</td>
<td>190 (94.5)</td>
</tr>
<tr>
<td>Men who have sex with men (MSM)</td>
<td>760 (5.0)</td>
<td>35 (4.6)</td>
<td>725 (95.4)</td>
</tr>
<tr>
<td>Others/undisclosed</td>
<td>5865 (38.2)</td>
<td>172 (2.9)</td>
<td>5693 (97.1)</td>
</tr>
<tr>
<td>Number of risk factors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>10685 (69.5)</td>
<td>656 (6.1)</td>
<td>10029 (93.9)</td>
</tr>
<tr>
<td>2–4</td>
<td>4473 (29.1)</td>
<td>1295 (29.0)</td>
<td>3178 (71.1)</td>
</tr>
<tr>
<td>&gt;4</td>
<td>208 (1.4)</td>
<td>136 (65.4)</td>
<td>72 (34.6)</td>
</tr>
</tbody>
</table>

HCV, hepatitis C virus; RDT, rapid diagnostic test.
non-PWID was 220 (164–279) days versus 197 (133–248) days, respectively (p=0.02) (online supplemental table 3).

**Cost of HCV testing**

In a cohort of 10 000 patients with an RDT-positive rate of 13.6% and viraemic rate among antibody positive participants of 84.5%, the total cost for testing per treated patient was US$136.21. Over a 30-year time period, the overall cost per 10 000 patients and quality-adjusted life-years (QALYs) were US$6 921 839 and US$172 036, compared with the cost and QALYs of no action of US$11 725 196 and US$170 774. Compared with no testing, a simplified decentralised HCV testing and treatment model in primary healthcare settings could result in cost savings of US$4.8 million per 10 000 persons tested over the span of 30 years. The disease burden avoided for decompensated cirrhosis, hepatocellular carcinoma and liver disease-related deaths, compared with the burden with no action, were 116, 68 and 117 cases, respectively (online supplemental table 4).

**DISCUSSION**

Overall, this project demonstrated the effectiveness and feasibility of a simplified, decentralised HCV testing and treatment model in primary care settings that targeted high-risk groups in Malaysia. Good outcomes were attained across most steps of the cascade of care when patients were offered treatment at decentralised sites compared with centralised hospitals, however, considerable attrition was reported for linkage to care.

A distinctive feature of this model was its demonstration that HCV case-finding at PHCs using RDTs is both feasible (reflected by the marked increase in testing uptake, with more than 15 000 individuals being tested in 10 months) and achieved a high rate of case-finding (prevalence 13.2%). This was achieved through a targeted HCV case-finding strategy of identifying high-risk patients within the PHC catchment population. The resultant enrolled population included high proportions of key populations including PWID, PLHIV, MSM, SW, intranasal illicit drug users, those who were previously in prisons as well as individuals with chronic liver disease or a history of invasive medical procedures. Targeting these populations resulted in an overall high yield of HCV-positive cases (13.2%).

While overall retention was good for most steps in the cascade, our findings also highlight some cascade steps where there was significant attrition and suboptimal linkage following a positive HCV antibody RDT that provide opportunities for improvement. There were 539 patients (26.7%) who did not have a confirmatory viral load test and a further 250 (20.1%) who had an HCV viral load test that was positive but did not receive pretreatment assessments (ie, a total of 789 (39.1%) of the HCV antibody-positive individuals). In addition, there was attrition of RNA positive patients initiating treatment, but markedly more so in patients that received treatment at hospitals compared with those treated at PHC (48.8% vs 71.0%, p<0.001).

It is likely that at both points in the cascade a key driver of attrition is the provision of services at hospitals. All
seropositive participants were referred up from PHCs to designated hospital sites for viral load testing and subsequent pretreatment assessment, rather than having on-site blood sample collection for HCV viral load and pretreatment assessment. This was due to the pre-enrolment requirements of the DNDi clinical trial (viral load and pretreatment assessment). During follow-up calls, study staff logged the following reasons for attrition from hospital visits; the distance participants had to travel to the hospital (online supplemental table 1); high transportation costs. In addition, it is likely that follow-up of patients was not carried out to the highest standard due to limited information exchange between hospital and PHC staff and poor tracking and tracing of patients lost. In addition, limited appointment availability and long lead-times for blood collection at the hospitals; and a reluctance to attend hospital appointments because of fear of stigmatisation in contrast to the ‘high-risk population-friendly’ PHCs were also likely causes of attrition of patients throughout the cascade.

These findings are consistent with evidence from a recent systematic review which reported lower rates of linkage to care and treatment uptake in partially decentralised models of care (29 studies) compared with fully decentralised models of care (ie, all testing and treatment provided at a single site). Although, this finding was only reported for key populations whereas results in the general population were heterogeneous. In addition, only 49% of studies included in this review were from low and middle-income countries.25 Other studies with similar models of partially decentralised HCV care assessed within existing public health systems have reported poorer retention between diagnosis of HCV and treatment 59.3% in the Cherokee nation HCV elimination programme and 73.7% for partially decentralised arm in the HEAD-Start Project Delhi.26 27 Whereas, high rates of retention have been reported in several studies where fully decentralised care is provided.28 29

Preliminary analyses of loss to follow-up led to changes in the national programme to allow for the provision of HCV treatment at PHCs for non-cirrhotic patients (including patients who were coinfected with HIV), from quarter 3 of 2019. This change enabled a subanalysis of patients, according to where their treatment was provided. We observed a significant improvement cascade of care retention when patients had treatment provided at a PHC compared with receiving treatment at a hospital. In addition, at six PHCs (in the state of Kedah), treatment of

Figure 3  Flowchart of treatment sites for cirrhotic versus non-cirrhotic patients. 1These compensated cirrhotic patients were referred for treatment (sofosbuvir/daclatasavir without ribavirin) at six PHCs in the state of Kedah. 2These compensated and decompensated cirrhotic patients were referred for treatment at hospitals. PHC, primary healthcare clinic; RDT, rapid diagnostic test; SVR, sustained virological response; Tx, treatment.
a small cohort of compensated cirrhotic patients (n=59, using sofosbuvir/daclatasvir without ribavirin) was successful.

There were several key limitations in this study: first, the study is observational in nature, with inherent challenges taking into account the many confounders affecting outcomes across the cascade of care, particularly when comparing PHCs versus hospitals; second, standard of care HCV practices evolved during the conduct of the study—decentralisation of HCV treatment under the MOH national programme for non-cirrhotic patients to PHCs, including patients who were coinfected with HIV and a small cohort of compensated cirrhotic patients, commenced in quarter 3 of 2019; third, the costing estimates did not take into account the differential costs of the HCV care pathway between PHCs and hospitals as well as the costs to the patients.

The major challenges encountered were due to the COVID-19 pandemic, which resulted in delays to treatment initiation (65 (24–112) days pre-COVID-19 vs 154 (127–211) days post-COVID-19, p<0.001). These delays may have contributed to increased numbers of patients lost to follow-up. In particular, loss to follow-up in treatment initiation, follow-up treatment visits and SVR testing during the COVID-19 outbreak may have been higher among key populations, such as PWID, who were reportedly less willing to travel to treatment sites amid increased police surveillance during COVID-19 lockdowns due to fear of arrest. Indeed, others have also reported access to all healthcare and other services for PWID was affected by COVID-19. In addition, HCV screening at PHCs was reduced, laboratory turnaround times were increased and an increase in SVR samples being misplaced was reported during the COVID-19 outbreak, due to prioritisation of laboratory resources for processing COVID-19 samples.

Initiatives by the MOH after the study started have led to a tremendous expansion in screening and treatment for HCV. The evidence from this study has catalysed plans for MOH to roll-out decentralised HCV care from the 25 sites to all PHCs nationwide, in a stepwise manner from quarter 1 of 2020. The model for scale-up builds on key aspects that were integral to this study design, including the use of RDTs for point of care results, optimal turnaround times and the use of DAA therapies at PHCs for non-cirrhotic and uncomplicated cases of HCV, where there is capacity present on-site. In addition, MOH has already recently further decentralised services by ensuring venous blood collection for HCV viral load confirmation and reflex biochemistry blood tests for pretreatment assessments, including AST to Platelet Ratio Index scores, will be carried out at PHCs rather than referring these patients to hospitals. This includes sending the sample for either HCVcAg or HCV RNA testing at a designated hospital or laboratory or use of on-site GeneXpert testing making the model a fully decentralised care package.

In addition to the scale-up of this fully decentralised model of HCV care at PHCs nationally, this study has provided evidence, with regards to the yield of

<table>
<thead>
<tr>
<th>Site</th>
<th>Total Median (days)</th>
<th>Hospital Median (days)</th>
<th>PHC Median (days)</th>
<th>PHC vs hospital Median difference (days)</th>
<th>Adjusted p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>RDT-RNA test specimen collection-RNA test specimen collection</td>
<td>25 15–33</td>
<td>33 1481 6</td>
<td>3–120 10 13</td>
<td>6 10 10</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
HCV RDT+, for the MOH to continue the successful approach of targeting high-risk groups of individuals for HCV screening. To this end, the MOH has also started programmes in prisons and drug rehabilitation centres and is developing plans for novel screening strategies, including self-testing, to further target key populations including MSM, transgender people and SW. To ensure successful HCV programmes can be implemented within these populations, the MOH has begun to drive the coordination of different government departments including primary care, public health, the Ministry of Home Affairs and relevant non-governmental organisations (NGOs).

Further lessons from this study that are being adopted for scale-up include an emphasis on the importance of developing robust monitoring and evaluation and data collection systems at every step of the HCV care cascade. The use of a central database for capturing data in a systematic way during this study can be translated for use in the national programme in simplified and practical ways. As well as the importance of strategies to raise community awareness, outreach activities and engagement with NGOs.

**CONCLUSIONS**

In conclusion, using an innovative model of partially decentralised care, this study demonstrated a high rate of case-finding for HCV-positive individuals. There were significantly higher levels of retention in the care cascade when patients were treated at PHCs compared with hospitals supporting existing evidence of improved outcomes using decentralised care. Several improvements were made during the study and in the national programme to address these limitations, including the decentralisation of confirmatory testing and pretreatment assessment and the provision of HCV treatment at PHCs. This optimised model of fully decentralised HCV care, is now being adopted by MOH as part of a scale-up nationwide and serves as a good model for implementation in other settings.

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**Acknowledgements**

The authors would like to thank Unitaid for the support and funding: study participants for their involvement, and partners and colleagues for the support and implementation of this study - study teams and their colleagues from the 25 PHCs, 5 hospitals and IMR, DNDI, Clinical Research Centre (CRM) and Clinical Research Centre; in particular: Dr Akhalma Yusof and the study coordinators from CRM; Family Medicine Specialists from the 25 PHCs - Dr Idris Ibrahim, Dr Zamri Mansor, Dr Siti Ashikh Juhari, Dr Habshoh Hat, Dr Fazlin Suhana Otman, Dr Jamilah Abdullah, Dr Norizain Hassan, Dr Tuan Zailina Tuan Ngah, Dr Rahiza Ab Rahman, Dr Nik Harlina Roza Nik Kazim, Dr Roshana Mohamed Yasin, Dr Norashidah Abdullah, Dr Mohd Sukarno Saud, Dr Nurul Aida Salleh. Dr Siti Rohani Mohamed Alias, Dr Noor Harzana Harun, Dr Husni Hussain, Dr Rafidah Mohd Rafie, Dr Radziah Jibril, Dr Nazhatulzima Suhaili, Dr Sheela Bai a/p Pannir Selvam, Dr Wan Noor Azlin Wan Idris, Dr Ziena Zufida Zainol Rashid, Dr Zti Akthar Supian, Dr Fauziah Ahmad and Dr Vickneswaran a/p Ayadurai; the clinical trial assistants, site supervisor and clinical research assistants from DNDI: Wan Nur Ilyana Wan Yusoff, Noor Annisa Darman, Muhammad Abidh Ab Wahab, Matron Wakiya Wahab, Nurul Amalina Md Zem, Nur Farahana Zakaria, Nur Alya Ahmat @ Ahmad, Nurul Fazira Basran, Muhammad Hafiz Idris, Putri Shafnaz Sharudin, Muhammad Tauifik Nasarudin and Khairul Fidaa Khairul Bazli; colleagues from DNDI: François Bompart, Molly Jagpal, Han Yang Chung, Muhammad Haif Mahmud Fauzi, Kamsiah Hasbullah, Azereza Abin, TiliKabu Ramanaidu, Nyap Ming Tim, Francisco Simon, Tania Bilyk and Guillaume Drapeau; and present and past colleagues from FIND: Catharina Boeheime, Bill Rodriguez, Zachary Katz, Francesco Marinucci, Violet Chihota, Natalie Jotikasthira, Cristina Dang, Jeremy O'Brien, Flavo Ambrogiani and Dominique Rabin. The authors would also like to thank the following civil society organisations and governmental agency for their support and contribution - Persatuan Cahiaya Harapan Negeri Kedah/Perlis, Persatuan Perantaraan Pesakit Kelantan, Persatuan Insaf Murni Malaysia, the Malaysian AIDS Council and the National Anti-Drug Agency; and the Director-General of Health, Malaysia, for his support throughout the conduct of this study and permission to publish the findings. Editorial support, under the direction of the authors and funded by FIND, was provided by Adam Bodley.

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JM designed data collection tools, implemented the study, monitored data collection for the study, cleaned and analysed the data, and drafted and revised the paper. She is guarantor. SShilton initiated the collaborative project, designed the study and data collection tools, implemented the study, monitored data collection for the study and drafted and revised the paper. She is guarantor. XHS designed data collection tools, implemented the study, monitored data collection for the study, cleaned and analysed the data, and drafted the draft paper. CHK revised the draft paper. RMS, ZZ, NAB, HG, SK and RH implemented the study and monitored data collection for the study. SSiva designed the study and data collection tools, implemented the study, monitored data collection for the study and revised the draft paper. RJR implemented the study and monitored data collection for the study. MG and AT wrote the statistical analysis plan, cleaned and analysed the data, and revised the draft paper. MA and JC analysed the data and revised the draft paper. J-IP initiated the collaborative project, implemented the study, and revised the draft paper. RMZ initiated the collaborative project, designed and implemented the study, and monitored data collection for the study. CM implemented the study, monitored data collection for the study, and revised the draft paper. FY, NHI, FI and RZ implemented the study. IA-M initiated the collaborative project, designed and implemented the study, and revised the draft paper. IA-M initiated the collaborative project, designed and implemented the study, and revised the draft paper. MRAH initiated the collaborative project, designed and implemented the study, monitored data collection for the study and revised the draft paper. All authors revised the paper critically for intellectual content and approved the final version.

**Funding**

This study was funded by Unitaid as part of HEAD-Start (Hepatitis Elimination through Access to Diagnostics).

**Map disclaimer**

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**Competing interests**

None declared.

**Patient consent for publication**

Not applicable.
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