EQUIP POLICY REPORT

OCTOBER, 2019

TREATMENT OUTCOMES AND COSTS OF A SIMPLIFIED ANTIVIRAL TREATMENT STRATEGY FOR HEPATITIS C IN MYANMAR

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ACROYNMS

AHRN	Asian Harm Reduction Network
APRI	AST-to-platelet ratio index
CPI	Community Partners International
DAA	Direct Acting Antiviral
DPH	Department of Public Health
DMR	Department of Medical Research
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HIV	Human Immuno Deficiency Virus
INR	International Normalized Ratio
LMICs	Low-Medium Income Countries
MANA	Myanmar Anti-Narcotic Association
MAT	Medically Assisted Therapy
MdM	Médecins du Monde
MLF	Myanmar Liver Foundation
MMK	Myanmar Kyat
MSFH	Medicins Sans Frontier Holland
NAP	National AIDS Programme
OST	Opiod Substitution Therapy
PEPFAR	U.S. President's Emergency Plan for AIDS Relief
PWID	People With Injectable Drugs
RBV	Ribavirin
RAS	Resistance-associated substitution
SVR	Sustained virologic response
SW	Sex Workers
SOF/VEL	Sofosbuvir/Velpatasvir
TDF	Tenofovir disoproxil fumarate
UCLA	University California Los Angeles
USAID	United States Agency for International Development
WHO	World Health Organization

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BACKGROUND

Hepatitis C Virus (HCV) infection is a deadly but curable disease that disproportionately affects people in low- and middle-income countries (LMICs). There are 70-80 million people with chronic HCV globally, of whom 50-60 million live in resource-limited settings where HCV prevalence often exceeds 3.5%[1-3]. HCV prevalence and genetic diversity (genotype) vary by population and region. HCV infection remains high among certain populations even in low prevalence settings, specifically people who inject drugs (PWID) and HIV-infected men who have sex with men (MSM)[4]. Chronic HCV infection is expected in 55% to 85% of untreated cases and is associated with liver cirrhosis, liver failure, hepatocellular carcinoma, and death. Despite the development of highly effective direct-acting antiviral (DAA) treatment, which can cure HCV infection with 8-12 weeks of therapy, HCV remains a leading cause of mortality worldwide, causing more than 350,000 deaths each year[3, 5].

The WHO's Global Health Sector Strategy sets goals of a 90% reduction in new HCV infections and a 65% reduction in HCV-related mortality by 2030[6]. Strategies for achieving these targets are similar to those for HIV: scaling up access to affordable testing and treatment combined with interventions for infection prevention (for HCV, these are mainly harm reduction and safe blood donation and injections). Progress in HCV treatment scale-up is encouraging, with more than 3 million treated globally with direct-acting antivirals since 2015. However, testing coverage and diagnosis rates are still less than 10% in LMICs[3].

The Nationwide Prevalence Survey of Hepatitis B & C conducted from May 2015 to November 2015 in Myanmar by the Department of Medical Research (DMR) and Department of Public Health (DPH) found the prevalence of HCV and hepatitis B virus (HBV) infection to be 2.7% and 6.5%, respectively[7]. Amongst those HIV-infected, HBV co-infection, HCV co-infection, and dual HBV+/HCV+ co-infection rates were estimated to be 2.2%, 20.1%, and 20.7%, respectively. The prevalence of HCV antibody positivity among PWID is estimated at 48.1%, with treatment access in the region under 1%[8]. HCV infection is estimated to account for 25% of hepatocellular carcinoma[4]. The most common HCV genotypes in Myanmar are 3 and 6, followed by genotype

1 [4] The HIV epidemic in Myanmar is concentrated among MSM, PWID, and female sex workers (SW) and ranks among the most serious in Asia[5]. HCV/HIV co-infection rates are estimated at about 22.8% with high risk among PWID.[9, 10]. A lack of adequate facilities and free-to-client services, combined with fear of prosecution for drug use and high stigma for key populations (particularly MSM), means that most individuals who present for treatment for HCV and HIV are already well advanced in their illness.

Treatment delivery is also dependent on access to laboratory assays. Most U.S. FDA-approved HCV direct-acting antiviral (DAA) therapies are genotype-specific, with limited efficacy for select genotypes, requiring genotype determination for their use. Fixed-dose combination Sofosbuvir/Velpatasvir (SOF/VEL) was the first FDA-approved interferon-free DAA regimen that is pan-genotypic, with activity against HCV genotypes 1-6. The addition of ribavirin has been recommended for select harder-to-treat groups if the Y93H resistance-associated substitution (RAS) is present or if resistance testing is not readily available [7] [11]). More recent data, however, suggest that high SVR rates can still be achieved in these harder to treat groups (cirrhotic, treatment-experienced, with baseline RASs) without the addition of ribavirin [12-16]. Thus, SOF/VEL alone for 12 weeks can provide high HCV cure rates for all genotypes, of particular relevance to resource-limited settings where access to genotyping and adequate laboratory and clinical personnel support for the monitoring of and management of ribavirin-associated toxicities (namely anemia and rash) are not readily available.

Delivery of HCV therapy requires a simplified approach which provides low cost laboratory testing and effective drugs and requires minimal infrastructure. Increased screening and access to treatment for HCV provides an opportunity for integrated screening, linkage, and follow up of HIV/HCV co-infected individuals and management of both HIV and HCV infections.

In August 2017, with support from USAID, EQUIP Innovation for Health launched a single arm demonstration project to evaluate an integrated, simplified protocol for testing and treating HCV and HIV among key populations in Myanmar (https://www.equiphealth.org/articles/hivhcv-co-infection). The project's purpose was to demonstrate the feasibility, acceptability, outcomes, and affordability of a clinic-based service to diagnose, treat, and monitor HCV treatment among key

populations, and to integrate HCV care with HIV testing and treatment services. A total of 814 patients eligible for HCV treatment were enrolled at three clinics in Myanmar, with follow up completed in April 2019. Participants were treated with a twelve-week course of SOF/VEL with or without weight-based ribavirin (RBV) as determined by their HCV genotype and cirrhosis status. Midway through the project, the protocol was revised to treat all participants with SOF/VEL alone, without ribavirin and regardless of HCV genotype (further details below, in Methods). Outcomes were determined at 24 weeks after study enrollment, when patients were assessed for sustained virologic response (SVR) at 12 weeks after end of treatment. This report describes the treatment outcomes and estimated costs for simplified HCV testing and DAA treatment with SOF/VEL with or without RBV for patients with and without HIV co-infection.

IMPLEMENTING PARTNERS

This is an EQUIP Hepatitis C project funded by USAID funded through Grant AID-OAAA-A-15-00070 under the U.S. President's Emergency Plan for AIDS Relief (PEPFAR) through EQUIP. It has full support from the local USAID mission. Right to Care, an EQUIP program consortium partner, implemented the EQUIP Myanmar HCV Project through the EQUIP mechanism. Community Partners International (CPI) is leading this project in Myanmar under the guidance of the National Hepatitis Control Program and the National AIDS Program and in partnership with the Department of Medical Research, the Myanmar Liver Foundation, and the Asian Harm Reduction Network (AHRN) to help control the growing HCV epidemic among key populations in Myanmar. CPI is also responsible for fund management, coordination with National Programs, obtaining of Ethical Review Committee approval, progress monitoring, data cleaning and validation, and assistance with analysis.

The strategic partners of the project are Boston University (responsible for the economic analysis), the David Geffen School of Medicine at the University California Los Angeles (UCLA), Cepheid, QODE ABL(SA), and Mylan Pharmaceuticals Inc.

METHODS

Study sites and population

Enrollment into the HCV/HIV demonstration project was conducted between December 2017 and December 2018. The participants were recruited at three clinical facilities in Myanmar (Figure 1): the Than Sitt Charity Clinic in Yangon and the Than Sitt Charity Clinic in Mandalay, both operated by the Myanmar Liver Foundation (MLF), and the Waimaw AHRN Clinic in Kachin. Patients were referred to the study sites by civil society groups, the General Practitioners Society, National AIDS Program, Myanmar Anti-Narcotic Association (MANA), Medicins Sans Frontier Holland (MSFH), and Médecins du Monde (MdM). In Kachin recruitment of participants was done through AHRN with support from MLF.

The target populations for the project were people who inject drugs (PWID), men who have sex with men (MSM), and commercial sex workers, although initial enrolment included populations outside of these, most of whom could not afford private treatment. Patients were screened for HCV, HBV, and HIV. If they were HCV-infected, they were enrolled for treatment if they met the eligibility criteria.

Eligible participants included in the treatment study were HCV viremic, HCV treatment naïve or experienced (prior pegylated interferon [PegIFN] and RBV only), and 18 years or older, with HCV genotype 1, 2, 3, 4, 5 or 6, with or without HIV-1 co-infection. Patients with compensated cirrhosis (Child-Pugh Class A) and HBV infection were eligible; those with decompensated cirrhosis (Child-Pugh Class B or C) or prior treatment with HCV DAAs were not eligible. Patients who were ineligible for HCV treatment through the project were referred to other treatment centers for care. All participants provided written informed consent.

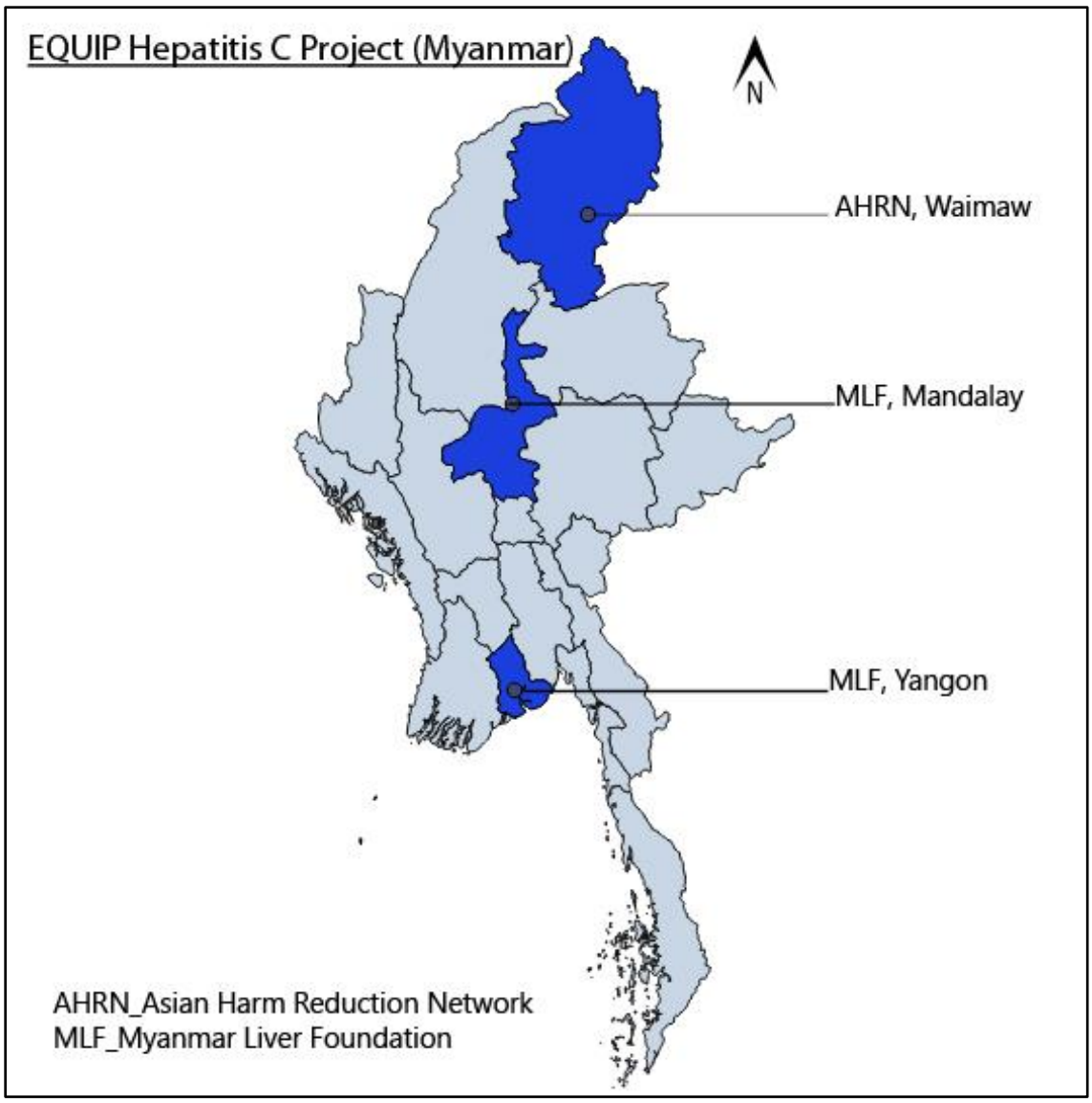


Figure 1: Treatment sites in Myanmar

Intervention description

The intervention combined HCV and HIV testing, HCV treatment, simplified HCV treatment monitoring, and HIV treatment initiation for those with co-infection not yet on antiretroviral therapy. HCV treatment was with fixed-dose combination sofosbuvir 400 mg/velpatasvir 100 mg (SOF/VEL) +/- weight-based ribavirin for 12 weeks and provided by the project. Ribavirin was initially included in the regimen for genotype 3 participants who were cirrhotic or who had previously failed an interferon-based treatment regimen, regardless of cirrhosis status.

In April 2018, 5 months into enrollment, based on more recent findings on treatment response rates with SOF/VEL without ribavirin for genotype 3 infection, including amongst PWID and in resource-limited settings in Asia [12-15], the protocol was revised to treat all participants with SOF/VEL alone, without ribavirin, for 12 weeks, regardless of genotype. With this revision, genotyping was not required prior to treatment initiation. This change allowed the inclusion of the third study site in rural Kachin called Waimaw, which faces barriers to obtaining timely genotyping and has limited resources to monitor for ribavirin-associated and other toxicities.

Participants with HBV co-infection and hepatitis B surface antigen positivity were concurrently treated with tenofovir disoproxil fumarate (TDF). HIV treatment was provided per Myanmar National AIDS Programme (NAP) recommendations. Provision of HIV and hepatitis B treatment was derived from national or USAID supported HIV treatment programs. The first line HIV treatment regimen in Myanmar—TDF/lamivudine (3TC)/efavirenz—posed a challenge as efavirenz could not be co-administered with velpatasvir due to drug-drug interactions. As such, the NAP supported the substitution of dolutegravir or another alternative (such as lopinavir/ritonavir) for efavirenz in the project. Switches in ART regimen for HIV/HCV co-infected participants were performed by an HIV specialist. Participants were followed for 24 weeks (through 12 weeks after treatment completion), including assessments of HCV and HIV treatment outcomes and safety. Intervention steps are illustrated in Figure 2.

Clinical and laboratory evaluations

Clinical evaluations

Screening evaluations were undertaken for treatment eligibility determination before initiation of treatment. Medical history and physical examination were undertaken at baseline and, at clinicians' discretion, at other follow-up visits. Clinical signs and symptoms presented by the patient were documented at all visits to track adverse events. All drugs prescribed for illness were documented in the concomitant medication log. Liver disease stage (cirrhosis vs non-cirrhosis) was defined based on either ultrasound (liver imaging consistent with cirrhosis [surface nodularity, heterogenous, course echotexture and enlarged caudate lobe]), AST-to-platelet ratio index (APRI) score ≥2.0, or Fibroscan ≥12.5kPa. For cirrhotic patients, Child-Pugh score was calculated to

determine if they had compensated or decompensated liver disease. Compensated cirrhosis was defined as Child-Pugh Score ≤6.

Laboratory evaluations

The screening laboratory evaluations included HCV RNA, haemoglobin, platelets, AST, ALT, total bilirubin, albumin, creatinine, blood urea nitrogen, pregnancy testing, prothrombin time/International Normalized Ratio (INR), point-of-care HBV serologies with WHO qualified SD Bioline (HBcAb, HBsAg, HBsAb), point-of-care rapid HIV testing (Determine, Unigold and Statpak) and CD4+ T cell count for HIV-infected participants. Laboratory results were also obtained from the medical record if reported within the specified window (namely HCV RNA at any time prior to study entry, HIV testing within 60 days prior to entry if negative and at any time prior to entry if positive, and CD4+ T-cell count within 90 days). HCV viral load testing was undertaken for all participants with positive HCV antibody results, using Cepheid GeneXpert-HCV Viral Load and/or Roche. HCV genotyping, subtyping, and resistance testing for all HCV viremic patients were performed. All participants who initiated HCV treatment had the following labs at week 24: HCV RNA, haemoglobin, platelets, AST, ALT, bilirubin, albumin, creatinine, blood urea nitrogen, prothrombin time/INR, and HIV RNA. Participants receiving ribavirin additionally had haemoglobin monitoring at weeks 2, 4, and 8. Pregnancy testing was required for all females of childbearing potential at screening and at weeks 4, 8, 12, and 24 for those assigned to ribavirin. Participants with eGFR<60 at screening and also receiving tenofovir had creatinine monitoring at weeks 4 and 12. Participants with isolated hepatitis B core Ab positivity (HBcAb+/HBsAg-/HBsAb-) additionally had hepatic function tests (AST, ALT, bilirubin) at weeks 4, 8, and 12 to assess for potential HBV reactivation.

Measurement of HCV viral load

Roche Real Time HCV quantitative viral load estimation was undertaken for the first 403 participants screened. Roche HCV viral load served as the standard of care viral load assay prior to validation of Xpert HCV viral load. As part of the validation process, GeneXpert (Cepheid, CA, USA) and Advanced Biological Laboratories (ABL) UltraGene-HCV assays (ABL SA.,

Luxembourg) for HCV viral load were conducted for patients at baseline and at 24 weeks in parallel (12 weeks post-treatment). The limits of quantification were 10 IU/mL for Xpert, 15 IU/mL for Roche, and 20 IU/mL for ABL. Clinical decisions to initiate HCV treatment and determination of SVR were based on Roche initially and then GeneXpert, after the performance of Xpert was found to be comparable to the Roche assay (Figure 4) . Dried Blood Spots (DBS) were collected at baseline, 4, 8, 12 and 24 weeks.

Genotyping and resistance

Genotyping was performed using DeepChek-HCV genotyping assay (ABL SA, Luxembourg, Luxembourg). The assay is a pan-genotypic method (HCV genotypes 1–6) and can discriminate HCV 1b/2k Chimera and the HCV subtype 1a and 1b.

Drug resistance testing was performed using DeepChek NS5A Drug Resistance Assay (ABL SA, Luxembourg, Luxembourg). It can detect all clinically relevant NS5A resistance-associated substitutions include several mutations in positions 28, 30, 31, 32, 58, 83 and 93. Sanger sequencing was performed using 1µL of the UltraGene HCV product and drug resistance was performed using 5µL of HCV RNA and the amplification step (RT-PCR) was performed using the DeepChek NS5A Drug Resistance.

The data generated from the Sanger instrument were analysed with the DeepChek-HCV software (ABL SA, Luxembourg, Luxembourg), and drug-resistance interpretations were assessed with antiretroviral drugs resistance algorithms: Geno2Pheno[17, 18].

Counseling

At each visit, counseling was provided by a social worker or peer counselor on study procedures and treatment adherence, HCV transmission and re-infection risks, and harm reduction, with referral to harm reduction services as appropriate for substance use comorbidities and HIV and HCV risk factors.

Outcomes

The two primary outcomes of the study were sustained virologic response (SVR) at 12 weeks after the end of treatment and cost per patient with SVR. Other secondary outcomes include comparison of conventional laboratory methods (Roche (standard of care) and ABL (potentially lower cost alternative with genotyping and resistance testing included)) and simplified testing (Xpert), and safety (adverse events) during the treatment period. Adverse events were monitored at all clinical visits.

For the cost analysis, we assigned each patient one of the following four outcomes at 24 weeks after treatment initiation:

- Treatment success (sustained virologic response 12 weeks after therapy completion (SVR12)
- Treatment failure (HCV viremia greater than the lower limit of quantification 12 weeks after therapy completion)
- Loss to follow up (did not return to clinic for 24-week evaluation)
- Death within 24-week study period.

Analysis of outcomes

We first describe baseline characteristics of the screened participants, including one or more risk categories for HCV infection, HCV genotype, and co-infections. Means (standard deviation) or medians (interquartile range) were calculated for continuous data. Differences in means or medians were calculated using t test or signed rank test. The proportion with SVR was calculated for each clinical site and overall, by intention to treat. Differences between those successfully treated (those who achieved SVR) compared to those who failed treatment were assessed by t test or chi-square test as appropriate, and by multivariable logistic regression. Data was analysed using STATA version 15 SE (StataCorp 2017. Stata Statistical Software: Release 15. College Station, TX: StataCorp LLC). Correlations and Bland Altman graphs were used to assess how ABL and Xpert compare with Roche as the gold standard method for HCV viral load measurements. The

sensitivity and specificity of the Xpert HCV and ABL viral load test were calculated using Roche as a gold standard.

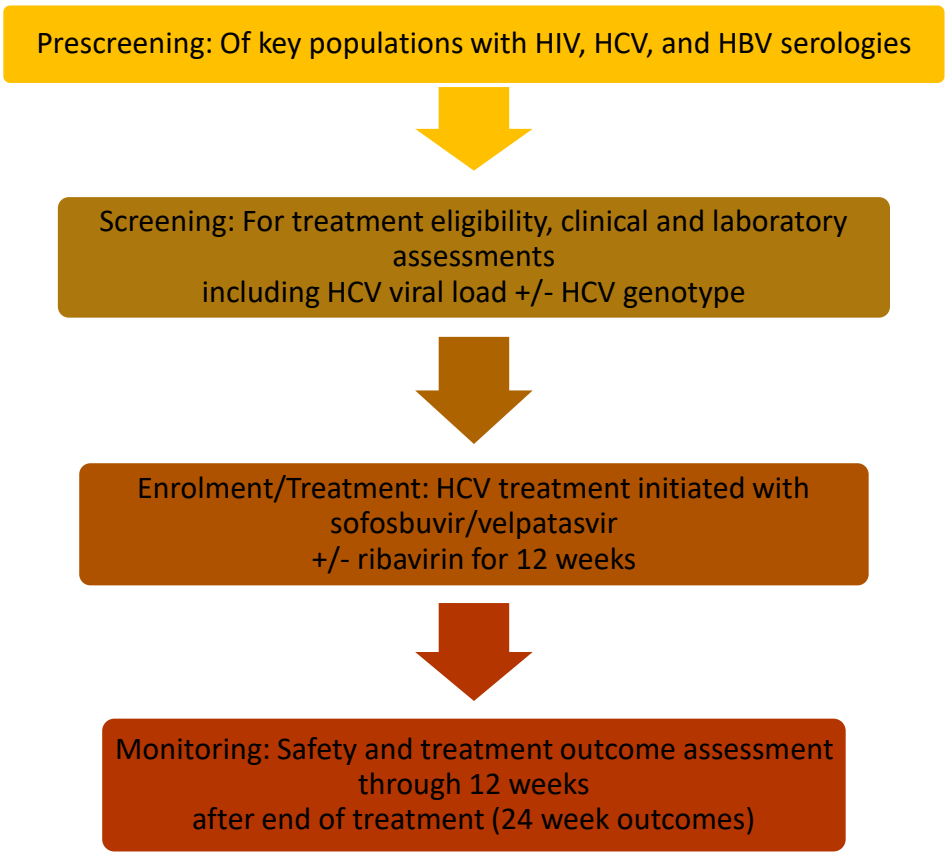


Figure 2: Intervention procedures

Analysis of costs

Cost estimates were made at two sites, Yangon and Mandalay, using data from patients enrolled at these sites. Costs were estimated from the provider perspective from initial screening date until assessment of cure at 12 weeks after HCV treatment completion (24 weeks total) using standard economic methods described previously[19, 20]. Resources incurring costs included: physical exams, counseling visits, laboratory testing, Fibroscan testing (supplies only), HCV and HBV medications, clinic staff, clinic space and overhead, equipment and supplies, and education and outreach. HIV medications were utilized but were paid for separately by the government HIV program and are excluded from the cost analysis. Equipment and technicians' time for Fibroscan testing were donated and are also excluded. We determined variable patient resource utilization from a de-identified dataset compiled from study participant case reporting forms and estimated resource utilization from average clinic site capacity and total annual visits. We then multiplied the quantity of each resource used by each patient by the associated unit cost to determine a total cost per patient.

We also evaluated the average resource utilization per patient by cost category, HCV treatment outcome, and HIV status and determined 95% confidence interval by outcome category. We calculated the production cost of a successful outcome by dividing the sum of all costs by the number of successful outcomes.

For the cost analysis, we considered four scenarios:

1) Observed costs excluding research related expenses (proxy for real world setting)
2) Observed costs including research expenses
3) Removed routine HCV genotype testing from scenario 1
4) Based on outcomes from one of the three study sites, increased the treatment failure rate from scenario 1 to 14% to simulate potential poorer treatment adherence and/or effectiveness in a real-world setting.

We applied the average exchange rate for 2018: 1.00 United States dollar (USD) = 1547.71 Myanmar Kyat (MMK).

The patient resource utilization matrix for this study was generated using SAS software, Version 9.3 (SAS Institute Inc., Cary, NC, USA). Study CRFs and patient data were managed with HepatiC® (ABL SA, Luxembourg). The costs of HCV treatment were estimated using the Healthcare Costs and Outcome Model (http://www.heroza.org/researchtools/the-healthcare-cost-and-outcomes-model-hcom) (HE^{2}RO, Johannesburg, South Africa). Economic models were generated with Excel 2011.

Ethical considerations

The study was reviewed by the Republic of the Union of Myanmar Ministry of Health and Sports Institutional Technical and Ethical Review Board, University of Public Health (ITERB-2017/Research/18), the Human Ethics Committee of the Myanmar Ministry of Health, the University of the Witwatersrand Human Research Ethics Committee (M17078), and the UCLA Medical Institutional Review Board (#18-00003). The Boston University Institutional Review Board approved analysis of a de-identified analytic dataset (H-37820). All patients provided written informed consent. The study is registered at ClinicalTrials.gov (NCT03579576).

RESULTS

Enrollment and patient characteristics

We screened 1007 patients and enrolled those eligible at the three study sites between 18th December 2017 and 17th December, 2018. We excluded 193 of those screened, for the reasons listed in Figure 1, including 112 who did not test positive for HCV RNA. A total of 814 (80.8%) patients were eligible for treatment under the project, of whom 803 initiated treatment and 764 (95.1% of those eligible) completed 24 weeks of follow up. Figure 3 illustrates study enrollment and retention.

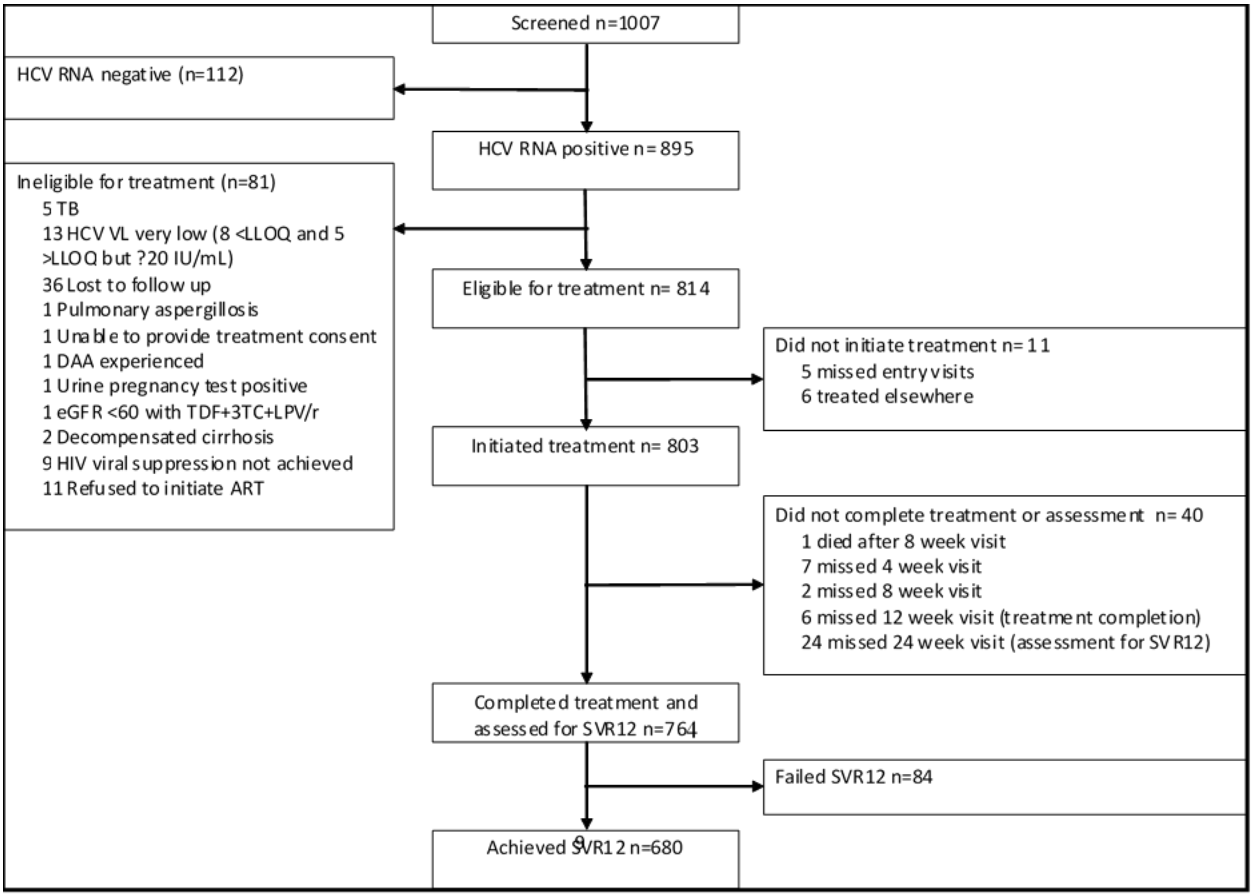


Figure 3: Study enrolment and retention

Characteristics of the cohort are described in Table 1. About 50% of the participants were HCV mono-infected, with most recruited from Yangon and Waimaw, Kachin, and a minority (17% of those screened) from Mandalay. Forty-seven peecent of participants were HIV coinfected (476/1007) and the majority of the HIV coinfected were (443/1007) participants from the AHRN clinic in Waimaw, Kachin.g, a significantly higher proportion than at the other two sites. Out of the 1007 screened participants, 650 were PWID and 402(97.57%) were recruited from Kachin. Most patients assessed were not cirrhotic, but 17% had compensated cirrhosis, mostly from the Yangon clinic. Six hundred eighty-six participants had HCV genotyping results available at the time of this report. Of these, the most common genotypes were 3 (47.9%) and 6 (40.7a %).

Table 1: Patient characteristics at screening, by site

Characteristic	Yangon n=427	Mandalay n=168	Kachin n=412	Total N=1007
Age (Median, Interquartile Range)	43(18 – 70)	35(19 – 71)	31(18 - 65)	36(18 -71)
Gender (%): Female	158(37.00)	17(10.12)	13(3.16)	188(18.67)
Education beyond Primary (%)	359(84.07)	152(90.48)	351(85.19)	862(85.60)
Risk Groups (%)				
MSM and other	11(2.58)	2(1.19)		13(1.29)
PWID and other	126(29.51)	122(72.62)	402(97.57)	650(64.55)
PLHIV / SW and other	17(3.98)	22(13.10)	10(2.43)	49(4.87)
Sexual partner of HCV	26(6.09)			26(2.58)
General Population	247(57.85)	22(13.10)		269(26.71)
Marital Status (%)				
Ever Married	54.4	57.1	67.7	60.5
Mean BMI (Kg/m^2) (Range)	22.4 (14.5 - 39.6)	20.2(12.5 - 31.0)	20.3 (13.8 – 31.2)	20.9 (12.5 -39.6)
Cirrhosis %				
Compensated	114(28.01)	16(9.64)	27(8.63)	157(17.82)
Decompensated			2(0.64)	2(0.23)
No Cirrhosis	293(71.99)	145(90.06)	284(90.73)	722(81.95)
Infection Status (%)				
HCV mono-infected	352(82.44)	99(58.93)	52(12.62)	503(49.95)
HCV/HIV	50(11.71)	65(38.69)	328(78.61)	443(43.99)
HCV/HBV	23(5.39)		5(1.21)	28(2.78)
HCV/HIV/HBV	2(0.47)	4(2.38)	27(6.55)	33(3.28)
Genotype (subtype)				
1	38(11.48)	14(13.73)	6(2.83)	58(8.99)
2	4(1.2)			4(0.62)
3 (3a/3b)	157(47.43)	42(41.18)	113(53.30)	312(48.37)
4	2(0.60)	1(0.98)		3(0.47)
5				
6	129(38.97)	45(44.12)	93(43.87)	267(41.40)
Mixed	1(0.3)			1(0.16)
Median HCV RNA, $Log_{10}IU/mL$	$1.40x10^6$ ($377 – 4.97x10^7$)	$2.01x10^6$ ($11 – 4.73x10^7$)	$2.5x10^6$ ($12 – 6.12x10^7$)	$1.89x10^6$ ($11 – 6.12x10^7$)
Haemoglobin (median, IQR)	13.6(5.3 – 19.1)	14.3(7.3 – 21.4)	13.8(7.2 – 17.7)	13.9(5.3 – 21.4)
Creatinine (Median, IQR)	0.9 (0.5 – 1.8)	0.9 (0.5 -1.6)	0.81(0.28 – 1.6)	0.83(0.28 – 1.8)
ALT (Median, IQR)	248(23 - 504)	240(40 – 409)	182(14 – 454)	226(14 – 504)

Bilirubin	0.5 (0.2 -2.6)	0.5(0.2 – 1.7)	0.46 (0.12 – 3.6)	0.5 (0.12 – 3.6)
Albumin	4.4 (3.1 -5.2)	4.4 (2.9 - 5)	4.08 (3 – 43)	4.3 (2.9 -43)
INR	0.86 (0.66 – 1.23)	0.9 (0.7 – 1.2)	1.2 (0.8 – 1.8)	0.91 (0.66 – 1.8)
Platelets	248 (23 – 504)	240 (40 – 409)	182 (14 -454)	226 (14 -504)

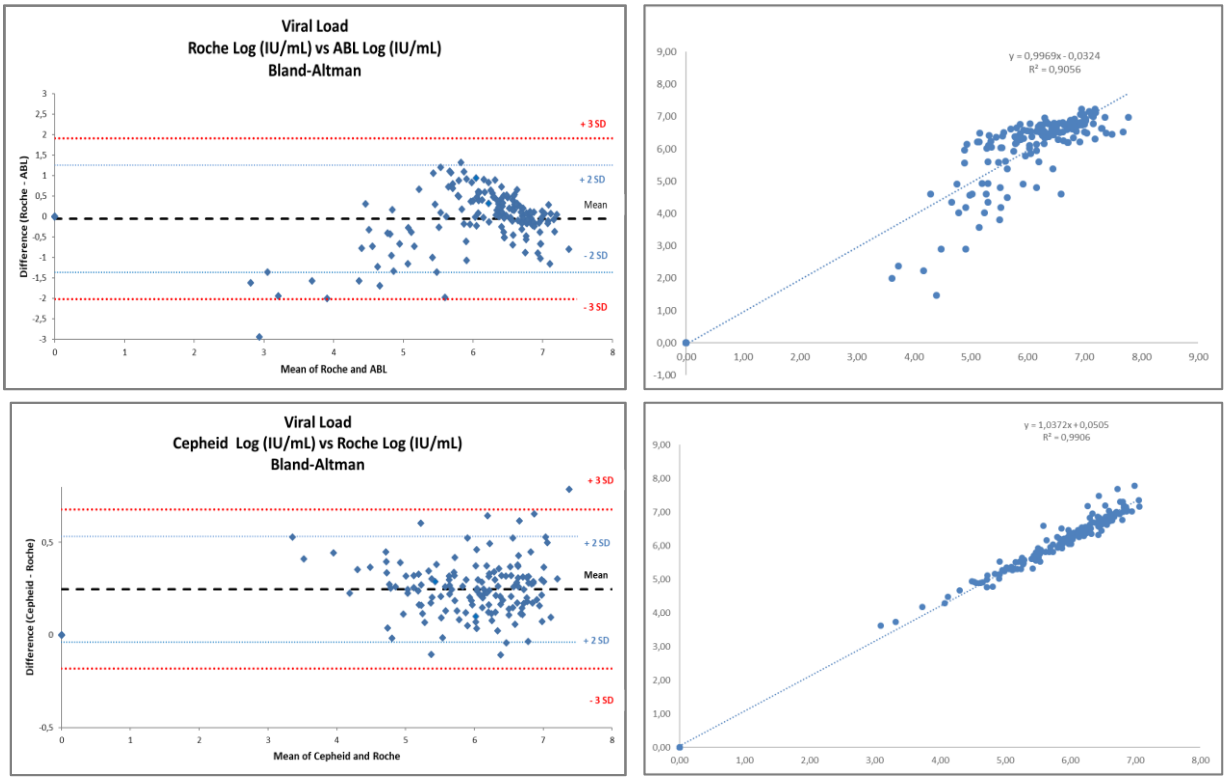
M = male, F = female, HCV = hepatitis C virus, PLHIV = people living with human immunodeficiency virus (HIV) infection, MSM = men who have sex with men, Partner + = sexual partner of HCV infected person, SW = sex worker, PWID = people who inject drugs, MAT= medication assisted treatment, HBV = hepatitis B virus

Genotyping

A total of 645 HCV viremic patients in Yangon, Mandalay, and the Kachin region had genotyping data available at the time of this report. The genotyping and subtyping results are summarized in Table 1, based on sequencing of the 5´UTR region.

Laboratory comparisons at baseline

Both ABL and Cepheid Gene-Xpert were highly correlated with Roche and against each other. There was generally agreement between ABL and Roche and between Xpert and Roche (Figure 4).



	Number of samples	Correlation coefficient R	P value	Critical value (outside + 3SD; -3SD)
Roche vs ABL	181	0,91 strong significant	p < 0.0001 Extremely significant	1
Cepheid vs ABL	164	0,91 strong significant	p < 0.0001 Extremely significant	1
Cepheid vs Roche	164	0,99 strong significant	p < 0.0001 Extremely significant	1

Figure 4: Laboratory assay correlations

Treatment outcomes

Treatment outcomes by site are reported in Table 2. Of the 803 patients who initiated HCV treatment, 12 were treated with ribavirin. There were two adverse events, neither of which was related to study treatment: one grade 3 event with hospitalization for low grade fever and hypokalaemia that was treated and resolved and one death due to tuberculosis. One participant in Kachin was found to be pregnant 8 weeks into treatment and elected to continue HCV treatment after the risks and benefits were reviewed.

After treatment initiation, 40 participants were counted as lost to follow with missing visits (see figure 3) 1 patient died, and 24 were known to have completed treatment but missed the week 24 SVR assessment. A total of 764 participants were assessed for SVR at 24 weeks. By intention-to-treat analysis, 123 failed with an overall treatment success rate of 680/803 (85%). SVR rates differed significantly by site, risk group, HIV coinfection with the greatest number of treatment failures (HCV viremia above the limit of quantification at week 24) and loss to follow up in Kachin.

Table 2: Study outcomes at 24 weeks after study enrollment, by site

Outcome (n, %)	Yangon	Mandalay	Kachin	Total
Treatment success (cure)	347 (96)	110 (83)	223 (72)	680 (85)
Treatment failure	8 (2)	9 (7)	67 (22)	84 (10)
Lost to follow up after treatment initiation	4 (1)	13 (10)	21 (7)	38 (5)
Died	1 (0)	0 (0)	0 (0)	1 (0)
Total	360 (100)	132 (100)	311 (100)	803 (100)

There were two adverse events, neither of which was related to study treatment: one grade 3 event with hospitalization for low grade fever and hypokalaemia that was treated and resolved and one death due to tuberculosis. A total of 764 were assessed for SVR at 24 weeks. Of these 680 (89%) achieved SVR by per protocol analysis. By intention-to-treat analysis, 124 failed with an overall treatment success rate of 680/803 (84.6%). SVR rates differed significantly by site, with the greatest number of treatment failures and loss to follow-up in Kachin. Treatment failure was more among the PWID than other groups. Out of 497 PWIDS assessed for SVR12, 76.8% achieved SVR. Those on Opiod Substitution Therapy were more likely to achieve SVR12. There were 231 patients where data was available regarding initiating OST and 297 without OST and of these 89.6% on OST achieved SVR12 compared to 76.4% who achieved SVR12 among those not on OST.

Predictors of SVR

In Tables 3 and 4, characteristics of participants are compared between the SVR group and the treatment failure group by per protocol (Table 3) and intention to treat analysis (Table 4). In both models, there were significant differences in the odds of achieving a successful treatment response by treatment site, age, being a PWID, gender, and HIV status. There was no association between HCV genotype and treatment response.

Table 3: Factors influencing success of therapy (per protocol, N=764)

Characteristic	Failure-Detected; n=84	Success-Undetected; n=680	Per Protocol N=764	Test Statistics, p-value	OR (95%CI)	p-value
Region				Chi-Square=72.94, p<0.001		
Kachin	67(79.76)	224(32.79)	290(37.96)		1.00 (ref)	
MLF Mandalay	9(10.71)	110(16.18)	119(15.58)		1.40(1.03-1.90)	0.030
MLF Yangon	8(9.52)	347(51.03)	355(46.47)		1.53(1.23-1.92)	0.001
Age (Median, Interquartile Range)	*30.5(19-65)*	*38(18-70)*	*37(18 -70)*	Z=5.278, p<0.001	1.10 (1.00 – 1.02)	0.027
Gender (%): Female	2(2.38)	161(23.71)	163(21.36)	Chi-Square=21.44, p<0.001	1.00 (ref)	
Male	81(96.63)	517(75.99)	597(78.24)		0.78 (0.61 – 1.00)	0.05
Transgender (M to F)	1(1.19)	2(0.29)	3(0.39)		0.51(0.79 -2.84)	0.444
Education				Chi-Square=0.0122, p=0.912		
Primary and below	12(14.29)	94(13.84)	106(13.89)		1.00 (ref)	
Beyond Primary	72(85.16)	585(86.16)	657(86.11)		1.01(0.75 - 1.35)	0.944
Risk Groups (%)				Fisher's Exact p<0.001		
MSM and other	1(1.19)	9(1.33)	10(1.31)		0.84(0.58-1.22)	0.363
PWID and other	78(93.86)	376(55.38)	454(59.50)		0.72(0.67-0.78)	<0.001
PLHIV / SW and other	2(2.38)	38(5.6)	40(5.24)		0.98(0.82-1.16)	0.780
Sexual partner of HCV		24(3.53)	24(3.15)		1.03(0.99-1.06)	0.082
General population	3(3.57)	232(34.17)	235(30.80)		1.00 (ref))	
Marital Status (%)				Chi-Square=5.90, p=0.015		
Single	42(50.00)	247(36.38)	289(37.88)		1.00 (ref)	
Ever Married	42(50.00)	432(63.62)	474(62.12)		1.13(0.92-1.39)	0.262
Mean BMI (Kg/m^2) (Range)	20.12(15.55 - 32.52)	21.37(12.55 - 39.56)	21.19(12.55-39.58)	z = 3.75, p=0.0002	1.019(0.99-1.05)	0.168
Cirrhosis %				Chi-Square=7.35, p=0.007		
Compensated	6(7.14)	130(19.15)	136(17.82)		1.00 (ref)	
Decompensated						

No Cirrhosis	78(92.86)	549(80.85)	627(82.18)		0.84(0.65-1.09)	0.188
Infection Status (%)				Fisher's Exact, p<0.001		
HCV mono-infected	9(10.71)	395(58.17)	404 (52.95)		1.00 (ref)	
HCV/HIV	70(83.33)	253(37.26)	323(42.33)		0.68(0.55 - 0.84)	0.0001
HCV/HBV		20(2.95)	20(2.95)		1.05(0.55 - 1.97)	0.891
HCV/HIV/HBV		11(1.62)	16(2.10)		0.55(0.26 - 1.15)	0.112
Genotype (subtype)				Fisher's exact = 0.332		
1	2(3.03)	55(10.15)	57(9.38)		1.00 (ref)	
2		4(0.74)	4(0.66)		1.07(0.26 - 4.50)	0.924
3 (3a/3b)	36(54.55)	256(47.23)	292(48.03)		0.84(0.56 - 1.25)	0.387
4		3(0.55)	3(0.49)		1.07(0.21 - 5.54)	0.933
5						
6	28(42.42)	224(41.33)	252(41.45)		0.86(0.57 - 1.29)	0.708
Mixed						
Median HCV RNA, Log_{10}IU/mL	$1.73x10^7$(50-6.12 $x10^7$)	$2.78x10^7$(1040-5.42 $x10^7$)	$1.97x10^7$(50-6.12 $x10^7$)	z = -1.85, p=0.0649		
Haemoglobin (median, IQR)	13.85(10 – 17.2)	13.9(5.3 – 21.4)	13.9(5.3 – 21.4)	z=0.621, p=0.5348	1.01(0.95 -1.07)	0.825
Creatinine (Median, IQR)	0.845(0.55 – 1.36)	0.84(0.28 -1.8)	0.84(0.28 -1.8)	z=0.406, p=0.6849	1.08(0.62 - 1.86)	0.792
ALT (Median, IQR)	38.5(8 - 149)	45(4.3 – 610)	44(4.3 – 610)	z=1.55, p=0.2073	1.01(0.99 - 1.00)	0.476
Bilirubin	0.405(.17 – 2.37)	0.5(0.2 – 2.3)	0.5(0.17 – 2.37)	z=1.55, p=0.1219	1.09(0.78 - 1.53)	0.616
Albumin			4.1(3.2 – 42.9)		0.99(0.97 - 1.01)	0.196
INR	1.2(0.66 – 1.58)	0.9(0.68 -1.8)	0.9(0.66 – 1.8)	z=-7.710, p<0.0001	0.43(0.27 – 0.69)	0.0001
Platelets	192(39-390)	229(14-504)	225(14-504)	z=3.83, p=0.0001	1.00(0.99 - 1.00)	0.118

Table 4: Factors influencing success of therapy (intention to treat, N=803).

Characteristic	Failure-Detected; n=124	Success-Undetected; n=680	Intention to Treat N=803	Test Statistics, p-value	OR (95%CI)	p-value
Region				Chi-Square=80.09, p<0.001		
Kachin	89(71.77)	223(32.70)	311(38.73)		1.00 (ref)	
MLF Mandalay	22(17.74)	110(16.20)	132(16.44)		1.31(0.97 – 1.75)	0.074
MLF Yangon	13(10.48)	347(51.10)	360(44.83)		1.68(1.35 – 2.09)	0.0001
Age (Median, Interquartile Range)	*30(19 -65)*	*38(18-70)*	*37(18 -70)*	z=-6.80, p<0.0001	*1.02(1.01 – 1.02)*	0.001
Gender (%): Female	2(1.61)	161(23.71)	163(20.30)	Chi-Square=32.11, p<0.001	1.00 (ref)	
Male	121(97.58)	516(75.99)	637(79.33)		0.70(0.55 - 0.89)	0.004
Transgender (M to F)	1(0.81)	2(0.29)	3(0.37)		0.51(0.09– 2.84)	0.444
Education				Chi-Square=0.82, p=0.366		
Primary and below	21(16.94)	94(13.84)	115(14.32)		1.00 (ref)	
Beyond Primary	103(83.06)	585(86.16)	688(85.68)		1.07(0.81 – 1.43)	0.626
Risk Groups (%)				Fisher's Exact, p<0.001		
MSM and other	1(0.81)	9(1.33)	10(1.25)		0.85(0.58-1.23)	0.386
PWID and other	116(93.55)	376(55.38)	492(61.27)		0.64(0.59-0.70)	<0.001
PLHIV / SW and other	3(2.42)	38(5.6)	41(5.11)		0.94(0.77-1.14)	0.516
Sexual partner of HCV		24(3.53)	24(2.99)		1.03(1.01-1.07)	0.044
Not available	4(3.23)	232(34.17)	236(29.39)		1.00 (ref))	
Marital Status (%)				Chi-Square=12.51, p<0.0001		
Single	66(53.23)	247(36.38)	313(38.98)		1.00 (ref)	
Ever Married	58(46.77)	432(63.62)	490(61.02)		1.21(0.99 – 1.49)	0.062
Mean BMI (Kg/m^2) (Range)	19.83(14.55 – 32.52)	21.37(12.55 - 39.56)	21.08(12.55-39.58)	z = -4.83, p<0.0001	1.03(1.00 – 1.06)	0.031
Cirrhosis %				Chi-Square=8.94, p=0.001		
Compensated	10(8.06)	130(19.15)	140(17.43)		1.00 (ref)	
Decompensated						
No Cirrhosis	114(91.94)	549(80.85)	663(82.57)		0.80(0.620-	0.098

					1.04)	
Infection Status (%)				Fisher's Exact, p<0.001		
HCV mono-infected	20(16.13)	395(58.17)	415(51.68)		1.00 (ref)	
HCV/HIV	98(79.02)	253(37.26)	351(43.71)		0.02 (0.51 - 0.77)	0.0001
HCV/HBV		20(2.95)	20(2.49)		1.10(0.58 – 2.07)	0.766
HCV/HIV/HBV	6(4.84)	11(1.62)	17(2.12)		0.53(0.25– 1.09)	0.086
Genotype (subtype)				Fisher's exact, p=0.152		
1	3(3.09)	55(10.15)	58(9.08)		1.00 (ref)	
2		4(0.74)	4(0.63)		1.11(0.27 – 4.65)	0.887
3 (3a/3b)	53(54.64)	256(47.23)	309(48.36)		0.78 (.53 – 1.17)	0.232
4		3(0.55)	3(0.47)		1.11(0.22 – 5.73)	0.902
5						
6	41(42.27)	224(41.33)	265(41.47)		0.81(0.54 – 1.22)	0.311
Mixed						
Median HCV RNA, Log_{10}IU/mL	$2.52x10^7$(541-5.42 $x10^{7)}$	$1.73x10^7$(50-6.12 $x10^{7)}$	$1.97x10^7$(50-6.12 $x10^{7)}$	z = 1.761, p=0.0783		
Haemoglobin (median, IQR)	13.9(10 – 17.2)	13.9(5.3 – 21.4)	13.9(5.3 – 21.4)	z=0.090, p=0.9280	0.99(0.94 – 1.06)	0.960
Creatinine (Median, IQR)	0.825(0.49 – 1.36)	0.84(0.28 -1.8)	0.83(0.28 – 1.8)	z=-1.077, p=0.2815	1.19(0.70 – 2.05)	0.521
ALT (Median, IQR)	40.85(8 - 252)	45(4.3 – 610)	44(4.3 - 610)	z=-0.722, p=0.4703	1.00(0.99 – 1.00)	0.571
Bilirubin	0.435(0.117 – 2.37)	0.5(0.2 – 2.3)	0.5(0.117 – 2.37)	z=-1.279, p=0.2010	1.09(0.78 – 1.52)	0.608
Albumin	4.1(3 – 42.9)	4.3(2.9 - 43)	4.3(2.9 – 43)	z=-2.56 ,p=0.0106	0.98(0.97 – 1.01)	0.143
INR	1.2(0.66 – 1.8)	0.9(0.68 -1.8)	0.91(0.66 – 1.8)	z=7.518, p<0.0001	0.39(0.24 - 0.62)	0.0001
Platelets	206(39 - 451)	229(14-504)	226(14 - 504)	z=-2.968, p=0.003	1.00(0.10 – 1.02)	0.178

Resource utilization and unit costs

As mentioned above, economic evaluation was limited to the Mandalay and Yangon sites. For each of the 492 participants from these sites included in the cost analysis dataset, we tabulated the number of physical exams, counseling visits, laboratory assessments, Fibroscan evaluations, and medications for HCV and HBV during the 24-week follow up period, as reported in Table 5. Actual resource utilization included more physician examinations than specified in the study protocol, while the remaining resources were as anticipated. HIV treatment costs were not included, beyond the initial HIV diagnostic test.

Figure 5: Median resource utilization per participant during the 24-week study period

Resource	Median number utilized per patient	Cost per unit (USD)
Physical exam	3	22.32
Counseling visit	4	5.39
Fibroscan (supplies only)	1	45.23
HCV RNA (Ni-Ni lab or GeneXpert)	2	80.00
HCV genotype (ABL)	1	50.00
Liver tests (ALT, AST, albumin, bilirubin)	2	8.00
CBC (Hb, Plt)	2	5.04
Creatinine	2	5.00
INR/Prothrombin time	2	2.00
HIV screening antibody rapid test	1	1.00
HBV rapid test (Surface Ab, Core Ab, Surface Ag)	1	1.00
SOF/VEL (HCV medication) (tablets; mean cost /24 week study period)	84	555.00
Ribavirin (HCV medication) (tablets; mean/24 week study period)*	123	83.00
HBV medication cost (mean/24 week study period)	84	33.60

HCV = hepatitis C virus, Ni-Ni = centralized processing lab and current standard of care at the time of study implementation, RNA = ribonucleic acid, ALT = alanine aminotransferase, AST = aspartate aminotransferase, CBC = complete blood count, Hb = hemoglobin, Plt = platelet count, INR = international normalized ratio, PT = prothrombin time, HIV = human immunodeficiency virus, HBV = hepatitis B virus, Ab = antibody, Ag = antigen

*12 patients were prescribed ribavarin at either 400 or 500mg/tablet

Cost per patient treated

Table 6 presents key results for the four scenarios modeled. A more detailed presentation of scenarios 1 and 2, which represent expenses incurred in implementation of the pilot project, is provided later in this section.

Table 5: Treatment and successful outcome production costs, by scenario

Scenario	Cost per patient treated (USD)	Production cost of successful outcome (USD)*
1) Research expenses removed	1,030	1,109
2) Actual demonstration project	1,129	1,216
3) Routine genotype testing removed	980	1,055
4) Increased treatment failure to 14%	1,030	1,248

*Production cost per successful outcome = all costs for cohort/number of successful outcomes

While there was not a great deal of variation in cost per patient or production cost of a successful outcome by scenario, removing both research expenses and routine genotype testing minimized the cost per patient. If the treatment failure rate increased to 14% (scenario 4), though, the production cost per successful outcome would climb substantially.

Scenario 1

Scenario 1, which reflects observed costs minus expenses related to research, represents the likely "real world" scenario for the protocol intervention. Costs under Scenario 1 by outcome, with average component, are shown in Table 7. Indirect costs include support staff/personnel, building costs, office supplies. Events include physical exams (physician visit), counseling visit, Fibroscan. Labs include HCV RNA modeled using the centralized laboratory pricing (Ni-Ni lab), HCV genotyping, HIV and HBV testing, pregnancy testing if applicable, PT/INR, and blood counts and chemistries. Cost for research staff, education and outreach activities, tariffs and shipping charges for supplies accrued during the research study were removed from this scenario.

Table 6: Cost/patient by outcome in Scenario 1 in USD, for n=492 included in cost analysis

Outcome*	N	%	Indirect costs	Events	Labs	Drugs	Mean (SD) cost per outcome
Success	457	93%	107	113	258	557	1,035 (20)
Failure	17	3%	113	115	264	555	1,047 (20)
Lost after treatment initiation	17	3%	79	86	156	555	876 (24)
Death	1	0%	74	84	152	555	864 (N/A)
All outcomes	492	100%	106	112	255	557	1,030 (20)

USD = United States dollar, SD = standard deviation. *Only patients at Yangon and Mandaley sites.

If all patients had successful outcomes, the average cost per patient in this scenario would be $1,035. As would be expected, losing patients before completion of treatment reduces costs, because they do not receive the full course of medications or other services, but it also utilizes resources that do not contribute to successful outcomes. This increases the production cost for a successful outcome by 7%.

Scenario 2

Scenario 2 also reflects observed costs but includes all in-country expenses for the project, not just those likely to be incurred under routine care (Scenario 1). The cost per patient under Scenario 2, by outcome and component, is shown in Table 8. Indirect costs include support staff/personnel, building costs, office supplies, education and outreach activities, tariffs and shipping charges for supplies. Events include physical exams (physician visit), counseling visits, and Fibroscans.

Table 7: Cost/patient by outcome in Scenario 2 in USD, for n=492 included in cost analysis

Outcome*	N	%	Indirect costs	Events	Labs	Drugs	Mean (SD) cost per outcome
Success	457	93%	208	113	258	557	1,136 (25)
Failure	17	3%	218	115	264	555	1,152 (27)
Lost after treatment initiation	17	3%	153	86	156	555	950 (38)
Death	1	0%	142	84	152	555	933
All outcomes	492	100%	187	101	252	461	1,129 (27)

USD = United States dollar, SD = standard deviation. *Only patients at Yangon and Mandaley sites.

As expected, indirect costs/outcome were substantially higher in Scenario 2, which captures the research costs of implementing and evaluating the demonstration project.

DISCUSSION

In a demonstration project of a simplified protocol for treating HCV among key populations in Myanmar, 85% of patients who initiated HCV treatment achieved SVR. Among those who did not, 10% failed therapy and 5% were lost to follow up before the final 24-week assessment of outcomes. Success varied widely by site, however, with Yangon achieving 96% SVR and Kachin only 72%. Greater treatment "failure" is in part explained by greater lost to follow-up rates in Mandalay and Kachin, where those lost to follow-up were considered treatment failures by intention to treat analysis, as SVR could not be assessed. While adherence to HCV treatment was not measured, it is suspected that poorer adherence to treatment in Mandalay and Kachin, where there were more PWID enrolled and amongst whom treatment adherence may be challenging, is also likely to have contributed. Of note, preliminarily, the SVR rate amongst PWID on MAT appears to be high and similar to rates amongst non-PWID, compared to the SVR rate amongst PWID not on MAT, suggesting that PWID status alone may not adversely impact treatment success if those persons are linked to substance use and harm reduction treatment.

The estimated average cost of treatment per patient initiated on HCV therapy was $1030, and cost per patient achieving SVR12, including resources used for patients who did not achieve this outcome, was $1,109. The small handful of patients who did not achieve sustained virologic response cost slightly more/patient. In case real-world effectiveness of our intervention country-wide is closer to that achieved by averaging SVR rates across all three sites (i.e. different treatment settings, including treatment settings such as Kachin, where SVR rates were substantially lower), we performed a sensitivity analysis using a reduced SVR rate of 86%. This resulted in a 12% increase in the production cost of a successful outcome, to an average of $1,248 to produce a successful outcome.

The production cost for a successful outcome reported here ($1109/patient) is modeled utilizing confirmatory HCV RNA pricing negotiated for the project through Ni-Ni labs. Other confirmatory HCV tests, including those that can be performed at or near the point of care, may allow further

reductions in the laboratory cost components, though difficulties with implementation of new technologies that rely on foreign imports for parts and servicing may offset cost savings. Since this demonstration project utilized a pan-genotypic drug, we also modeled further reductions in the laboratory cost component with elimination of genotype testing, reducing the cost/patient to the lowest in the analysis.

For budgeting purposes, under the assumption of no genotype testing and decreased real-world effectiveness (lower SVR and retention rates), an average cost of $1250/patient is likely a reasonable estimate for this intervention. Costs will decrease if programs can reduce loss to follow up and failure rates. The cost/patient, though, does not include costs for scaling up or maintaining the treatment program, such as procurement, training, management, and oversight, or costs of screening and confirmatory testing for those who do not further engage in care. Although much less than seen in high-income countries, a cost of $1250/patient will likely be challenging to pay for a country with per capita health expenditures estimated at $62/year[21]; assistance in the form of drug donations from manufacturers and/or foreign donor investments will likely be needed for scale up of treatment.

This analysis had several limitations. As with any intention to treat analysis, given the loss to follow-up and inability to assess SVR in some participants, the true SVR rate is likely slightly underestimated in this report. As such some patients, completed treatment but were not able to be assessed for SVR12 due to complexes circumstances such as imprisonment. While the four cost scenarios presented aimed to provide a reasonable estimate of the costs across a range of treatment, resource, and population settings in Myanmar, the cost results were based on Yangon and Mandalay treatment outcomes and costs only, excluding those from Kachin. The poorer treatment outcomes and likely higher cost of resource inputs in Kachin, resulting from its more remote location, were not taken into account.

Conclusions

Overall, SVR rates with pan-genotypic SOF/VEL were high for diverse and key populations bearing the burden of HCV infection in Myanmar. These SVR rates were high even with treatment implemented in regions with limited resources for HCV testing and treatment monitoring. HCV

viral load testing remains a limitation to identifying persons eligible for treatment (i.e. HCV viremic patients) and may be improved with a point of care assay to detect HCV viremia or antigenemia, particularly in regions such as Kachin, where access to laboratory instruments is limited. Though being PWID was a risk factor for treatment failure, concurrent MAT during the period of HCV treatment improved SVR rates. Linkage to substance use disorder treatment services is critical to HCV elimination in this population.

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