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Epidemiological characteristics and real-world treatment outcomes of hepatitis C among HIV/HCV co-infected patients in Myanmar: A prospective cohort study

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Abstract

Background and Aims: In Myanmar, public sector treatment programs for hepatitis C virus (HCV) infection were nonexistent until June 2017. WHO highlights the importance of simplification of HCV service delivery through task-shifting among health workers and decentralization to the primary health care level. Between November 2016 and November 2017, a study was conducted to describe the epidemiological data and real-world outcomes of treating HIV/HCV coinfected patients with generic direct acting antiviral (DAA) based regimens in the three HIV clinics run by nonspecialist medical doctors in Myanmar.

Methods: HCV co-infection among people living with HIV (PLHIV) from two clinics in Yangon city and one clinic in Dawei city was screened by rapid diagnostic tests and confirmed by testing for viral RNA. Nonspecialist medical doctors prescribed sofosbuvir and daclatasvir based regimens (with or without ribavirin) for 12 or 24 weeks based on the HCV genotype and liver fibrosis status. Sustained virologic response at 12 weeks after treatment (SVR12) was assessed to determine cure.

Results: About 6.5% (1417/21,777) of PLHIV were co-infected with HCV. Of 864 patients enrolled in the study, 50.8% reported history of substance use, 27% history of invasive medical procedures and 25.6% history of incarceration. Data on treatment outcomes were collected from 267 patients of which 257 (96.3%) achieved SVR12, 7 (2.6%) failed treatment, 2 (0.7%) died and 1 (0.4%) became loss to follow-up.

Conclusion: The study results support the integration of hepatitis C diagnosis and treatment with DAA-based regimens into existing HIV clinics run by nonspecialist medical doctors in a resource-limited setting. Epidemiological data on HIV/HCV

co-infection call for comprehensive HCV care services among key populations like drug users and prisoners in Yangon and Dawei.

KEYWORDS
epidemiology, hepatitis C, HIV, Myanmar, sustained virologic response

1 | INTRODUCTION

The hepatitis C virus (HCV) is a major public health problem worldwide. The World Health Organization (WHO) estimated that there were 58 million people with chronic HCV infection worldwide in 2019, with about 1.5 million new infections annually.[1,2] To eliminate viral hepatitis as a public health threat by 2030, WHO has set targets to diagnose 90% of the people infected with HCV and treat 80% of eligible HCV infected people by 2030.[1,2] In 2019, only about 21% of people (15.2 million) with hepatitis C knew their HCV status and about 62% of people (9.4 million) diagnosed with chronic HCV infection had been treated with direct-acting antivirals (DAA).[1,2]

Challenges in access to diagnostics and treatment for HCV disproportionately affect developing countries. In low-income countries, less than 10% of people infected with HCV had been diagnosed, compared to over 40% in high-income countries.[3] Although second-generation DAA-based regimens with very high efficacy and great safety profiles became available in 2014,[4] many people with hepatitis C remain untreated because of inadequate funding and varying costs of testing and treatment.[2,3] For efficiency, WHO highlights the importance of simplification of HCV service delivery through task-shifting among health workers and decentralization to primary health-care level.[5]

The HCV burden is concentrated among people who inject drugs (PWID), prisoners, men who have sex with men (MSM) and other vulnerable populations like migrants, refugees, and indigenous peoples.[5] Moreover, approximately 2.3 million (6.2%) people living with HIV (PLHIV) have current or past co-infection with HCV and many of them are from low- and middle-income countries.[2,6,7] Because of the shared modes of transmission of the viruses, a HIV/HCV co-infection is very common among PWID. In Myanmar, the HCV prevalence among PWID was estimated to be 56% compared to 2.7% among the general population[8,9] and about 26.8% of PWID had a HIV/HCV co-infection.[9] Untreated HCV co-infection among PLHIV can cause rapid progression to significant liver damage, hepatocellular carcinoma and untimely death.[10] Therefore, WHO prioritizes the integration of HCV care into shared programs like HIV clinics and harm reduction facilities to increase access to hepatitis C testing and treatment in low- and middle-income countries.[5]

Myanmar Ministry of Health and Sports (MoHS) established the National Hepatitis Control Program (NHCP) in 2014 which primarily focused on the preventive services for viral hepatitis.[11] Public sector free-of-charge treatment programs for hepatitis C with DAA-based regimens only started in June 2017.[11–13] Between November 2016 and November 2017, Médecins Sans Frontières (MSF) conducted a study to describe the real-world outcomes of the integration of hepatitis C diagnosis and treatment with DAA-based regimens into three existing HIV clinics run by nonspecialist medical doctors in Yangon and Dawei cities of Myanmar. The study also intended to provide the epidemiological data such as prevalence and risk factors associated with HCV infection among PLHIV so that more contextualized hepatitis C control activities can be carried out in these two resource-limited and distinct geographic areas.

2 | METHODS

2.1 | Study sites and population

In 2014, MSF, in collaboration with NHCP, set up a systematic screening for HCV of PLHIV in the three MSF HIV clinics: Thaketa and Insein clinics in Yangon, and Myittar Yeik (MTY) clinic in Dawei. Between November 2016 and November 2017, a prospective cohort study on the treatment of hepatitis C among PLHIV in the three MSF HIV clinics was conducted.

Thaketa and Insein clinics are in the periphery of Yangon, the largest port city in Myanmar, and both clinics applied the same treatment protocol for HCV under the supervision by a common medical team. The two clinics had a combined cohort of approximately 17,000 PLHIV during the study period. Likewise, MTY clinic in Dawei city of Tanintharyi Region in the south-eastern part of Myanmar was providing care for about 2400 PLHIV during the study period.

2.2 | Inclusion and exclusion criteria

Adult PLHIV with an active HCV infection who gave informed consent were included in the study. The only exclusion criterion was minors under 18 years. Eligibility for the treatment of hepatitis C was not linked to the inclusion into the study and the treatment was considered for all adult patients with an active HCV infection, including those with the history of treatment for hepatitis C. Patients ineligible for treatment at the time of the study included those with hepatocellular carcinoma (HCC), terminal illnesses, uncontrolled opportunistic infections, uncontrolled severe psychiatric disease, poor adherence to medication, lactating women, pregnant women, and women planning to get pregnant or unwilling to use contraception during the course of the treatment of hepatitis C.

2.3 | Model of HCV care

In MSF clinics, multidisciplinary teams were trained to provide care for HIV, related comorbidities and co-infections including HCV. There were 11 nonspecialist medical doctors (eight in Yangon and three in Dawei) who provided the hepatitis C treatment integrated into the routine HIV care. Nurses (22 in Yangon and 7 in Dawei) did consultations on stable PLHIV with undetectable HIV VL and referred patients with opportunistic infections or co-infections to medical doctors. Health promotion counselors (10 in Yangon and 9 in Dawei) ensure the proper screening for HIV and HCV using rapid diagnostic tests (RDTs), pretreatment counseling for both HIV and HCV, adherence management, tracing of patients missing a scheduled appointment, and post-treatment counseling for HCV. Specialist MSF medical advisors and one national hepatologist from MoHS provided support to the clinic teams for complex cases.

Integrated into the routine HIV care, our patients received a comprehensive care package based on the 2015 recommendations of the European Association for the Study of the Liver (EASL).[14] All PLHIV attending the three MSF clinics were screened for HCV antibody using OraQuick® HCV test (OraSure Technologies). For patients tested positive for HCV antibody, an active HCV infection was confirmed by the presence of HCV RNA using a near point-of-care platform, Cepheid's Xpert® HCV Viral Load test (Cepheid) with a lower limit of quantification at 10 IU/mL. Cepheid's Xpert® platform was already in use in the three MSF HIV clinics for the detection of HIV viral load (VL) as part of the routine monitoring of HIV care and for the detection of rifampicin resistance among new cases of tuberculosis. HCV VL above 800,000 IU/L was considered a high baseline value.[15] HCV genotype results were used to guide treatment options for treatment-eligible patients. As genotyping was not widely unavailable in Myanmar at the time of the study, HCV genotyping was done in the Geneva University Hospitals in Switzerland (HUG) and the University Medical Center Utrecht in the Netherlands (UMC Utrecht) by using dried blood spots (DBS). Nucleic acid was extracted from eluted DBS using EMAG extraction plate-form (bioMérieux) in HUG and MagNA Pure 96 DNA and Viral NA large volume kit (Roche) in UMC Utrecht according to respective manufacturer's instructions. RT-PCR was then performed to obtain amplicons from the core, NS5A, and NS5B regions. The resulting DNA products were sequenced by applying Sanger sequencing method. For DNA sequencing, HUG used BigDye® Terminator on ABI 3500XL (Thermo Fisher Scientific) and UMC Utrecht used DeepChek® SingleRound RT-PCR and Sequencing NS5B/5'UTR Assay, and DeepChek® Assay CORE v1 (Advanced Biological Laboratories). The sequences obtained were aligned and analyzed using SmartGene IDNS (SmartGene) in HUG, and ReCall v2.30.1 (University of British Columbia) in UMC Utrecht. A threshold for similarity of a minimum of 85% was used to consider the genotype or subtype.

Before treatment initiation, patients with an active HCV infection were clinically and biologically assessed. Screening for depressive symptoms and alcohol dependency was done using the Patient Health Questionnaire-9 (PHQ9) and the Alcohol Use Disorders Identification Test (AUDIT) scales. Patients were screened for hepatitis B virus surface antigen (HBsAg) using RDTs and if positive, tenofovir-based antiretroviral regimen was provided to patients who were not already taking it to prevent the reactivation of hepatitis B virus (HBV). Several laboratory tests including complete blood count, CD4 count, HIV VL, liver and renal function tests, glucose, and pregnancy test were performed.

Liver fibrosis was evaluated by trained medical doctors using a noninvasive transient elastography method with FibroScan®. The METAVIR fibrosis stages for HIV/HCV co-infected patients were set at F0-F1 (<7 kPa), F2 (<11.5 kPa), F3 (11.5 to <14 kPa) and F4 (14 kPa or greater).[16] Patients with F3 and F4 were prioritized for treatment due to limitations in the availability of medication at the time of the study while those with less advanced fibrosis stages were registered on a waiting list until more medication became available. To evaluate cirrhosis status, F4 patients were tested additionally for INR, total bilirubin and albumin. Compensated cirrhosis was defined as a Child-Pugh score ≤6. Ultrasound was used to assess HCC when suspected based on a combination of clinical and laboratory findings.

Eligible patients were initiated with sofosbuvir (SOF) 400 mg and daclatasvir (DCV) 60 mg, with or without ribavirin for 12 or 24 weeks depending on their HCV genotype and liver fibrosis status. Daclatasvir dose was adjusted according to the HIV treatment regimen: 90 mg for patients receiving efavirenz or nevirapine and 30 mg for those taking atazanavir/ritonavir and cobicistat-containing antiretroviral regimens. Ribavirin dose was adjusted according to body weight, hematological and renal conditions. Follow-up visits after treatment initiation included clinical and laboratory monitoring to detect adverse events. In particular, hemoglobin values, renal and liver functions were monitored regularly. Other laboratory tests were performed based on clinical findings and clinician's recommendations. HCV VL was done at the end of the treatment course with an additional test 12 weeks after for the evaluation of final treatment outcomes.

During each visit, all patients also accessed existing MSF patient support, education and counseling services where health promotion counselors provided individual counseling sessions to ensure good adherence to medication and health advice on HCV infection. Patients could also discuss with counselors about social and psychological challenges encountered throughout the treatment course. The total follow-up duration for study patients ranged from 24 weeks to 36 weeks once the treatment had started depending on the assignment of 12- or 24-week DAA based regimen.

2.4 | Data collection

Demographic characteristics such as age, gender, marital status and HCV risk factors were collected by medical doctors during a baseline interview using standardized questionnaires. In addition, data on clinical signs, and laboratory results were collected both at baseline and follow-up visits. All the data were transferred electronically to Research Electronic Data Capture (REDCap) software using a password-protected account.

2.5 | Outcomes

The primary outcome was a sustained virologic response 12 weeks after treatment completion (SVR12). SVR12 was defined as an unquantifiable HCV VL 12 weeks post-treatment using the Xpert® platform. Other outcomes included loss to follow-up (LTFU) before or after treatment completion, and death before or after treatment completion. LTFU was defined as patients not showing up for follow-up 2 months after the last clinical appointment excluding deaths or transferred patients. We also described adverse events during the treatment of hepatitis C.

2.6 | Data analysis

Baseline characteristics of all patients enrolled in the study were compared across two study sites, Yangon and Dawei. Thaketa and Insein clinics were merged into one site category, Yangon. Where appropriate, differences in proportions were calculated using Pearson's χ^2 test and differences in medians were measured using Mann–Whitney U test. A two-sided $p < 0.05$ was considered statistically significant. Comparison of baseline characteristics between the patients included in the study and those who did not provide consent was done to assess the nonresponse bias during the enrollment into the study.

Proportions of SVR12 achieved along with their 95% confidence intervals were calculated for all treated patients (intention-to-treat analysis) and were displayed across treatment sites and baseline characteristics. A modified analysis was also done among patients who had an SVR12 evaluation. Stata version 17 (StataCorp. 2021. Stata Statistical Software: Release 17. College Station, TX: StataCorp LLC) was used for all statistical analyses.

2.7 | Ethical considerations

Ethical approval to conduct the study was given by the MSF Ethics Review Board (MSF ERB ID 1523) in June 2015 and by the Department of Medical Research, Myanmar Ministry of Health and Sports (MoHS) in October 2016 (Ethics/DMR/2016/139). Before the study enrollment, written informed consent was obtained from all patients. All biological and clinical data were anonymized with only the program committee and the investigators having access to the coded databases.

3 | RESULTS

3.1 | Selection of the study population

Among 21,777 PLHIV (17,047 from Yangon clinics and 4730 from Dawei clinic) screened for HCV antibody, 1417 (1038 from Yangon and 379 from Dawei) were tested positive with an overall positivity rate of 6.5% (Figure 1). Of the 1417 HCV antibody positive patients from all clinics, 1298 (91.6%) had their HCV VL assessed. Active HCV infection was confirmed in 1143/1298 (88.1%) patients, while 155/1298 (11.9%) had undetectable HCV VL. Out of 1143 patients with an active HCV infection, 1051 (92%) were enrolled in the treatment program. When invited for the study, 186 patients did not give informed consent and 1 did not complete the baseline interview resulting in the final study population size of 864. During a nonresponse bias analysis, we did not find a difference in baseline characteristics between the patients enrolled in the study and those excluded from the study.

3.2 | Baseline descriptions of the study population

3.2.1 | Demography and risk factors

Of the 864 study patients, 657 (76%) came from Yangon clinics and 207 (24%) from Dawei clinic (Table 1). Most study patients were male (654/864, 75.7%) and there were fewer proportions of male patients in Yangon clinics than Dawei clinic (73.7% vs. 82.1%; $p = 0.013$). Overall, the median age (IQR) of the study patients was 43 years (IQR: 39–48 years). The youngest age of the study patient was 20 years and the oldest was 65 years. Proportionally, Dawei had more manual laborers (40.1% vs. 8.4%), more fishermen (19.3% vs. 0.5%), fewer sellers (4.8% vs. 13.4%), fewer drivers (5.3% vs. 12.2%), fewer patients with other occupation (12.6% vs. 33.7%) and less unemployment (17.9% vs. 31.8%) compared to Yangon ($p < 0.001$).

Overall, 410/807 (50.8%) study patients reported history of drug use among which 346 (84.4%) were PWID and 12 (2.9%) were active drug users. Higher proportions of patients with history of drug use in Yangon reported being PWID compared to Dawei (88.1% vs. 77.3%; $p = 0.004$). 229/847 (27%) study patients reported history of invasive medical procedures and 217/847 (25.6%) had history of spending time in prison. In comparison, fewer proportions of patients from Yangon than Dawei reported history of invasive medical procedures (21.9% vs 43%; $p < 0.001$), history of incarceration (16.4% vs. 54.1%; $p < 0.001$), history of substance use (44.8% vs. 68.4%; $p < 0.001$), being a sex worker (0.9% vs. 6.3%; $p < 0.001$), and being MSM (1.8% vs. 4.8%; $p = 0.035$).

3.2.2 | Characteristics of HCV

HCV genotyping results was available in 640/864 (74%) enrolled study patients. Overall, the most common HCV genotype was genotype 3 (317/640, 49.5%) followed by genotype 1 (206/640, 32.2%), genotype 6 (115/640, 18%), genotype 2 (1/640, 0.2%), and genotype 4 (1/640, 0.2%). In comparison, Yangon had fewer proportions of patients with genotype 1 (26.6% vs. 44.1%), and more proportions of patients with genotype 6 (23.6% vs. 5.9%) than Dawei ($p < 0.001$). Overall, 842/864 (97.5%) study patients had FibroScan® results. The distribution of METAVIR fibrosis staging was as follows: 352/842 (41.8%) F0-F1, 215/842 (25.5%) F2, 65/842

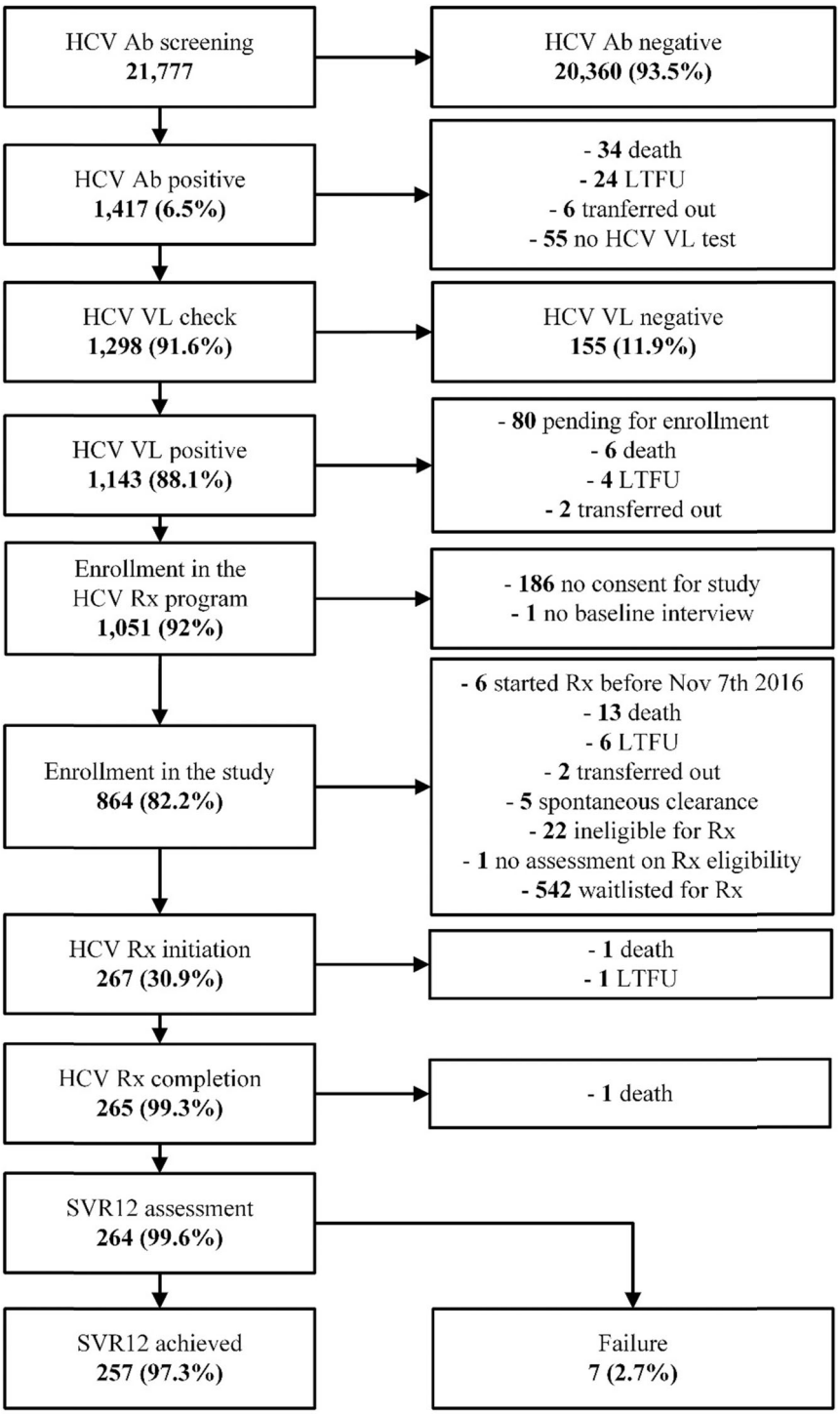

FIGURE 1 Flowchart of PLHIV during the HCV screening and diagnosis (January 2014–November 2017), and treatment (November 2016–2017) in the three MSF clinics in Myanmar. Ab, antibody; HCV, hepatitis C Virus; LTFU, loss to follow-up; MSF, Medecins Sans Frontieres; PLHIV, people living with HIV; Rx, treatment; SVR12, sustained virologic response 12 weeks after treatment completion; VL, viral load.

(7.7%) F3, 210/842 (24.9%) F4. No difference in fibrosis staging categories between Yangon and Dawei clinics was found ($p = 0.782$).

3.2.3 | Additional comorbidities

About 82% (707/864) of study patients had HBsAg test results and 7.8% (55/707) of them were co-infected with HBV, HCV, and HIV (triple infection). There was no difference in proportions of patients with the triple infection of HBV, HCV, and HIV between Yangon and Dawei (8.4% vs. 6.3%; $p = 0.35$). There was no difference in proportions of patients with anemia between Yangon and Dawei (35.8% vs. 43.5%; $p = 0.054$). Diabetes mellitus was found in 1.3% (8/627) of Yangon patients and 3.5% (6/172) of Dawei patients ($p = 0.05$). Fewer proportions of patients in Yangon had tuberculosis than Dawei (0.9% vs. 2.9%; $p = 0.035$). Overall, 493/848 (58.1%) patients had normal BMI, 255/848 (30.1%) were underweight, 83/848 (9.8%) were

TABLE 1 Baseline characteristics of enrolled study participants ($N = 864$) in the three MSF clinics in Myanmar.

Characteristics at baseline	Total ($N = 864$)		Yangon ($N = 657$)		Dawei ($N = 207$)	Pearson's χ^2 test[a]/Wilcoxon rank-sum test	
	N	*n* (%)	*N*	*n* (%)	*N*	*n* (%)	*p* Value
Sociodemographics							
Sex, male	864	654 (75.7)	657	484 (73.7)	207	170 (82.1)	0.013
Age in years, median [IQR]	864	43 [39–48]	657	43.9 [39–48.5]	207	42 [39.6–46]	0.095
Marital status	841		635		206		0.5
Married		458 (54.5)		350 (55.1)		108 (52.4)	
Single		383 (45.5)		285 (44.9)		98 (47.6)	
Occupation	848		641		207		<0.001
Manual laborer		137 (16.2)		54 (8.4)		83 (40.1)	
Fisherman		43 (5.1)		3 (0.5)		40 (19.3)	
Seller		96 (11.3)		86 (13.4)		10 (4.8)	
Driver		89 (10.5)		78 (12.2)		11 (5.3)	
Employed, others		242 (28.5)		216 (33.7)		26 (12.6)	
Unemployed		241 (28.4)		204 (31.8)		37 (17.9)	
Risk factors							
History of blood transfusion	844	156 (18.5)	637	115 (18.1)	207	41 (19.8)	0.572
History of invasive medical procedures	847	229 (27.0)	640	140 (21.9)	207	89 (43.0)	<0.001
Previous time in prison	847	217 (25.6)	641	105 (16.4)	206	112 (54.1)	<0.001
History of drug use	807	410 (50.8)	601	269 (44.8)	206	141 (68.4)	<0.001
Current drug use	410	12 (2.9)	269	10 (3.7)	141	2 (1.4)	0.232
Mode of drug use	410		269		141		0.004
Injecting		346 (84.4)		237 (88.1)		109 (77.3)	
Noninjecting		64 (15.6)		32 (11.9)		32 (22.7)	
Sex worker	841	19 (2.3)	634	6 (0.9)	207	13 (6.3)	<0.001
MSM	625	16 (2.6)	457	8 (1.8)	168	8 (4.8)	0.035
HCV characteristics							
HCV viral load >800,000 IU/ml	864	523 (60.5)	657	384 (58.4)	207	139 (67.1)	0.026
HCV genotype	640		436		204		<0.001
Type 1		206 (32.2)		116 (26.6)		90 (44.1)	
Type 2		1 (0.2)		1 (0.2)		0 (0)	
Type 3		317 (49.5)		215 (49.3)		102 (50.0)	
Type 4		1 (0.2)		1 (0.2)		0 (0)	
Type 6		115 (18.0)		103 (23.6)		12 (5.9)	
Fibrosis staging category[b]	842		637		205		0.782
F0–F1		352 (41.8)		266 (41.8)		86 (42.0)	
F2		215 (25.5)		158 (24.8)		57 (27.8)	
F3		65 (7.7)		51 (8.0)		14 (6.8)	
F4		210 (24.9)		162 (25.4)		48 (23.4)	

TABLE 1 (Continued)

Characteristics at baseline	Total (*N* = 864)		Yangon (*N* = 657)		Dawei (*N* = 207)	Pearson's χ^2 test[a]/Wilcoxon rank-sum test	
	N	*n* (%)	*N*	*n* (%)	*N*	*n* (%)	*p* Value
Comorbidities							
Anemia[c]	740	281 (38.0)	533	191 (35.8)	207	90 (43.5)	0.054
HBsAg positive	707	55 (7.8)	501	42 (8.4)	206	13 (6.3)	0.35
Diabetes mellitus	799	14 (1.8)	627	8 (1.3)	172	6 (3.5)	0.05
Tuberculosis	856	12 (1.4)	649	6 (0.9)	207	6 (2.9)	0.035
Body Mass Index	848		641		207		<0.001
Underweight (<18.5 kg/m^2)		255 (30.1)		219 (34.2)		36 (17.4)	
Normal (18.5–24.9 kg/m^2)		493 (58.1)		342 (53.4)		151 (72.9)	
Overweight (25–29.9 kg/m^2)		83 (9.8)		67 (10.5)		16 (7.7)	
Obese (30 kg/m^2 and above)		17 (2.0)		13 (2.0)		4 (1.9)	

Abbreviation: HBsAg, hepatitis B surface antigen.

[a]Fisher's exact test was used for variables whose cells had $n < 5$.

[b]F0–F1 = < 7 kPa; F2 = 7-<11.5 kPa; F3 = 11.5 -<14 kPa; F4 = 14+ kPa.

[c]Anemia (Hb: male <13 g/dL, female <12 g/dL).

overweight and 17/848 (2%) were obese. The patients from Yangon had more proportions of underweight patients than those from Dawei (34.2% vs. 17.4%; $p < 0.001$).

3.3 | Treatment outcomes

Of the 864 patients included in the study, 267 (30.9%) received treatment for hepatitis C during the study period. Most of the remaining patients, 542/864 (62.7%), were put on the waiting list (Figure 1). According to the intention-to-treat analysis, 257/267 (96.3%) achieved SVR12. The SVR12 proportions ranged from 92% to 100% for all baseline characteristics including liver fibrosis status and DAA-based regimens (Table 2). High SVR12 proportions were observed among patients with history of drug use including PWID (139/145, 95.9%) and patients with history of incarceration (79/80, 98.8%). The SVR12 proportions among patients with HCV genotype 1, 3, and 6 were 96.6% (86/89), 96.7% (146/151), and 92% (23/25) respectively.

Of the 10 remaining patients with unfavorable outcomes, seven (2.6%) failed to achieve SVR12, one (0.4%) became LTFU before treatment completion, one (0.4%) died before treatment completion, and one (0.4%) died after treatment completion but with undetected HCV VL at the end of treatment. Both patients who died were due to non-HCV related causes. The SVR12 proportion among study patients who had a proper HCV VL evaluation at 12 weeks after treatment completion (modified analysis) was 257/264 (97.3%).

Of the seven patients who failed to achieve SVR12 (virologic failure), four (57.1%) were from Yangon and three (42.9%) from Dawei. For cirrhotic status, 4/7 (57.1%) patients had compensated cirrhosis while the remaining 3/7 (42.9%) had no cirrhosis. Regarding HCV genotype, there were 3/7 (42.9%) patients with genotype 1, 2/7 (28.6%) with genotype 3 and 2/7 (28.6%) with genotype 6 (Figure 2). Regarding the treatment regimen, 4/7 (57.1%) were on a 12-week treatment of sofosbuvir and daclatasvir without ribavirin, 2/7 (28.6%) on a 24-week treatment of sofosbuvir and daclatasvir without ribavirin, and 1/7 (14.3%) on a 24-week treatment of sofosbuvir and daclatasvir with ribavirin (Figure 2).

3.3.1 | Treatment safety and adverse events

Overall, 23/267 (8.6%) patients presented an anemia during treatment with 15 of them from Yangon and 8 from Dawei. All of them were taking a ribavirin-containing regimen. Ribavirin dose was reduced in 18/23 (78.3%) cases and was stopped in 5/23 (21.7%) cases. Serious adverse event (SAE) was identified among three cases (Hb <7 g/dL) in Yangon and all of them completed the treatment for hepatitis C after modifications in ribavirin doses. Among the remaining 20 patients with anemia, one developed thrombocytopenia, one had an increase in alanine transaminase (ALT) compared to the baseline, and one developed both thrombocytopenia and an increase in ALT from the baseline.

TABLE 2 SVR12 among participants initiated with HCV treatment in the three MSF clinics in Myanmar (intention-to-treat analysis).

Characteristics	Total (*N* = 267) DAA initiation (*n*)	SVR12 achieved (*n*)	SVR12 (%)	(95% CI)
Clinic sites				
Both	267	257	96.3	(93.2–98.2)
Yangon	160	154	96.3	(92–98.6)
Dawei	107	103	96.3	(90.7–99)
Sociodemographics at enrollment				
Sex				
Male	215	206	95.8	(92.2–98.1)
Female	52	51	98.1	(89.7–100)
Marital status				
Married	144	138	95.8	(91.2–98.5)
Single	121	117	96.7	(91.8–99.1)
Missing	2	2	100	(22.4–100)
Occupation				
Employed	200	192	96	(92.3–98.3)
Unemployed	65	63	96.9	(89.3–99.6)
Missing	2	2	100	(22.4–100)
Risk factors[a]				
History of blood transfusion	46	44	95.7	(85.2–99.5)
History of invasive medical procedures	74	73	98.6	(92.7–100)
Previous time in prison	80	79	98.8	(93.2–100)
History of drug use	145	139	95.9	(91.2–98.5)
Current drug use	1	1	100	(5–100)
Mode of drug use				
Injecting	121	116	95.9	(90.6–98.6)
Noninjecting	24	23	95.8	(78.9–99.9)
Sex worker	8	8	100	(68.8–100)
Men who have sex with men	8	8	100	(68.8–100)
HCV characteristics				
Baseline HCV viral load >800,000 IU/mL	166	159	95.8	(91.5–98.3)
HCV genotype				
Type 1	89	86	96.6	(90.5–99.3)
Type 3	151	146	96.7	(92.4–98.9)
Type 4	1	1	100	(5–100)
Type 6	25	23	92	(74–99)
Unknown	1	1	100	(5–100)
Baseline fibrosis staging category[b]				
F0–F1	33	32	97	(84.2–99.9)

Characteristics	Total (*N* = 267) DAA initiation (*n*)	SVR12 achieved (*n*)	SVR12 (%)	(95% CI)
F2	63	60	95.2	(86.7–99)
F3	40	38	95	(83.1–99.4)
F4	130	126	96.9	(92.3–99.2)
Missing	1	1	100	(5–100)
Cirrhosis status				
No	136	130	95.6	(90.6–98.4)
Compensated	119	115	96.6	(91.6–99.1)
Decompensated	6	6	100	(60.7–100)
Indeterminate	6	6	100	(60.7–100)
DAA-based regimens				
12 weeks Sof+ Dac	50	46	92	(80.8–97.8)
24 weeks Sof+ Dac	40	37	92.5	(79.6–98.4)
12 weeks Sof+ Dac + Rib	79	79	100	(96.3–100)
24 weeks Sof+ Dac + Rib	98	95	96.9	(91.3–99.4)
Comorbidities at enrollment				
Anemia[c]	97	94	96.9	(91.2–99.4)
Creatinine clearance <60 mL/min	47	46	97.9	(88.7–99.9)
Tuberculosis				
Confirmed	3	3	100	(36.8–100)
Unknown	1	1	100	(5–100)
Body mass index				
Underweight (<18.5 kg/m^2)	63	60	95.2	(86.7–99)
Normal (18.5–24.9 kg/m^2)	167	161	96.4	(92.3–98.7)
Overweight (25–29.9 kg/m^2)	29	28	96.6	(82.2–99.9)
Obese (30 kg/m^2 and above)	8	8	100	(68.8–100)

Abbreviations: CI, confidence interval; DAA, direct acting antiviral medication; DCV, daclatasvir; HCV, hepatitis C Virus; MSF, Medecins Sans Frontieres; Rib, ribavirin; SOF, sofosbuvir; SVR12, sustained virologic response 12 weeks after treatment completion.

[a]Variables with missing values (*n* = 7–10).

[b]F0–F1 ≤ 7 kPa; F2 = 7-<11.5 kPa; F3 = 11.5-<14 kPa; F4 = 14+ kPa.

[c]Anemia (Hb: male <13 g/dL, female <12 g/dL).

4 | DISCUSSION

With 96.3% of study patients initiated with DAA-based regimens achieving SVR12, our study supports the real-world effectiveness of the treatment of hepatitis C with DAA-based regimens among HIV/HCV co-infected patients within existing HIV clinics in Myanmar. The high treatment success reported by this study coincides with the results of other studies that use DAA-based regimens to treat hepatitis C in HIV-positive populations.[17–19] Recent studies on the treatment effectiveness of DAA-based regimens in HCV infected patients in Myanmar have shown mixed SVR12 achievements ranging from 77% to 98.6%.[20–25] Most of them studied on general populations[20–24] with only one study having more than half of their study patients as HIV/HCV co-infected patients[25] making our study a valuable addition to the existing evidence of the real-world effectiveness of DAA-based regimens among HIV/HCV co-infected patients in Myanmar.

Our study also supported the management of HCV care among HIV/HCV co-infected patients by nonspecialized health staff or general practitioners. Previous studies had shown high SVR12

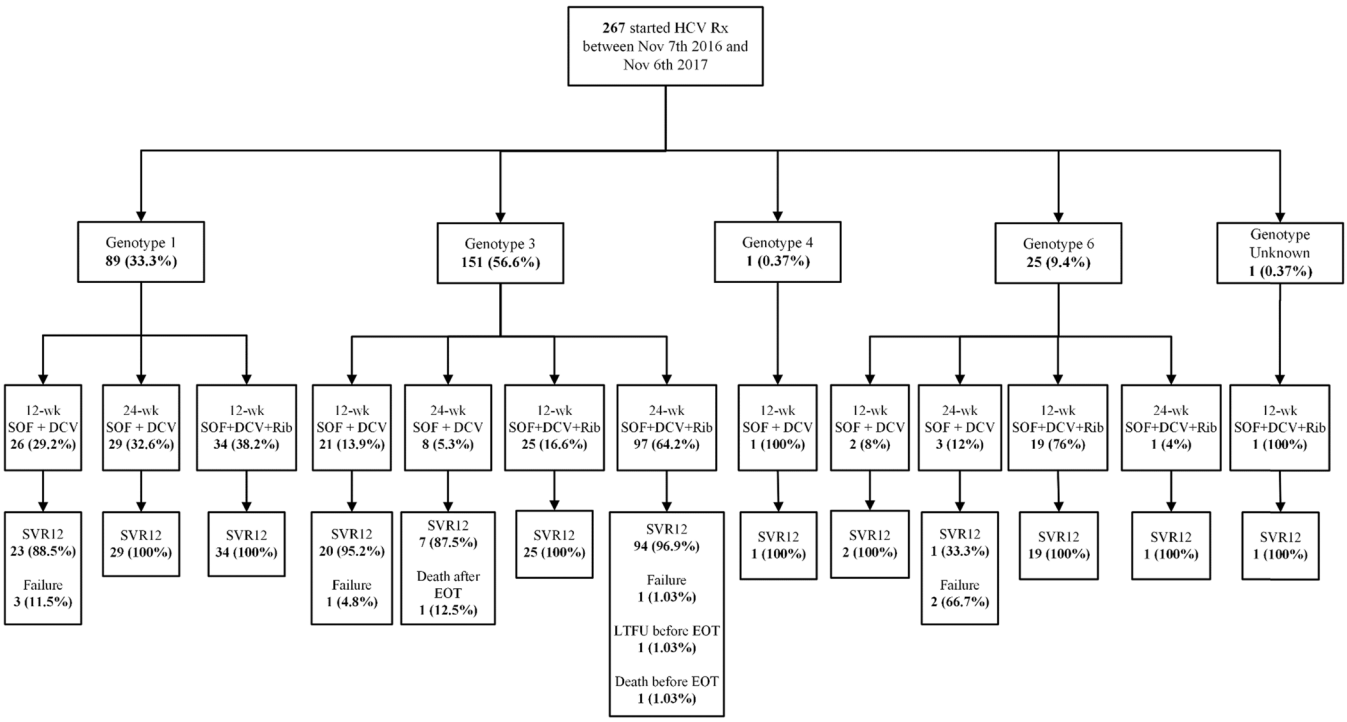

FIGURE 2 Outcomes per HCV genotypes and treatment regimens for patients initiated with DAA-based regimens in the three MSF clinics in Myanmar. DAA, direct acting antiviral medication; DCV, daclatasvir; EOT, end of treatment; HCV, hepatitis C Virus; LTFU, loss to follow-up; MSF, Medecins Sans Frontieres; Rib, ribavirin; Rx, treatment; SOF, sofosbuvir; SVR12, sustained virologic response 12 weeks after treatment completion.

achievements with general practitioners as the primary providers of the treatment of hepatitis C but they excluded or had less than 5% of HIV/HCV co-infected patients in their study cohorts.[20,26] However, our model of care involved multiple rounds of visits from the patients. This is because the real-world evidence of the effectiveness of DAA-based regimens for the treatment of hepatitis C in Myanmar was lacking in 2016 and close monitoring was required. In February 2017, Myanmar MoHS published the first simplified treatment guideline for treatment of HCV with pangenotypic DAA; its second edition was released in July 2019.[12,27] These simplified treatment guidelines for hepatitis C have led to a more affordable model of care that allows general practitioners to provide treatment, requires less frequent consultation visits from patients, and does not need expensive laboratory tests like HCV genotyping.

Globally, 6.2% of PLHIV are co-infected with HCV[7] which is comparable to our finding of 6.5% but this estimate is slightly higher than 5.3% found in a study in Myanmar between 2005 and 2012.[28] We also found that a high proportion (7.8%) of HIV/HCV co-infected study patients were tested positive for HBsAg (triple infection). This calls for the importance of providing PLHIV in Myanmar with comprehensive HCV and HBV care services that include universal screening and linkage to care for treatment.

Substance use and incarceration are closely related factors with almost half of prisoners in Myanmar being detained for drug-related offenses.[29] Additionally, these key populations are subject to social stigma resulting in exclusion from health care in some instances.[6] Higher proportions of patients from Dawei reported risk factors for HCV infection than those from Yangon. This might be because of inherent differences in the socioeconomic conditions of the patient populations between Yangon and Dawei that predispose them to engage in more risky behaviors for HCV infection. For instance, it was reported that HIV/HCV co-infected fishermen in Dawei were more likely to inject drugs and engage in commercial sex work.[30] However, it is also important to know that a higher proportion of drug users in Yangon were PWID compared to Dawei. Programs aimed at harm reduction measures, awareness raising for social stigma and safe medical procedures are required for the prevention and care of new HIV/HCV co-infections in our study settings.

There were several limitations to this study. Only about 31% (267/864) of study patients had their treatment outcomes analyzed and 64% (170/267) had liver fibrosis stages F3 and F4. This is because the study duration was limited to 1 year during which the study ERB was valid. We also prioritized patients with advanced fibrosis for the hepatitis C treatment during the beginning of the study after which the remaining treatment-eligible patients were treated on a routine basis. All the treatment-eligible patients on the waitlist were eventually provided with the DAA-based regimens beyond the study period. As a result, our treatment outcome results in this study pose a selection bias toward patients with advanced fibrosis. A follow-up study on the treatment outcomes of the entire patient cohort will be needed for a more comprehensive report on the effectiveness of hepatitis C treatment with DAA-based regimens

among PLHIV in our study settings. Also, our study did not look at factors associated with treatment success in a multivariate analysis because only 10 out of 267 treated study patients had negative treatment outcomes. Another limitation was missing data during collection. Variables included in the standardized baseline questionnaires that had more than 5% of missing data were omitted from the baseline descriptive analysis but critical variables like risk factors, HCV genotype, HBsAg status, diabetes mellitus and anemia were retained. However, variables like HBsAg status and diabetes mellitus were dropped during the treatment outcome analysis because more than 10% of treated patients had missing data.

5 | CONCLUSION

The study findings support the integration of comprehensive HCV care that involves the diagnosis and treatment of hepatitis C with DAA-based regimens into an existing HIV program run by non-specialist medical doctors in a resource-limited setting. Our findings favor the idea of one-stop health services for HIV/HCV coinfected populations. The epidemiological data on the HIV/HCV co-infection prevalence, and risk factors for HCV infection also reinforce the importance of providing comprehensive HCV care services to key populations like drug users and prisoners in Yangon and Dawei.

AUTHOR CONTRIBUTIONS

Thein Min Swe: Conceptualization; data curation; formal analysis; methodology; software; validation; visualization; writing—original draft; writing—review & editing. **Derek. C. Johnson**: Conceptualization; methodology; writing—original draft; writing—review & editing. **Htay Thet Mar**: Data curation; project administration; resources; writing—review & editing. **Phone Thit**: Data curation; project administration; resources; writing—review & editing. **Tobias Homan**: Writing—review & editing. **Cherry May Chu**: Data curation; project administration; resources. **Phyu Ei Mon**: Data curation; resources. **Thin Thin Thwe**: Data curation; project administration; resources; writing—review & editing. **Kyi Pyar Soe**: Data curation; project administration; resources; writing—review & editing. **Win Le Shwe Sin Ei**: Data curation; project administration; resources; writing—review & editing. **Nyan Lynn Tun**: Data curation; project administration; resources. **Kyaw Zay Lwin**: Data curation. **Hayk Karakozian**: Project administration; resources; supervision. **Khin Sanda Aung**: Conceptualization; supervision; writing—review & editing. **Aude Nguyen**: Investigation; methodology; writing—review & editing. **Iza Ciglenecki**: Methodology; resources; writing—review & editing. **Natalia Tamayo**: Project administration; resources; writing—review & editing. **Anne Loarec**: Conceptualization; funding acquisition; methodology; resources; supervision; writing—review & editing. All authors have read and approved the final version of the manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

TRANSPARENCY STATEMENT

The lead author Thein Min Swe affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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