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High sustained viral response rate in patients with hepatitis C using generic sofosbuvir and daclatasvir in Phnom Penh, Cambodia

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Abstract

Safe and efficacious pan-genotypic direct-acting antiviral (DAA) regimens, such as sofosbuvir and daclatasvir (SOF + DCV), facilitate simplified models of care for hepatitis C virus (HCV). However, in Cambodia access to HCV testing and treatment has typically been low. In response, Médecins Sans Frontières (MSF) implemented a HCV testing and treatment pilot project in Phnom Penh, Cambodia in 2016. This project provides the first real-world evidence of SOF + DCV effectiveness across a large patient cohort using a simplified care model in Cambodia. Patients treated with SOF + DCV from September 2016 to June 2019 were included in the analysis. Medical standard operational procedures (SOPs) were simplified significantly across the study period. Treatment effectiveness was assessed by sustained viral response at 12 weeks post-treatment (SVR12) according to a modified intention-to-treat methodology. Treatment safety was assessed by clinical outcome and occurrence of serious and nonserious adverse events (S/AE). Of 9158 patients, median age was 57 years and 39.6% were male. At baseline assessment, 27.2% of patients had compensated cirrhosis and 2.9% had decompensated cirrhosis. Genotype 6 was predominant (53.0%). Among patients analysed according to modified intention to treat (n = 8525), treatment effectiveness was high, with 97.2% of patients achieving SVR12. Occurrence of SAE was low (0.7%). Treatment effectiveness and safety was not affected by the iterative simplification to treatment modality. In conclusion, in this large treatment cohort in Phnom Penh, Cambodia, the SOF + DCV regimen showed high rates of treatment effectiveness and safety across patient sub-groups and during progressive simplification.

KEYWORDS

Cambodia, Daclatasvir, Hepatitis C, Sofosbuvir, SVR12

1 | INTRODUCTION

Introduced in 2013, direct-acting antivirals (DAA) have drastically simplified the management of HCV-infected patients and altered the landscape of traditional hepatitis C virus (HCV) treatment.[1,2] Previous interferon-based treatments, due to poor tolerability, high toxicity and limited efficacy, required hepatologist consultation, often provided in tertiary or private settings, that posed accessibility barriers to many people living with HCV.[3-5] Real-world efficacy studies have shown DAA treatment to be well tolerated and successfully curing over 90% of patients.[2,6] In particular, pan-genotypic DAA regimens, such as sofosbuvir and daclatasvir (SOF + DCV) therapy, can cure most patients regardless of HCV genotype.[6,7] Current DAA treatments combined with reliable, rapid point-of-care diagnostics [1] allows simplified models of HCV testing and treatment.[1,8] Simplified models of care, ideally in decentralized and integrated community-based clinics, are intended to remove barriers imposed by lengthy, complex diagnostic algorithms and tertiary level treatment.[8,9] There is evidence that such models improve HCV cascade outcomes,[8] and some international governments are now making their own recommendations for simplified HCV care,[10] but it is acknowledged that more evidence on different models of care, adapted to different contexts, is needed.[8]

The Cambodian HCV epidemic is poorly understood.[11-13] No population-level prevalence studies exist, and sample-specific prevalence estimates range between 2.8% and 14.7% antibody positivity and 1.9- 3.5% RNA positivity, with differences across rural and urban populations and study samples.[12-14] However, these studies do provide some characterization of the epidemic. Nouhin et al (2019) recently described the characteristics of over 3000 Cambodian patients receiving HCV treatment using data from a project implemented by Médecins Sans Frontières (MSF) (the same project from which this study is drawn).[12] The average age of the cohort was 55, with slightly more females (59%). Predominant risk factors for infection were having undergone invasive medical procedures, previous blood transfusions, having a partner with HCV, or being a healthcare worker.[12] These findings correspond to previous epidemiological work, describing a disease reservoir largely situated among older individuals.[13,15] The long-time absence of a functioning health system caused by the Cambodia civil war is thought to explain Cambodia's higher HCV prevalence compared to surrounding countries, mainly as a result of historic iatrogenic causes.[11,13,14,16] As a result, hepatocellular carcinoma is a growing problem in the country, and HCV (and hepatitis B) infection is among the major causative factors.[17]

Despite the existing context, access to HCV testing and treatment in Cambodia has typically been low [11]; with the cost of treatment borne by the patient.[11] Tellingly, nearly all patients (94.2%) in the Nouhin et al study were treatment-naïve.[12] In response, MSF implemented a HCV screening and treatment pilot project in Phnom Penh, Cambodia, in 2016. Recognizing the limited health infrastructure and barriers to access among potential patients, MSF aimed to develop a simplified model of free-of-charge HCV care provided by general practitioners, nursing staff and pharmacists, with few restrictions on patient access.

In this paper, we describe the treatment outcomes for 9158 patients enrolled in the MSF treatment cohort and prescribed SOF + DCV regimens. Reduced effectiveness of SOF + DCV regimens has been described when treating cirrhotic HCV genotype 3[18]; however, Nouhin et al reported no genotype 3 among their cohort.[12] This study provides the first real-world treatment evidence of SOF + DCV (or indeed, any DAA regimen) effectiveness in Cambodia.

2 | METHODS

2.1 | Patient cohort

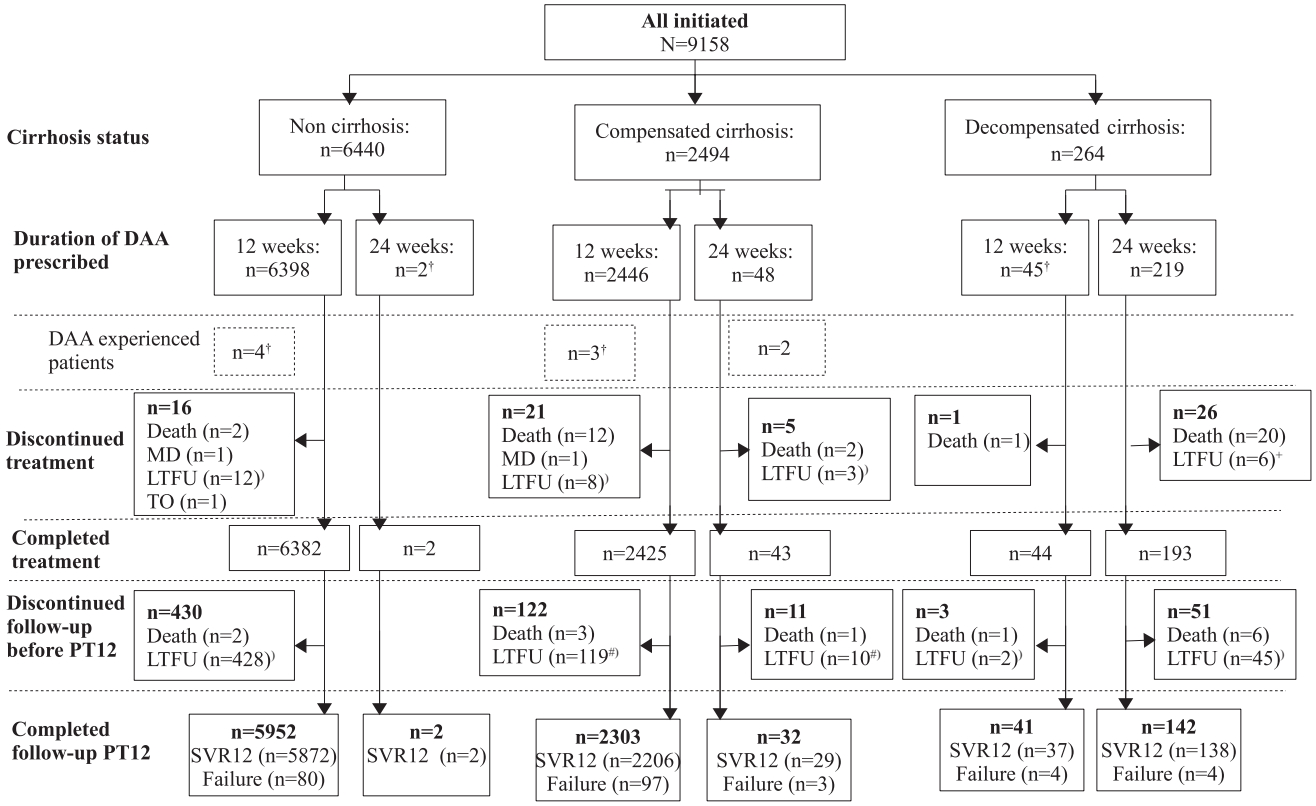
Patients were initiated on DAA treatment via MSF's HCV treatment project in Phnom Penh, Cambodia from September 2016 to June 2019. The project established a new HCV clinic in collaboration with the Hepato-Gastroenterology Department of Cambodia-China Friendship Preah Kossamak Hospital (PKH)—a government-run national hospital in Phnom Penh. The MSF clinic was situated in the PKH precinct.

Patients eligible for this study cohort were those screened through the Hepatology Department out-patient services at PKH or via participating screening programs at collaborating NGOs (AIDS Health Care Foundation & Mopotsyo for people with diabetes), and the Diabeto-Department of PKH; those who had a valid cirrhosis status result; and those initiating HCV treatment between September 2016 and December 2018, to allow for treatment completion prior to project handover to the Cambodian Ministry of Health in June 2019.

There were 9210 patients initiated during the study period. After excluding 12 patients who did not provide informed consent and 40 patients without valid cirrhosis status, a total of 9158 patients were included in this analysis (Figure 1).

2.2 | Baseline evaluation for DAA therapy

During the study period, the medical standard operating procedure (SOP) was altered to simplify treatment modality (as described in the 'changes to treatment modality' section); however, there were common procedures across SOPs. Baseline patient evaluation for DAA initiation was conducted by a general practitioner and included liver fibrosis staging evaluation by transient elastography using FibroScan®, and laboratory blood testing of random blood sugar, hepatitis B virus (HBV) surface antigen and HIV antibody. In addition, comprehensive blood tests including complete blood count (CBC), serum creatinine, bilirubin, albumin, alanine aminotransferase (ALT), clotting profile and other examinations (ie endoscopy and ultrasounds) were provided according to doctor's discretion and the relevant SOP at the time of patient evaluation.



†Assigned outside of standard operation procedure.
)Excluded for SVR12 analysis among patients with known outcomes
MD: medical decision to discontinue treatment; LTFU: lost to follow-up; TO: transfer-out; SVR12: sustained viralogical response at 12 weeks post-treatment

FIGURE 1 Patient cohort treatment flow

The presence of decompensated cirrhosis was a determinant of treatment course. Across treatment modalities, a Fibroscan result higher than 14Kpa was used to identify cirrhosis (either compensated or decompensated). Decompensated cirrhosis was defined using the Child-Pugh score or clinical examination for signs of decompensation, depending on treatment modality.

All patients living with HIV needed to be on antiretroviral treatment for at least 3 months prior to DAA initiation. Patients with poor overall clinical condition and in need of palliative care were referred to a collaborating organization (Douleurs Sans Frontieres). Patients unwilling or unable to comply with treatment visits or medicine regimen were not eligible to receive treatment, but could return to the clinic once better able to meet treatment requirements.

2.3 | Treatment and monitoring

Patients were treated with generic SOF (400 mg/d) and DCV (60 mg/d) with dosage adjusted according to potential interactions with other medications (such as HIV treatment). Thirteen patients were initially prescribed ribavirin (RBV) but this was ceased due to nonsevere adverse events (in analysis, these patients are considered no different from other SOF + DCV patients). According to the relevant medical SOP, patients were prescribed a 12-week treatment, unless diagnosed with decompensated cirrhosis or had a previous history of DAA treatment in which case 24-week treatment was prescribed.

Treatment safety was assessed by biological and clinical follow-up, and reporting and monitoring of adverse events (AEs). AEs were defined as events leading to temporary or permanent treatment discontinuation or modification of treatment. Serious adverse events (SAEs) were defined as events leading to hospitalization, prolonging hospitalization or death, occurring anytime between treatment initiation and 12-weeks post-treatment testing (PT12). AEs and SAEs could be classified regardless of the events' association with receiving DAA treatment. All SAE cases were reported to the Cambodia National Ethical Committee for Health Research (NECHR) for review.

2.4 | Treatment effectiveness

Treatment effectiveness was evaluated at PT12. HCV cure was defined as sustained viral response at PT12 (SVR12)—being beneath the lower limit of quantification range of the viral load according to the testing assay in use (≤10-17 IU/mL depending on testing assay). Treatment failure was defined as higher than lower limit of quantification range of viral load at SVR12 testing.

2.5 | Changes to treatment modality

During the study period, there were five major periods of patient management, operating under different medical SOPs with the first *Full model* implemented in September 2016, progressing to the final *simplified model 3* in October 2018 (Appendix S1). Across models, there were significant changes to medical SOPs, implemented according to accrued experience within the project and emerging innovations and evidence in the HCV testing and treatment.

In summary, patients were initially required to attend at least 15 visits from screening to treatment outcome with either a general practitioner or a nurse counsellor (depending on the consultation). HCV diagnosis was initially performed by ELISA and HCV RNA PCR (COBAS AmpliPrep/CobasTaqMan® HCV Test V2.0 Virus Quantitative detection kit [Roche]) at an external laboratory. All patients received blood tests including CBC, ALT and serum creatinine at baseline and had follow-up ALT testing during treatment and at PT12. Decompensated cirrhosis was diagnosed by Child-Pugh score B or C among F4 patients. HCV genotype testing was performed for an initial 3352 patients [see Nouhin et al (2019)[12]], with testing stopped once numbers were sufficient to describe genotype distribution across the cohort. Further, due to the pan-genotypic indication of SOF + DCV, and the confirmation of the very low prevalence of genotype 3 [which requires longer treatment regimens[20]], genotype testing was considered unnecessary in future medical SOPs.

Subsequent treatment models were simplified step by step. From *simplified model 3* onwards, diagnosis was performed using rapid HCV antibody diagnostic tests (SD Bioline or Oral Quick) at the HCV clinic and HCV RNA performed by GeneXpert (Cepheid) or InnuPure®C16 qTOWER3® HCV quantitative test (Analytik Jena) at the hospital laboratory. Only selected patients (ie patients ≥ 50 years old, FibroScan result ≥ 20kPa, HBV co-infected) were assessed with additional laboratory tests including CBC, creatinine and ALT per relevant SOP. The number of consultations required was also greatly reduced, with noncomplicated patients (the majority of patients) receiving only three appointments (including assessment for DAA initiation) with the general practitioner, and two further assessments at treatment months one and two completed by the MSF pharmacist when patients refilled medication. Decompensated cirrhosis was no longer diagnosed by Child-Pugh scoring. Instead, clinical examination for signs of decompensation was used. Further, as project monitoring showed consistently high SVR12 achievement, patients were provided a PT12 appointment date, but tracing was abandoned for patients not attending, to reduce staff workload and travel time/expenses for patients.

2.6 | Data collection and statistical analysis

Data on patient characteristics, laboratory findings and treatment outcomes were collected using Research Electronic Data Capture (REDCap, Vanderbilt University, USA). Analysis was performed using Statistical Analysis Software (SAS, SAS Institute Inc, USA).

Pre-treatment patient demographic and clinical characteristics were described by cirrhosis status (noncirrhotic, compensated cirrhosis and decompensated cirrhosis) at baseline using medians with inter-quartile ranges (IQR) for continuous variables and count with percentage for categorical variables.

Treatment outcomes were analysed according to modified intention-to-treat methodology, whereby treatment effectiveness was assessed for patients experiencing pre-defined 'known outcomes'. Known outcomes included achieving SVR12, treatment failure at PT12, death from any cause at any point up to PT12, patient transfer out of the treatment cohort and discontinuation from treatment. LTFU was not considered a known outcome and was excluded from treatment effectiveness analysis. All known outcomes other than SVR12 were considered as treatment failure in analysis.

SVR12 rates as a percentage of known outcomes were described across patient demographic and clinical characteristic sub-groups. More detailed effectiveness comparison was provided for different cirrhosis status. Confidence intervals (CI) for SVR12 were calculated using the Clopper-Pearson method.

2.7 | Ethics

Written informed consent was obtained from patients prior to enrolment. Ethical approval was obtained from the French Comités de Protection des Personnes of Saint-Germain-en-Laye (Saint-Germain-en-Laye Ethical Review Board, Reference: 16049) and the Cambodian National Ethical Committee for Health Research (Reference: 031NECHR).

3 | RESULTS

3.1 | Patient characteristics

Median patient age was 57 years (IQR: 48, 63) and 39.6% (n = 3631) of patients were male (Table 1). At baseline assessment, 6400 (69.9%) patients were without cirrhosis, 2494 (27.2%) had compensated cirrhosis, and 264 (2.9%) had decompensated cirrhosis. Among 2517 patients who had genotype testing, 53.0% (n = 1334) were genotype 6, followed by genotype 1 (32.3%, n = 814) and genotype 2 (7.9%, n = 198), and two genotype 3. There were 219 (2.4%) patients co-infected with HBV, 108 (1.2%) co-infected with HIV, and six patients co-infected with both HBV and HIV. Thirty-eight HBV-positive patients required initiation on tenofovir whilst receiving DAA treatment. Most patients were HCV treatment-naïve; 188 (2.1%) and nine (0.1%) had previously received interferon-based treatment or at least one prior DAA treatment, respectively.

Most patients (n = 8889, 97.1%), were treated with SOF + DCV 12-week course, including 45 decompensated cirrhotic patients who were assigned outside of SOP (Figure 1). Two-hundred and sixty-nine (2.9%) patients were treated with SOF + DCV 24-week course, including two noncirrhotic patients (again, outside SOP); 48 cirrhotic patients with Child-Pugh A and signs of clinical decompensation,

TABLE 1 Baseline characteristics of 9158 enrolled patients, breakdown by cirrhosis status

	N (%)	Noncirrhosis, n (%)	Compensated cirrhosis, n (%)	Decompensated cirrhosis, n (%)
Total	9158	6400	2494	264
Male	3631 (39.6)	2471 (38.6)	1046 (41.9)	114 (43.2)
Age (year)				
Median (IQR)	57 (48, 63)	55 (46, 62)	59.4 (54, 65)	61 (57, 66.5)
<45	1568 (17.1)	1434 (22.4)	128 (5.1)	6 (2.3)
45-54	2321 (25.3)	1737 (27.1)	548 (22)	36 (13.6)
55-64	3467 (37.9)	2150 (33.6)	1189 (47.7)	128 (48.5)
≥65	1802 (19.7)	1079 (16.9)	629 (25.2)	94 (35.6)
HCV VL (IU/mL)				
Log_{10} Median (IQR)	6.2 (5.5, 6.7)	6.2 (5.5, 6.7)	6.1 (5.4, 6.5)	5.6 (4.9, 6.1)
<6 million	7428 (81.1)	5001 (78.1)	2173 (87.1)	254 (96.2)
≥6 million	1730 (18.9)	1399 (21.9)	321 (12.9)	10 (3.8)
HCV genotype[a]				
1	814 (32.3)	628 (34.6)	169 (25.8)	17 (36.2)
2	198 (7.9)	144 (7.9)	50 (7.6)	4 (8.5)
3	2 (0.1)	2 (0.1)	0 (0)	0 (0)
6	1334 (53)	922 (50.8)	391 (59.7)	21 (44.7)
Indeterminate	169 (6.7)	119 (6.6)	45 (6.9)	5 (10.6)
Liver stiffness (kPa)				
Median (IQR)	9 (6.2, 16.6)	7.2 (5.6, 9.6)	22.3 (17.3, 33.3)	44.8 (29.9, 65.2)
No valid result	22 (0.2)	0 (0)	0 (0)	22 (8.3)
F0: 0-2	1028 (11.2)	1028 (16.1)	0 (0)	0 (0)
F1: 2.1-8	2144 (23.4)	2144 (33.5)	0 (0)	0 (0)
F2: 8.1-9	1603 (17.5)	1603 (25)	0 (0)	0 (0)
F3: 9.1-14	1625 (17.7)	1625 (25.4)	0 (0)	0 (0)
F4: ≥14.1	2736 (30.0)	0 (0)	2494 (100)	242 (91.7)
Body-mass index (kg/m^2)				
Median (IQR)	23.2 (20.8, 25.8)	23 (20.7, 25.5)	23.8 (21.2, 26.6)	22.7 (20.6, 25.4)
Missing	12 (0.1)	9 (0.1)	3 (0.1)	0 (0)
<23	4363 (47.6)	3174 (49.6)	1048 (42)	141 (53.4)
23-27.4	3552 (38.8)	2479 (38.7)	989 (39.7)	84 (31.8)
≥27.5	1231 (13.5)	738 (11.6)	454 (18.2)	39 (14.8)
Co-infection				
HBV	219 (2.4)	154 (2.4)	61 (2.4)	4 (1.5)
HIV	108 (1.2)	72 (1.1)	33 (1.3)	3 (1.1)
HIV&HBV	6 (0.1)	4 (0.1)	2 (0.1)	0 (0)
Diabetes				
Previously diagnosed diabetes[b]	1123 (12.3)	519 (8.1)	561 (22.5)	43 (16.3)
No diabetes history but baseline RBS ≥ 200mg/mL[c]	251 (2.7)	134 (2.1)	103 (4.1)	14 (5.3)
Hypertension[d]	1322 (14.4)	784 (12.3)	512 (20.5)	26 (9.8)
HCV treatment experience				
Naive	8961 (97.8)	6271 (98)	2430 (97.4)	260 (98.5)
DAA	9 (0.1)	4 (0.1)	5 (0.2)	0 (0)

(Continues)

TABLE 1 (Continued)

	N (%)	Noncirrhosis, n (%)	Compensated cirrhosis, n (%)	Decompensated cirrhosis, n (%)
IFN, pegIFN, RBV	188 (2.1)	125 (1.9)	59 (2.4)	4 (1.5)
Regimen				
12 weeks	8889 (97.1)	6398 (100)	2446 (98.1)	45 (17.0)
24 weeks	269 (2.9)	2 (0)	48 (1.9)	219 (83.0)

Abbreviations: HCV, hepatitis C virus; VL, viral load; HBV, hepatitis B virus; HIV, human immunodeficiency virus; RBS, random blood sugar; DAA, direct-acting antivirals; IFN, interferon; pegIFN, pegylated interferon; RBV, ribavirin.

[a]HCV genotype testing was performed for an initial 3352 patients, with testing stopped once numbers were felt to be sufficient to describe the genotype distribution across the ongoing cohort. The table only shows 2517 patients included in the study and have done the genotype test, and 6641 patients without genotype test were not included in the table.

[b]Patients' self-reported diabetes history, with/without blood sugar controlled.

[c]Patients did not report with diabetes history; however, baseline random blood sugar level is higher than 200 mg/mL.

[d]Patients self-reported hypertension history, with/ without blood pressure controlled.

but were not diagnosed with decompensated cirrhosis based on the medical SOPs used at the time (Child-Pugh B and C were the measures for diagnosis); and 219 patients with decompensated cirrhosis as per definition of the SOP in use at the time.

3.2 | Adverse events

Nonserious AEs were observed in 13 patients leading to modification of treatment regimen. These patients were those originally prescribed SOF + DCV with RBV. All required RBV cessation (12 due to decreased haemoglobin, one due to deterioration in condition due to decompensated cirrhosis), with three discontinuing treatment, one LTFU and the remaining nine achieving SVR12.

A total of 66 SAEs (0.7%) occurred among 63 patients (one patient experienced two SAEs, one patient experienced three SAEs). SAE occurrence was 0.1% (n = 7) among patients without cirrhosis; 1.1% (n = 26) among patients with compensated cirrhosis, and 11.7% (n = 30) among patients with decompensated cirrhosis (Table 2). The most common causes of SAEs were decompensation/ ascites/ pleural effusion (n = 29), and oesophageal varices rupture or gastrointestinal bleeding (n = 15). Other causes of SAE included cardiovascular disease (n = 5), hepatocellular carcinoma (n = 4), nonliver cancer or tumour (n = 3), infection (n = 4), severe appetite loss (n = 1) and unknown cause (n = 5). All of the SAEs were determined to be consistent with a worsening of underlying disease than related to SOF + DCV treatment, following clinical evaluation by the project medical activity manager. Among all patients experiencing SAEs, two (3.4%) discontinued treatment, 50 (78%) died either during or after treatment, and four (6.8%) were LTFU either during or after treatment. Seven patients with occurrence of a SEA eventually achieved SVR12 (11.9%). No patient with a SAE who reached PT12 experienced treatment failure.

3.3 | Treatment outcomes

Of the 9158 patients in the study cohort, only 69 (0.8%) did not complete treatment. Noncompletion was a result of treatment

TABLE 2 Cause of severe adverse event by cirrhosis status

Cause of SAE	NonCirrhosis (n = 6400)	Compensated cirrhosis[a] (n = 2494)	Decompensated cirrhosis[b] (n = 264)	SAE occurrence by cause (%) (N = 9158)
Cardiovascular disease	2	3	0	5 (0.1)
Decompensation/ascites/pleural effusion	0	7	22	29 (0.3)
Oesophageal varices rupture/GI bleeding	2	11	2	15 (0.2)
HCC	0	1	3	4 (0)
Nonliver cancer or tumour	1	1	1	3 (0)
Infection	1	2	1	4 (0)
Severe and prolong appetite loss	1	0	0	1 (0)
Unknown	0	3	2	5 (0.1)
SAE occurrence (%)	7 (0.1)	28 (1.1)	31 (11.7)	66 (0.7)

Abbreviations: GI, gastrointestinal; HCC, hepatocellular carcinoma; SAE, serious adverse event.

[a]One patient had three SAE occurrences.

[b]One patient had two SAE occurrences.

TABLE 3 SVR12 rate among patients with known outcomes by baseline characteristics

	SVR12/patients with known outcome[a]	SVR12 rate (95%CI)
Total	8284/8525	97.2 (96.8, 97.5)
Sex		
Male	3209/3346	95.9 (95.2, 96.6)
Female	5075/5179	98 (97.6, 98.4)
Age (year)		
<45	1420/1435	99 (98.3, 99.4)
45-54	2139/2187	97.8 (97.1, 98.4)
55-64	3154/3263	96.7 (96, 97.2)
≥65	1571/1640	95.8 (94.7, 96.7)
HCV VL (IU/mL)		
<6 million	6705/6903	97.1 (96.7, 97.5)
≥6 million	1579/1622	97.3 (96.4, 98.1)
HCV genotype		
1	771/780	98.9 (97.8, 99.5)
2	191/194	98.5 (95.6, 99.7)
3	2/2	100 (15.8, 100)
6	1239/1292	95.9 (94.7, 96.9)
Indeterminate	163/167	97.6 (94, 99.3)
Not tested	5918/6090	97.2 (96.7, 97.6)
Liver stiffness (kPa)		
No Valid result	13/18	72.2 (46.5, 90.3)
F0: 0-2	936/947	98.8 (97.9, 99.4)
F1: 2.1-8	1951/1978	98.6 (98, 99.1)
F2: 8.1-9	1464/1489	98.3 (97.5, 98.9)
F3: 9.1-14	1523/1546	98.5 (97.8, 99.1)
F4: ≥14.1	2397/2547	94.1 (93.1, 95)
Body-mass index (kg/m^2)[b]		
<23	3895/4004	97.3 (96.7, 97.8)
23-27.4	3264/3347	97.5 (96.9, 98)
≥27.5	1114/1163	95.8 (94.5, 96.9)
Co-infection		
HCV mono-infection	7986/8218	97.2 (96.8, 97.5)
HBV	193/197	98 (94.9, 99.4)
HIV	99/104	95.2 (89.1, 98.4)
HIV&HBV	6/6	100 (54.1, 100)
Diabetes		
No diabetes history and baseline RBS < 200 mg/mL	7075/7256	97.5 (97.1, 97.9)
Previously diagnosed diabetes	981/1038	94.5 (92.9, 95.8)
No diabetes history but baseline RBS ≥ 200mg/mL	228/231	98.7 (96.3, 99.7)
Hypertension		
No hypertension	7052/7243	97.4 (97, 97.7)
Diagnosed hypertension	1232/1282	96.1 (94.9, 97.1)
HCV treatment experience		
Naive	8096/8335	97.1 (96.8, 97.5)
DAA	7/8	87.5 (47.3, 99.7)
IFN, pegIFN, RBV	181/182	99.5 (97, 100)
Regimen		
12 weeks	8115/8320	97.5 (97.2, 97.9)
24 weeks	169/205	82.4 (76.5, 87.4)

(Continues)

TABLE 3 (Continued)

Abbreviations: HCV, hepatitis C virus; VL, viral load; HBV, hepatitis B virus; HIV, human immunodeficiency virus; RBS, random blood sugar; DAA, direct-acting agent; IFN, interferon; pegIFN, pegylated interferon; RBV, ribavirin.

[a]Patients with known outcomes (SVR12, virological failure, discontinuation of treatment, transfer out of treatment, death at anytime during follow-up), excluding patients lost to follow-up.

[b]Patients with known outcomes but missing BMI (n = 11) were not included.

discontinuation due to SAEs (n = 2), death during treatment (n = 37), LTFU during treatment (n = 29) and one HIV-positive patient transferred out of the MSF project to a HIV treatment provider to continue HCV care. A total of 9089 (99.2%) patients, therefore, completed DAA treatment (Figure 1).

Of these, 8472 (92.5% of total cohort) returned for PT12 (Figure 1). Among patients not reaching PT12 after treatment completion, 13 died and 604 were LTFU [with 549 (90.9%) LTFU patients occurring after PT12 tracing was stopped]. Consequently, there were 8525 patients defined as having a known outcome. Of the 8472 patients completing PT12, 8284 (97.8%) achieved SVR12, and 188 (2.2%) experienced treatment failure. There were 53 other known outcomes, being patients who died (n = 50), were discontinued (n = 2) or were transferred out of treatment (n = 1).

The SVR12 rate across the total study cohort was 90.4%. When analysed according to known outcomes (n = 8525, with 633 LTFU excluded), the SVR12 rate was 97.2% (95%CI: 96.8, 97.5) (Table 3). Known outcome SVR12 rate according to cirrhosis status was 98.6% (95%CI: 98.2, 98.8) among patients without cirrhosis, 94.9% (95%CI: 94.0, 95.8) among patients with compensated cirrhosis, and 82.9% (95%CI: 77.2, 87.8) among patients with decompensated cirrhosis (Table 4).

Across all baseline demographic and clinical characteristics, SVR12 rate was consistently high, except among patients on 24-week regimens (82.4%, 95% CI: 76.5, 87.4) (Table 3). SVR12 rate was also low among patients with previous DAA treatment experience (87.5%, 95% CI: 47.3, 99.7), and patients with an invalid FibroScan result (72.2%, 95% CI: 46.5, 90.3) although numbers in both these sub-groups were too small to be statistically meaningful.

TABLE 4 SVR12 rate by cirrhosis status

	Noncirrhosis	Compensated cirrhosis	Decompensated cirrhosis
SVR12 among patients with known outcomes[a]			
n/N	5874/5960	2235/2354	175/211
% (95% CI)	98.6 (98.2, 98.8)	94.9 (94.0, 95.8)	82.9 (77.2, 87.8)
SVR12 among all initiated patients			
n/N	5874/ 6400	2235/2494	175/264
% (95% CI)	91.8 (91.1, 92.4)	89.6 (88.4, 90.8)	66.3 (60.2, 72)
Treatment failure[b]			
n (%)	80 (1.3)	100 (4.0)	8 (3.0%)

Abbreviations: SVR12, sustained viral response at post-treatment 12 weeks.

[a]Patients with known outcomes (SVR12, virological failure, discontinuation of treatment, transfer out of treatment), excluding patients lost to follow-up.

[b]Proportion of treatment failure was calculated among all initiated patients.

TABLE 5 SVR12 rate among patients with known treatment outcomes by treatment model

Model	Full	Transition	Simplified 1	Simplified 2	Simplified 3
Patients with known outcomes[a]	326	1002	1200	4759	1238
SVR12 rate % (95%CI)	97.5 (95.2, 98.9)	95.5 (94, 96.7)	96.4 (95.2, 97.4)	97.7 (97.2, 98.1)	97.2 (96.1, 98)
Completed follow-up					
SVR12	318	957	1157	4649	1203
Treatment failure	6	42	26	92	22
Did not complete follow-up					
Death	2	3	16	16	13
MD/TO	0	0	1	2	0
LTFU[b]	2	9	28	388	206

Abbreviations: SVR12, sustained viral response at post-treatment 12 weeks; MD/TO, medical decision to discontinue treatment/transfer out; LTFU, lost to follow-up.

[a]Patients with known outcomes (SVR12, virological failure, discontinuation of treatment, transfer out of treatment, death at anytime during follow-up), excluding patients lost to follow-up.

[b]LTFU was not included in 'patients with known outcomes'.

SVR12 rates across medical SOPs were largely similar, with SVR12 achievement ranging between 95.5% and 97.7% suggesting there was no loss to treatment effectiveness as a result of model simplification (Table 5).

4 | DISCUSSION

Among this large treatment cohort in Phnom Penh, Cambodia, high levels of treatment effectiveness were observed; 90.4% of all patients initiating treatment, and 97.2% of patients with a known outcome, achieved SVR12. These results are comparable with previous clinical trials[3,18] and real-world studies[18,19] assessing the effectiveness of SOF + DCV regimens. Results also accord with the WHO's recommendation of SOF + DCV regimens as pan-genotypic treatment for patients with and without cirrhosis.[20]

Treatment effectiveness was high across patient demographic and clinical sub-groups, irrespective of patient gender, age, BMI, genotype, initial liver stiffness, co-infection or diabetic status. Actual treatment failure was low, with 188 (2% of patients with known outcome) patients experiencing this outcome. Importantly, high treatment effectiveness (95.9%, 95% CI: 94.7, 96.9) was demonstrated among patients with genotype 6. International evidence of the effectiveness of SOF + DCV in treating HCV in patients with genotype 6 is emerging,[21,22] but currently limited. This outcome contributes to this existing knowledge gap, informing international HCV treatment programs.

There was an incremental decrease in treatment effectiveness across cirrhotic classification, although effectiveness was low only for patients with decompensated cirrhosis. This observation was attributable to the frequency of patient deaths (n = 28), rather than treatment failure. The condition of some patients with decompensated cirrhosis will deteriorate during treatment, and it is impossible to prospectively identify these patients.[20] If treatment outcomes were restricted to those completing PT12, effectiveness among patients with decompensated cirrhosis was 95.6%. Similarly, lower effectiveness among 24-week regimen patients is due to nearly all

being decompensated patients. Whilst acknowledging the role of comorbidities, coinfections and alcohol consumption on disease progression, severity of disease (including decompensated cirrhosis) will not always be mitigated by DAA treatment alone. This, however, need not be a contraindication for treatment,[20] with the additional care required for patients in the MSF project with greater disease severity provided by increased patient monitoring. Even so, it must be remembered that the duration of HCV infection is a determinant of disease severity, with liver fibrosis potentially accelerated among older individuals,[23,24] and the management of severe liver cirrhosis and disease requires substantial medical resources often unavailable for resource-limited countries like Cambodia. Measures to screen and treat individuals at an early stage of infection are vital to reduce the impact of disease severity and conserve vital resources.

AEs occurred in a minority of patients (0.7%), and again, these were largely experienced by those with decompensated cirrhosis (47% of all SAEs) at treatment initiation. No AEs (either serious or nonserious) were determined to be a direct result of the prescribed SOF + DCV treatment.

This study supports the established safety profile and effectiveness of SOF + DCV regimens,[20] in this case, among a very large cohort of typically older patients with probable long-standing HCV infection in Cambodia. Importantly, the MSF Cambodian project is also an evaluation of a simplified model of treatment. The treatment algorithms employed by the project became progressively simplified over time, with patients at the end of the study period required to receive far fewer initiation diagnostics and attend far fewer appointments than patients at the beginning. Via the simplified model, MSF was able to scale-up the number of patients treated without increasing staff or other project resources, or at the expense of patient safety or efficacy, thereby demonstrating a safe and effective method of delivering HCV treatment which can be replicated across other resource-limited settings. MSF is already adapting and expanding this model of care into rural settings in Cambodia's Battambang province, where they have integrated HCV screening and treatment via basic rural health centres primarily managed by nursing and pharmacy staff (with support from general practitioners at the local reference hospital). These projects, along with the Cambodian government's recently released National Strategic Plan for HCV and HBV,[25] will hopefully bring substantial decreases in existing national HCV prevalence and reduce the disease burden among affected populations.

Recent advances in HCV diagnostics and treatment mean that HCV-positive patients can now be identified quickly and cured with relatively little observation in community settings and few restrictions on patient eligibility.[1,8] It is imperative that screening and treatment models capitalize on the opportunity afforded by these technological advances with equally innovative models of care. By reducing the volume of diagnostic and treatment testing, the number of consultations and the need for specialist oversight, simplified models of care greatly reduce the time, work and financial burden to patients and medical staff. Program budgets also benefit greatly, allowing for expanded programs that can treat more patients. Further, simplified, decentralized models of care are recommended within WHO guidelines.[20] Despite the benefits, many HCV treatment models remain unnecessarily complex, limiting their potential to expand.[8] One limitation is that although simplified models of HCV care are becoming more common globally, disseminated evidence is lacking.[8] This evidence is vital to inform implementation of large-scale screening and treatment programs, particularly for national programs in resource-limited contexts. This project therefore makes an important contribution to the international evidence base.

This MSF project used generic DAAs, produced under the voluntary licence, with prices more affordable compared with branded medication, thereby providing MSF far greater monetary resource for project scale-up. In similar resource-limited settings, generic DAAs help reduce the cost of treatment considerably, increasing the number of patients that can potentially be treated.

There are limitations associated with this study cohort, principally being the change in treatment modality over time, the potential bias in patient-type across the span of the study period, and the number of patients LTFU to PT12 (as a direct result of model changes).

As described, across the study period, the MSF project underwent an incremental, but significant, simplification process, meaning there were differences in care provision between patients. Due to the changes in treatment modality, patients at the start of the study period received a more detailed package of care than those at the end of the study period. Additionally, there were more patients with advanced cirrhosis at the start of the study period (85% F3-F4 patients in the first treatment model compared to 43% F3-F4 patients in the last treatment model), as patients with more advanced disease were prioritized for treatment due to limited treatment capacity when the project first started. Regardless, there was no substantial difference in SVR12 rates across models (Table 5). Finally, as part of the simplification process, it was decided to stop tracing LTFU patients between treatment completion and PT12. The cumulative number of LTFU patients across the study period accounts for the progressively reduced efficacy rates among all initiated patients. When rates were calculated among those with known outcome, thereby excluding those LTFU, there was no difference in efficacy. There is no reason to presume patients not returning for PT12 did not achieve similarly high rates of cure.

In this particularly large treatment cohort in Phnom Penh, Cambodia, the SOF + DCV regimen displayed high rates of treatment effectiveness across patient sub-groups, including among genotype 6 patients, a sub-group with a currently limited body of evidence for SOF + DCV effectiveness. Adverse events were few in number and in keeping with DAA use elsewhere and considered unrelated to the provision of DAA treatment. These outcomes were maintained throughout the three years of the study period, during progressive simplification of treatment care which reduced testing, work and financial burden for patients, medical staff and the MSF budget. This experience makes a significant contribution to the international HCV treatment literature, helping to inform local and international project implementers and health policy makers engage (often) limited resources most effectively. Simplified models of HCV care can diagnose and treat patients earlier in their

infection and reduce treatment burdens on both staff and patients, without compromising patient safety or treatment effectiveness.

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CONFLICT OF INTEREST

None.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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