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ORIGINAL RESEARCH

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Hepatitis C treatment program in Maputo, Mozambique, the challenge of genotypes and key populations: A 5-year retrospective analysis of routine programmatic data

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Abstract

Background and Aims: Hepatitis C (HCV) programs face challenges, especially linked to key populations to achieve World Health Organization (WHO) goals of eliminating hepatitis. Médecins Sans Frontières and Mozambique's Ministry of Health first implemented HCV treatment in Maputo, in 2016 and harm reduction activities in 2017.

Methods: We retrospectively analyzed routine data of patients enrolled between December 2016 and July 2021. Genotyping was systematically requested up to 2018 and subsequently in cases of treatment failure. Sustainable virological response was assessed 12 weeks after the end of treatment by sofosbuvir-daclatasvir or sofosbuvir-velpatasvir.

Results: Two hundred and two patients were enrolled, with 159 (78.71%) males (median age: 41 years [interquartile range (IQR): 37.10, 47.00]). Risk factors included drug use (142/202; 70.29%). One hundred and eleven genotyping results indicated genotype 1 predominant (87/111; 78.37%). Sixteen patients presented genotype 4, with various subtypes. The people who used drugs and HIV coinfected patients were found more likely to present a genotype 1. Intention-to-treat analysis showed 68.99% (89/129) cure rate among the patients initiated and per-protocol analysis, 88.12% (89/101) cure rate. Nineteen patients received treatment integrated with opioid substitution therapy, with a 100% cure rate versus 59.37% (38/64) for initiated ones without substitution therapy ($p < 0.001$). Among the resistance testing performed, NS5A resistance-associated substitutions were found in seven patients among the nine tested patients and NS5B ones in one patient.

Conclusion: We found varied genotypes, including some identified as difficult-to-treat subtypes. People who used drugs were more likely to present genotype 1. In addition, opioid substitution therapy was key for these patients to achieve cure. Access to second-generation direct-acting antivirals (DAAs) and integration of HCV care with harm reduction are crucial to program effectiveness.

KEYWORDS
developing countries, genotype, harm reduction, hepatitis C, retrospective studies

1 | INTRODUCTION

Direct-acting antivirals (DAAs) have revolutionized care for hepatitis C virus disease (HCV).[1] With the availability of DAAs, treatment can be scaled up, potentially with the aim of curing the 58 million people worldwide affected by the disease.[2] In 2016, the World Health Organization (WHO) issued a call to eliminate viral hepatitis as public health treat by 2030. Many countries are already moving toward this goal.[2,3]

Access to pan-genotypic treatment and simplification of care are crucial to achieve HCV elimination.[3] Six genotypes (GTs) predominate as the most clinically important.[4] However, natural and acquired treatment resistance, related to GTs and subtypes, may compromise the goal of elimination, particularly in low- and middle-income countries (LMIC).[5,6]

Most clinical trials thus far have been conducted in high-income countries, potentially leading to biased estimates of treatment efficacy, given that such studies may neglect GTs and subtypes present in LMIC.[7] GT4 is predominantly found in Central Africa and presents high phylogenetic diversity.[8,9] Previous work has shown that GT4 subtypes present NS5A resistance-associated substitutions (RAS), leading to low cure rates after treatment with first-generation DAAs (sofosbuvir combined with ledipasvir or daclatasvir).[10,11]

Furthermore, wider implementation of HCV programs reveal the diversity of population affected by HCV, linked with varying risk factors. In a similar way to Human Immunodeficiency virus (HIV), stigma is a greater burden for some HCV subpopulations, such as people who use drugs (PWUD). In countries where harm reduction (HR) programs are insufficient or nonexistent, the efficacy of HCV care is endangered by inadequate support.[12,13]

In sub-Saharan Africa, an estimated nine million patients are infected with HCV, with various GT and subtypes identified as difficult-to-treat.[2,14] In this region, the population of people who inject drugs (PWID) is estimated at 1.4 million.[2] Lack of epidemiological data, as well as other medical priorities, compromise the goal of HCV elimination. Nevertheless, some countries have launched HCV elimination programs with success.[15]

In Mozambique, until 2016, HCV screening was conducted only for blood transfusion safety purposes and for population-specific surveys.[16] In 2016, Médecins sans Frontières (MSF) launched the country's first HCV care program in collaboration with the Ministry of Health (MoH) in the capital, Maputo. Set up in a referral center for patients with advanced HIV, we found the prevalence of HCV serology of 1.15% among HIV patients, with a high proportion of PWUD among these.[17] In collaboration with local partners, MSF launched an HR program in 2017, providing screening activities, access to care, social support, and syringe-needle distribution, via outreach activities and a community center. In 2020, opioid substitution therapy (OST) was added to provide a full HR package.[18] It was the first OST program in the country. In the community center, HCV screening revealed HCV prevalence at 8% among PWUD overall and at 25.2% among PWID.[19] Therefore, HCV care was integrated into the HR program.

We analyzed the results of HCV care activities to inform further national and international strategies. We described patient characteristics, and we explored possible associations between GTs and patient characteristics and between outcomes and patient characteristics.

2 | METHODS

2.1 | Setting & study design

We report a retrospective analysis of patients enrolled consecutively in HCV care between December 2016 and July 2021. MSF first offered HCV care to HIV–HCV coinfected patients and then included HIV-negative patients in 2018. No other exclusion criteria were applied. The patient's follow-up data were censored in November 2022.

Patients were referred to the HIV clinic, providing HCV integrated care, after positive serological tests (Bioline HCV®, Abbott Diagnostics Korea), from the HIV clinic, the PWUD community center, or from external partners. HCV RNA viral load (VL) testing was initially performed by a local private laboratory (using Cobas 6800 system© platform, Roche Diagnostics) with a turn-around-time of 1 month and then on-site, using Xpert® HCV VL (Cepheid AB), providing same-day results. The limits of detection were 15 and 12 IU/mL, respectively. In February 2020, the OST clinic opened, located within the HIV clinic compound, providing a one-stop service covering HR, HIV, and HCV care. From then on, OST was proposed to PWUD patients using opioids, before HCV treatment.

Nonspecialist doctors were trained to follow patients confirmed by detectable HCV VL. Counsellors and nurses supported patient screening, linkage to care, and follow-up.

2.2 | Baseline assessment

For patients with unknown status, counsellors performed point-of-care HIV screening using serial testing strategies per national protocols and Hepatitis B Virus (HBV) serological screening tests (Determine HBsAg 2, Abbott Diagnostics Korea). Nurses collected blood to assess full blood count, liver and renal functions, and CD4 count if HIV-positive. Tuberculosis screening was performed.

HCV GT was performed systematically up to August 2018, after which it was performed only after treatment failure in case of suspicion of treatment resistance, following new international recommendations.[20] As no in-country genotyping available, dried blood samples were sent to the virology laboratory (Hôpitaux

Universitaires de Genève). GT, sequencing, and resistance profiles were determined as previously described.[21] RAS were reported according to international recommendations.[1]

To assess liver fibrosis, clinicians calculated AST-to-platelet ratio index (APRI) score, and graded liver stiffness using FibroScan402® (Echosens), first systematically then as of 2020, only for patients with APRI score>1.[22] Elasticity threshold for cirrhosis (METAVIR fibrosis 4 stage) was set at 13 kPA following Echosens® recommendations for HIV coinfected patients and EASL 2018 recommendations.[20]

2.3 | Treatment

Limited treatment availability and procurement difficulties meant that at times the medical team had to prioritize patients for treatment. This was done in relation to liver fibrosis and comorbidity, but also considering treatment adherence and active drug consumption. The medical team reevaluated noninitiated patients every 6 months. HCV treatment was initiated after tuberculosis treatment when indicated, and after 6 months of antiretroviral therapy for newly diagnosed HIV-positive patients. In the case of HBV positive test, HIV patients were switched to a tenofovir-based regimen; non-HIV patients were referred to the hepatology department of the central hospital of Maputo, after HCV treatment completion. Patients ineligible for treatment included those with suspicion of hepatocellular carcinoma, terminal illnesses, or uncontrolled opportunistic infections.

Following 2016 recommendations, sofosbuvir-daclatasvir (SOF/DAC) was the first-line treatment. Treatment duration (either 12 or 24 weeks), was decided according to patient GT and liver stiffness (e.g., 24-week treatment for patients presenting cirrhosis).[23] Daclatasvir dose was adjusted to account for drug interactions with HIV regimen. Sofosbuvir-velpatasvir (SOF/VEL) regimens were available as of 2021 for patients with suspected or confirmed RAS. To avoid medicine expiry, some patients received SOF/VEL first-line. From 2020, OST with methadone was available for active PWUD using opioids.

Medical teams adapted the frequency of medical consultations to patient profile and adherence. They systematically reviewed patients at the end of treatment and 12 weeks after that. HCV cure was defined as the sustained virological response at 12 weeks after treatment (SVR12).

In cases of treatment failure, the team evaluated adherence and requested resistance profiling. Retreatment was provided with SOF/VEL in cases of RAS or with SOF/DAC, in cases of adherence problems and absence of RAS.

A patient was considered as lost to follow-up (LTFU) after 6 months without a visit or phone contact.

2.4 | Data collection

The medical team collected routine individual data at each medical consultation, using standardized forms. Nationality was defined as the country of birth; information about stays in other countries was not collected. Status of drug users was defined as past or current drug use. History of risk factors were collected without time limits. Cirrhosis status was defined based on the first liver stiffness measurement or if unavailable, on the APRI score (APRI ≥ 2).

After anonymization, data clerks entered files in a secure database, to Research Electronic Data Capture (REDCap) software using a password-protected account.[24]

2.5 | Statistical analysis

No sample size was defined; we included all patients enrolled in HCV care during the studied period. Baseline patient characteristics were described across HCV GTs: demographic characteristics (gender, age, nationality), biological characteristics (HCV VL, APRI, liver stiffness, and cirrhosis status), comorbidities (HIV, HBV, tuberculosis, diabetes, and renal impairment) and risk factors (past or current drug use, history of imprisonment, of blood transfusion, of invasive procedure and status of health worker). Case definitions and categories for characteristics were based on international recommendations and scientific evidence.

We first tested the hypothesis that there is a difference of characteristics for the patients GT1 versus the other GTs (GT 2, 3, 4, 5). Associations between the GTs and the baseline characteristics were also assessed. The choice of two GT groups was done considering field observations from the medical team and treatment impact. Patients with unknown GTs were not considered in the analysis, considering that systematic genotyping was stopped following new international recommendations during the studied period.

Then, we assessed associations between treatment outcomes and different variables: age, gender, HIV status, groups of GT (as defined above), drug use history, HIV status, cirrhosis status, and received regimen. The variables were selected based on the literature. The primary outcome was a sustained virologic response 12 weeks after treatment completion (SVR12). Failure was defined as virological failure. Per-protocol analysis included patients with available virological results at 12 weeks posttreatment. Intention to treat (ITT) analysis included all initiated patients and failure was defined as virological failure, death, LTFU or transferred out.

Finally, in a subgroup analysis, we described the outcomes of the PWUD patients, with or without OST treatment, and assessed potential statistical evidence of difference.

Differences in proportions were calculated using Pearson χ^2 test or Fisher's exact test for categorical variables. The difference in medians were measured using Mann–Whitney *U* test. A two-sided *p*-value less than 0.05 was considered statistically significant.

We performed univariate and multivariate logistic regressions to measure potential associations between GT groups or treatment outcomes and patient characteristics. The results are presented with the strength estimates (odds ratios [OR]) and their precision (95% confidence interval [95% CI]). Missing information was not included

in the analysis; the denominators reflect the number of informative observations.

We performed data analysis using STATA version 13.1 (StataCorp. 2013. Stata Statistical Software: Release 13.: StataCorp LLC).

3 | RESULTS

3.1 | General description

From December 2016 to July 2021, 202 patients were enrolled in the HCV activities (Figure 1). The median age was 41 years (IQR: 37.10, 47.00), 159 (78.71%) were male; 197 (97.52%) were Mozambican. Regarding risk factors for transmission, 70.29% (142/202) reported current or past drug consumption, 47.40% (82/173) a history of imprisonment, 33.91% (59/174) a history of invasive procedure, and 19.07% (33/173) a history of blood transfusion. Only 1.73% of the enrolled patients (3/173) were health workers. Among the PWUD, 77.46% (110/142) reported injection practices (Table 1).

In relation to comorbidities, out of the 202 patients, 118 (58.42%) were coinfected with HIV, and 7 (3.46%) presented HBsAg-positive results. In addition, 9.90% (20/202) presented with tuberculosis disease at baseline consultation.

Fibroscan® was performed for 111 patients (54.95%); 14.41% (16/111) presented an F4 stage. Out of 181 patients with APRI score, 150 (82.87%) had an APRI < 1, 19 (10.50%) an APRI between 1 and 2, and 12 (6.63%) an APRI > 2. Among all enrolled patients, 18 (18/202, 8.91%) presented with cirrhosis, based on Fibrobroscan© or APRI. Median HCV VL at admission was 6.00 log IU/mL (IQR: 5.37, 6.48).

3.2 | GTs

Out of 202 enrolled patients, 111 patients (54.95%) had GT testing before treatment (Table 2). GT 1a was found in 72.97% (81/111), and GT1b in 5.41% (6/111) of patients. GT 4 was found in 16 patients with various subtypes: GT4b (n:3), GT4d (n:3), GT4r (n:4), GT4v (n:1), GT4w (n:3) and indeterminate subtype (n:2). The other reported GTs were GT2b (n:1), GT3a (n:4), GT3 with indeterminate subtype (n:2) and GT5a (n:1). The patient's characteristics per GT are presented in Table 1. We assessed the difference of demographic characteristics between GT1 and the other GTs. In a univariate analysis, we saw

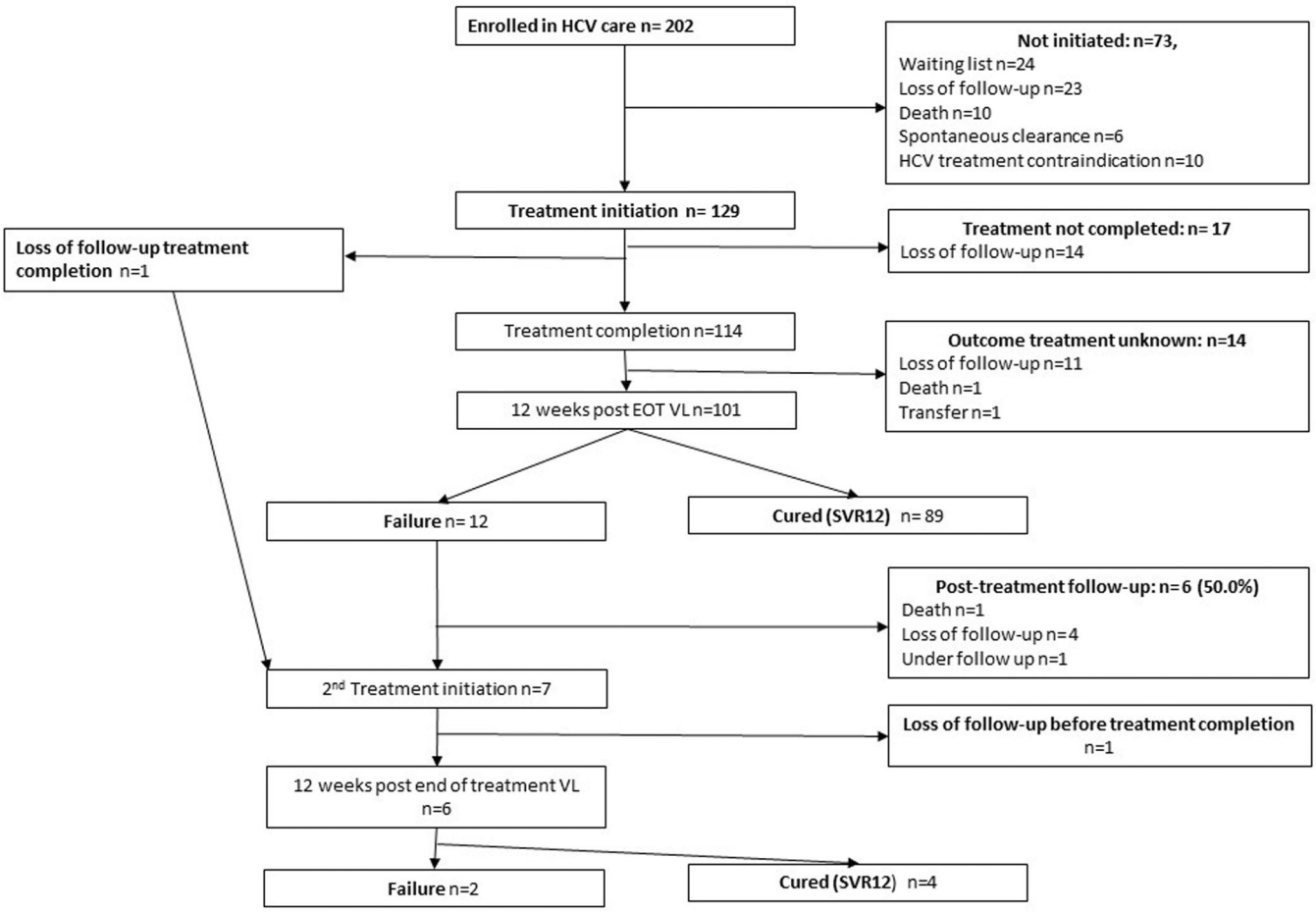

FIGURE 1 Flowchart of patients enrolled in Hepatitis C care activities, Maputo, between 2016 and 2021. EOT, end of treatment; HCV, hepatitis C virus; SVR12, sustainable virological response 12 weeks posttreatment; VL, viral load.

TABLE 1 Sociodemographic, risk factors and biological characteristics of patients enrolled in Hepatitis C care activities in Maputo, between 2016 and 2021.

Characteristics	unknown GT n/N (%) or median (IQR)	GT1 n/N (%) or median (IQR)	GT2 n/N (%) or median (IQR)	GT3 n/N (%) or median (IQR)	GT4 n/N (%) or median (IQR)	GT5 n/N (%) or median (IQR)	Crude OR [95%CI][a]	*p* value[b]
Sociodemographic characteristics								
Age[c]	42.10 (36.4, 47.00)	39.35 (37.25, 43.70)	47	51.45 (45.80, 58.00)	46.55 (36.00, 50.90)	65	0.94 [0.89, 0.98]	0.022
Gender								
Male	71/91 (78.02)	72/87 (82.76)	1/1 (100)	2/6 (33.33)	12/16 (75.00)	1/1 (100)	2.40 [0.87, 6.62]	0.057
Nationality								
Mozambican	91/91 (100)	84/87 (96.55)	1/1 (100)	4/6 (66.67)	16/16 (100)	1/1 (100)	2.55 [0.40, 16.18]	0.295
Risk factors (History)								
PWUD								
Yes	60/91 (65.93)	74/87 (85.06)	1/1 (0.00)	3/6 (50.00)	4/16 (25.00)	0/1 (0.0)	11.38 [4.05, 31.99]	<0.001
Invasive procedures								
Yes	24/79 (30.38)	24/74 (32.43)	1/1 (100)	3/5 (60.00)	7/14 (50.00)	0/1 (0.0)	0.44 [0.16, 1.17]	0.094
Blood transfusions								
Yes	10/76 (13.16)	18/76 (23.68)	0/1 (0.00)	2/5 (40.00)	2/14 (14.29)	1/1 (100)	0.99 [0.32, 3.09]	0.990
Health Workers								
Yes	1/78 (1.28)	1/74 (1.35)	0/1 (0.00)	1/5 (20.00)	0/14 (0.00)	0/1 (0.00)	0.27 [0.02, 4.58]	0.395
Prisoner								
Yes	31/78 (39.74)	47/75 (62.67)	1/1 (100)	1/5 (20.00)	2/13 (15.38)	0/1 (0.00)	6.71 [2.04, 22.10]	0.001
Comorbidities								
Positive HIV status	43/91 (47.25)	66/87 (75.86)	0/1 (0.00)	2/6 (33.33)	7/16 (43.75)	0/1 (0.00)	5.24 [2.00, 13.70]	<0.001
Positive HBsAg	3/91 (3.30)	3/87 (3.45)	0/1 (0.00)	1/6 (16.67)	0/16 (0.00)	0/1 (0.00)	0.82 [0.08, 8.27]	>0.99
Tuberculosis disease	6/91 (6.59)	14/87 (16.09)	0/1 (0.00)	0/6 (0.00)	0/16 (0.00)	0/1 (0.00)	1	0.037
Renal impairment[d]	3/91 (3.30)	2/87 (2.30)	0/1 (0.00)	0/6 (0.00)	0/16 (0.00)	0/1 (0.00)	1	>0.99
Diabetes[d]	3/91 (3.30)	3/87 (3.45)	0/1 (0.00)	1/6 (16.67)	0/16 (0.00)	0/1 (0.00)	0.82 [0.08, 8.27]	>0.99

(Continues)

TABLE 1 (Continued)

Characteristics	unknown GT n/N (%) or median (IQR)	GT1 n/N (%) or median (IQR)	GT2 n/N (%) or median (IQR)	GT3 n/N (%) or median (IQR)	GT4 n/N (%) or median (IQR)	GT5 n/N (%) or median (IQR)	Crude OR [95%CI][a]	*p* value[b]
Biological characteristics								
HCV Viral Load mean Log10[c]	6.00 (5.34, 6.37)	6.05 (5.41, 6.55)	6.68	5.86 (5.54, 5.93)	5.74 (4.72, 6.28)	6.63	1.23 [0.76, 1.99]	0.368
APRI[d]								
<1	57/76 (75.00)	75/82 (91.46)	1/1 (100)	4/6 (66.67)	12/15 (80.00)	1/1 (100)		0.040
1–2	13/76 (17.11)	5/82 (6.10)	0/1 (0.00)	0/6 (0.00)	1/15 (6.67)	0/1 (0.00)		
'>2	6/76 (7.89)	2/82 (2.44)	0/1 (0.00)	2/6 (33.33)	2/15 (13.33)	0/1 (0.00)		
Liver stiffness[d]								
F0–F3	25/33 (75.76)	59/62 (95.16)	0/1 (0.00)	2/4 (50.00)	9/10 (90.00)	0/1 (0.00)		0.008
F4	8/33 (24.24)	3/62 (4.84)	1/1 (100)	2/4 (50.00)	1/10 (10.00)	1/1 (100)		
Cirrhosis status[e]								
Cirrhosis	9/77 (11.69)	3/84 (3.57)	1/1 (100)	2/6 (33.33)	2/15 (13.33)	1/1 (100)	0.10 [0.02, 0.46]	0.003

Abbreviations: APRI, aspartate aminotransferase-to-platelet ratio index; F0-F4, METAVIR fibrosis stage; GT, genotype; HIV, human immunodeficiency virus; HBsAg, hepatitis B surface antigen; IQR, interquartile range; OR, odds ratios; PWUD, people who use drugs; 95% CI, 95% confidence interval.

[a]Univariate analysis of the association between GT1 patients and the other GTs (GT2, GT3, GT4, GT5).

[b]Pearson's χ^2 test/Fisher's exact test (variables whose cells had $n < 5$)/Wilcoxon rank-sum test.

[c]No missing observation, median, and IRQ calculated on the entire group.

[d]Categories based on international recommendations, F4 ≥ 13 kPa.

[e]Cirrhosis status based on liver stiffness, or if absent on APRI score.

TABLE 2 Genotype distribution and treatment outcomes among patients enrolled in Hepatitis C care in Maputo, between 2016 and 2021.

Genotype	Subtype	Subtype[a] *n* (%)	1st treatment N, regimen	SVR12[b] n/N (%)	2nd treatment N, regimen	SVR12[b] n/N (%)
1	a	81 (72,97)	52 SOF DAC	35/43 (81.40)	5 SOF-DAC	4/4 (100)
			1 SOF-VEL			
	b	6 (5,41)	4 SOF DAC	4/4 (100)	0	NA
			1 SOF-VEL			
2	b	1 (0,90)	1 SOF-DAC	NA	0	NA
3	a	4 (3,60)	3 SOF-DAC	3/3 (100)	0	NA
	undeterminate	2 (1,80)	0	NA	0	NA
4	b	3 (2,70)	2 SOF-DAC	1/1 (100)	0	NA
	d	3 (2,70)	2 SOF-DAC	1/2 (50.00)	0	NA
			1 SOF-VEL			
	r	4 (3,60)	4 SOF-DAC	3/4 (75.00)	1 SOF-VEL	0/1 (0.00)
	v	1 (0,90)	1 SOF-LED	1/1 (100)	0	NA
	w	3 (2,70)	3 SOF-DAC	0/2 (0.00)	1 SOF-VEL	0/1 (0.00)
	undeterminate	2 (1,80)	0	NA	0	NA
5	a	1 (0,90)	1 SOF-DAC	1/1 (100)	0	NA
GT unknown	NA	91 (NA)	51 SOF-DAC	40/40 (100)	0	NA
			2 SOF-VEL			

Abbreviations: DAC, daclatasvir; GT, Genotype; LED, ledipasvir; NA, not applicable; SOF, sofosbuvir; SVR12, sustained virological response at 12 weeks after treatment; VEL, velpatasvir.

[a]Percentage calculated among patients with known genotype.

[b]Percentage calculated among the patients with posttreatment VL available (per protocol analysis).

statistically significant evidence of difference in the median age between the two GT groups (*p*: 0.022; 39.95 [95% CI: 37.25, 43.7) versus 47.15 (95% CI: 36.55, 51.85]). GT1 patients were more likely to report drug consumption (74/87, 85.06%) in comparison to other patients (8/24, 33.33%; odds ratio [OR]: 11.38, 95% CI: 4.05, 31.99). GT1 patients were more likely to have a history of imprisonment (62.67% [47/75] vs. 20.00% [4/20]; OR: 6.71; 95% CI: 2.04, 22.10). The OR of GT1 being detected was 5.24 (95% CI: 2.00, 13.70) for HIV-positive (66/87;75.86%) versus HIV-negative patients (9/24; 37.5%). GT1 patients were less likely to present with cirrhosis (3.57% [3/84] vs. 26.09% (6/23; OR: 0.10, 95% CI: 0.02, 0.46) (Table 1).

When adjusting for age, gender, PWUD status, prison history, HIV status, and cirrhosis, only PWUD and HIV status remained statistically significantly associated with GT1 (OR: 7.18, 95% CI: 1.30, 39.52; OR:4.18, 95% CI: 1.14, 15.36).

3.3 | Treatment

Among 202 patients enrolled, 73 (36.14%) were not initiated on treatment. Six patients, out of the 202 patients (2.97%) presented with spontaneous clearance, 10 (4.95%) patients died, 23 (11.39%) were LFTU before initiation, and 10 (4.95%) patients were transferred out to other specialized facilities with other severe disease. At the time of writing, 24 patients (24/202;11.88%) were still waiting for treatment (Figure 1).

One hundred and twenty-nine patients (129/202, 63.86%) were initiated on treatment. The majority of patients were treated with SOF/DAC. One patient with GT4v was treated with SOF/LED, given in India but the patient received all follow-up in Maputo. SOF/VEL was given to five patients as first-line therapy due to short expiration date of these drugs.

Before the end of treatment, 10.85% (14/129) of the patients were LTFU. One LTFU patient was enrolled again later.

After initiation, 88.37% (114/129) of the patients completed treatment and 88.60% (101/114) of these had VL available 12 weeks after treatment completion. In ITT analysis, among the 129 initiated patients, 89 patients (68.99%) achieved SVR12, and 12 patients (9.30%) were considered as virological failure. In addition, one patient was transferred out, one died, and 15 and 11 patients were LTFU, respectively, before and after treatment completion. Per-protocol analysis, the success rate was 88.12% (89/101) (Table 3).

We analyzed the outcome of treatment, stratified by age, gender, GT1, cirrhosis, HIV status, treatment regimen, and PWUD status. We were unable to demonstrate a difference between

TABLE 3 Treatment outcomes (1st initiation) among the patients initiated with Hepatitis C treatment, in Maputo between 2016 and 2021.

Column1	SVR12 N: 89 n (%) or median (IQR)	Virological Failure N: 12	OR (95%CI)[a] (Per Protocol)	P value[b] (Per Protocol)	Failure Outcome[c] N: 40	OR (95%CI)[a] (Intention-to-treat)	P value[b] (Intention-to-treat)
Age	41.8 (37.9, 49.00)	39.2 (37.75,48.00)	1.02 (0.96, 1.09)	0.482	40.2 (36.3, 48.00)	1.02 (0.95, 1.05)	0.482
Gender							
Male	64 (71.91)	11 (91.67)	0.23 (0.03, 1.90)	0.179	32 (80.00)	0.64 (0.26, 1.58)	0.330
Female	25 (28.91)	1 (8.33)	reference		8 (20.00)	reference	
Genotype							
GT 1	39 (43.82)	8/12 (66.67)	1.95 (0.49, 7.80)	0.445	19 (47.50)	1.64 (0.56, 4.83)	0.267
Other GTs[d]	10 (11.24)	4/12 (33.33)	reference		8 (20.00)	reference	
Unknown GT	40 (44.94)	0 (0.00)	NA		13 (32.50)	NA	
PWUD							
Yes	57 (64.04)	9 (75.00)	0.59 (0.15,2.35)	0.536	26 (65.00)	0.96 (0.43, 2.09)	0.917
No	32 (35.96)	3 (25.00)	reference		14 (35.00)	reference	
Cirrhosis[e]							
Yes	12 (13.95)	1/12 (8.33)	1.78 (0.21, 15.10)	1	4 (10.26)	1.42 (0.43, 4.71)	0.774
No	74 (86.05)	11/12 (91.67)	reference		35 (89.74)	reference	
HIV Status							
Positive	51 (57.30)	10 (83.33)	0.27 (0.06, 1.30)	0.118	20 (50)	1.23 (0.58, 2.64)	0.441
Negative	38 (42.70)	2 (16.67)	reference		20 (50)	reference	
TTT							
SOF-DAC/LED	85 (95.51)	12 (100)	1	>0.99	39 (97.50)	1.84 (0.20, 16.96)	>0.99
SOF-VEL	4 (4.49)	0 (0.00)	reference		1 (2.5)	reference	

Note: Intention-to-treat and Per analysis.

Abbreviation: DAC, daclatasvir; GT, genotype; HIV, human immunodeficiency virus; IQR, interquartile range; LED, ledipasvir; NA, not applicable; OR, odds ratios; PWUD, people who use drugs; SOF, sofosbuvir; SVR12, sustainable virological response; VEL, velpatasvir; 95% CI, 95% confidence interval.

[a]Univariate analysis of the association between treatment outcomes and the patient's characteristics.

[b]Pearson's χ^2 test/Fisher's exact test (variables whose cells had $n < 5$)/Wilcoxon rank-sum test.

[c]Final outcome includes virological failure, death, LTFU or transferred out.

[d]Other genotypes included Genotype 2, 3, 4,5.

[e]Cirrhosis status based on liver stiffness, or if absent on APRI score.

outcome groups either in ITT analysis or in per-protocol analysis (Table 3).

Considering patients with available posttreatment VL results (per protocol analysis), all patients with GT1b, GT3a, GT4b, GT5a achieved SVR12 (Table 4). The GT4v patient, treated with SOF/LED was also cured. For GT1a, 81.39% of the patients presented an SVR12 (n:35/43), 50% of the GT4d patients (n:1/2), 75% of the GT4r patients (n:3/4). The two GT4w patient failed to achieve SVR12.

Patients without GT at baseline achieved an SVR 12 per PP analysis of 100% (40/40).

Eighty-three patients with a history or current drug consumption were initiated on HCV treatment. Among them, 19 were initiated on HCV treatment while on OST; all completed follow-up and achieved SVR12. For the PWUD initiated without OST, the ITT and PP analysis found an SVR12 at 59.37% (38/64), and 80.85% (38/47), respectively. There was statistical evidence of difference between patients on and without OST for the ITT analysis ($p < 0.001$), but we were unable to demonstrate a statical evidence for the PP analysis ($p = 0.050$).

3.4 | Resistance testing

Resistance testing was performed in nine patients with virological failure after initial SOF/DAC treatment (Table 4). Testing was not done for three patients with treatment failure due to a clear lack of adherence or LTFU. NS5A RAS were found in seven patients out of the nine tested patients and NS5B RAS (282 T/C) in one GT4w patient (Table 3). To note, four RAS (28 V, 30 S, 58 P, 93 S) were detected in the three patients with GT4w.

Some patients became LTFU before a possible retreatment; second-line treatment for some patients presenting with RAS was also not available for all.

3.5 | Second treatment

Seven patients received a retreatment course, two with SOF/VEL and five with SOF/DAC (Table 2). Among the six patients with VL available 12 weeks after treatment completion, two patients (showing GT4r and GT4w, neither PWUD), failed again to achieve SVR12 despite completion of the SOF/VEL regimen. Four GT1a patients achieved SVR12 with SOF/DAC regimen, including two patients with concurrent OST. Considering small numbers of retreated patients, no further analysis was performed.

4 | DISCUSSION

We successfully implemented the first HCV care activities in Mozambique, integrated with HIV and HR programs. This analysis provided information about the distribution of HCV GTs, patient characteristics and treatment outcomes, in Mozambique. Importantly, our data show a large variety of identified GTs and we described the effectiveness of concurrent OST, to achieve high HCV cure rates.

4.1 | GTs and patient characteristics

We found five different GTs in the studied population, with GT1a in the majority. These GTs have already been reported in Mozambique and in neighboring countries, but data are scarce and lack detail on subtypes.[25,26] GT1 was associated with PWUD status. GT1a and GT1b were previously reported as predominant in PWUD worldwide and in South Africa, and among HIV coinfected individuals.[27,28] In other studies, GT4 was more often identified in PWUD.[29,30] Nevertheless, the presence and the amplification of the GTs in a population were reported to be linked to social, behavioral, and

TABLE 4 Description of resistance-associated substitutions for patients with virological failure, in Hepatitis C care activities in Maputo, between 2016 and 2021.

Patient No	Genotype/subtype	HCV treatment	RAS NS5A	RAS NS5B	Outcome after re-treatment
1	1a	SOF/DAC	28 V	none	Lost to follow-up
2	1a	SOF/DAC	28 V	none	Failure (SOF/DAC)
3	1a	SOF/DAC	none	none	SVR12 (SOF/DAC)
4	1a	SOF/DAC	26E,31 M	none	Lost to follow-up
5	4d	SOF/DAC	30 R, 58 P	none	Lost to follow-up
6	1a	SOF/DAC	none	none	Failure (SOF/DAC)
7	4w	SOF/DAC	28 V,30 S,58 P,93 S	282 T/C	Lost to follow-up
8	4w	SOF/DAC	28 V,30 S,58 P,93 S	none	Lost to follow-up
9	4w	SOF/DAC	28 V,30 S,58 P,93 S	none	Failure (SOF/VEL)

Abbreviations: DAC, daclatasvir; HCV, hepatitis C virus; RAS, resistance-associated substitutions; SOF, sofosbuvir; SVR12, sustainable virological response; VEL, velpatasvir.

demographic factors, leading to different prevalence in different populations infected by different routes of transmission.[26]

Our data highlighted the presence of GT4, predominant in Central Africa.[8] The subtypes GT4a and GT4d are the most disseminated and studied in clinical trials, in comparison to the other subtypes.[5] In our analysis, a variety of GT4 subtypes was found, including 4b, 4d, 4r, 4 v, 4w.

Due to the recruitment of patients from an HIV cohort and HR program, the prevalence of coinfection was high (41.58%). No studies reported specific association between GT1 and HIV status. Our findings may be mostly related to initial eligibility criteria and a probable cluster of HCV infections within the HIV population, receiving care in the facility.

4.2 | Treatment outcomes

The overall cure rate was 68.99% (89/129) in the ITT analysis, and 88.12% (89/101) in per-protocol analysis. These findings were lower than SVR12 reported within clinical trials.[1] In this cohort, we had a high proportion of PWUD, therefore patients more likely to face adherence problems without proper support and access to an HR program. This population is highly stigmatized, usually criminalized, and has needs not addressed by health systems. Nevertheless, several studies have shown that with adapted and integrated provision of care, adherence in such groups could be similar to the non-PWUD population.[12] Destigmatised and flexible approaches, without restrictive criteria, are key to linkage and retention in care for PWUD.[31–33]

In Maputo, we set up specific counselling support, adapted flow, and provided a one-stop service, both for harm-reduction services and care for comorbidities. In 2020, the inclusion of OST was key to achieve adequate adherence; all patients with concurrent methadone treatment achieved SVR12. However, bias in recruitment may overestimate this success, as patients receiving HCV treatment were already adherent to methadone treatment. Nevertheless, several studies have recognized the importance of HR, including OST, to ensure adherence to and success of HCV or HIV treatment.[34] A full HR package is crucial for this high-risk population, to achieve cure and to stop transmission.[35]

Second, patients enrolled in this analysis presented subtypes, often considered as more difficult to treat, especially with first-generation DAAs.[36] We noted a low success rate in the initial treatment of GT4 patients: 6/10 (60.00%). Previous publications reported lower cure rates for these GTs.[10,37,38] Bi-therapy and tri-therapy of second-generation associations have been recommended.[1] SOF/VEL, combined with voxilaprevir in cases of retreatment, has been shown to be safe and effective with an SVR12 at 97% for GT4 in Rwanda.[39,40] In our center, during retreatment with SOF/VEL alone, GT4r and GT4w patients did not achieve SVR12. Few clinical trials have included patients with unusual GT4 subtypes, and effectiveness of the newer drugs remains uncertain.

Access to resistance testing is limited in LMIC. In collaboration with the Laboratory of Virology (Geneva University Hospital), we documented RAS after treatment failure. Detected NS5A RAS have already been reported in the literature in patients with daclatasvir virological failure.[36,41]

Nevertheless, today, most of the countries in sub-Saharan Africa do not have access to these regimens due to a lack of registration by the originator and generic manufacturers, and high prices, which endanger the implementation of national strategies.[42] SOF/VEL now has quality-assured generic formulations from two different companies, although is not yet registered widely in LMICs. Another second-line option could be glecaprevir/pibrentasvir (G/P) but despite a license from the Medicines Patent Pool, it has yet to be developed by generic companies. Both SOF/VEL and G/P are included in the WHO essential medicines list, while sofosbuvir/velpatasvir/voxilaprevir is not. International funders, such as the Global Fund to fight Tuberculosis, AIDS, and Malaria, have supported procurement of DAAs for key populations and for HIV patients with coinfections.[43]

Accessible and affordable pan-genotypic drugs are crucial to scaling up HCV care. Genotyping is not widely accessible in LMICs, risk factors should be considered to evaluate the risk of resistance to first-association treatment regimen. Highly effective drugs allow for simplification of diagnostic flow, removing the need for genotyping, and for simplification of medical follow-up, facilitating decentralization of HCV care with the potential for task-shifting to nurses.[44] In Mozambique, we succeeded in the implementation of HCV care with nonspecialized doctors, and in involving nurses and counsellors for patient follow-up.

4.3 | Limitations

In this analysis, several limitations need to be considered. First, HCV activities were conducted in only one health facility in Maputo City. The risk factors and GT distribution may be different in other parts of Mozambique or in neighboring countries. Mozambique has very high HIV prevalence and increasing drug use, which influences viral transmission and care strategies.[45] Due to difficulties in accessing treatment, enrolment of HCV patients was limited. Wait time to enrolment and receipt of treatment may have biased patient recruitment and impacted retention in care. Patients enrolled may have been more likely to be adherent to HCV treatment. We might also have missed patients who were too sick to continue the follow-up. The studied patients may not be representative of all screened positive patients.

The population size studied was limited. In addition to the lack of representation, the analysis may have neglected some associations both for GT distribution and outcomes. Furthermore, we retrospectively analyzed routine programmatic data, prone to suboptimal quality and completeness. The impact of these biases is difficult to evaluate as epidemiological data on HCV are lacking in the southern Africa region.

Finally, we did not perform sequencing at baseline; it is unclear therefore if RAS observed after virological failure might already have been present at baseline. Moreover, we could not discriminate

virological failure from possible reinfection, which might be a major problem among the PWUD.

4.4 | Next steps

The National Hepatitis Program developed a national guideline for HCV and HBV, supported by this MSF-MoH collaboration.[46] The guideline was developed before evidence became available about the presence of difficult-to-treat subtypes; this guideline would require also revision to include second-generation DAAs, conditioned by access to affordable drugs. The MoH has also succeeded in including HCV care and HR care in the current Global Fund grant.

This analysis will inform further adapted, simplified, and cost-effective strategies, crucial to achieve the WHO call for hepatitis elimination.

5 | CONCLUSIONS

This HCV care project was successfully implemented in Mozambique as a one-stop service, integrated into existing primary healthcare. GT1 was the most prevalent GT. Nevertheless, the presence of difficult-to-treat GTs and high-risk populations need to be considered in the national strategy to ensure success. An integrated approach with HR services was highlighted as crucial to achieve high cure rates and avoid new infection or reinfection in this high-risk clustered population. To simplify diagnostic flow and ensure treatment success, access to affordable pan-genotypic treatment should be prioritized, to achieve HCV elimination in LMIC.

AUTHOR CONTRIBUTIONS

Anne Loarec: Conceptualization; data curation; formal analysis; funding acquisition; investigation; methodology; supervision; validation; writing—original draft. **Ana Gabriela Gutierrez**: Supervision; validation; writing—review & editing. **Gil Muvale**: Supervision; writing—review & editing. **Aleny Couto**: Supervision; validation; writing—review & editing. **Aude Nguyen**: Conceptualization; methodology; writing—review & editing. **Sabine Yerly**: Investigation; validation; writing—review & editing. **Yolanda Pinto**: Investigation; writing—review & editing. **Natercia Madeira**: Investigation; software. **Alan Gonzales**: Funding acquisition; supervision; writing—review & editing. **Lucas Molfino**: Resources; supervision; writing—review & editing. **Iza Ciglenecki**: Conceptualization; methodology; writing— original draft; writing—review & editing. **Natalia Tamayo Antabak**: Conceptualization; investigation; methodology; project administration; resources; supervision; writing—original draft; writing—review & editing. All authors have read and approved the final version of the manuscript.

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CONFLICTS 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. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

ETHICS STATEMENT

This analysis was granted ethical approval from the Mozambican National Committee for Bioethics in Health (56CNBS/2021), with informed consent waiver, due to the retrospective nature of the analysis of routine programmatic data, and fulfilled the exemption criteria set by the MSF Ethics Review Board (ERB) for a posteriori analyses of routinely collected clinical data; thus was deemed to not require MSF ERB review.

TRANSPARENCY STATEMENT

The lead author Anne Loarec 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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