

Retreatment of Chronic Hepatitis C Infection: Real-World Regimens and Outcomes From National Treatment Programs in Three Low- and Middle-Income Countries

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Access to recommended second-line treatments is limited for patients who fail initial hepatitis C virus (HCV) therapy in low- and middle-income countries. Alternative regimens and associated outcomes are not well understood. Through a pooled analysis of national program data in Egypt, Georgia, and Myanmar, we observed SVR rates >90% for alternative retreatment regimens.

Keywords. hepatitis C; HCV; retreatment; treatment failure; low- and middle-income countries.

Achievement of hepatitis C virus (HCV) elimination in low- and middle-income countries (LMICs) relies upon a simplified public health approach and affordable generic direct acting antiviral (DAA) regimens. DAAs recommended as initial therapy combinations and available from generic manufacturers, such as sofosbuvir/daclatasvir (SOF/DCV), cure about 95% of those treated [1] and are available in over 100 countries [2]. Patients who fail initial treatments should be retreated with second-line therapy. Sofosbuvir/velpatasvir/voxilaprevir (SOF/VEL/VOX) is the only evidence-based retreatment option in resource-limited settings recommended by the World Health Organization (WHO), based on trials showing 96–98% sustained virologic response at 12 weeks (SVR12, ie, cure) in

patients previously treated with another DAA-based regimen [3]. However, SOF/VEL/VOX is not available as a generic formulation and is not widely accessible in LMICs [2, 4].

As access to HCV treatment in LMICs grows and more people are treated, the volume of patients requiring second-line therapy will increase. These patients need timely and effective retreatment to prevent progression of liver disease and secondary HCV transmission [5]. In the absence of recommended regimens (eg, SOF/VEL/VOX) for retreatment, clinicians in LMICs have utilized alternative therapeutic regimens and durations, typically based on SOF in combination with the NS5A inhibitors ledipasvir (LDV) or DCV for 12–24 weeks with or without the addition of ribavirin (RBV). Retreatment studies have been conducted with SOF/VEL+RBV and glecaprevir/pibrentasvir (G/P) in high-income countries for genotypes (GT)-1, 2, and 3 [6–9]. Studies of alternative options for HCV retreatment in LMIC settings are sparse [10–12].

Data are needed regarding the effectiveness of alternative and widely available retreatment regimens readily available in LMICs in achieving HCV cure among patients who initially failed treatment on a DAA-based regimen. The aim of this analysis was to pool de-identified program data across LMICs to assess the most common treatment regimens that have been used to retreat patients who failed initial DAA-based therapies and to determine SVR12 rates by treatment regimen and duration among patients who failed initial DAA-based therapies.

METHODS

Existing HCV treatment programs in LMICs were invited to participate in this study via partners in the Coalition for Global Hepatitis Elimination and Clinton Health Access Initiative country programs. A centralized, secure data portal was established for LMIC HCV treatment programs to share previously collected, de-identified data on HCV patients with failure of initial DAA treatment. Failure to primary DAA regimen was defined by a detectable HCV RNA at or after 12 weeks following the end of treatment course. Patients were not eligible for inclusion if suspected of having reinfection 1) as suspected by local clinicians, or 2) due to a negative HCV RNA at or after SVR12 time point followed by a positive HCV RNA at a later date.

Data included initial therapy and second-line therapy regimens and durations, patient demographic and clinical characteristics, and retreatment outcomes. Given that this retrospective analysis used de-identified data, this study was given a Non-Human Subject Research determination (Advarra IRB Pro00041396, Georgian National Center for Disease Control and Public Health IRB 2020-004). National

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programs from Egypt, Georgia, and Myanmar and clinical sites from Rwanda contributed data on initial therapy failures, retreatments with second-line therapy, or both; data from Rwanda (N = 37) included only initial therapy failures and were not included in the final analysis. All reported data from Georgia and Egypt were from the public sector, whereas data from Myanmar were from both public and private facilities. Descriptive statistics were used to assess patient demographic and clinical characteristics and second-line therapy regimens, as well as SVR12.

RESULTS

De-identified data on 1462 HCV infected patients with confirmed virologic relapse after initial DAA therapy and retreated with second-line therapy were shared from Egypt (N = 639), Georgia (N = 807), and Myanmar (N = 16) (Table 1). The median age of retreated patients was 53 (interquartile range [IQR]: 47–59) years, and 73.8% were male (N = 1079). Of retreated patients, 73.2% (N = 1061) were cirrhotic. The breakdown of genotypes for the 823 retreated patients in Georgia and Myanmar was as follows: GT-1: 50.8%, GT-2: 21.6%, GT-3:

Table 1. Patient Characteristics and Treatment Regimens Across Countries and SVR12 by Retreatment Regimen

	Egypt		Georgia		Myanmar		All Sites		SVR12 Achieved With Retreatment (All Sites)	
	N	%	N	%	N	%	N	%	n/N	%
Total N	639		807		16		1462		1004/1070	93.8%
Sex										
Female	258	40.4%	125	15.5%	0	0.0%	383	26.2%		
Age in years, median (IQR)	639	54 (47–59)	807	52 (46–58)	16	44 (40–49)	1462	53 (47–59)		
Known HIV-positive	103	16.1%	0	0.0%	16	100.0%	119	8.1%		
Known HBV-positive	2	0.3%	20	2.5%	0	0.0%	22	1.5%		
History of injecting drugs	82	10.2%	82	10.2%		
Genotype										
1	414	51.3%	4	25.0%	418	50.8%	217/229	94.8%
2	178	22.1%	0	0.0%	178	21.6%	115/120	95.8%
3	215	26.6%	8	50.0%	223	27.1%	97/111	87.4%
6	0	0.0%	4	25.0%	4	0.5%	0/0	N/A
Cirrhotic	495	77.5%	565	70.1%	1	25.0%	1061	73.2%		
Duration of initial treatment										
12 weeks	294	36.4%	14	87.5%	308	37.4%		
24 weeks	391	48.5%	2	12.5%	393	47.8%		
Other	122	15.1%	0	0.0%	122	14.8%		
Initial therapy										
SOF/LDV	0	0.0%	102	12.6%	0	0.0%	102	7.1%	39/46	84.8%
SOF/LDV+RBV	0	0.0%	144	17.8%	0	0.0%	144	10.0%	57/58	98.3%
SOF+RBV	384	62.5%	556	68.9%	0	0.0%	940	65.4%	678/719	94.3%
SIM/SOF	110	17.9%	0	0.0%	0	0.0%	110	7.7%	99/104	95.2%
SOF/DCV	55	9.0%	0	0.0%	16	100.0%	71	4.9%	51/55	92.7%
SOF/DCV+RBV	63	10.3%	0	0.0%	0	0.0%	63	4.4%	55/61	90.2%
Other	2	0.3%	5	0.6%	0	0.0%	7	0.5%	0/2	0.0%
Second-line therapy and duration selection										
12 weeks										
SOF/LDV+RBV	0	0.0%	77	9.5%	0	0.0%	77	5.3%	61/62	98.4%
SOF/DCV+RBV	79	12.4%	0	0.0%	0	0.0%	79	5.4%	71/77	92.2%
SOF+SIM+DCV+RBV	77	12.1%	0	0.0%	0	0.0%	77	5.3%	75/77	97.4%
Other ^a	34	5.3%	40	5.0%	4	25.0%	78	5.3%	56/57	98.3%
24 weeks										
SOF/LDV+RBV	0	0.0%	465	57.6%	0	0.0%	465	31.8%	266/291	91.4%
SOF/DCV+RBV	449	70.3%	0	0.0%	0	0.0%	449	30.7%	395/422	93.6%
SOF/VEL+RBV	0	0.0%	201	24.9%	3	18.8%	204	14.0%	64/68	94.1%
Other ^b	0	0.0%	24	3.0%	9	56.3%	33	2.3%	16/16	100.0%

Abbreviations: DCV, daclatasvir; HBV, hepatitis B virus; HIV, human immunodeficiency virus; IQR, interquartile range; LDV, ledipasvir; RBV, ribavirin; SIM, simeprevir; SOF, sofosbuvir; SVR12, sustained viral response at 12 weeks; VEL, velpatasvir.

^aAmong patients with SVR12 received.

^bOther regimens were as follows: SOF/VEL, SOF/DCV, SOF/LDV, SOF/LDV+RBV+PegIFN, SOF/VEL/VOX, SOF/VEL/VOX+RBV, SOF/PAR/OMB+RBV, SOF/SIM, SOF+RBV+PegIFN.

27.1%, GT-6: 0.5%. Genotype data were not available in Egypt. About 10% (N = 82) of retreated patients were persons who injected drugs (this variable was only collected in Georgia), 8.1% (N = 119) were known to be human immunodeficiency virus (HIV)-positive, and 1.5% (N = 22) were known to be hepatitis B virus (HBV)-positive. Of 823 patients in Georgia and Myanmar, 47.8% (N = 393) received 24 weeks of initial therapy, 37.4% (N = 308) were prescribed a 12-week regimen of therapy, and 14.8% (N = 122) were prescribed other initial treatment durations. The most common initial therapy regimens were SOF+RBV (65.4%) and SOF/LDV+RBV (10%). There was some use of SOF/LDV+RBV as first-line therapy for GT-2 (N = 30) and GT-3 (N = 99), despite this regimen not being recommended by WHO guidelines for these genotypes.

A total of 37.7% (N = 546) of retreated patients initiated second-line therapy within 6 months after completion of initial therapy. Of the 1462 patients retreated for HCV infection, the most common second-line therapy regimens and treatment durations were SOF/LDV+RBV for 24 weeks (31.8%), SOF/DCV+RBV for 24 weeks (30.7%), SOF/VEL+RBV for 24 weeks (14.0%), SOF/DCV+RBV for 12 weeks (5.4%), SOF/LDV+RBV for 12 weeks (5.3%), and SOF+simeprevir (SIM)+DCV+RBV for 12 weeks (5.3%). SOF/VEL/VOX or SOF/VEL/VOX+RBV was used for 11 patients (0.2%; all patients were in Myanmar).

At the time of analysis, 89.8% (N = 1313) of the 1462 retreated patients had completed second-line therapy. Of 1070 (81.5% of 1313) patients who completed retreatment and received SVR12 testing, the proportion of patients who achieved SVR12 was at least 91.4% for all regimens (range: 91.4–100%). Overall, 93.8% of the 1070 retreated patients who received SVR12 testing were cured. Cure rates were high for GT-2 (13/13; 100%) and GT-3 (39/40; 97.5%) patients treated with SOF/LDV+RBV, despite this not being a WHO-recommended regimen.

DISCUSSION

This retrospective analysis revealed that despite the unavailability of WHO-recommended regimens for HCV second-line therapy in 3 LMICs, alternative therapeutic regimens are available, are being used by clinicians, and resulted in over 93% of patients cured of HCV infection upon retreatment. The most commonly used second-line therapy regimens were SOF/LDV+RBV, SOF/DCV+RBV, and SOF/VEL+RBV for 24 weeks. Although the quality of this evidence is lower than that for the WHO-recommended regimen, these strategies of extending existing therapies to 24 weeks and/or adding ribavirin are consistent with commonly used practices in HCV treatment. All retreatment regimens used in Egypt and Georgia achieved SVR rates of more than 90%.

This analysis was limited by its observational, retrospective design. Direct comparison of SVR rates across retreatment regimens was not possible due to the potential for confounding

across regimens and settings. More than 20% of patients in the data set did not have SVR12 data reported, and these patients may have had a lower cure rate than that described here or may have experienced adverse events. Moreover, genotype data were not available from Egypt, although it has been well documented that the primary genotype in this population is 4a [13]. Most patients (65.4%) were initially treated with SOF+RBV, which is no longer the primary initial therapy in LMICs, and virologic failure after this regimen may be less likely to provoke NS5A resistance and possibly influence retreatment success. However, even when restricting analysis to only NS5A-containing initial regimens (SOF/LDV and SOF/DCV), SVR12 after retreatment was 89.1%, in line with the broader conclusions of the analysis. SOF/LDV+RBV was given to some genotype 2 and 3 patients as initial therapy, despite not being recommended by WHO guidelines. For these patients with SVR12 data, the retreatment outcomes were still favorable: GT-2: 100% cured; GT-3: 97.5% cured. No patients in this data set were treated with glecaprevir/pibrentasvir (G/P), as G/P is not currently widely available in LMICs. Retreatment outcomes may differ for failures of first-line regimens not included in this dataset.

Data on tolerability/adverse events were not systematically collected at all sites and therefore this topic was outside of the scope of this analysis. Additional data should be collected to assess the strengths and limitations of these second-line therapeutic options. For example, there are drawbacks of a ribavirin-based therapy, especially for 24 weeks, including a higher side effect profile, increased ribavirin monitoring needs, more challenges with adherence, and potential issues with availability of ribavirin. A prospective, randomized controlled trial in LMICs is needed to establish high-quality evidence on preferred second-line therapy regimens. Still, useful information may be gleaned by analyzing routinely collected, real-world data from active HCV programs in LMICs.

In the absence of a recommendation on affordable and accessible regimens for retreatment in international guidelines, clinicians in LMICs must use their own judgement based on second-line therapy options available or make the difficult decision to defer retreatment. Patients who defer retreatment may go on to develop advanced liver disease or primary liver cancer. These preliminary data suggest that currently available second-line therapy options have high cure rates. These alternative second-line therapy regimens are affordable at a cost as low as US \$28 for locally approved SOF/DCV and US \$63 for RBV for a 12-week treatment course [14, 15].

The World Health Organization set global targets for hepatitis elimination in 2030, and patients who experience initial therapy failures should not be forgotten on the quest to elimination.

Notes

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