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# RESPONDING TO DIFFICULT-TO-TREAT HCV SUBTYPES PREVALENT IN SUB-SAHARAN AFRICA

## INTRODUCTION

All people living with hepatitis C virus (HCV) infection have a right to effective treatment. To fulfill this right and meet World Health Organization (WHO) targets to eliminate HCV as a public health threat by 2030, countries, donors, and researchers must act to ensure that all people with HCV have access to the tests and curative direct-acting antivirals (DAAs) they need. Newer pangenotypic DAAs may be more effective at curing emerging, difficult-to-treat subtypes of HCV.<sup>1</sup> In 2019, it was estimated that **5.5 million people in sub-Saharan Africa could be infected with difficult-to-treat subtypes, accounting for half of those with chronic HCV in sub-Saharan Africa and 8 percent of the global patient population.**<sup>2</sup> People from the region also reside as migrants around the world, and their countries of residence must also prepare to diagnose and treat these subtypes.

## EMERGING DIFFICULT-TO-TREAT HCV SUBTYPES

The late recognition of difficult-to-treat subtypes and their prevalence in sub-Saharan Africa is the direct result of the failure to conduct clinical trials for regulatory approvals in the region. Data on the efficacy of DAAs from HCV test-and-treat programs in sub-Saharan countries have only recently become available. Viral genotype subtypes previously thought rare are prevalent in sub-Saharan Africa. In Rwanda, the **4r subtype** has been linked to lower-than-expected cure rates. The SHARED study reported that just 56 percent (27/48) of patients with 4r subtype achieved sustained virologic response (SVR), or effective cure, with 12 weeks of sofosbuvir/ledipasvir (SOF/LDV). In addition, some of the 4r patients were initially identified as having genotype 1 or mixed 1/4 genotype by existing assays.<sup>3</sup> A retrospective study from France—which included migrants from sub-Saharan Africa—revealed that subtype 4r has specific mutations associated with resistance to DAAs. These mutations have been shown to increase resistance to the **NS5A inhibitors** ledipasvir and daclatasvir (DAC).<sup>4</sup>

Analysis of samples from Uganda and the Democratic Republic of Congo have identified additional subtypes: 4k, 4p, 4q, 4s, and genotype 7, including a previously uncharacterized genotype 7 subtype.<sup>5</sup> A French cohort study known as GEMHEP also revealed increasing subtype diversity, likely among migrants from sub-Saharan Africa. Among patients with genotype 4, 27.5 percent had subtype 4a, with other poorly understood subtypes also observed.<sup>6</sup> Data on the efficacy of DAAs against all these newly identified subtypes is lacking.

In one United Kingdom study, 47 of 91 (52 percent) people of African origin who had been treated for HCV had rare or previously uncharacterized subtypes, labeled as “**non-1a/1b**” by researchers. The majority of these non-1a/1b subtypes (82 percent) were also found to have NS5A resistance profiles, with only 75 percent (21/28) of these patients achieving SVR. Notably, treatment failures were associated with SOF/LDV, and none of the patients had initially been treated with newer pangenotypic regimens such as sofosbuvir/velpatasvir (SOF/VEL) or glecaprevir/pibrentasvir (G/P). At the time of writing, five of these patients had begun retreatment with G/P or sofosbuvir/velpatasvir/voxilaprevir, with four achieving SVR.<sup>7</sup>

## IMPLICATIONS FOR DIAGNOSTICS AND TREATMENT SCALE-UP

Access to DAAs in sub-Saharan Africa remains extremely limited for a number of reasons: lack of funding for universal test-and-treat programs, lack of national registration of generic medications under voluntary licenses, lack of diagnostics and treatment infrastructure, and lack of epidemiological data at the national level. Access to newer regimens such as SOF/VEL and G/P, which could better address these more difficult-to-treat subtypes, is even more limited.

It is understandable that global health authorities and national ministries of health committed to addressing HCV have focused their efforts on delivering first-line treatments for the majority of patients. Concerns regarding difficult-to-treat HCV subtypes that may

predominate in sub-Saharan African countries must not slow efforts to implement ambitious test-and-treat programs. Rather, the emergence of these subtypes should spur investment in HCV elimination in the region, including to catalyze the uptake of diagnostics and of SOF/VEL and G/P regimens. The challenge of these difficult-to-treat subtypes also provides opportunities for the development of novel algorithms, potentially novel combinations of existing DAAs, and diagnostic tools with sensitivity and specificity<sup>8</sup> to subtypes prevalent in sub-Saharan Africa. Shared resistance profiles must be characterized for patients living in or originating from sub-Saharan Africa, and clinical trials must be initiated to test and determine optimal treatment regimes. Waiting for patients with difficult-to-treat subtypes to fail is unacceptable.

### Recommendations for Action:

#### Generic Companies:

- Manufacturers must immediately register SOF/VEL and G/P for production in all countries covered under voluntary licenses, and negotiate affordable pricing with national governments, regional procurers, and donors.

#### National Governments and Donors:

- Universal treatment with pangenotypic DAAs in the sub-Saharan Africa region using generic SOF/VEL and G/P must be scaled up without delay.
- Governments must expedite national regulatory approvals, negotiate affordable access pricing from suppliers, and procure at volume to meet local needs.
- Donors and governments must support production and procurement of generic SOF/VEL to achieve a target price that is no more than US\$120/treatment course—or double the best price available for generic SOF/DAC—to the public health system, at minimal or no cost to patients, as part of a comprehensive package of services.

#### Diagnostic Companies and Donors:

- Donors and diagnostics developers must invest with direct funding in the development of affordable point-of-care assays for low- and middle-income countries to rapidly detect and triage difficult-to-treat subtypes such as 4r and non-1a/1b.

- Diagnostic companies must develop affordable tools to identify and analyze resistance profiles.

#### Clinical Providers:

- Treatment programs must confirm cure at 12 or 24 weeks after treatment and put systems in place to prevent loss to follow-up before SVR confirmation.
- Programs must strive to find patient-friendly approaches to retain patients in care who do not achieve SVR; programs must provide appropriate retreatment.
- Clinicians must document and create registries of 4r and non-1a/1b patients who do not achieve SVR in their first treatment course.
- Programs must pool patient resistance profiles and treatment data at national and regional levels to guide the development of optimal treatment protocols for difficult-to-treat subtypes.

This brief is current as of February 2020. Please check for more current resources at [www.treatmentactiongroup.org](http://www.treatmentactiongroup.org).

### ENDNOTES

<sup>1</sup> Treatment Action Group. HCV genotypes. 2017 February. <https://www.treatmentactiongroup.org/publication/hcv-genotypes/>.

<sup>2</sup> Gupta N, Kateera F, Desalegn H, et al. Is resistance to direct-acting antivirals in sub-Saharan Africa a threat to HCV elimination? Recommendations for action. *J Hepatol*. 2019 Dec 10;S0168-8278(19)30644-0. doi: 10.1016/j.jhep.2019.10.017.

<sup>3</sup> Gupta N, Mbituyumuremyi A, Kabahizi J, et al. Treatment of chronic hepatitis C virus infection in Rwanda with ledipasvir-sofosbuvir (SHARED): a single-arm trial. *Lancet Gastroenterol Hepatol*. 2019 Feb;4(2):119–26. doi: 10.1016/S2468-1253(18)30382-0.

<sup>4</sup> Fourati S, Rodriguez C, Hézode C, et al. Frequent antiviral treatment failures in patients infected with hepatitis C virus genotype 4, subtype 4r. *Hepatology*. 2019 Feb;69(2):513–23. doi: 10.1002/hep.30225.

<sup>5</sup> Davis C, Mgomella GS, da Silva Filipe A, et al. Highly diverse hepatitis C strains detected in sub-Saharan Africa have unknown susceptibility to direct-acting antiviral treatments. *Hepatology*. 2019 Apr;69(4):1426–41. doi: 10.1002/hep.30342.

<sup>6</sup> Semenova T, Nemoz B, Thibault V, et al. Hepatitis C subtype distribution in chronically infected patients with mild liver fibrosis in France: the GEMHEP study. *Epidemiol Infect*. 2019 Jan;147:e234. doi: 10.1017/S0950268819001225.

<sup>7</sup> Childs K, Davis C, Cannon M, et al. Suboptimal SVR rates in African patients with atypical genotype 1 subtypes: Implications for global elimination of hepatitis C. *J Hepatol*. 2019 Dec;71(6):1099–1105. doi: 10.1016/j.jhep.2019.07.025.

<sup>8</sup> Treatment Action Group. Hepatitis C virus (HCV) diagnostics fact sheet. 2015 December. <https://www.treatmentactiongroup.org/publication/hepatitis-c-virus-hcv-diagnostics-fact-sheet/>.