Editorial

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# DAA failures in African patients with "unusual" HCV subtypes: Hey! Didn't you know there was another world?

Jean-Michel Pawlotsky[1,2,*]

[1]National Reference Center for Viral Hepatitis B, C and D, Department of Virology, Hôpital Henri Mondor, Université Paris-Est, Créteil, France; [2]INSERM U955, Créteil, France

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We all agree: the field of hepatitis C has experienced an unprecedented therapeutic revolution. Since the discovery of hepatitis C virus (HCV) in 1989, the rates of cure of the infection have jumped from approximately 6% after 1 year of standard interferon-alpha administered 3 times per week – at the cost of numerous and often serious side effects – to nearly 98% on average after 8 to 16 weeks of oral treatment nowadays.[1] Current direct-acting antiviral (DAA) combination regimens are pangenotypic, easy to take (1 to 3 pills once per day), highly efficacious and well tolerated. In this context, the World Health Organization (WHO) set the goal to eliminate hepatitis C as a major public health threat (*i.e.* to reduce the incidence of new infections by 90% and HCV-related mortality by 65%) by 2030. However, as of today, only a few countries are on track to eliminate HCV by 2030.[2–4] Many high-income countries are not expected to achieve HCV elimination before 2050, while the vast majority of low- and middle-income countries have not yet started addressing the issue.[2–4] Reasons commonly evoked to explain the difficulties in implementing efficient elimination policies include the lack of political will, the absence of national or regional action plans, insufficient funding, the lack of screening policies, poor linkage-to-care strategies, and treatment restrictions.

Insidiously, another danger weighs on the hope for global HCV elimination: our HCV DAA combinations may not be as pangenotypic as claimed. Indeed, in the current issue of the *Journal of Hepatology*, Childs *et al.*[5] report from a London hospital on suboptimal rates of sustained virological response (SVR) in patients of African origin who were infected with HCV genotype subtypes unusually found in Western Europe. Among 2,211 patients with chronic hepatitis C seen between 2010 and 2018 in their center, the authors identified 91 individuals (4.1%) who were born in (mostly sub-Saharan) Africa. Thirty-five of them (38.5%) were infected with unusual HCV genotype 1 subtypes, including 1e, 1g, 1h, 1l or unassigned genotype 1 (from which 15 new subtypes were identified by full-length HCV open reading frame sequencing). In addition, 12 of the 91 African patients (13.1%) were infected with unusual HCV genotype 4 subtypes, including 4c, 4e, 4f, 4k and 4r[5]. In contrast, patients not of African origin were infected with HCV genotypes usually found in the area, including 1a, 1b or 3a, except 3.3% infected with an unassigned genotype 1 subtype. After treatment, only 75% of African patients infected with unusual genotype 1 subtypes achieved SVR, whereas a high rate of response was achieved in those infected with usual subtypes. Factors associated with the lack of SVR in patients of African origin in multivariate analysis were unusual HCV genotype 1 subtype and NS5A inhibitor-based *vs.* protease inhibitor-based treatment regimens.[5] Failures of NS5A inhibitor-containing treatments were explained by the frequency of NS5A resistance-associated substitutions (RASs) present as natural polymorphisms at baseline in African subtypes, particularly at amino acid positions 24, 30 and 31. Most patients had been treated before the implementation of last-generation pangenotypic regimens, but all of those who failed had received treatment combinations supposed to carry pan-genotype 1 activity (sofosbuvir/ledipasvir, grazoprevir/elbasvir, or ombitasvir/paritaprevir/ritonavir plus dasabuvir). One of 3 patients retreated with glecaprevir/pibrentasvir failed to achieve SVR, while 2 patients retreated with sofosbuvir/velpatasvir/voxilaprevir cured the infection.[5]

These results echo our recent report of frequent antiviral treatment failures in patients of African origin infected with HCV subtype 4r.[6] In our experience, out of 537 patients treated with DAAs who experienced a virological failure between 2015 and 2018, 22.5% were infected with genotype 4 (whereas genotype 4 represents only 13.7% of HCV-infected patients in France[7]), and among them, 22.3% were infected with subtype 4r, a very rare subtype in the French general population. All patients infected with subtype 4r were born in sub-Saharan Africa.[6] This overrepresentation of subtype 4r among patients failing to achieve SVR was in keeping with a Rwandan study showing an SVR rate of only 56% in patients infected with subtype 4r treated with sofosbuvir/ledipasvir, significantly lower than the 93% SVR rate in patients infected with other genotype 4 subtypes.[8] Low SVR rates in patients infected with genotype 4r receiving sofosbuvir and an NS5A inhibitor were explained by the presence at baseline of multiple NS5A RASs (L28M/V

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* Corresponding author. Address: Department of Virology, Hôpital Henri Mondor, 51 avenue du Maréchal de Lattre de Tassigny, 94010 Créteil, France. Tel.: +33 1 4981 2827; fax: +33 1 4981 4831.
*E-mail address:* jean-michel.pawlotsky@aphp.fr.

+ L30R ± L31M), conferring substantially reduced susceptibility to NS5A inhibitors, and of fit viral populations harboring S282C/T RASs in their polymerase sequence, conferring reduced susceptibility to sofosbuvir.[6]

The implementation of the most recent pangenotypic regimens did not solve the issue: our laboratory is now receiving samples from patients of African origin infected with unusual subtypes of genotypes 1, 2 or 4 who carried NS5A RASs on their baseline genome sequences and failed to achieve SVR after sofosbuvir/velpatasvir or glecaprevir/pibrentasvir (unpublished).

Sub-Saharan Africa is not the only region where HCV subtypes that are unusual in the Western world have been found to be less responsive to DAA combinations. Genotype 3, subtype 3b is prevalent in South-East Asia, accounting for 9.7% of cases in a recent study from Thailand[9] and 8.9% in a report from mainland China including 27 provinces or municipalities across the country.[10] In a Chinese single-arm, open-label, phase III trial, 89% of patients infected with subtype 3b without cirrhosis (25/28) and only 50% of those with cirrhosis (7/14 patients) achieved SVR after 12 weeks of sofosbuvir/velpatasvir.[11] Resistance analysis indicated that subtype 3b is inherently resistant to NS5A inhibitors, due to the presence at baseline of the A30K + L31M RAS combination that confers high-level resistance to daclatasvir, elbasvir and velpatasvir and intermediate-level resistance to pibrentasvir.[12]

These findings must make us think more deeply about our biased vision of the world and its influence on the way we develop new medications in the 21st century. The United States and Western Europe are, by far, the biggest markets for the drug industry. As a result, new medications are developed essentially in the United States and Europe to target these highly profitable markets. Treatments for HCV were no exception. Currently approved HCV DAAs are all manufactured by American drug companies. Pangenotypic drugs have been designed and optimized to be efficacious against the HCV genotypes and subtypes most commonly found in these regions, including genotypes 1a, 1b, 2a, 2c, 3a and 4a. Fortunately, they were also active against genotypes 5a and 6a, frequent in South Africa and in some areas in South-East Asia, respectively, allowing them to be called "pangenotypic". The vast majority of clinical trials and real-world studies with the new HCV DAAs have been performed in the United States, Europe and in some selected countries in the Asia-Pacific region (Japan, New Zealand, Australia). The high SVR rates obtained in these studies were considered sufficient to definitively halt HCV drug development several years ago.

Like for many centuries, and although some of us thought these times were over, the Western world keeps thinking that what is good for him will also be good for the "other" world. Nevertheless, this "other world" displays an incredibly rich heterogeneity of human beings and diseases that often have little to do with what is found in the Western world. It should not be a surprise that Africa and Asia harbor a high genetic diversity of HCV strains, as this diversity was described very soon after the virus discovery. In 2005, Simmonds *et al.* published a consensus proposal for a unified system of nomenclature of HCV genotypes. At that time, subtypes 1a to 1l, 2a to 2q, 3a to 3i, 4a to 4t, 5a, and 6a to 6q were already known.[13] In the 2014 update, classification of confirmed HCV subtypes was provided up to 1l, 2r, 3k, 4w, 5a, 6xa and 7a.[14] Complete coding region sequences had been obtained for each of the different subtypes from at least 3 independent strains; they included sequences from genome regions targeted by current HCV DAAs, *i.e.* NS3 protease, NS5A and NS5B polymerase.[14] Thus, it has been well known for decades that, in many parts of the world, HCV strains carrying RASs conferring high-level resistance to DAAs as natural polymorphisms are circulating and unlikely to respond to at least several of the available DAA regimens. Was this considered during the long HCV drug development process? No, never...

Epidemiological studies describing the prevalence of the different HCV genotypes and subtypes in low- and middle-income countries of Africa and Asia are lacking. Precise subtyping requires technologies that are generally not available in these regions. Almost no clinical trials have been performed in these areas. In real-world studies, scarce data from these areas have been reported, generally with old-generation drug combinations, sometimes using generics. It is ironic that we had to wait for studies performed in Western Europe, such as the report by Childs *et al.* in the present issue of the *Journal*[5] or our own data, to "discover" that patients born in Africa, who by chance immigrated to Europe and had access to HCV drugs, could be naturally resistant to DAA therapy. Sadly, HCV drug development has now been halted as the needs of the Western world have been fulfilled. Thus, no new HCV drugs will be commercialized.

What should we do? First, we must think of the world as global and diverse, with consideration for all needs, wherever they come from. Secondly, it is key to identify funding mechanisms by which profits made in the West benefit those who live elsewhere. Thirdly, we must treat the "other" world like ours, perform careful epidemiological studies to establish the prevalence of the different HCV genotypes and subtypes and perform clinical trials to define simplified first-line therapeutic strategies that allow for optimal access to care and high efficacy in any region. In this respect, it will be essential to assess whether first-line treatment should be based on a triple combination of sofosbuvir, an NS5A inhibitor and a protease inhibitor in regions where a significant proportion of patients are unlikely to respond to a dual combination including an NS5A inhibitor. Finally, access to cheap generic drugs that fit with the local needs, *i.e.* that provide equal efficacy against usual and "unusual" HCV subtypes present in the area, must be provided as part of local elimination strategies.

One size never fits all. The WHO goal to eliminate HCV may be achievable, although probably much later than in 2030 at the global level, but this will require that specific objectives and means are tailored to local situations. This will now be the mission of the HCV community. There are many worlds in the global world, and they are equally important. We must take good care of them all.

## Conflict of interest

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Please refer to the accompanying ICMJE disclosure forms for further details.

## Supplementary data

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