Letter to the Editor

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Is resistance to direct-acting antivirals in sub-Saharan Africa a threat to HCV elimination? Recommendations for action

To the Editor:

Safe and highly effective direct-acting antiviral (DAA) medications are urgently needed for the treatment of chronic HCV infection in sub-Saharan Africa (SSA), which is home to an estimated 15% of viremic infections worldwide.[1] Fortunately, advocacy to ensure voluntary licensing of these medications has resulted in rapid price reductions for low-income countries. Although financing for diagnostics and medications remain formidable challenges, treatment experience with DAAs in SSA is slowly accumulating, and several studies have demonstrated acceptable overall rates of treatment success.[2,3]

However, there are early signs that baseline resistance to DAAs may exist in high concentration in SSA. In the *Journal of Hepatology*, Childs *et al.* reported that immigrants from SSA accounted for a disproportionate percentage of treatment failures in a UK center, primarily following treatment with earlier generation NS5A inhibitors, such as daclatasvir and ledipasvir.[4] These patients had a higher proportion of HCV genotype 1 and 4 subtypes, labeled as "non-1a/b" and "non-4a/d", which are less commonly encountered in highly developed treatment centers or clinical trials. Prospective data from SSA have shown lower treatment success with sofosbuvir and ledipasvir, particularly in genotype 4 subtypes.[5] Although these subtypes may be considered "*unusual*" or "*rare*" in high-resource settings, this is not the case in large populations in SSA. Such subtypes actually *predominate* or, in some cases, represent the *entirety* of HCV infections in countries such as Ethiopia, the Democratic Republic of Congo, Cameroon, Uganda, and Rwanda.[6–8] Based on regional estimates of HCV viremic infections,[1] we estimate that roughly half of all individuals with chronic HCV infection in SSA would harbor "non-1a/b" or "non-4a/d" subtypes, representing an estimated 5.5 million infections or almost 8% of the global epidemic.

The only currently approved re-treatment for individuals failing NS5A inhibitor based DAA regimens is sofosbuvir/velpatasvir/voxilaprevir. There is some evidence for the success of this regimen in genotype subtypes particular to the SSA region,[9] and results from 2 trials underway in SSA are expected by 2020 (NCT02405013; NCT03888729). However, this regimen is not currently produced generically nor within reach of viral hepatitis control programs in SSA. Treatment centers in highly developed settings without access to sofosbuvir/velpatasvir/voxilaprevir rely on viral sequencing to guide customized regimens, which is not available for routine clinical care in SSA. Based on limited data, the newer pangenotypic NS5A inhibitors velpatasvir and pibrentasvir may be more effective in genotype subtypes, particular those in SSA.[10] Steps are underway to improve the availability of these medications in SSA; however, neither medication is currently affordable nor accessible in this setting for national programs and clinical experience with these regimens to treat subtypes particular to SSA is needed.

Consequently, re-treatment of DAA failures in SSA is non-standardized and haphazard. Most re-treatment is dependent on available NS5A inhibitor (daclatasvir or ledipasvir)-based regimens for 24 weeks with the potential addition of ribavirin, where available. Based on current resources in resource-constrained settings, this is a reasonable approach and endorsed by recent WHO guidelines. However, such regimens have clear disadvantages, including paucity of data in subtypes particular to this region, known side effects and teratogenicity of ribavirin, additional duration and costs of treatment, and added complexity for guidelines, training, monitoring, and reporting tools. In our anecdotal experience from the region, it is not uncommon for patients to simply receive a repeat 12-week course of a failed NS5A inhibitor due to resource constraints and drug availability.

Rapid scale-up of DAAs in SSA is paramount; however, for a large population in SSA, baseline NS5A resistance will not be *unusual* and treatment failures with currently used DAAs will not be *rare*. Fortunately, there is an opportunity to ensure that this does not emerge as a threat to HCV elimination without slowing the HCV response. To achieve this, several actions are needed. Firstly, clinicians should ensure rigorous implementation and documentation of test-of-cure at 12 to 24 weeks following the end of treatment. Secondly, treatment centers should provide active follow-up, meticulous retention, and registration or reporting of individuals with treatment failure. Second-line regimens and their outcomes should be documented and pooled through national programs and regional networks. Thirdly, national treatment programs should sample genotype subtypes and resistance profiles, leveraging research collaborations and surveillance networks established through the HIV response. Fourthly, given the likely need for re-treatment of substantial numbers of DAA treatment failures in SSA under currently available treatment regimens, steps should be taken to ensure access to validated and approved pangenotypic regimens for both first-line treatment and re-treatment. Such measures, including access pricing, voluntary licensing, generic manufacturing, and country-based regulatory approvals should be accelerated. The impact that such measures have already had for DAA availability cannot be understated but remain incomplete without newer pangenotypic regimens. We believe these actions can mitigate the risk that high baseline resistance to currently used DAAs may present to ambitious long-term targets for HCV elimination in SSA.

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Conflict of interest

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Authors' contributions

NG conducted the literature review and prepared the first draft of the manuscript. All authors critically revised the manuscript and approved the final version.

Supplementary data

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