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

To the Editor:

We thank Gupta *et al.* for their letter[1] responding to our article 'Suboptimal SVR rates in African patients with atypical genotype 1 subtypes: Implications for global elimination of Hepatitis C?'.[2] We agree that our results in conjunction with other studies and the available epidemiological data are cause for potential concern. Our study may be something of a canary in the coalmine; the data are derived from a relatively small number of individuals, in a migrant African population, yet have potentially important implications beyond our centre's experience. Our findings in an African diaspora are not a substitute for evaluating the prevalence of these polymorphisms in different countries and regions of sub-Saharan Africa (SSA). Despite the fact that 14% of the global HCV burden is located in SSA there has been an almost total absence of registration trials of DAAs conducted in the region.[3] Trials of treatments for globally prevalent infections, including HCV and HBV need to encompass regional diversity. The concentration of trials hitherto conducted in Europe and North America points to a failure of the pharmaceutical industry to recognise the significant burden of disease beyond high-income countries.

Further studies of the local prevalence of different subtypes and their associated resistance-associated substitution (RAS) profile are urgently needed. However, our published analysis assists in drawing attention to the need to avoid the risk of resistance that could be engendered by first generation NS5A inhibitors as first-line therapies in the region.

Gupta *et al.* make the point that in the sub-Saharan African setting, these genotypes are far from unusual. We wholeheartedly endorse this view. We chose this nomenclature for clarity, "unusual" connotating these genotypes as remarkable and different variants, rather than uncommonly occurring. These genotypes are seldom seen in Europe, but as we discuss in our paper, are not unusual in Africa. A more useful terminology may be 'distinct African subtypes' denoting that the genotypic HCV distribution and relative prevalence of certain subtypes in Africa is distinct and different from that described elsewhere. There is a lack of large scale prevalence studies on the genotypic distribution of HCV in African countries, but compiling the available evidence suggests that non 1a/1b and non 4a/4d subtypes are common.[4,5]

Secondly, evidence is accumulating from ours and other studies that extensive viral diversity is present in these subtypes; they show a high prevalence of baseline RAS; response rates of these 1 and 4 'African subtypes' to first line NS5A inhibitors are suboptimal in the DAA era. These data include the study conducted in Rwanda where patients with genotype 4r, who accounted for 15% of patients, only experienced a 56% sustained virological response (SVR) rate; similarly in a French cohort subtype 4r accounted for 5% of all treatment failures,[6,7] with similar results in a recently published analysis from South Africa.[8]

These subtypes are difficult to characterise and treat even in well-resourced Western settings. We relied on next generation sequencing to fully characterize the sub-genotype, a methodology which is not routinely available in SSA. It is indeed important to document SVR rates in African programs. It is imperative, as we and Gupta *et al.* suggest, that effective treatments are used in the first-line setting: African countries should avoid the temptation to be the beneficiaries of generic first-line NS5A inhibitors, despite their low price, in regions of high intrinsically-resistant subtype prevalence. Recall of patients for retreatment after unsuccessful DAA treatment will be difficult. This evidence should induce policymakers and the pharmaceutical industry to facilitate access to the most potent pan-genotypic regimens in Africa. Finally, the efficacy of second generation NS5A inhibitors and even triple regimens against the prevalent subtypes requires validation.

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Conflict of interest

The authors declare no conflicts of interest that pertain to this work.

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Authors' contributions

K.C. and G.D. wrote the first draft, all other authors reviewed, contributed and commented.

Supplementary data

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Kate Childs[1,*]
Mary Cannon[1]
Christopher Davis[2]
Emma C. Thompson[2]
Geoff Dusheiko[1]
Kosh Agarwal[1]
[1]*Institute of Liver Studies, King's College Hospital Trust, London, United Kingdom*
[2]*MRC-University of Glasgow Centre for Virus Research, Glasgow, United Kingdom*
* Corresponding author. Address: Institute of Liver Studies, King's College Hospital Trust, London, United Kingdom.
E-mail address: kate.childs@nhs.net (K. Childs)

UDCA therapy in intrahepatic cholestasis of pregnancy?

To the Editor:

We read the recent grand round by de Vries and Beuers with great interest.[1] We congratulate the authors for an in-depth discussion about the safety and indications of ursodeoxycholic acid (UDCA) in pregnancy. A most frequent indication for UDCA in pregnancy is intrahepatic cholestasis of pregnancy (ICP). ICP is a reversible condition of cholestasis with an increased risk of adverse perinatal outcomes. The standard therapeutic approach includes UDCA for maternal symptoms and early term delivery to prevent fetal morbidity. Various society guidelines proposed UDCA as the only disease-modifying drug, and the supporting evidence was weak.[2] UDCA improves pruritus, liver biochemical tests, and an earlier meta-analysis suggested beneficial effects on fetal outcomes.[3,4] An earlier RCT of UDCA in patients with ICP reported significant reductions in alanine aminotransferase, gamma glutamyltransferase, and bilirubin, but not in bile acid concentrations.[5] Recently, Ovadia *et al.* carried out an interesting individual patient data meta-analysis in which 27 eligible studies, including 5,557 ICP cases and 165,136 controls, were analyzed, which is the largest to date.[6] Serum bile acid levels were very well correlated with the fetal outcomes (>100 μM/L), and peak bile acid concentration predicted the outcomes irrespective of treatment with UDCA. Furthermore, UDCA therapy did not significantly affect the association between bile acid levels and fetal outcomes. In a recent large multicenter placebo-controlled trial (PITCHES), treatment with UDCA did not reduce perinatal outcomes in women with ICP.[7] The authors suggested reconsidering the routine use of UDCA in ICP. Moreover, treatment with UDCA did not affect pruritus and serum bile acid concentration. So, the latest evidence suggests that a patient with ICP and high serum bile acids has no definitive therapy. Therefore, despite established safety, UDCA treatment in patients with ICP is not advisable. Further research is needed to understand the mechanisms of pruritus and adverse perinatal outcomes.

Conflict of interest

The authors declare no conflicts of interest that pertain to this work.

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Supplementary data

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