Editorial

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An appraisal of the WHO hepatitis B treatment guidelines applicability to Africans

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Chronic hepatitis B (CHB) remains an important cause of mortality and morbidity in Africa, due to its high prevalence, low awareness of the disorder, limited screening and treatment interventions, and consequent late presentation of disease with decompensated cirrhosis and hepatocellular carcinoma (HCC). In 2015, the World Health Organization (WHO), cognisant of the need to improve the outlook from CHB in low- and middle-income countries issued guidelines for the management of CHB with treatment criteria adapted to the resource-constrained settings.[1] These criteria are based on a clinical diagnosis of cirrhosis or aspartate aminotransferase (AST) to platelet ratio index (APRI) greater than 2 and raised serum alanine aminotransferases (ALT) (19 or 30 U/L for women or men, respectively) and hepatitis B virus (HBV) DNA concentrations greater than 20,000 IU/ml. In resource-limited regions where HBV DNA measurement is often not feasible, the WHO proposes the use of these criteria without HBV DNA assessment.

In a large cohort of patients with CHB in Ethiopia, Aberra and co-authors[2] have interrogated the applicability of the WHO criteria, including HBV DNA level. Eligibility for antiviral therapy was benchmarked against the European Association for the Study of the Liver (EASL) 2017 clinical practice guidelines.[3] The cohort was drawn from a referral hospital in Addis Ababa, Ethiopia; 1,190 treatment naïve, adult patients with CHB were analysed. Coinfections with human immunodeficiency virus and hepatitis D virus were relatively rare and not material in this analysis. All patients underwent standardized investigations, including fasting transient elastography (Fibroscan®) based on previously validated cut-offs in Africa;[4] a reading of greater than 7.9 kPa was used to define significant liver fibrosis, and greater than 9.9 kPa, to define cirrhosis.

In this study, the data provide important implications for African patients. First, the authors report a relatively high proportion of patients eligible for treatment irrespective of the criteria (25.2% and 15.3% according to the EASL and WHO criteria, respectively). This rate is higher than the rate previously reported in the general African population infected with HBV (5%)[5] or even in selected vulnerable populations (10%).[6] Since the patients were recruited in a hospital and were mainly symptomatic, this figure may reflect a degree of referral bias. However, the proportion of HBV-infected patients in need of antiviral therapy has been insufficiently analysed in Africans. Secondly, the authors underline not only the poor concordance between the EASL and WHO criteria (Cohen's kappa 0.518, p value <0.001) but also the low performance of the WHO criteria to correctly identify HBV-infected patients in need of immediate antiviral therapy in Ethiopia. The WHO criteria missed half of the patients eligible for treatment according to the EASL criteria. Interestingly, the 153 ineligible patients by WHO criteria but eligible by EASL were mainly males, relatively young (median age of 30 years) with median transient elastography scores of 9.4 kPa, a median HBV DNA level of 6,100 IU/ml, and 52% had ALT levels greater than 19 IU/L or 30 IU/L in females or males, respectively. Only 1.3% of those fulfilling the WHO criteria were HBeAg positive and older than 30 years. Most patients (52%) who fulfilled the WHO criteria had decompensated cirrhosis. This suggests the WHO criteria overlook the opportunity to treat and protect sufficient patients with CHB from hepatic complications. The sensitivity of the WHO criteria was low (49%) despite a high specificity (96%). If a higher transient elastography threshold of 11.7 kPa was used to define cirrhosis, fewer patients were eligible according to the EASL 2017 guidelines and the sensitivity of the WHO criteria marginally improved from 49% to 51%.

The use of the EASL treatment guidelines in Africa raises 2 main concerns: i) the criteria have been mainly developed from non-African studies, and whether they are applicable to the African patients with CHB is unknown; ii) these criteria require HBV DNA measurement and transient elastography, tests whose accessibility is severely limited in African countries. Unfortunately, the authors did not analyse the WHO criteria without HBV DNA measurement. We can, however, anticipate poor performance of these criteria as previously reported by the Prevention of Liver Fibrosis and Cancer in Africa (PROLIFICA) group,[7] as the WHO criteria mainly target patients with cirrhosis. Moreover, the APRI score in this population underestimates cirrhosis. In 135 Gambian patients with a liver biopsy, an APRI cut-off of 2 had a sensitivity of 25% with an area under the receiver operating characteristic curve of 0.70 (0.55 to 0.86).[4,8]

Is it judicious for low-income countries to prioritise HBV antiviral treatment for those with advanced fibrosis and

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cirrhosis? Guidelines in African countries should encompass criteria that would steer treatment toward obviating the development of cirrhosis, thus preventing the onset of decompensated cirrhosis, and, based on evidence in other population cohorts, reducing the risk of HCC to that of HBV surface antigen (HBsAg)-positive patients without cirrhosis.[9] We should no longer hold to the tenet that such a disadvantageous ranking, specifying treatment mainly for those with ominous advanced hepatic fibrosis or hepatocellular failure, should inevitably apply in resource-limited sub-Saharan Africa. There is of course a caveat: many high prevalence countries in Africa suffer major deficiencies in overall health care infrastructures and are resource constrained. It is correct that extending treatment to patients without advanced fibrosis or decompensated cirrhosis would have major financial implications for countries with constrained health care budgets. However, the advent of generic low-cost antiviral drugs makes it possible for low-income, high-prevalence countries to advocate and promulgate up-to-date generic maintenance suppressive nucleoside analogue treatment for $35–$50 per year – a cost which should induce governments in African countries to facilitate and extend treatment for CHB, including the provision of assistance for self-payers. Some economic models support the benefit of a fiscal analysis of national plans for treatment of hepatitis B, and scrutiny of the proportional burden and impact of the management of viral hepatitis on national budgets. The costs of disability-adjusted life years may be less than the benchmark of half of per capita gross domestic product.[10] Such illustrations support an investment case approach based on value for money, and indicate that policy makers should promote awareness, screening and the initiation of timely therapy.[11]

Failure to implement the appropriate interventions incurs an opportunity cost. The WHO criteria will need refining and closer pairing with other internationally accepted guidelines. However, defining treatment criteria in a vacuum, devoid of the appropriate diagnostic evaluation of CHB, particularly the imperative to assess the level of HBV viremia, poses major but not insurmountable difficulty. The unavoidable conclusion is that HBsAg-positive patients on the continent need more widespread access to measurement of serum HBV DNA and serum aminotransferases, outside of urban centres, to match eligibility for treatment applicable in other regions of the world.[12,13] It might be argued that antiviral treatment of hepatitis B has not been shown to reduce the incidence of HCC in Africans, but our current understanding and the advances over the past half century, make it unreasonable and irrational to withhold treatment for African patients at risk of progressive disease due to hepatitis B.

Simple tools may suffice to determine treatment – such as the recent TREAT-B score developed in West Africa that might be effective where HBV DNA testing is not available.[7] In the latter score, ALT levels divided into 4 categories (<20, 20–39, 40–79, ≥80 IU/L) and HBeAg sero-positivity were independent predictors of treatment eligibility. The score requires validation in other African countries in whom most patients are HBeAg− negative.

The advent of several recent innovative and inventive nucleic acid micro-engineering platforms promises to change the field and provide rational, applicable and equitable criteria for treatment of hepatitis B in sub-Saharan Africa. Thus, there is an imperative to develop and introduce more widespread, affordable, reliable, simple to use and highly portable point of care tests for HBV DNA or consider widespread use of dried blood spot nucleic acid testing. A quantitative or semi-quantitative test for HBV DNA with perhaps a lower limit of quantitation of 2,000 (or 20,000) IU/ml, coupled with aminotransferase testing and basic clinical evaluation, may provide the most practical differentiation between relatively benign, low replicative hepatitis B not requiring immediate treatment *vs.* replicative HBV infection and disease at risk of progression, enhancing the pathway of interventions required for screening, diagnosis, staging, treatment and monitoring. More widespread use of portable transient elastography in larger centres may become possible with improved leasing finance.

To increase treatment coverage to 80% of those requiring treatment of CHB by 2030 as requested by the WHO,[14] it is likely that African countries will have to adapt screening and treatment strategies. People living in both urban and rural areas will need access to simplified, workable but more accurate diagnostic and monitoring algorithms. This Ethiopian study[2] combined with other recent studies from West Africa[5,7] represent an important opportunity for the WHO and African countries to formulate apposite guidelines for the management and treatment of hepatitis B in Africans.

Conflict of interest

G.D. reports grants and personal fees from Gilead and Abbott; personal fees from Janssen, Springbank and Arbutus; grants from Lumiera, during the conduct of the study. M.L. reports no conflict of interest. Please refer to the accompanying ICMJE disclosure forms for further details.

Supplementary data

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