Research Article
Viral Hepatitis

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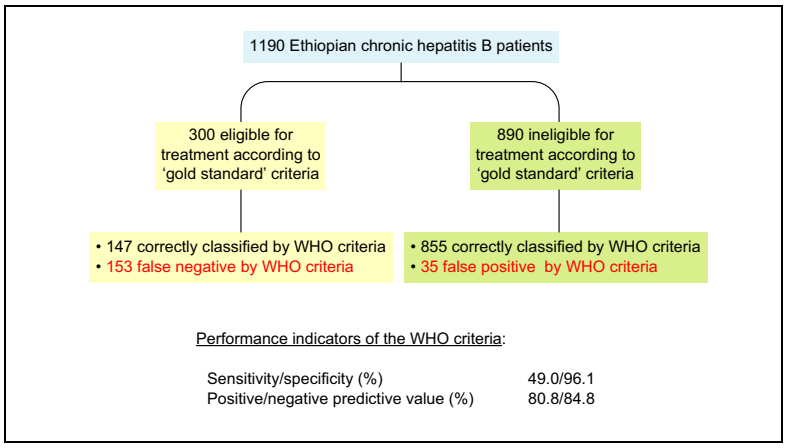
The WHO guidelines for chronic hepatitis B fail to detect half of the patients in need of treatment in Ethiopia

Graphical abstract



Highlights

- In 2015, the WHO launched treatment guidelines for chronic hepatitis B.
- Little is known about the performance of the WHO guidelines in sub-Saharan Africa.
- In a large Ethiopian cohort, the WHO criteria failed to detect half of those in need of treatment.
- Most patients identified by the WHO criteria had decompensated cirrhosis.
- A revision of the WHO guidelines should take into account local data from Africa.

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Lay summary

Antiviral therapy prevents disease progression and death in patients with chronic hepatitis B (CHB), but the identification of patients in need of treatment is a challenge in low- and middle-income countries. The World Health Organization (WHO) has suggested treatment eligibility criteria for use in such settings, but in our study the WHO criteria detected less than half of those in need of therapy in a large Ethiopian cohort of 1,190 patients with CHB. Our findings suggest that the WHO criteria might be unsuitable in sub-Saharan Africa.

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The WHO guidelines for chronic hepatitis B fail to detect half of the patients in need of treatment in Ethiopia

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See Editorial, pages 1043–1045

Background & Aims: In 2015, the World Health Organization (WHO) issued guidelines for the management of chronic hepatitis B (CHB) in low- and middle-income countries, but little is known about the applicability of the WHO treatment criteria in sub-Saharan Africa. The aim of this study was to evaluate the diagnostic performance of the WHO guidelines in a large CHB cohort in Ethiopia.

Methods: Treatment-naïve adults who attended a public CHB clinic in Addis Ababa were included in this analysis. All patients underwent a standardized evaluation at recruitment, including blood tests and transient elastography (Fibroscan®). A Fibroscan result >7.9 kPa was used to define significant fibrosis and >9.9 kPa to define cirrhosis. Treatment eligibility was assessed using the most recent guidelines from the European Association for the Study of the Liver (EASL) as the 'gold standard'.

Results: Out of 1,190 patients with CHB, 300 (25.2%) were eligible for treatment based on the EASL 2017 guidelines and 182 (15.3%) based on the WHO 2015 guidelines. The sensitivity and specificity of the WHO criteria were 49.0 and 96.1%, respectively. Most patients (94 of 182; 51.6%) who fulfilled the WHO criteria had decompensated cirrhosis and might have a dismal prognosis even with therapy. Only 41 of 115 patients (35.7%) with compensated cirrhosis, who are likely to benefit the most from therapy, were eligible for treatment based on the WHO criteria.

Conclusions: The WHO guidelines for CHB failed to detect half of the patients in need of treatment in Ethiopia, implying the need for a revision of the WHO treatment criteria.

Lay summary: Antiviral therapy prevents disease progression and death in patients with chronic hepatitis B (CHB), but the identification of patients in need of treatment is a challenge in low- and middle-income countries. The World Health Organization (WHO) has suggested treatment eligibility criteria for use in such settings, but in our study the WHO criteria detected less than half of those in need of therapy in a large Ethiopian cohort of 1,190 patients with CHB. Our findings suggest that the WHO criteria might be unsuitable in sub-Saharan Africa.

Trial registration number: NCT02344498 (ClinicalTrials.gov identifier). Registered 16 January 2015.

Introduction

Chronic infection with hepatitis B virus (HBV) continues to be a significant health problem globally. Worldwide, around 2 billion people have evidence of past or present infection with HBV and an estimated 257 million are chronically infected.[1,2] Almost half of the world's population resides in areas of high HBV endemicity, with the highest prevalence in Africa and East Asia. In sub-Saharan Africa, 5–10% of the adult population is living with chronic hepatitis B (CHB).[3] Annually, an estimated 887,000 deaths occur as a result of CHB, mainly due to its late complications *viz* cirrhosis and hepatocellular carcinoma (HCC).[1] Between 1990 and 2013 the number of HBV-related deaths due to liver cirrhosis and/or HCC increased by 33% globally.[4]

CHB has a variable spectrum of disease and its natural history ranges from an inactive carrier state with excellent prognosis to progressive liver fibrosis leading to cirrhosis with end-stage liver disease and a markedly increased risk of HCC. The natural course depends on both host and viral factors, and in the absence of treatment an estimated 15–40% of patients infected with HBV will die prematurely.[5] The challenge in clinical practice, therefore, is to avoid unnecessary treatment in patients who have a benign course even without therapy, and to reliably identify patients at risk of developing complications so that antiviral treatment can be timely initiated. By achieving a sustained suppression of HBV viral load levels in patients with progressive liver disease, it has been shown that liver fibrosis can be reversed and the risk of cirrhosis, liver failure, HCC and death markedly reduced.[6–9]

Various international liver societies have issued guidelines for the treatment of CHB.[10–13] Generally, treatment is recommended in patients with moderate or severe liver inflammation and/or fibrosis and ongoing viral replication. Although there are some differences, all guidelines base the decision to commence

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treatment on a combined assessment of liver fibrosis stage, serum level of alanine aminotransferase (ALT), and HBV viral load. In 2015, the World Health Organization (WHO) published guidelines for the prevention, care and treatment for persons with CHB, with an emphasis on resource-limited settings.[14] However, most of the evidence used to develop the WHO guidelines was based on studies from Asia, North America and Western Europe, and little is known about the accuracy and applicability of the WHO treatment criteria in sub-Saharan Africa.

Ethiopia is a low-income country in east Africa and is one of the most populous nations on the continent with a population size of around 100 million.[15] Based on different clinical studies, the overall prevalence of CHB is estimated to be 7.4%.[16] In 2015, we set up a prospective cohort study in the capital city of Addis Ababa in order to study the feasibility and efficacy of modern CHB treatment in a resource-limited setting. In the current analysis we evaluated the performance of the WHO treatment eligibility criteria in this cohort, which is one of the first and largest treatment programs for CHB in sub-Saharan Africa. The treatment eligibility criteria in the most recent guidelines of the European Association for the Study of the Liver (EASL) were used as the 'gold standard'.[11] Since this is one of few CHB studies from sub-Saharan Africa we believe our results are vital to inform policy makers and direct treatment guidelines on the continent.

Patients and methods

Study setting, participants and ethical considerations

St. Paul's Hospital Millennium Medical College is a referral hospital located in Addis Ababa, Ethiopia. Between February 9 and December 14, 2015, a total of 1,303 patients with CHB, defined by the carriage of hepatitis B surface antigen (HBsAg) for more than 6 months, were enrolled in a prospective cohort study. HBsAg positive patients were referred from other hospital departments based on symptomatic liver disease, or from blood banks and antenatal care clinics based on a positive screening test.

For the purpose of the present analysis, data from 1,190 treatment-naïve adult patients (aged ≥18 years) were included. One-hundred-and-twenty-three patients were excluded from the analysis for the following reasons: previous exposure to antiviral treatment (n = 66), missing HBV viral load measurements at baseline (n = 23), concurrent HCC (n = 12), and human immunodeficiency virus (HIV) co-infection (n = 12).

Ethical clearance was obtained from the Regional Committee for Medical and Health Research Ethics in Norway and the National Research Ethics Review Committee in Ethiopia, as well as the pertinent institutional ethical review boards. The study was conducted in accordance with the Declaration of Helsinki, and all patients gave written informed consent to participate in the study.

Data collection

All patients were interviewed and examined using a standardized form. Baseline demographic data and presence of comorbid conditions was recorded. Past medical history included previous liver disease (and previous serological data if available), alcohol abuse, consumption of khat (*Catha edulis*) and other substances. Harmful alcohol use was defined as more than 30 g/day for men and 20 g/day for women for 6 months or more, and khat abuse was defined as current use of khat regardless of the quantity. Physical examination included liver stigmata, such as spider angiomas, jaundice and ascites.

Laboratory analyses

Blood samples were collected at enrollment for hematology, biochemistry and standard serology testing. Routine laboratory investigations were carried out using the following kits and assays: hematology (HumaCount 30, Human, Germany), biochemistry (Humalyzer 3000, Human, Germany), and serology (HBsAg/anti-HIV/anti-hepatitis C virus [HCV], Elisys Uno, Human, Germany). HBsAg was screened on-site at enrollment using a WHO approved rapid diagnostic test (Determine™, Alere Inc., USA). HIV testing was done in accordance with the National algorithm, *i.e.* using a WHO approved rapid diagnostic test kit (HIV 1+2 antibody colloidal gold [KHB], Shanghai Kehua Bioengineering co., China) for screening, and another rapid diagnostic test kit (HIV 1/2 STAT-PAK, Chembio Diagnostics, USA) for confirmation.

Hepatitis D virus (HDV) antibodies were detected using an enzyme-linked immunosorbent assay (ELISA) method (ETI-AB-DELTAK-2, Diasorin, Italy) from EDTA plasma samples. A second anti-HDV ELISA assay (Dia.Pro Diagnostic Bioprobes Srl, Milan, Italy) was used to confirm indeterminate or weak positive results obtained with the Diasorin assay, as suggested by the manufacturer when plasma is used instead of serum. These analyses were performed at the Centre national de référence des hépatites B, C et Delta, Hôpitaux universitaires de Paris-Seine-Saint-Denis, Bobigny, France.

Hepatitis B e antigen (HBeAg), anti-HBe and HBV DNA viral load were performed at the Norwegian Institute of Public Health, Oslo, Norway. HBeAg/anti-HBe testing was done using an enzyme-linked fluorescent immunoassay (VIDAS HBe/anti-HBe, BioMérieux, Marcy l'Etoile, France). HBV DNA viral load was measured using the Abbott RealTime HBV assay (Abbott Molecular, Des Moines, USA).

Aspartate aminotransferase to platelet ratio index (APRI) was calculated by the following equation: (AST [U/L]/upper limit of normal of AST)/platelet count (10^9/L) × 100.[17] For the purpose of calculating APRI the upper limit of normal for AST was set at 40 U/L. FIB-4 was calculated by the following equation: (age [years] × AST [U/L])/(platelet count [10^9/L] × (ALT [U/L])$^{1/2}$).[18]

Assessment of liver fibrosis

Transient elastography (Fibroscan® 402, Echosens, France) was used to assess liver fibrosis and was part of the baseline evaluation in all patients. The procedure was performed by trained personnel per the manufacturer's instruction after at least 2 h of fasting. Transient elastography was missing or invalid in 97 individuals because of pregnancy (n = 57), ascites (n = 12), obesity (n = 16), or other reasons (n = 12).

A transient elastography threshold of 7.9 kPa was used to define significant fibrosis (Metavir score ≥F2) and 9.9 kPa to define cirrhosis (Metavir score F4), based on a meta-analysis of Asian and European patients and a study from West Africa.[19,20] In patients with grossly elevated ALT, transient elastography measurements were repeated later since liver stiffness can be overestimated in this situation.[21]

Treatment eligibility criteria

For low- and middle-income countries, the WHO 2015 guidelines recommend antiviral treatment for CHB in patients who fulfill any of the following 3 criteria:[14]

a) Clinically diagnosed cirrhosis
b) APRI >2.0
c) Age ≥30 years and ALT >19/30 U/L (women/men) and viral load >20,000 IU/ml

A clinical diagnosis of cirrhosis was made in the presence of any of the following: i) Past or current evidence of ascites, either by clinical examination or by ultrasonography. Although ultrasonography was not performed routinely in the present program, many patients had been examined prior to enrollment and presented written radiology reports. ii) Esophageal varices. Endoscopy was not routinely performed in our setup, but some patients had undergone gastroscopy prior to enrollment. iii) Jaundice on physical examination. iv) Other clinical signs of advanced liver disease on physical examination, including hepatomegaly, splenomegaly and a firm liver on palpation.

The WHO treatment eligibility criteria were compared to a 'gold standard' *viz* the most recent guidelines from the EASL. The EASL 2017 guidelines recommend treatment based on the following criteria:[11]

a) Cirrhosis and detectable viral load
b) Significant fibrosis and viral load >2,000 IU/ml
c) ALT >80 U/L and viral load >20,000 IU/ml
d) Metavir ≥A2 and viral load >2,000 IU/ml
e) HBeAg positive and age ≥30 years
f) Family history of HCC or cirrhosis

Cirrhosis was diagnosed either in the presence of signs of decompensated liver disease *viz* ascites, esophageal varices, or jaundice as defined above, or by transient elastography using the threshold described previously. Significant fibrosis was defined by transient elastography. Point d) could not be assessed since liver biopsies were not performed.

The present treatment program in Ethiopia was established prior to the release of the WHO guidelines from 2015 and the Ethiopian viral hepatitis guidelines from 2016; hence, we based treatment eligibility criteria on the EASL guidelines from 2012 with some modifications as previously described.[22] The following treatment eligibility criteria were used ('St. Paul criteria'):

a) Decompensated cirrhosis
b) Compensated cirrhosis
c) Significant fibrosis and viral load >2,000 IU/ml
d) ALT >80 U/L and viral load >2,000 IU/ml
e) Family history of HCC and viral load >2,000 IU/ml

Decompensated cirrhosis was diagnosed in the presence of ascites, esophageal varices, or jaundice, as defined above. Compensated cirrhosis was defined by transient elastography using the threshold described previously. Significant fibrosis was defined by transient elastography. Patients who met more than one treatment indication were only registered once.

Statistical analysis

Descriptive statistics were used to summarize baseline demographics of study participants. Cohen's kappa coefficient with the interpretation scale of Landis-Koch was employed to determine agreement between the various treatment guidelines.[23] The performance of the WHO 2015 criteria and the St. Paul criteria were assessed using the EASL 2017 criteria as the 'gold standard', and the sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were calculated.

A *post hoc* sensitivity analysis was performed using a higher Fibroscan threshold to define cirrhosis. The cut-off value at 11.7 kPa identified in a large meta-analysis of 2,772 patients with CHB was employed.[19]

All tests were 2-sided and a p value <0.05 was considered statistically significant. Statistical analysis was performed using SPSS for Windows version 25.0 (SPSS Inc., Chicago, USA). Results were reported in accordance with the Standards for Reporting of Diagnostic Accuracy.[24]

Results

Baseline characteristics

Out of 1,190 treatment-naïve patients included in this analysis, 682 (57.3%) were men, the median age was 31 (interquartile range [IQR] 26–39) years, 39 (3.3%) reported harmful alcohol use, and 105 (9.6%) reported current khat use. Baseline characteristics are summarized in Table 1.

Co-infections were rare; 28 patients (2.7%) were anti-HCV positive and 17 (1.4%) were anti-HDV positive. Twelve patients with HCV and/or HDV co-infection had cirrhosis; however, this was a relatively modest contribution to the total of 209 patients diagnosed with cirrhosis in this cohort.

Table 1. Baseline characteristics of 1,190 patients with chronic hepatitis B, Addis Abba, Ethiopia.

Characteristic	Median (IQR)/n (%)
Men	682 (57.3)
Age (years)	31 (26–39)
Body mass index (kg/m2)	22.4 (19.6–25.3)
TE (kPa)[1]	5.8 (4.6–7.6)
≤7.9	842 (77.0)
8.0–9.9	62 (5.7)
>9.9	189 (17.3)
HBV viral load (IU/ml)	1,330 (275–14,300)
≤2,000	666 (56.0)
2,001–20,000	247 (20.8)
>20,000	277 (23.3)
ALT (U/L)	29 (21–48)
≤40	967 (81.3)
41–80	161 (13.5)
>80	62 (5.2)
AST (U/L)	25 (20–34)
≤40	997 (83.8)
41–80	131 (11.0)
>80	62 (5.2)
Platelets ($\times 10^9$/L)[2]	276 (222–326)
<150	95 (8.7)
≥150	1,001 (91.3)
APRI[2]	0.23 (0.17–0.36)
≤2.0	1,067 (97.4)
>2.0	29 (2.6)
Cirrhosis assessment	
No cirrhosis	981 (82.4)
Compensated cirrhosis[3]	115 (9.4)
Decompensated cirrhosis[4]	94 (8.2)

ALT, alanine aminotransferase; APRI, aspartate aminotransferase to platelet ratio index; AST, aspartate aminotransferase; HBV, hepatitis B virus; IQR, interquartile range; TE, transient elastography.
[1] Missing or invalid result in 97 patients.
[2] Platelet counts were missing (and APRI could not be calculated) in 94 patients.
[3] Defined as transient elastography >9.9 kPa and absence of features of decompensation.
[4] Defined as the presence of ascites, esophageal varices, or jaundice.

Treatment eligibility

The number of patients eligible for treatment was 300 (25.2%) based on the EASL 2017 criteria, 182 (15.3%) based on the WHO 2015 criteria, and 275 (23.1%) based on the St. Paul criteria. Indications for treatment based on the different guidelines are summarized in Table 2.

Most of the patients (94 of 182; 51.6%) who fulfilled the WHO criteria had decompensated cirrhosis. Only 41 of 115 patients (35.7%) with compensated cirrhosis were eligible for treatment according to the WHO criteria.

Of note, APRI – at the WHO recommended threshold of 2.0 – failed to identify most patients in need of treatment, with a sensitivity of 8.5% and a specificity of 99.3% compared to the EASL guidelines. Lowering the APRI threshold, however, improved the sensitivity without a substantial decrease in specificity:

- APRI >1.5: sensitivity 12.0% and specificity 98.5%
- APRI >1.0: sensitivity 21.2% and specificity 98.0%
- APRI >0.5: sensitivity 46.6% and specificity 94.8%

Other simple non-invasive markers were also explored. FIB-4 at the higher threshold of 3.25 yielded a sensitivity and specificity of 10.2 and 99.0%, respectively, whereas the lower threshold of 1.45 yielded a sensitivity and specificity of 30.4 and 95.4%, respectively. Platelet count < 150 $x10^9$/L yielded a sensitivity and specificity of 21.9 and 95.9%, respectively. Newer indices such as the gamma-glutamyltransferase to platelet ratio (GPR) and TREAT-B could not be calculated since gamma-glutamyltransferase and HBeAg status were unavailable in a large proportion of patients.

Comparison of the different treatment criteria

The level of agreement between the WHO 2015 criteria and the EASL 2017 criteria was only moderate (Cohen's kappa 0.518, p <0.001), whereas the agreement between the St. Paul criteria and the EASL criteria was excellent (Cohen's kappa 0.924, p <0.001). The sensitivity, specificity, PPV and NPV of the different guidelines are summarized in Table 3.

In a sub-analysis, excluding 94 patients with decompensated cirrhosis, the performance of the WHO criteria was even more dismal (Table 4). The agreement between the WHO 2015 criteria and the gold standard in this analysis was poor (Cohen's kappa 0.279, p <0.001), whereas the agreement between the St. Paul criteria and the gold standard was still good (Cohen's kappa 0.897, p <0.001).

Sensitivity analysis

When a higher Fibroscan threshold was used to define cirrhosis, the total number of patients eligible for treatment using the EASL 2017 criteria was reduced from 300 to 285. This resulted in a slightly improved performance of the WHO 2015 criteria; the sensitivity, specificity, PPV, NPV and proportion correctly classified was 51.6, 96.1, 80.8, 86.3 and 85.5%, respectively. The St. Paul criteria were virtually unchanged; the sensitivity, specificity, PPV, NPV and proportion correctly classified were 89.5, 99.6, 98.5, 96.8 and 97.1%, respectively.

Clinical characteristics of patients ineligible for treatment by the WHO criteria

A total of 153 patients who were eligible for treatment based on the EASL 2017 criteria were excluded from treatment by the WHO 2015 guidelines. The majority of these (n = 105, 68.6%) had significant fibrosis based on transient elastography measurements, and 74 (48.4%) had cirrhosis. Characteristics of the 153 patients who were not detected by the WHO 2015 criteria are summarized in Table 5.

None of the 74 patients with cirrhosis in Table 5 had clinical signs of advanced liver disease; instead they were diagnosed based on a transient elastography result above 9.9 kPa (median 13.0; IQR 10.9–17.9). The 31 patients with significant fibrosis (but not cirrhosis) in Table 5 had a transient elastography result in the range 8.0 to 9.9 kPa (median 8.5; IQR 8.3–8.9).

Discussion

In the present study, carried out in one of the first and largest CHB treatment programs in sub-Saharan Africa, we found a poor concordance between the WHO 2015 and the EASL 2017 treatment eligibility criteria. Indeed, only half of the patients in need of antiviral therapy were eligible for treatment using the WHO guidelines, and most of the patients who fulfilled the WHO criteria were patients with decompensated cirrhosis, indicating that their prognosis might be dismal even with effective therapy. Although antiviral therapy is beneficial even in decompensated cirrhosis,[6] the risk of HCC, hepatic decompensation and death is still high in this group.[25] Hence, using the current WHO guidelines for CHB, many patients in need of therapy will not be detected until they have end-stage liver disease, and opportunities to prevent liver failure and death are being lost.

Although the sensitivity of the WHO 2015 criteria was low compared with the EASL 2017 guidelines, the specificity was found to be high. This implies that few patients would start lifelong antiviral therapy unnecessarily, which is of prime importance in settings with limited resources. Even though clinical data and cost-effectiveness analyses from low- and middle-income countries are scarce, it seems reasonable in such settings to prioritize treatment to those with the highest chance of benefiting from therapy, which usually would signify patients with advanced fibrosis but preserved liver function.[14] Timely initiation of therapy in such patients has been shown to lead to reversal of liver fibrosis and an excellent clinical outcome. Indeed, Marcellin *et al.* found significant improvement in fibrosis scores in repeated liver biopsies after 1 and 5 years of TDF treatment, even in patients who had compensated cirrhosis at baseline.[8] Moreover, Papatheodoridis *et al.* recently reported that long-term antiviral therapy significantly reduces the risk of HCC in patients with compensated cirrhosis;[26] however, this has not yet been investigated in an African setting.

The challenge in resource-limited settings, where liver biopsies are generally unrealistic and transient elastography too costly, is to find simple and reliable tools to accurately predict significant liver fibrosis. An ideal tool should be simple, affordable and easy-to-use, and should have a high sensitivity and specificity to detect patients with advanced liver fibrosis. In our study, the WHO recommended APRI score demonstrated a very low sensitivity and was able to detect less than 10% of patients in need of treatment, using the higher threshold of 2.0. This concords with a study by Lemoine *et al.* showing that APRI had a poor diagnostic accuracy compared to liver biopsy in a cohort of West African patients with CHB; indeed, the sensitivity of APRI to detect significant fibrosis was 0% in Senegal and 9% in Gambia, whereas the sensitivity to detect cirrhosis was 25%.[20] Results from our own cohort suggest that APRI might still be of use, provided that the decision threshold is set lower than the cut-off at 2.0 currently recommended by the WHO.[27]

Table 2. Comparison of treatment eligibility criteria among treatment-naïve patients with chronic hepatitis B, Ethiopia (n = 1,190).

EASL 2017		St. Paul		WHO 2015	
Criteria	**n**	**Criteria**	**n**	**Criteria**	**n**
Cirrhosis and detectable VL	208	Decompensated cirrhosis	94	Clinical evidence of cirrhosis	107
Fibrosis and VL >2,000 IU/ml	35	Compensated cirrhosis	115	APRI >2.0[2]	14
ALT >80 U/L and VL >20,000 IU/ml	11	Fibrosis and VL >2,000 IU/ml	35	Age ≥30 years and ALT >19 (women)/30 (men) U/L and VL >20,000 IU/ml	61
Metavir ≥A2 and VL >2,000 IU/ml[1]	0	ALT >80 U/L and VL >2,000 IU/ml	14		
HBeAg positive and age ≥30 years	9	Family history of HCC and VL >2,000 IU/ml	17		
Family history of HCC or cirrhosis	37				
Total	**300**	**Total**	**275**	**Total**	**182**

ALT, alanine aminotransferase; APRI, aspartate aminotransferase to platelet ratio index; EASL, European Association for the Study of the Liver; HBeAg, hepatitis B e antigen; HCC, hepatocellular carcinoma; VL, viral load.
[1] Liver biopsy was not performed; hence, none fulfilled this criterion.
[2] Platelet counts were missing and APRI could not be calculated in 94 patients.

Lowering the APRI threshold to 1.0 nearly tripled the sensitivity without a significant decline in specificity. Recently, Shimakawa *et al.* reported that the WHO simplified criteria, *i.e.* based on clinical assessment, APRI and ALT but without HBV viral load, had a specificity no better than chance; instead, the authors developed a new score (TREAT-B) based on ALT and HBeAg which appeared to have good diagnostic properties.[28] A number of other non-invasive markers have been proposed, but so far none of them have performed much better than APRI.[20,27,29]

The main strength of this study was the sample size; indeed, the present program comprises one of the largest cohorts of patients with CHB in sub-Saharan Africa, together with the PROLIFICA study in West Africa.[30] All patients underwent a comprehensive panel of tests at baseline, including transient elastography, liver function tests and viral load. The WHO acknowledges the lack of data from sub-Saharan Africa as a limitation in the development of the WHO 2015 guidelines for CHB,[14] and we believe results from our study can provide valuable evidence to be used in a future revision of the WHO guidelines. Indeed, our study emphasizes that CHB guidelines for resource-limited settings in sub-Saharan Africa must, whenever possible, be based on local data from African CHB cohorts.

The study also had its limitations. First, the use of the EASL 2017 guideline as a gold standard might be questioned, since this by no means is the ultimate answer to which patients would need therapy. Comparison of any new diagnostic method (*i.e.* treatment guideline in this specific study) to an imperfect gold standard will inevitably lead to an imprecise estimate of the performance of the new method.[31] This limitation should be kept in mind when interpreting our results. Second, Fibroscan which was used to diagnose fibrosis and cirrhosis in the present program has its inherent limitation, as both ALT flares, congestive heart failure, extrahepatic cholestasis and recent food intake might lead to falsely elevated Fibroscan values.[32] Hence, some patients might have been 'false positive' by the EASL criteria rather than 'false negative' by the WHO criteria. Although we tried to minimize this problem by instructing patients to fast for at least 2 h prior to the examination, and excluding Fibroscan readings with grossly elevated ALT, it is still possible that some patients were misclassified. Moreover, since the Fibroscan threshold used to identify cirrhosis (9.9 kPa) was lower than in many other studies, it is possible that the prevalence of (compensated) cirrhosis was overestimated resulting in an underestimation of the performance of the WHO criteria. However, in a sensitivity analysis using a higher threshold to define cirrhosis (11.7 kPa), the performance of the WHO criteria was only minimally improved. Third, the use of ascites to define decompensated cirrhosis could have led to some degree of misclassification, since other causes of ascites such as abdominal tuberculosis were not systematically ruled out. If anything, this would have led to an overestimation of the performance of the WHO criteria. Fourth, the lack of liver biopsies in the present program probably led to an underestimation of the proportion of patients eligible for treatment according to the EASL 2017 guidelines, since one of the treatment criteria is based on Metavir score.[11] Thus, the sensitivity of the WHO guidelines could be slightly inflated in our study. Fifth, the treatment eligibility criterion pertaining to HCC or cirrhosis in close family members might be inaccurate in a low-income setting where

Table 3. Performance of the different treatment guidelines compared to the EASL 2017 criteria (n = 1,190).

	WHO 2015	St. Paul
Sensitivity/specificity (%)	49.0/96.1	90.3/99.6
PPV/NPV (%)	80.8/84.8	98.5/96.8
Correctly classified (%)	84.2	97.2

PPV, positive predictive value; NPV, negative predictive value.

Table 4. Performance of the different treatment guidelines compared to the EASL 2017 criteria in the non-decompensated population (n = 1,096).

	WHO 2015	St. Paul
Sensitivity/specificity (%)	25.7/96.1	85.9/99.6
PPV/NPV (%)	60.2/84.8	97.8/96.8
Correctly classified (%)	82.8	97.0

PPV, positive predictive value; NPV, negative predictive value.

many people die without a verified diagnosis. Whether the 37 patients who were eligible for treatment according to this criterion with the EASL 2017 criteria were an over- or underestimation is uncertain; hence, it remains unclear which effect this had on the estimated performance of the WHO criteria. Sixth, the present study was carried out at a referral hospital in the capital city, where patients with advanced liver disease were overrepresented. Based on the sub-analysis where patients with decompensated cirrhosis were excluded, it is likely that the WHO criteria would be even less accurate in the general HBV positive population in Ethiopia. Finally, we used laboratory results from the baseline evaluation, rather than repeated measurements, to compare the different guidelines which may not reflect the dynamic nature of the disease; hence, changes in ALT and viral load over time are not captured in this analysis.

In conclusion, the present study demonstrated that the WHO 2015 criteria for CHB treatment failed to detect roughly half of the patients in need of treatment according to the EASL 2017 guidelines. Specifically, the non-invasive marker APRI – at the WHO recommended threshold – had poor sensitivity to identify individuals with significant liver fibrosis and cirrhosis. Of concern, using the WHO guidelines, the majority of those who start therapy will be patients with decompensated cirrhosis, who might have a poor prognosis even with access to therapy. Our results suggest that the WHO guidelines might be unsuitable in an African setting, and that a future revision should take into account local data from real-life CHB cohorts in sub-Saharan Africa.

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Conflicts of interest

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

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

Authors' contributions

AJ conceived the study and wrote the protocol with significant contributions from NB and SGG. HA, HD and BM were responsible for patient enrollment and data acquisition. AJ, HA and GM did the statistical analysis. HA and AJ drafted the manuscript, and all authors critically revised it and approved the final version.

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Table 5. Characteristics of 153 patients who were eligible for treatment by the EASL 2017 criteria but ineligible by the WHO 2015 criteria.

Characteristic	Median (IQR)/N (%)
Men	100 (65.4)
Age (years)	30 (25–40)
TE (kPa)[1]	9.4 (7.3–12.9)
Viral load (IU/ml)	6,100 (770–330,000)
Viral load >20,000 IU/ml	58 (37.9)
ALT (U/L)	28 (21–49)
ALT >19/30 U/L (women/men)	81 (52.9)
Viral load >20,000 IU/ml and ALT >19/30 U/L (women/men), but age <30 years	37 (24.2)
APRI[2]	0.30 (0.20–0.54)
APRI >1.0	8 (5.2)
EASL 2017 criteria fulfilled	
Cirrhosis and detectable viral load	74 (48.4)
Fibrosis and viral load >2,000 IU/ml	31 (20.3)
ALT >80 U/L and viral load >20,000 IU/ml	10 (6.5)
HBeAg positive and age ≥30 years	2 (1.3)
Family history of HCC or cirrhosis	36 (23.5)

ALT, alanine aminotransferase; APRI, aspartate aminotransferase to platelet ratio index; EASL, European Association for the Study of the Liver; HBeAg, hepatitis B e antigen; HCC, hepatocellular carcinoma; IQR, interquartile range; TE, transient elastography.
[1] Missing or invalid result in 8 patients.
[2] Platelet counts were missing and APRI could not be calculated in 9 patients.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2019.01.037.

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