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Observational Study

Chronic hepatitis B virus monoinfection at a university hospital in Zambia

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Abstract

AIM

To characterize antiviral therapy eligibility among hepatitis B virus (HBV)-infected adults at a university hospital in Zambia.

METHODS

Hepatitis B surface antigen-positive adults ($n = 160$) who were HIV-negative and referred to the hospital after a routine or clinically-driven HBV test were enrolled. Alanine Aminotransferase (ALT), Aspartate Aminotransferase (AST), platelet count, hepatitis B e-antigen, and HBV DNA were measured. Liver fibrosis/cirrhosis was assessed by physical examination, AST-to-platelet ratio index, and transient elastography. In antiviral therapy-naïve individuals, we described HBV stages and antiviral therapy eligibility per World Health Organization (WHO) and by HBV test (routine *vs* clinical). Elevated ALT was > 19 in women and > 30 U/L in men. Among treatment-experienced individuals, we described medication side effects, adherence, and viral suppression.

RESULTS

The median age was 33 years, 71.9% were men, and 30.9% were diagnosed with HBV through a clinically-driven test with the remainder identified *via* routine testing (at the blood bank, community events, *etc.*). Among 120 treatment-naïve individuals, 2.5% were categorized as immune tolerant, 11.7% were immune active, 35.6% were inactive carriers, and 46.7% had an indeterminate phenotype. Per WHO guidelines, 13 (10.8%) were eligible for immediate antiviral therapy. The odds of eligibility were eight times higher for those diagnosed at clinical *vs* routine settings (adjusted odds ratio, 8.33; 95%CI: 2.26-29.41). Among 40 treatment-experienced HBV patients, virtually all took tenofovir, and a history of mild side effects was reported in 20%. Though reported adherence was good, 12 of 29 (41.4%) had HBV DNA > 20 IU/mL.

CONCLUSION

Approximately one in ten HBV-mono-infected Zambians were eligible for antivirals. Many had indeterminate phenotype and needed clinical follow-up.

Key words: Hepatitis B virus; Liver fibrosis; Treatment; Tenofovir; Africa

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Core tip: Data to inform the scale-up of hepatitis B testing and treatment in Africa are badly lacking. Among 120 recently diagnosed hepatitis B surface antigen-positive and HIV negative adults in Zambia, Southern Africa, 10% met the WHO's criteria for immediate antiviral therapy and an additional 40% had an "indeterminate" hepatitis B virus (HBV) phenotype with either elevated alanine aminotransferase or HBV DNA > 2000 IU/mL. Among 40 additional patients who were antiviral therapy-experienced (primarily with tenofovir), tolerability and adherence were good; however, nearly half had incomplete HBV DNA suppression. Effective approaches to retain antiviral-ineligible HBV patients in care will be important in Zambia.

Vinikoor MJ, Sinkala E, Kanunga A, Muchimba M, Nsokolo B, Chilengi R, Wandeler G, Mulenga J, Chisenga T, Bhattacharya D, Saag MS, Foster G, Fried MW, Kelly P. Chronic hepatitis B virus mono-infection at a university hospital in Zambia. *World J Hepatol* 2018; 10(9): 622-628 Available from: URL: <http://www.wjgnet.com/1948-5182/full/v10/i9/622.htm> DOI: <http://dx.doi.org/10.4254/wjh.v10.i9.622>

INTRODUCTION

In Africa, approximately 60 million individuals are chronically infected with hepatitis B virus (HBV). Informed by Asian and European data, international recommendations were developed to guide policymakers and implementers on diagnosis and treatment of chronic HBV in resource-constrained settings^[1-3]. In settings with hepatitis B surface antigen (HBsAg) positivity $> 2\%$, both general population testing and targeted testing of populations with higher disease burden are recommended; however, limited real world data from Africa are available. In addition, understanding the proportion of patients diagnosed with chronic HBV infection who would benefit from antiviral therapy in African settings is not well-established.

Several recent studies have informed scale-up of HBV treatment in Africa. In Zambia, integration of HBsAg testing into a population-based HIV survey revealed 5.6% of adults and 1.3% of children to be HBsAg-positive (Zambian Ministry of Health, 2016 #599). A research program in Gambia demonstrated the feasibility of community screening, linkage to a comprehensive liver evaluation, and initiation of antiviral treatment^[4]. Among potential key populations (sex workers and men who have sex with men) in West Africa and adults in Ethiopia, approximately 10% met criteria for antiviral therapy but another 50% had markers requiring longitudinal follow-

up^[5]. Building on these and other studies, we established an observational cohort study at a referral hospital in Lusaka, Zambia. We described where Zambians are currently being tested for HBV and among those with no prior HBV treatment, we categorized patients into the classical stages of HBV using biochemical, virological, and non-invasive markers of liver fibrosis. We also estimated patient eligibility for antivirals according to international guidelines. Among patients already taking antiviral therapy, we described medication side effects, adherence, and viral suppression.

MATERIALS AND METHODS

Study setting and participant recruitment

In Zambia, 5.6% of adults and 1.3% of children are estimated to be HBsAg-positive^[6], and HBV genotypes A1 and E are present at nearly equal proportions^[7]. HBsAg testing is part of the evaluation of signs or symptoms of liver disease, and routine testing in Zambia occurs at several settings, including at the blood bank, during community screening events (sometimes integrated with HIV testing), and as part of medical check-ups to obtain a driving license, enroll in college, start a new job, *etc.* Following an HBsAg-positive diagnosis, some Lusaka area residents are referred to University Teaching Hospital (UTH), a public tertiary care and academic medical facility with > 1000 inpatient beds located in Zambia's capital of Lusaka. At UTH, the Department of Internal Medicine hosts a weekly liver clinic that is staffed by three gastroenterology-trained physicians and provides specialty care for patients with acute and chronic liver disease, hepatic lesions, and portal hypertension.

From August 23, 2016 to August 18, 2017, after obtaining the required ethical and government approvals, 160 HBsAg-positive HIV-negative adults (18+ years old) were enrolled in a cohort study at the UTH liver clinic. HIV-HBV coinfecting individuals identified during recruitment for the cohort were referred for immediate linkage to and initiation of antiretroviral therapy according to national guidelines^[8]. We excluded patients from provinces outside of Lusaka to reduce losses to follow-up. Participants provided written informed consent to be followed for up to five years.

Study measures

Although specific HBV management guidelines are limited in Zambia, international standards of care are followed. At cohort enrollment, we performed a complete physical examination, including vital signs and body mass index (BMI), and extracted data from participants' medical records related to HBV testing, treatment, laboratory and imaging tests, and liver biopsy results when available. A standardized questionnaire was used to document sociodemographic information, comorbid conditions, and to screen for and quantify alcohol consumption using the alcohol use disorders identification

test-consumption (AUDIT-C)^[9]. Among those already on antiviral drugs for HBV at cohort enrollment, we assessed current or prior drug side effects and self-reported medication adherence in the past 7 d.

Blood was collected for measurement of serum transaminases, hemoglobin, platelet count, hepatitis B e-antigen (HBeAg), and HBV viral load, which was determined using either the Roche COBAS AmpliPrep/COBAS Taqman platform (Pleasanton, CA, United States) or an in-house real time PCR assay^[10]. We measured liver stiffness non-invasively with the Aspartate Amino-transferase (AST)-to-platelet ratio index^[11] and with transient elastography (TE; Fibroscan 402, Echosens, Paris, France). TE was performed by a nurse or physician trained according to manufacturer guidelines and with experience performing > 500 tests. Testing for hepatitis C and hepatitis delta was not routinely performed as they are rare in Zambia^[12,13].

Statistical analysis

Among treatment-naïve patients (*i.e.*, no prior history of antiviral therapy), we described demographics and clinical features stratified by type of HBsAg test (clinical or routine). We compared baseline characteristics measured on categorical scale between clinical and routine diagnosis using Fisher's exact test. For comparison of median between the two groups, we used Wilcoxon rank sum test. Obesity was BMI > 30 and unhealthy alcohol consumption was AUDIT-C of 4+ for men and 3+ for women. Among antiviral naïve participants, we described HBV viral loads, HBeAg, serum transaminase levels, and the proportion of patients with cirrhosis. In our primary analysis, we defined elevated ALT as > 30 U/L for men and > 20 U/L for women per WHO recommendations^[3]. We defined persistently elevated ALT as any degree of baseline ALT elevation plus an elevated measurement at > 60 d prior to baseline. Significant fibrosis (equivalent to Metavir fibrosis stages F2-4) was defined as liver stiffness measurement (LSM) of 7.9-9.5 kPa based on a validation study in West Africa^[14]. We defined cirrhosis as having at least one of the following: APRI > 2.0^[11], LSM > 9.5 kPa^[14], or decompensated cirrhosis on physical examination defined by the presence of ascites.

Using ALT, HBeAg, and HBV DNA at enrollment, we categorized treatment-naïve participants into one of the classical stages of chronic HBV infection. Immune tolerant stage was defined as HBeAg-positivity, normal ALT, and HBV DNA > 20000 IU/mL. Immune active HBV was defined as either HBeAg-positive, elevated ALT, and HBV DNA > 20000 IU/mL or HBeAg-negative/unknown with elevated ALT and HBV DNA > 2000 IU/mL. Inactive carriers were those with HBeAg-negative/unknown status, normal ALT, and HBV DNA < 2000 IU/mL. Participants not categorized into one of these three stages were considered to have an indeterminate phenotype^[15]. We repeated this categorization using the "conventional" ALT upper limit of normal (*i.e.*, 40 IU/mL). We compared unhealthy alcohol use and obesity

between indeterminate patients with HBV DNA < 2000 and ALT elevation and inactive carriers using a χ^2 test.

We determined eligibility for antiviral therapy if patients met one of these criteria based on WHO guidelines: (1) decompensated cirrhosis; (2) APRI > 2.0; or (3) HBV DNA > 20000 IU/mL with ALT elevation and age > 30 years. We also assessed treatment eligibility per European Association for Study of the Liver (EASL) criteria^[2] as follows: (1) cirrhosis by physical examination (with or without decompensation) and detectable HBV DNA; (2) HBeAg-positive and age > 30 years; (3) LSM > 7.9 and HBV DNA > 2000 IU/mL, or (4) ALT > 80 U/L and HBV DNA > 20000 IU/mL. We compared treatment eligibility, per WHO criteria, between those who were diagnosed with a clinically-driven vs routine HBsAg test using logistic regression and adjusting for age and sex.

Among treatment experienced patients, we described antiviral therapies received, time on therapy, history of side effects, and self-reported adherence. We reported the proportion with viral suppression (VS) defined as HBV DNA < 20 IU/mL among those on therapy for 2+ years. Analyses were performed using Stata version 14 (Statacorp, College Station, TX, United States). The statistical review of the study was performed by a biomedical statistician. The cohort was approved by the ethics committees at University of Zambia (Lusaka, Zambia) and University of Alabama at Birmingham (Birmingham, AL, United States).

RESULTS

Median age was 33 years (IQR, 26-42), 115 (71.9%) were men, and the majority ($n = 84$, 52.6%) were recently diagnosed with HBV. The majority were diagnosed at routine HBsAg testing during community/routine medical check-ups ($n = 58$; 36.2%) or at the blood bank, while 49 (30.6%) were tested due to signs/symptoms of possible liver disease (*i.e.*, clinical test). Current alcohol consumption at "unhealthy levels" was reported by 19 (12.2%) participants. At enrollment, 120 (75.0%) were antiviral therapy naïve. Serum transaminases were available for 145 (90.6%) and 104 (65.0%) had a prior ALT measurement available at a median of 308 d (IQR, 62-469) before enrollment. HBeAg testing was performed for 143 (89.4%), 149 (93.1%) had an HBV DNA measurement, and 97 (60.6%) underwent TE. A description of treatment naïve patients by HBsAg test type (routine vs clinical) is shown in Table 1.

Among 120 treatment naïve patients, 5 (4.2%) had decompensated cirrhosis (*i.e.*, ascites) by physical examination. Among the 62 with sufficient data, median APRI was 0.29 (IQR, 0.18-0.51) and 4 (6.4%) had APRI > 2.0. Among the 69 that underwent TE, median LSM was 6.3 kPa (IQR, 4.8-8.3), 6 (8.7%) had LSM suggestive of significant fibrosis, and 14 (20.3%) had LSM suggestive of cirrhosis. A cumulative 17 (14.2%) patients had cirrhosis by either physical examination,

APRI, or TE. Median ALT was 23 (IQR, 17-36) and 44 (40.7%) had an elevated ALT at enrollment based on WHO-recommended thresholds. Among the 66 with serial ALT levels, 30 (45.4%) had persistently normal ALT, 20 (30.3%) had intermittently elevated ALT, and 16 (24.2%) had persistently elevated ALT. Median HBV DNA level was 232 IU/mL (IQR, 23-3495) and viral loads were low (*i.e.*, < 2000 IU/mL) for 77 patients (69.4%), moderate (2000-20000 IU/mL) for 16 (14.4%), and high (> 20000 IU/mL) for 18 (16.2%). HBeAg-positivity was present in 18 (18.9%), and among HBeAg-positives, 9 (50.0%) had high and 5 (27.8%) had moderate HBV DNA levels with 4 at HBV DNA < 2000 IU/mL.

Using baseline ALT, HBV DNA, and HBeAg, we categorized 3 (2.5%) treatment-naïve patients as immune tolerant, 14 (11.7%) as immune active, 47 (35.6%) as inactive carriers, and 56 (46.7%) as having indeterminate stage. While 18 of 56 were considered indeterminate due to a missing ALT, HBV DNA, or HBeAg, 29 had HBV DNA < 20000 IU/mL with elevated ALT and 7 had HBV DNA > 20000 with normal ALT. Elevated ALT in patients with indeterminate stage could not be attributed to overweight/obesity or unhealthy alcohol use, as rates of these were similar to those of inactive carriers (data not shown). After applying the conventional ALT threshold (*i.e.*, 40 IU/mL), there were 6 (5.0%) immune active patients, 10 (8.3%) immune active patients, 65 (54.2%) inactive carriers, and 39 (32.5%) with an indeterminate phenotype.

According to WHO guidelines, 13 (10.8%) treatment naïve patients were deemed to be eligible for antiviral therapy at cohort enrollment (Table 2). Of these, five became eligible for decompensated cirrhosis, two for APRI > 2.0, and six for HBV DNA > 20000 IU/mL with ALT elevation and age > 30 years. Among patients diagnosed during a routine HBsAg-test, 4 (4.6%) met WHO treatment criteria vs 9 (29.0%) of those with clinically-driven HBsAg testing. After adjusting for age and sex, there was 8 times higher odds of treatment eligibility for clinically vs routinely-diagnosed patients (adjusted odds ratio, 8.33; 95%CI: 2.26-29.41). By EASL guidelines, 21 (17.5%) were eligible for antiviral therapy.

Among 40 treatment-experienced patients, 31 were currently taking antivirals at enrollment with the majority (85%) on fixed dose combination TDF plus 3TC. Median time on therapy was 12.2 mo (IQR, 5.0-24.3). Although complete medical records were not available for all patients, many treatment-experienced patients had a history of significant fibrosis/cirrhosis at time of initiation. A minority of patients ($n = 6$; 20.0%) reported at least one side effect in the past/present attributed to antivirals, including nausea, diarrhea, skin rash, itchiness, dizziness, drowsiness, or mild headache. Among those on therapy at enrollment, 17 of 29 (58.6%) had complete HBV DNA suppression including 5 of 9 with 2+ years on treatment. Among the four individuals with HBV DNA non-suppression during long-term

Table 1 Baseline characteristics of treatment-naïve hepatitis B mono-infected adults referred to a university hospital in Zambia according to setting of hepatitis B virus diagnosis

	Clinical diagnosis (<i>n</i> = 31)	Routine diagnosis (<i>n</i> = 89)	<i>P</i> value
Median age, in years	37 (29-42)	33 (26-41)	0.15
Male sex	22 (71.0)	63 (70.8)	0.99
Education level completed			0.05 ^a
None to 6 th grade	5 (16.1)	3 (3.4)	
7 th to 12 th grade	14 (45.2)	49 (55.1)	
College	12 (38.7)	37 (41.6)	
Lifetime alcohol abstinence	13 (41.9)	36 (40.9)	0.92
Herbal medicine use, past month	7 (31.8)	14 (16.3)	0.10
Body mass index			
< 25	23 (76.7)	56 (62.9)	0.35
25-30	5 (16.7)	20 (22.5)	
> 30	2 (6.7)	13 (14.6)	
HBV DNA level, IU/mL			0.12
< 20	4 (15.4)	21 (24.7)	
20-1999	10 (38.5)	42 (49.4)	
2000-19199	4 (15.4)	12 (14.1)	
≥ 20000	8 (30.8)	10 (11.8)	
HBeAg positive	11 (37.9)	11 (14.5)	0.008 ¹
Median ALT, in U/L (IQR)	22 (17-28)	23 (17-36)	0.82
Elevated ALT	8 (32.0)	36 (43.4)	0.31
AST-to-platelet ratio index ≥ 2.0	4 (21.1)	0	0.002 ¹
Liver stiffness measurement in kPa			
< 7.9	4 (25.0)	45 (84.9)	< 0.001 ¹
7.9-9.5	2 (12.5)	4 (7.6)	
> 9.5	10 (62.5)	4 (7.6)	

¹Data with statistical significance. HBV: Hepatitis B virus; ALT: Alanine aminotransferase. All values are *n* (%) or median (IQR).

therapy, all HBV DNA levels were < 2000 IU/mL. Among those currently on antivirals, median adherence was 100% but 12.5% reported missing at least one dose in the prior 7 d.

DISCUSSION

Approximately 1 in 10 Zambian adults with HBV mono-infection met international guidelines for immediate antiviral therapy, and an additional half had either elevated ALT or HBV DNA > 2000 IU/mL, suggesting the need for further follow-up. Participants diagnosed on suspicion of having HBV were more likely to require therapy compared to those HBsAg tested at routine settings. Antiviral therapy was well tolerated among treatment-experienced participants; however, a subset had HBV DNA non-suppression. These data are some of the first data on modern HBV treatment in Southern Africa and provide insights around the scale-up of testing for and treatment of chronic HBV infection in Africa.

While many chronic HBV patients in Zambia had elevated ALT, relatively few qualified for immediate antiviral therapy when we applied international guidelines. By WHO guidelines around 10% of treatment-naïve patients met criteria and by EASL criteria this was closer to 20%. These results are supported by Gambian data where 4.4% in the community and 9.7% of blood donors met EASL criteria^[4]. In a smaller study of female sex workers, men who have sex with men, and inmates

in West Africa, 10.0% were also treatment-eligible based on modified WHO criteria^[5]. Taken together these research data suggest that the WHO criteria are very stringent and might be missing some patients who could benefit from antiviral therapy. Although not surprising, we also observed that symptomatic patients were more likely to meet treatment eligibility compared to those tested in routine settings. Further data are needed to understand the most efficient way to identify HBV patients who would benefit from antiviral therapy in Zambia and similar settings.

Based on their enrollment values, 35% of our participants were classified as inactive carriers and half had indeterminate HBV phenotypes. Identification of inactive carriers, a group at low risk to progress to cirrhosis or develop HCC^[16], is useful in programmatic settings in Africa. For example, at an HBV treatment program in Ethiopia, inactive carriers (also representing around one-third of patients) will be discharged from care after one year in order to focus resources on those more likely to benefit from therapy^[17]. Unfortunately, our cohort and others have reported that a substantial percentage of patients cannot be initially categorized as needing or not needing therapy (*i.e.*, indeterminate phenotype). In Senegal, 53% did not qualify for antivirals but had either significant fibrosis, raised ALT, or significant HBV DNA levels^[5]. In the HBV Research Network (HBRN) in North America, 38% had indeterminate phenotype at baseline and will be followed longitudinally^[15]. Similar to the HBRN, most patients with indeterminate disease stage

Table 2 Hepatitis B virus stage and eligibility for immediate antiviral therapy among treatment-naïve Zambian adults with chronic hepatitis B virus infection *n* (%)

		Overall (<i>n</i> = 120)	Clinical diagnosis (<i>n</i> = 31)	Routine diagnosis ¹ (<i>n</i> = 89)	<i>P</i> ²
HBV stage	Immune tolerant	3 (2.5)	2 (6.4)	1 (1.1)	0.16
	Immune active	14 (11.7)	4 (12.9)	10 (11.2)	0.8
	Inactive carrier	47 (35.6)	7 (20.0)	40 (41.2)	0.02 ³
	Indeterminate	56 (46.7)	18 (58.1)	38 (42.7)	0.14
Eligibility for immediate therapy per guidelines	WHO 2015 guidelines	13 (10.8)	9 (29.0)	4 (4.5)	< 0.01 ³
	EASL 2017 guidelines	21 (17.5)	12 (38.7)	9 (10.1)	< 0.01 ³

¹Routine diagnosis was defined as being tested for hepatitis B surface antigen at the blood bank, antenatal care, a community screening event, or as part of a routine medical check-up; ²A χ^2 test was used to compare clinically and routinely HBV-diagnosed participants; ³Data with statistical significance. HBV: Hepatitis B virus; WHO: World Health Organization; EASL: European Association for Study of the Liver.

in Zambia had elevated ALT with HBV DNA < 20000 IU/mL, suggesting non-HBV reasons for ALT elevation. Although we did not find that they were correlated with having indeterminate stage, fatty liver and hazardous alcohol use are potential causes of elevated ALT in HBV patients. Longitudinal follow-up to ascertain whether patients of indeterminate stage develop treatment indications or become inactive carriers is needed in Africa to guide HBV policy^[5].

Our data from treatment-experienced Zambians with chronic HBV monoinfection support the feasibility of longitudinal treatment with antiviral therapy in African settings. TDF + XTC was the most common regimen as this fixed-dose combination drug is found in large supply in Zambia to treat and prevent HIV/AIDS. We documented HBV DNA non-suppression among the small group on long-term therapy which requires further follow-up. We presumed suboptimal adherence as the mechanism, although most of our patients self-reported good adherence in the prior week. Our data are contrasted by the PROLIFICA study in the Gambia where 43 of 47 (91.5%) tenofovir-treated HBV mono-infected individuals achieved viral suppression at one year^[4]. Lower HBV DNA suppression in our cohort may reflect differences in study design (clinical trial vs hospital cohort) or could reflect HBV genotypic differences as Gambia has predominantly HBV genotype E and Zambia has both E and A1, a genotype that rapidly developed lamivudine-resistance in Malawi^[18].

This study has several limitations. Most importantly, our cohort is based at one site in Zambia and may not represent other HBV-infected populations. Our cohort is hospital-based and enriched for sicker patients evidenced by the fact that participants referred from clinical settings were eight times more likely to be treatment-eligible compared to other HBsAg-positives. To offset this, we also characterized a subset of participants diagnosed at routine settings such as the blood bank and a population-based survey. Finally, we had incomplete laboratory and clinical data that led to incomplete evaluation of some patients and inflated our estimate of the proportion with indeterminate HBV. We believe the missing data occurred at random and would not have introduced bias into the distribution of HBV stages.

In summary, an HBV monoinfection cohort was established at a referral hospital in Zambia to begin to answer a number of clinical and operational questions around HBV treatment in Africa. We observed that 1 in 10 patients who underwent comprehensive assessment met the WHO criteria for therapy, although the number was higher among those with signs/symptoms and lower among those diagnosed during routine HBsAg testing. These data support scale-up of HBV testing and treatment in Africa, but further operational and clinical research is needed to define the most effective and efficient way to reduce HBV-related mortality and morbidity.

ARTICLE HIGHLIGHTS

Research background

Africa has 60 million individuals living with chronic hepatitis B virus (HBV) infection yet limited data to inform how to identify, link to care, and treat them to reduce the burden of cirrhosis and liver cancer.

Research motivation

Not all HBV patients need antivirals. Estimates on how many do will guide policy implementation. Also, few data are available on patient adherence, retention, and viral suppression with current antiviral drugs.

Research objectives

Our objective was to perform a comprehensive clinical assessment on chronic HBV-infected adults in Zambia and apply international criteria to learn what percentage may need antiviral drugs. In those already on antivirals, we measured the viral control.

Research methods

At a university hospital in Zambia, a cross-sectional assessment of adults (18+ years old) who were hepatitis B surface antigen positive and HIV negative was undertaken during 2016-2017. We used tests available in upper-income settings such as HBV DNA testing and transient elastography to assess HBV in these patients.

Research results

One hundred and sixty enrolled in the study, including 120 who were recently diagnosed with HBV and 40 already on antiviral drugs. The average age was 33, and 72% were men. We found that 1 in 10 met the World Health Organization guidelines to start antivirals; however, nearly 1 in 2 had at least one finding that would need clinical follow-up. Patients diagnosed because of signs or symptoms of HBV were slightly more likely to need antivirals compared to those diagnosed via routine testing (such as at the blood bank). Among those

already on the antivirals, few had side effects; however, 41% did not completely control their viral load.

Research conclusions

This is the first Southern African study to apply international HBV criteria.

Research perspectives

Additional data are needed on whether those with high ALT or viral loads at baseline will later need antivirals. HBV testing that focuses on symptomatic individuals could be more efficient (than routine testing for all) to find those needing treatment but more information is needed.

REFERENCES

- 1 **Terrault NA**, Bzowej NH, Chang KM, Hwang JP, Jonas MM, Murad MH; American Association for the Study of Liver Diseases. AASLD guidelines for treatment of chronic hepatitis B. *Hepatology* 2016; **63**: 261-283 [PMID: 26566064 DOI: 10.1002/hep.28156]
- 2 **European Association for the Study of the Liver**. EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection. *J Hepatol* 2017; **67**: 370-398 [PMID: 28427875 DOI: 10.1016/j.jhep.2017.03.021]
- 3 **WHO Guidelines Approved by the Guidelines Review Committee**. Guidelines for the Prevention, Care and Treatment of Persons with Chronic Hepatitis B Infection. Geneva: World Health Organization; 2015 [PMID: 26225396]
- 4 **Lemoine M**, Shimakawa Y, Njie R, Taal M, Ndow G, Chemin I, Ghosh S, Njai HF, Jeng A, Sow A, Toure-Kane C, Mboup S, Suso P, Tamba S, Jatta A, Sarr L, Kambi A, Stanger W, Nayagam S, Howell J, Mpabanz L, Nyan O, Corrah T, Whittle H, Taylor-Robinson SD, D'Alessandro U, Mendy M, Thursz MR; PROLIFICA investigators. Acceptability and feasibility of a screen-and-treat programme for hepatitis B virus infection in The Gambia: the Prevention of Liver Fibrosis and Cancer in Africa (PROLIFICA) study. *Lancet Glob Health* 2016; **4**: e559-e567 [PMID: 27443781 DOI: 10.1016/S2214-109X(16)30130-9]
- 5 **Jaquet A**, Nouaman M, Tine J, Tanon A, Anoma C, Inwoley A, Attia A, Ekouevi DK, Seydi M, Dabis F, Wandeler G. Hepatitis B treatment eligibility in West Africa: Uncertainties and need for prospective cohort studies. *Liver Int* 2017; **37**: 1116-1121 [PMID: 28561454 DOI: 10.1111/liv.13484]
- 6 **Zambian Ministry of Health**, Centers for Disease Control and Prevention, ICAP Columbia University, Central Statistics Office [Zambia]. Zambia Population-based HIV Impact Assessment. Lusaka, Zambia: 2016. Available from: URL: http://phia.icap.columbia.edu/wp-content/uploads/2016/09/ZAMBIA-Factsheet_FIN_.pdf
- 7 **Wandeler G**, Musukuma K, Zürcher S, Vinikoor MJ, Llenas-García J, Aly MM, Mulenga L, Chi BH, Ehmer J, Hobbins MA, Bolton-Moore C, Hoffmann CJ, Egger M; IeDEA-Southern Africa. Hepatitis B Infection, Viral Load and Resistance in HIV-Infected Patients in Mozambique and Zambia. *PLoS One* 2016; **11**: e0152043 [PMID: 27032097 DOI: 10.1371/journal.pone.0152043]
- 8 **Zambian Ministry of Health**. Zambia consolidated guidelines for treatment and prevention of HIV infection. Lusaka, Zambia: 2016. Available from: URL: https://aidsfree.usaid.gov/sites/default/files/zambia_hiv_gl2016.pdf
- 9 **Bush K**, Kivlahan DR, McDonell MB, Fihn SD, Bradley KA. The AUDIT alcohol consumption questions (AUDIT-C): an effective brief screening test for problem drinking. Ambulatory Care Quality Improvement Project (ACQUIP). Alcohol Use Disorders Identification Test. *Arch Intern Med* 1998; **158**: 1789-1795 [PMID: 9738608 DOI: 10.1001/archinte.158.16.1789]
- 10 **Garson JA**, Grant PR, Ayliffe U, Ferns RB, Tedder RS. Real-time PCR quantitation of hepatitis B virus DNA using automated sample preparation and murine cytomegalovirus internal control. *J Virol Methods* 2005; **126**: 207-213 [PMID: 15847939 DOI: 10.1016/j.jviromet.2005.03.001]
- 11 **Wai CT**, Greenon JK, Fontana RJ, Kalbfleisch JD, Marrero JA, Conjeevaram HS, Lok AS. A simple noninvasive index can predict both significant fibrosis and cirrhosis in patients with chronic hepatitis C. *Hepatology* 2003; **38**: 518-526 [PMID: 12883497 DOI: 10.1053/jhep.2003.50346]
- 12 **Wandeler G**, Mulenga L, Hobbins M, Joao C, Sinkala E, Hector J, Aly M, Chi BH, Egger M, Vinikoor MJ. Absence of Active Hepatitis C Virus Infection in Human Immunodeficiency Virus Clinics in Zambia and Mozambique. *Open Forum Infect Dis* 2016; **3**: ofw049 [PMID: 27047986 DOI: 10.1093/ofid/ofw049]
- 13 **Vinikoor MJ**, Sinkala E, Chilengi R, Mulenga LB, Chi BH, Zyambo Z, Hoffmann CJ, Saag MS, Davies MA, Egger M, Wandeler G; IeDEA- Southern Africa. Impact of Antiretroviral Therapy on Liver Fibrosis Among Human Immunodeficiency Virus-Infected Adults With and Without HBV Coinfection in Zambia. *Clin Infect Dis* 2017; **64**: 1343-1349 [PMID: 28158504 DOI: 10.1093/cid/cix122]
- 14 **Lemoine M**, Shimakawa Y, Nayagam S, Khalil M, Suso P, Lloyd J, Goldin R, Njai HF, Ndow G, Taal M, Cooke G, D'Alessandro U, Vray M, Mbaye PS, Njie R, Mallet V, Thursz M. The gamma-glutamyl transpeptidase to platelet ratio (GPR) predicts significant liver fibrosis and cirrhosis in patients with chronic HBV infection in West Africa. *Gut* 2016; **65**: 1369-1376 [PMID: 26109530 DOI: 10.1136/gutjnl-2015-309260]
- 15 **Di Bisceglie AM**, Lombardero M, Teckman J, Roberts L, Janssen HL, Belle SH, Hoofnagle JH; Hepatitis B Research Network (HBRN). Determination of hepatitis B phenotype using biochemical and serological markers. *J Viral Hepat* 2017; **24**: 320-329 [PMID: 27917600 DOI: 10.1111/jvh.12643]
- 16 **Chen CJ**, Yang HI, Su J, Jen CL, You SL, Lu SN, Huang GT, Iloeje UH; REVEAL-HBV Study Group. Risk of hepatocellular carcinoma across a biological gradient of serum hepatitis B virus DNA level. *JAMA* 2006; **295**: 65-73 [PMID: 16391218 DOI: 10.1001/jama.295.1.65]
- 17 **Aberra H**, Desalegn H, Berhe N, Medhin G, Stene-Johansen K, Gundersen SG, Johannessen A. Early experiences from one of the first treatment programs for chronic hepatitis B in sub-Saharan Africa. *BMC Infect Dis* 2017; **17**: 438 [PMID: 28629395 DOI: 10.1186/s12879-017-2549-8]
- 18 **Aoudjane S**, Chaponda M, González Del Castillo AA, O'Connor J, Noguera M, Beloukas A, Hopkins M, Khoo S, van Oosterhout JJ, Geretti AM. Hepatitis B virus sub-genotype A1 infection is characterized by high replication levels and rapid emergence of drug resistance in HIV-positive adults receiving first-line antiretroviral therapy in Malawi. *Clin Infect Dis* 2014; **59**: 1618-1626 [PMID: 25100867 DOI: 10.1093/cid/ciu630]

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