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Screening for hepatocellular carcinoma among adults with HIV/HBV co-infection in Zambia: a pilot study

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Abstract

Background and aims: Chronic hepatitis B virus (HBV) infection is the main cause of hepatocellular carcinoma (HCC) in sub-Saharan Africa (SSA). An HCC screening initiative was

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Author contributions

CR, MV and GW designed the study. CR and GW wrote the first draft of the manuscript. CR, HC, GM, BC and VS collected data. CBM supported study implementation. All authors contributed to interpretation of data, critically reviewed the manuscript, and agreed on its final version.

Conflict of interest statement

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Ethical approval

The Ethics Committees of the University of Zambia (Lusaka) and the University of Alabama at Birmingham approved the protocol, and all patients signed informed consent forms to participate in the study.

piloted in an established cohort of individuals co-infected with human immunodeficiency virus (HIV) and HBV on antiretroviral therapy (ART) at two outpatient clinics in Lusaka, Zambia.

Methods: All patients underwent abdominal ultrasound (AUS) and transient elastography.

Results: Among 279 patients co-infected with HIV/HBV, 165 (59.1%) were men, median age was 34 years [interquartile range (IQR) 28–39 years] and median CD4 count was 246 cells/μL (IQR 112–355 cells/μL) at ART initiation. While 102 (55.7%) individuals had elevated transaminases, 114 (59.7%) had HBV levels >2000 IU/mL and 59 (24.6%) had significant fibrosis. At their first AUS measurement, 75 (26.9%) participants had hepatomegaly and 69 (24.7%) had periportal fibrosis. Five patients had a liver lesion >1 cm, an indication for confirmatory imaging.

Conclusions: In one of the first HCC screening initiatives in SSA, 2% of patients co-infected with HIV/HBV had significant liver lesions, and one-quarter had findings suggestive of schistosomiasis-induced liver damage.

Keywords

Hepatocellular carcinoma; sub-Saharan Africa; Screening; Hepatitis B Virus; HIV

Introduction

Chronic hepatitis B virus (HBV) infection is the single most important cause of end-stage liver disease and hepatocellular carcinoma (HCC) worldwide (Akinyemiju et al., 2017). Its burden is particularly high in sub-Saharan Africa (SSA), where approximately 10% of the general population has chronic HBV infection (Schweitzer et al., 2015; Yang et al., 2017). Several additional factors, such as environmental exposure to aflatoxin B1, co-infection with human immunodeficiency virus (HIV) and unhealthy alcohol use, are common and may exacerbate the risk of HCC in HBV-infected individuals in the region (Kew, 2003; Nikolopoulos et al., 2009; Nouaman et al., 2018). According to the World Health Organization (WHO), the elimination of HBV as a public health problem by 2030 requires a 65% reduction in hepatitis-related mortality, which is mainly driven by HCC (World Health Organization, 2017). However, due to the lack of diagnostic capacity and incomplete cancer registries, epidemiological data on the incidence of HCC in SSA are scarce.

The early diagnosis of HCC is key to reduce HBV-related mortality, and can be achieved with the implementation of screening programmes using 6-monthly abdominal ultrasound (AUS) measurements. If hepatic lesions are detected during AUS, further diagnostic procedures, including four-phase computer tomography (CT) or repeat AUS, are needed to confirm the diagnosis, depending on the size of the lesions (European Association for the Study of the Liver, 2018). Although the presence of liver cirrhosis is the most important risk factor for the development of HCC among patients with chronic HBV, age, ethnicity and the presence of additional risk factors play a role. Current international guidelines recommend HCC screening for all HBV-infected patients of African origin after the age of 20 years, independent of the presence of cirrhosis (European Association for the Study of the Liver, 2018). Importantly, data on the incidence of HCC and risk factors among patients co-infected with HIV/HBV on tenofovir-containing antiretroviral therapy (ART) are very

limited: in a large study from Europe, age at initiation of tenofovir was the most important predictor of this outcome, besides cirrhosis (Wandeler et al., 2019). However, given the low number of patients of African origin included in the study, it remains unclear if the same risk factors should guide clinical decision-making on eligibility for HCC screening in African HIV clinics.

In light of the many structural challenges affecting healthcare systems in SSA, the collection of primary HCC incidence data is key to inform risk stratification and eligibility for HCC screening. As such, an ultrasound-based HCC screening programme was piloted in a long-term prospective cohort of individuals co-infected with HIV/HBV at two primary care clinics in urban Zambia. This article presents the results of the first AUS measurements from all patients included in the screening programme, and describes the main characteristics of individuals with at least one significant liver nodule.

Methods

Study population

From 2013, consecutive adults (aged ≥18 years) co-infected with HIV/HBV were enrolled into a prospective cohort study at two public sector outpatient primary care clinics in Lusaka, Zambia (Vinikoor et al., 2017). All participants were HBsAg-positive (Alere Determine, Waltham, MA, USA) and initiated ART containing tenofovir disoproxil fumarate, as per standard of care in Zambia. From January 2015, all participants were invited to join the pilot HCC screening programme. The Ethics Committees of the University of Zambia (Lusaka) and the University of Alabama at Birmingham approved the protocol, and all patients signed an informed consent form to participate in the study.

Study procedures

Detailed information on demographic and clinical characteristics, as well as laboratory measurements, were collected prior to the initiation of ART and at 3–6-monthly intervals thereafter using standardized data collection forms. The following laboratory tests were performed at least annually: full blood count; alanine aminotransferase (ALT; normal <19 U/L for women and <30 for men); creatinine; CD4+ cell count; and hepatitis B e-antigen (HBeAg). HBV viral load (VL) was measured annually using COBAS AmpliPrep/COBAS Taqman Version 2.0 (Roche Molecular Systems, Pleasanton, CA, USA). Screening for the presence of anti-hepatitis C virus antibodies was undertaken using a rapid test (OraQuick, OraSure Technologies, Bethlehem, PA, USA) (Wandeler et al., 2016). Alpha-fetoprotein (AFP) was measured in all participants with available stored serum samples at time of first AUS. AUDIT-C questions were used to assess level of alcohol consumption, and unhealthy alcohol use was defined as an AUDIT-C score >3 for women and >4 for men. Liver stiffness measurements (LSM) were taken annually using transient elastography (Fibroscan 402, Echosens, Paris, France) and results were categorized according to the METAVIR liver fibrosis stage: F0–F1 if LSM <7.1 kPa, F2–3 if LSM=7.1–11 kPa, and F4 if LSM >11.0 kPa, as established previously (World Health Organization, 2015). An examination was deemed successful if at least 10 valid LSM were obtained, and was considered very reliable if the

interquartile range divided by the median (IQR/M) was <0.1, reliable if IQR/M was 0.1–0.3, and poorly reliable if IQR/M was >0.3 (Boursier et al., 2013).

HCC surveillance protocol

In line with international recommendations, in January 2015, participants were asked to join the pilot HCC screening programme, and AUS imaging commenced in all individuals co-infected with HIV/HBV (European Association for the Study of the Liver, 2018). As AUS imaging at cohort clinics was inconsistent, patients were transported to the University Teaching Hospital (UTH), Lusaka's main referral hospital, located approximately 8 km away. AUS examinations were performed in the early afternoon, prior to lunch, by one of three experienced radiographers in the Department of Radiology. The following characteristics were described using a standardized case report form: liver mid-axillary diameter; portal vein diameter; and presence of splenomegaly, ascites, intraabdominal lymphadenopathy and peri-portal fibrosis. Liver cirrhosis was diagnosed in the presence of at least one of the following: surface nodularity; overall coarse and heterogeneous echotexture; atrophy; or segmental hypertrophy. Liver steatosis was diagnosed in the presence of increased echogenicity in comparison to the right kidney parenchyma and beam attenuation. The number, quality (hypo-, hyper- or mixed echogenicity) and location of liver lesions were described, and the largest lesion was measured (in cm). When a liver nodule >1 cm was documented on AUS, a four-phase CT scan was performed at UTH. LI-RADS Version 2017 was used to standardize interpretation and reporting for diagnostic imaging (LI-RADS®, Version 2017).

Results

Patient characteristics

Of 303 adults co-infected with HIV/HBV in the study cohort with a visit after January 2015, 279 (92.1%) had at least one AUS measurement. The median age of participants was 34 years (IQR 28–39 years), and 40.9% were female. At ART initiation, 118 (42.6%) participants reported unhealthy alcohol use, 53 (19%) were smokers, and 30 (10.8%) were overweight or obese (body mass index >25.5 kg/m^2). The median CD4 count was 246 cells/μL (IQR 112–355 cells/μL), and 100 (37.3%) were classed as WHO clinical stage 3 or 4 at ART initiation. Of all individuals with available data at the time of ART initiation, 102 (55.7%) had elevated ALT levels, 114 (59.7%) had HBV DNA levels >2000 IU/mL, and 103 (38.0%) had a positive HBeAg test. Overall, 59 (24.6%) participants had LSM compatible with significant fibrosis (METAVIR ≥F2), of whom 16 (6.7%) had liver cirrhosis (METAVIR F4). Of 147 patients with measured AFP levels, three had AFP levels >20 ng/mL.

Liver ultrasound findings

At their first AUS, participants had been on tenofovir-containing ART for a median of 8 months (IQR 0–16 months). Efavirenz was the third agent for 97.1% of participants, whereas 2.9% were receiving a nevirapine-based ART regimen. In this cross-sectional analysis, 75 (26.9%) participants had hepatomegaly and 69 (24.7%) had periportal fibrosis, whereas six individuals (2.2%) had signs of cirrhosis and four (1.4%) had liver steatosis

(Figure 1). Only one of 16 individuals with liver stiffness compatible with cirrhosis had signs of liver cirrhosis on AUS. Liver lesions ≥1 cm were documented in five (1.8%) patients, mostly appearing with a hyperechoic pattern (Figure 2, Panel A). One patient had multiple lesions. All participants with liver lesions were male and aged <50 years, two were HBeAg-positive, four (80.0%) had elevated ALT levels, and two had HBV DNA levels >2000 IU/mL at ART initiation. None of the five individuals with liver lesions had an elevated AFP level at the time of AUS. According to the updated nomenclature of the European Association for the Study of the Liver, one individual would have been classified as HBeAg-positive chronic HBV infection (Patient 1), three as HBeAg-negative chronic HBV infection (Patients 2–4), and one as HBeAg-positive chronic hepatitis (Patient 5). At the time of their first AUS measurement, all five patients had HBV VL <100 IU/mL.

Two patients with focal lesions >1 cm (Patients 1 and 5; Figure 2A) were referred for further investigation by four-phase CT scan. According to the LI-RADS categorization, lesions from both patients had a low probability of HCC on CT scan. Figure 2B shows radiological examinations of Patient 5, who had HBeAg-positive chronic hepatitis B with a high VL at baseline and liver cirrhosis. On ultrasound, a heterogeneous echotexture, surface nodularity of the liver, and multiple focal hypo- and hyperechoic focal lesions were noted. On four-phase CT scan, these lesions did not present any diagnostic HCC hallmarks, and were most likely haemangiomas. In two participants, there was a delay in recognizing the need for CT, and liver lesions were no longer visible on the next AUS (Patient 3) or had decreased in size on the next AUS (Patient 4). Finally, one patient withdrew from the study for personal reasons before a CT scan could be performed (Patient 2).

Discussion

Within a cohort of individuals co-infected with HIV/HBV in Zambia, 279 were successfully engaged in one of the first liver cancer screening initiatives for HBV-infected persons in SSA. At their first assessment, approximately 2% of patients had a liver lesion that warranted further diagnostic testing with a four-phase CT scan. Given the high proportion of participants with active hepatitis B, unhealthy alcohol use, and periportal fibrosis suggestive of schistosomiasis-induced liver damage, there is a need for continued evaluation of the incidence of HCC in this population.

This study demonstrated that imaging-based screening for HCC is feasible in resource-constrained settings, provided there are dedicated staff, skilled radiologists and access to adequate infrastructure. AUS was straightforward to perform at the referral centre; however, decentralized and integrated access to AUS at front-line facilities would further increase feasibility. Although the study population consisted mainly of young individuals co-infected with HIV/HBV receiving tenofovir-containing ART, a significant proportion had relevant risk factors for the development of HCC: 7% had liver stiffness consistent with liver cirrhosis and 60% had high HBV VL at the time of ART initiation. The prevalence of liver cirrhosis among people with HBV in this study is in line with the results of a recent meta-analysis, which showed similar estimates across SSA, and did not find evidence of a significant difference between HIV-infected and -uninfected individuals (Surial et al., 2020). Interestingly, most individuals with liver stiffness compatible with cirrhosis did not

have signs of liver cirrhosis on ultrasound. This finding could be explained by the higher sensitivity of elastography to diagnose cases of early, well-compensated cirrhosis, or by the impact of schistosomiasis on liver stiffness (Hashim and Berzigotti, 2021). The prevalence of additional HCC risk factors was also high in this population: 43% of individuals reported unhealthy alcohol use, and regular exposure to aflatoxin is widespread in the region. The need for HCC surveillance in non-cirrhotic patients treated with potent antiviral therapy is debated, as long-term suppression leads to the regression of liver fibrosis and cirrhosis, and reduces the incidence of HCC (Marcellin et al., 2013; Wandeler et al., 2019). However, given the high burden of HCC risk factors in SSA, HCC surveillance recommendations will have to be informed by prospective HBV cohorts with long-term HCC surveillance, such as described here.

In this cross-sectional analysis, five (2%) patients co-infected with HIV/HBV had an indication to undergo liver CT scan because of a liver lesion >1 cm on AUS. In two participants, this procedure was able to help exclude HCC. One patient was lost to follow-up before a CT scan could be performed, and a CT scan was not performed in the other two participants as the size of the lesions had reduced in subsequent AUS examinations. None of the participants showing liver lesions on AUS had elevated levels of AFP at the time of AUS. In resource-limited settings, access to four-phase CT scan to confirm or rule out HCC is limited due to the required infrastructure, including consistent power supply, supplies, specific contrast and syringes, and the necessary expertise in using and maintaining the device. Furthermore, the four-phase protocol, which involves complex timing of contrast injection, is rarely used in SSA and hence additional training is needed. Finally, the interpretation of contrast enhancement during the different phases of the procedure and standardized reporting require an experienced radiologist familiar with these procedures. Given the many challenges associated with the implementation of four-phase CT or magnetic resonance imaging in low-income countries, the use of potential HCC biomarkers should be evaluated to strengthen risk stratification and diagnosis of HCC.

A proportion of individuals in this study had periportal fibrosis, which is suggestive of schistosomiasis. The prevalence of schistosomiasis reaches 88% in endemic parts in Zambia, and related non-cirrhotic portal hypertension is a major cause of variceal bleeds in the region (Sinkala et al., 2020). Schistosomiasis may potentiate hepatic injury in the presence of HBV or hepatitis C virus infections, and experimental and clinical studies have suggested that schistosomiasis promotes the development of HCC (El-Tonsy et al., 2013). However, biomolecular mechanisms explaining the link between *Schistosoma mansoni* infection and HCC are still unknown, and it remains unclear whether schistosomiasis needs to be considered as an additional risk factor for the development of HCC. The systematic assessment of exposure to schistosomiasis should be included in studies assessing risk factors for HCC in endemic regions.

This study provides data from one of the first HCC screening initiatives among individuals with HBV infection in SSA. The following aspects make this clinical research platform unique in the region: (i) the patients had a comprehensive diagnostic work-up, including HBV virological analyses, alcohol assessment and transient elastography, before initiation of HCC screening; (ii) selection bias was avoided by securing the participation of the large

majority of patients with weekly transport to the radiology department; (iii) ultrasound examinations were conducted by one of three experienced radiologists who reported their results on a standardized form; (iv) the diagnosis of HCC was confirmed with a state-of-the-art four-phase CT scan protocol; and (v) AFP measurements were performed when stored samples were available at the time of AUS. However, the cross-sectional nature of this analysis and the absence of cases of HCC in the first round of AUS assessments meant that it was not possible to draw conclusions on the burden of end-stage liver disease in this population. An inherent limitation of the use of AUS is its low sensitivity for small tumours, which may have led to underestimation of the proportion of patients with clinically relevant nodules. Furthermore, AFP measurements were only available in 53% of patients. Finally, the characterization of risk factors for liver disease could have been improved by systematic measurement of aflatoxin B1 and schistosomal infection.

In summary, high prevalence rates of liver cirrhosis and periportal fibrosis were found among adults co-infected with with HIV/HBV, and 2% had liver lesions warranting a CT scan during the initial phases of this HCC surveillance initiative in urban Zambia. It was possible to include the majority of patients in the cohorts in the HCC screening programme due to the dedication of the study staff and the collaboration with a highly motivated tertiary care radiology department. Considering the logistical and financial challenges that need to be addressed for such a programme to be sustainable, the inclusion of participants based on optimized risk stratification and simplification of diagnostic tools will be key. Therefore, assessment of the diagnostic accuracy of AFP and new promising biomarker panels in larger prospective cohorts in the region is crucial. As HCC events are expected to occur frequently in young people with non-cirrhotic HBV infection in SSA, it will be crucial to assess the incidence of HCC and identify related risk factors in prospective studies with systematic surveillance programmes, such as in this Zambian cohort.

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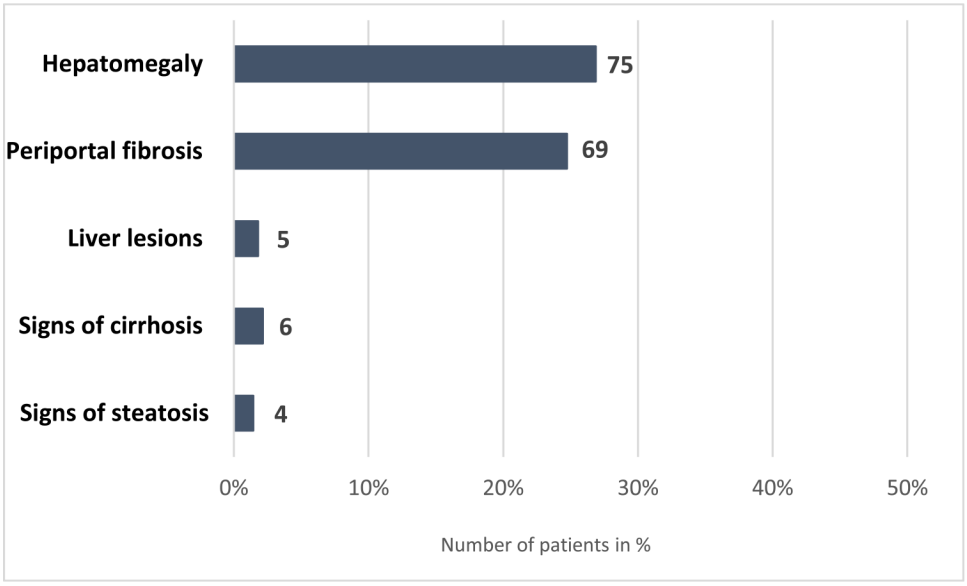

Figure 1.

Main findings at first ultrasound screening (*N*=279). Hepatomegaly was defined as liver diameter >15 cm. Patterns of periportal fibrosis were registered and graded according to the Niamey classification [15]. Signs of cirrhosis were defined as any of the following: surface nodularity; overall coarse and heterogeneous echotexture; atrophy or segmental hypertrophy. Steatosis was defined as increased liver echogenicity compared with right kidney parenchyma and beam attenuation.

Panel A.

Patient	Characteristics at ART start							Ultrasound findings			
	Sex	Age	CD4+ Count (cells/ul)	HBe Ag	ALT, U/L (IQR)	HBV DNA (IU/mL)	TE	Cirrhosis	Type lesion	No. lesions	Largest lesion (cm)
1	M	35	135	pos	38	52	F0	no	Hyperechoic	Single	2.2
2	M	29	174	neg	27	missing	F0	no	Hyperechoic	Single	1.7
3	M	38	237	neg	52	16600	F0	no	Hyperechoic	Single	1.4
4	M	47	259	neg	30	171	F0	no	Hyperechoic	Single	1
5	M	34	171	pos	71	39356310	F4	yes	Hypo- and Hyperechoic	Multiple	2.1

Abbreviations: HBeAg, hepatitis B surface antigen; HBV, hepatitis B virus; DNA, deoxyribonucleic acid; TE, transient elastography; M, male; pos, positive; neg, negative.

Fibrosis stage F0-F4 was graded according to the METAVIR scoring system.

Panel B.

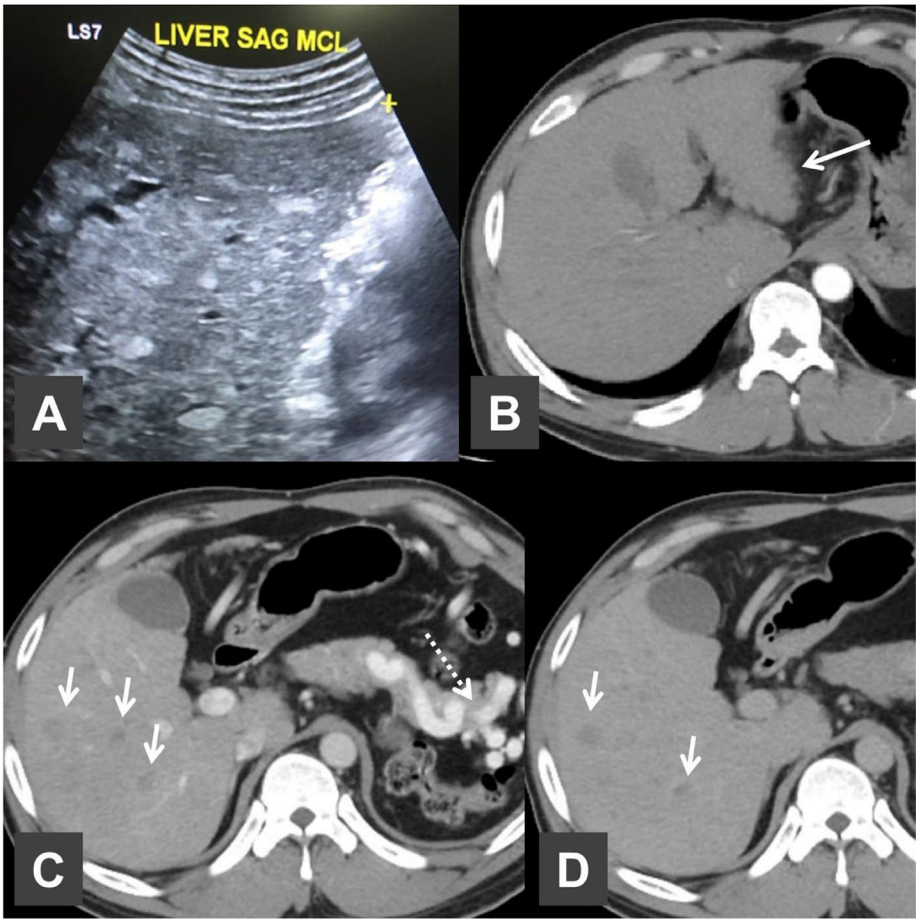

Figure 2.

Summary of patients with liver lesions. Main characteristics of the five patients with liver lesions (Panel A) and radiological examinations (US and 4-phase CT) of patient 5 (Panel B) Imaging findings in patient 5: The liver tissue is highly cirrhotic and shows an inhomogeneous hypo- and hyperechogenic structure in b-mode ultrasound (A). In the multiphase CT scan (B-D), the arterial phase (B) reveals a cirrhotic nodular surface of the liver (arrow in B), however, there are no focal lesions with an arterial hyperperfusion. Comparable to the ultrasound examination, the liver tissue is highly inhomogeneous with

multiple nodules also in the portal venous (small arrows in C) and the late contrast phase (small arrows in D). Due to an elevated portal venous pressure, large portocaval collaterals can be seen (dotted arrow in C).