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## Liver fibrosis in treatment-naïve HIV-infected and HIV/HBV co-infected patients: Zambia and Switzerland compared

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### SUMMARY

**Objective:** To examine the association between hepatitis B virus (HBV) infection and liver fibrosis in HIV-infected patients in Zambia and Switzerland.

**Methods:** HIV-infected adults starting antiretroviral therapy in two clinics in Zambia and Switzerland were included. Liver fibrosis was evaluated using the aspartate aminotransferase-to-platelet-ratio index (APRI), with a ratio  $>1.5$  defining significant fibrosis and a ratio  $>2.0$  indicating cirrhosis. The association between hepatitis B surface antigen (HBsAg) positivity, HBV replication, and liver fibrosis was examined using logistic regression.

**Results:** In Zambia, 96 (13.0%) of 739 patients were HBsAg-positive compared to 93 (4.5%) of 2058 in Switzerland. HBsAg-positive patients were more likely to have significant liver fibrosis than HBsAg-negative ones: the adjusted odds ratio (aOR) was 3.25 (95% confidence interval (CI) 1.44–7.33) in Zambia and 2.50 (95% CI 1.19–5.25) in Switzerland. Patients with a high HBV viral load ( $\geq 20\,000$  IU/ml) were more likely to have significant liver fibrosis compared to HBsAg-negative patients or patients with an undetectable viral load: aOR 3.85 (95% CI 1.29–11.44) in Zambia and 4.20 (95% CI 1.64–10.76) in Switzerland. In both settings, male sex was a strong risk factor for significant liver fibrosis.

**Conclusions:** Despite the differences in HBV natural history between Sub-Saharan Africa and Europe, the degree of liver fibrosis and the association with important risk factors were similar.

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### 1. Introduction

The increasing availability of antiretroviral therapy (ART) for HIV-infected individuals has led to a dramatic reduction in AIDS-related mortality and to the emergence of liver-related complications of hepatitis B virus (HBV) and hepatitis C virus (HCV)

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infections as a major cause of death.<sup>1</sup> Worldwide, HBV infection is the single most important cause of liver cirrhosis and causes over 50% of cases of hepatocellular carcinoma (HCC).<sup>2</sup> HIV infection accelerates the progression of HBV-related liver fibrosis, especially if cellular immunity is impaired or in the absence of adequate treatment of HBV infection.<sup>3</sup> A recent study from Nigeria showed that HIV/HBV co-infected individuals were five times more likely to have advanced liver fibrosis compared to HIV monoinfected people.<sup>4</sup>

Although the mechanisms of HBV-related fibrogenesis are not fully understood, recent results from prospective cohorts in Europe, North America, and Asia have provided new insights into its main determinants.<sup>5</sup> Several host and viral risk factors, including male sex, old age, high HBV viral load, and specific HBV genotypes, have been associated with the development of liver fibrosis, cirrhosis, and HCC. However, data from Sub-Saharan Africa (SSA), where HBV prevalence is highest, are scarce. In SSA, most infections occur during early childhood, in contrast to Western Europe, where the majority of patients are infected as adults.<sup>6</sup> As HBV transmission patterns and the duration of infection may influence the development of liver fibrosis and HCC, HIV/HBV co-infected patients in SSA could be at high risk of developing early liver disease.<sup>5</sup> In addition, the burden of HBV-related complications might be increased by the presence of concurrent infections such as hepatitis delta virus (HDV) and schistosomal infections, as well as environmental exposures such as aflatoxins.<sup>7–9</sup>

Several non-invasive measurements have been used for the staging of liver fibrosis in HIV-infected and HIV/HBV co-infected individuals.<sup>10,11</sup> The aspartate aminotransferase-to-platelet ratio index (APRI), which has been associated with mortality in SSA,<sup>12</sup> is recommended by the World Health Organization (WHO) for the assessment of the presence of liver fibrosis where liver biopsy is unavailable.<sup>13,14</sup> In this study, the stages of liver fibrosis were compared between HIV-infected and HIV/HBV co-infected individuals in cohorts from Zambia and Switzerland using the APRI. This provided a unique opportunity to assess the impact of HBV transmission patterns on the development of liver fibrosis and to evaluate its most important clinical and biological determinants in two distinct epidemiological contexts.

## 2. Methods

### 2.1. HIV cohorts in Zambia and Switzerland

Analyses were based on two HIV cohorts in Zambia and Switzerland.

HIV-infected adults receiving ART in two urban clinics in Lusaka, where care was provided to the standard of the national program, were included.<sup>15</sup> Routine baseline examinations included a medical history, physical examination, and laboratory measurements (CD4 cell count, full blood count, serum creatinine, and aminotransferases). In addition, all patients were tested for hepatitis B surface antigen (HBsAg) and anti-HCV antibodies, and HBV sequencing as well as viral load measurements were performed in HBsAg-positive individuals within the framework of a sub-study of the IeDEA-SA (International Epidemiological Databases to Evaluate AIDS in Southern Africa).<sup>16</sup> All data were entered into an electronic database for clinical care, monitoring, evaluation, and reporting purposes. Written informed consent was obtained from all patients. The Biomedical Research Ethics Committee of the University of Zambia School of Medicine and the Institutional Review Board of the University of North Carolina at Chapel Hill, USA, approved the study.

Established in 1988, the Swiss HIV Cohort Study (SHCS, <http://www.shcs.ch>) is a prospective nationwide cohort study with

ongoing enrolment of HIV-infected adults. It covers approximately 50% of the cumulative number of HIV infections reported to the Swiss public health authorities and 75% of patients receiving ART in Switzerland.<sup>17</sup> Detailed information on demographics, mode of HIV acquisition, risk behaviour, clinical events, co-infections, and treatment is collected using a standard protocol at registration and then at 6-monthly intervals. All participants are screened for HBV infection at study entry. Positive HBsAg tests are confirmed with an HBV DNA measurement. The local ethics committees at all participating study sites approved the study, and written consent was obtained from all participants.

### 2.2. Inclusion criteria and definitions

All adults with measurements of HBsAg, alanine aminotransferase (ALT), aspartate aminotransferase (AST), and platelets before ART initiation were included. Patients who tested positive for anti-HCV antibodies were excluded. Liver fibrosis was evaluated using the APRI, a non-invasive score originally validated in HIV/HCV co-infected patients and previously used in studies of HIV-infected and HIV/HBV co-infected individuals.<sup>11,12,18,19</sup> The following cut-offs were used, as recommended by the WHO: 0.5 and 1.5 to rule-out and confirm significant fibrosis (equivalent to METAVIR stages 2 and above), respectively, and 1.0 and 2.0 to rule-out and confirm cirrhosis (METAVIR stage 4), respectively.<sup>13</sup> Grade 1 ALT elevation (1.25–2.5 times the upper limit of normal (ULN)) was defined according to Division of AIDS criteria.<sup>20</sup>

In the SHCS, alcohol intake has been assessed routinely at 6-month intervals since 2005.<sup>21</sup> In Zambia, alcohol consumption was investigated in all patients at ART initiation using the AUDIT-C tool.<sup>22</sup> At-risk alcohol intake was defined according to the National Institute on Alcoholism and Alcohol Abuse (NIAAA) as an average daily consumption above one standard drink (10 g of pure alcohol) for women and above two standard drinks for men.

### 2.3. Laboratory analyses

HBsAg-positivity was assessed using the point-of-care Determine rapid test (Alere, Yavne, Israel) in Zambia and recommended commercial serological assays in Switzerland. HCV infection was evaluated using the anti-HCV antibody rapid test OraQuick (OraSure Technologies Inc., Bethlehem, PA, USA) in Zambia and the ARCHITECT anti-HCV assay (Abbott Diagnostics, Wiesbaden, Germany) in Switzerland. HBV DNA testing was performed using real-time PCR (Roche COBAS AmpliPrep/Taqman HBV test) in both countries. All measurements were performed before the initiation of ART, or within the first month of ART.

### 2.4. Statistical analyses

Differences in baseline demographic characteristics and clinical and liver-related parameters at ART initiation between HBsAg-positive and HBsAg-negative individuals in the two cohorts were tested using the Chi-square test and Mann–Whitney test. Logistic regression was used to evaluate the association between HBsAg positivity and significant liver fibrosis (APRI  $\geq 1.5$ ). The following potential confounders were adjusted for in multivariable models: sex, age (below vs. above 40 years), country (Zambia vs. Switzerland), CD4 cell count (below vs. above 200 cells/ $\mu$ l), clinical stage of HIV disease (advanced vs. not advanced, with advanced defined as WHO stages III or IV for Zambia and CDC stage C for Switzerland), and alcohol consumption (at-risk consumption vs. no or not-at-risk consumption). The logistic regression analysis was repeated after stratification by country. As some of the comparisons of HBV-related determinants between patients from Zambia and Switzerland might have been biased by the presence of

patients of African origin in the SHCS, the main analyses were also repeated after excluding the latter.

To evaluate the role of HBV replication on the degree of liver fibrosis, the logistic regression analyses were repeated including levels of HBV replication in three categories: (1) no HBV infection or HBV infection with an HBV viral load <20 IU/ml, (2) HBV viral load between 20 and 19 999 IU/ml, and (3) HBV viral load ≥20 000 IU/ml. The association between HBV viral load and significant fibrosis and cirrhosis was further explored by repeating the analyses after excluding HIV/HBV co-infected patients with high viral loads but normal aminotransferases (as a proxy for the immune-tolerant profile). All statistical analyses were performed using Stata 12.0 (Stata Corp, College Station, TX, USA).

### 3. Results

#### 3.1. Demographic and clinical characteristics

In Zambia, 96 (13.0%) of 739 HIV-infected patients were HBsAg-positive compared to 93 (4.5%) of 2058 patients in Switzerland ( $p < 0.001$ ). The age and sex distribution were similar in HBsAg-positive and HBsAg-negative patients (Table 1). The prevalence of advanced disease and median CD4 counts were also similar in HBsAg-positive and HBsAg-negative patients in the two cohorts, but patients in Zambia had more advanced disease and lower CD4 cell counts. The prevalence of at-risk alcohol use was somewhat higher in HBsAg-positive patients than HBsAg-negative patients in both Zambia and Switzerland, but the differences failed to reach statistical significance ( $p > 0.20$ ). At-risk alcohol intake was more common in Zambia than in Switzerland (24.9% vs. 9.9%,  $p < 0.001$ ). In Switzerland, 26.9% of HIV/HBV co-infected individuals were of African origin, whereas this group represented only 15.6% of HBsAg-negative patients.

#### 3.2. Liver-related parameters

In both countries, HIV/HBV co-infected individuals were approximately twice as likely to have a grade 1 ALT elevation or higher as HIV monoinfected patients (Table 1). As shown in Figure 1, the proportion of patients with significant liver fibrosis (APRI >1.5) was higher in HIV/HBV co-infected patients than in HIV monoinfected patients (10.4% vs. 3.6% in Zambia, 14.0% vs. 4.4% in Switzerland). The proportion of individuals with liver cirrhosis was below 3% in all groups except in HIV/HBV co-infected

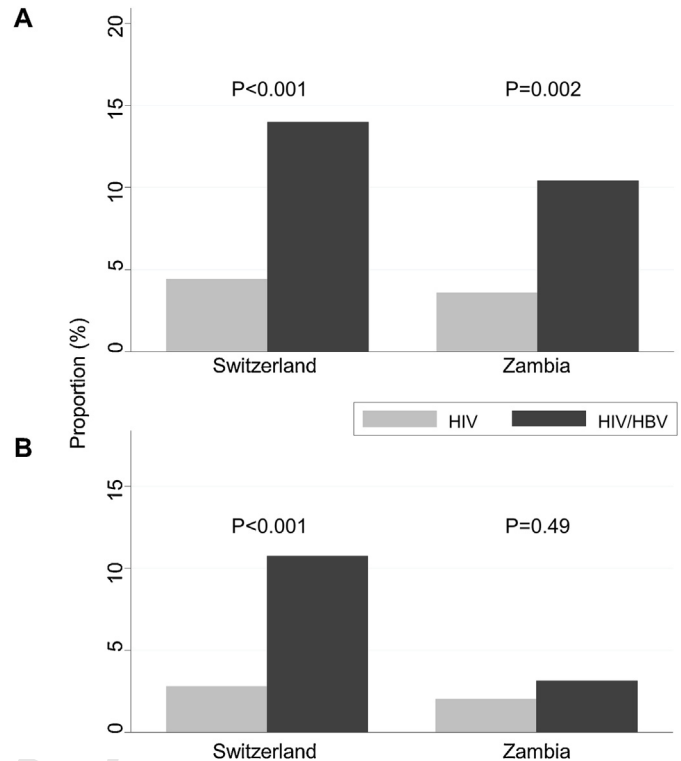


Figure 1. Proportion of patients with significant fibrosis (A) and cirrhosis (B), by country and HBV status.

patients in Switzerland, in whom the prevalence was 10.8% (Figure 1). Based on the lower APRI cut-off for cirrhosis (APRI >1.0), cirrhosis could be excluded in over 90% of HIV monoinfected patients, as well as in 84.4% and 76.3% of HIV/HBV co-infected patients in Zambia and Switzerland, respectively.

#### 3.3. Determinants of significant liver fibrosis

In adjusted analyses, HBsAg-positive patients were approximately three times more likely to have significant liver fibrosis compared to HBsAg-negative individuals (adjusted odds ratio (aOR) 2.75, 95% confidence interval (CI) 1.61–4.74; Table 2). The estimates were similar when each cohort was analyzed separately

Table 1

Baseline characteristics of the patients, by cohort

	Zambia			Switzerland		
	HIV (n=643)	HIV/HBV (n=96)	p-Value	HIV (n=1965)	HIV/HBV (n=93)	p-Value
General characteristics						
Female (%)	346 (53.8)	42 (43.8)	0.07	447 (22.8)	21 (22.6)	0.97
African origin (%)	643 (100)	96 (100)	0.99	306 (15.6)	25 (26.9)	0.004
Age, years, median (IQR)	34 (29–41)	34 (29–39)	0.30	39 (32–46)	38 (31–45)	0.38
At-risk alcohol intake (%)	155 (24.1)	29 (30.2)	0.20	191 (10.7)	12 (14.6)	0.26
Advanced HIV disease (%)	288 (45.4)	38 (40.0)	0.32	216 (11.0)	8 (8.6)	0.47
CD4, cells/ $\mu$ l, median (IQR)	226 (121–330)	233 (114–361)	0.59	277 (178–381)	293 (170–413)	0.64
Creatinine, $\mu$ mol/l, median (IQR)	80 (70–92)	79 (70–91)	0.72	76 (66–87)	75 (64–88)	0.84
Platelets, $\times 10^9$ /l, median (IQR)	250 (197–316)	246 (190–303)	0.35	205 (168–252)	199 (165–242)	0.41
Liver-related characteristics						
Grade 1 ALT elevation or above (%)	49 (7.6)	14 (14.6)	0.02	215 (10.9)	23 (24.7)	<0.001
APRI, median (IQR)	0.36 (0.26–0.53)	0.44 (0.29–0.76)	0.01	0.39 (0.29–0.59)	0.50 (0.37–0.89)	<0.001
HBV viral load category (%)						
<20	NA	11 (12.2)	NA	NA	12 (16.2)	NA
20–19 999	NA	40 (44.4)	NA	NA	29 (39.2)	NA
≥20 000	NA	39 (43.3)	NA	NA	33 (44.6)	NA

HBV, hepatitis B virus; IQR, interquartile range; ALT, alanine aminotransferase; APRI, aspartate aminotransferase-to-platelet-ratio index; NA, not applicable.

**Table 2**

Risk factors for significant liver fibrosis

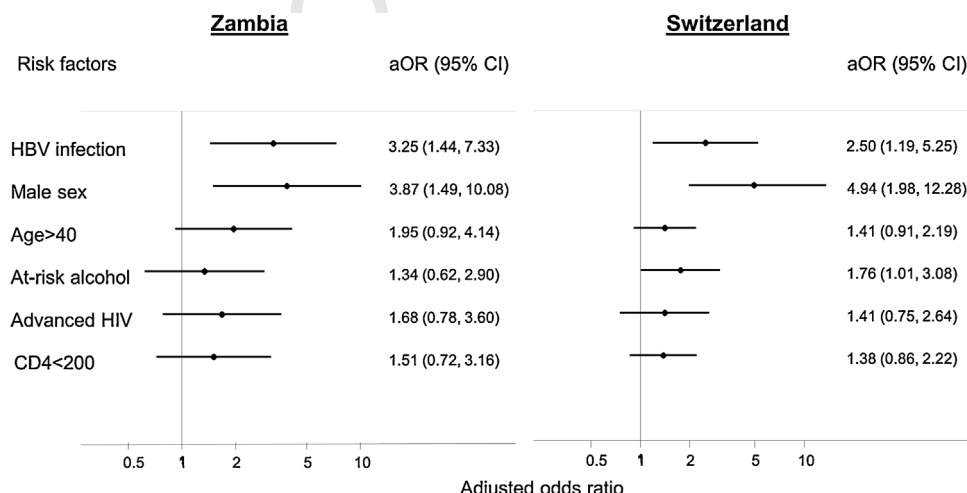
	No. (%) with significant fibrosis	Univariable analysis (95% CI)	Multivariable analysis (95% CI)
HBV co-infection			
No	110 (4.2)	1	1
Yes	23 (12.2)	3.15 (1.95–5.06)	2.75 (1.61–4.74)
Sex			
Female	12 (1.4)	1	1
Male	121 (6.3)	4.68 (2.57–8.51)	4.38 (2.30–8.32)
Age, years			
16–40	65 (3.9)	1	1
>40	68 (6.0)	1.57 (1.11–2.23)	1.54 (1.05–2.25)
At-risk alcohol intake			
No	93 (4.2)	1	1
Yes	30 (7.8)	1.93 (1.26–2.95)	1.55 (0.98–2.44)
Advanced HIV disease			
No	95 (4.3)	1	1
Yes	38 (6.9)	1.67 (1.13–2.47)	1.48 (0.92–2.38)
CD4+ count, cells/ $\mu$ l			
$\geq 200$	75 (4.0)	1	1
<200	58 (6.2)	1.56 (1.10–2.21)	1.40 (0.94–2.08)
Country			
Zambia	33 (4.5)	1	1
Switzerland	100 (4.9)	1.09 (0.73–1.63)	1.10 (0.66–1.81)

(3.25, 95% CI 1.44–7.33 in Zambia and 2.50, 95% CI 1.19–5.25 in Switzerland; [Figure 2](#)). Male sex was another strong predictor of significant liver fibrosis in pooled (OR 4.38, 95% CI 2.30–8.32) and stratified analyses (3.87, 95% CI 1.49–10.08 in Zambia and 4.94, 95% CI 1.98–12.28 in Switzerland). Associations with age above 40 years, at-risk alcohol intake, advanced HIV disease, and a CD4 count <200 cells/ $\mu$ l were weaker and further attenuated on multivariable analysis ([Table 2](#)). At-risk alcohol consumption predicted significant liver fibrosis in Switzerland (OR 1.78, 95% CI 1.01–3.08), but not in Zambia (OR 1.34, 95% CI 0.62–2.90). The results of the analysis in the SHCS after the exclusion of patients of African origin ( $n = 331$ ) remained similar, including the association between HBV and liver fibrosis (OR 2.64, 95% CI 1.20–5.82).

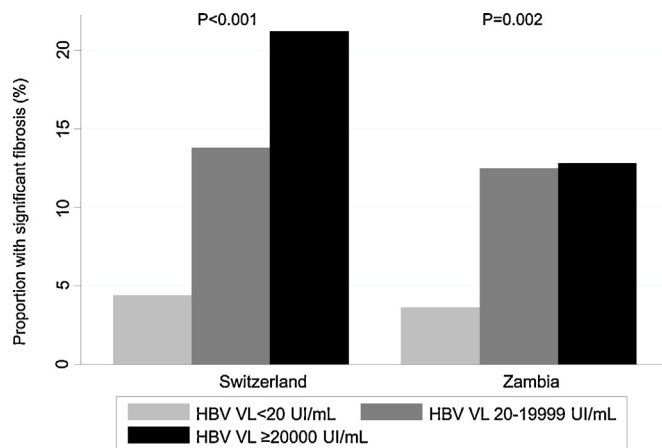
### 3.4. HBV viral load and liver fibrosis

Of 96 HIV/HBV co-infected individuals in Zambia, 90 (94%) had an available HBV viral load before the initiation of ART and the median HBV viral load was 1186 (interquartile range (IQR) 53–1.94e+06) IU/ml. Among the 93 HIV/HBV co-infected individuals in Switzerland, 74 (80.0%) had an available measurement and

the median HBV viral load was 7299 (90–1.62e+08) IU/ml ( $p$ -value for the comparison between the two countries = 0.07). A similar proportion of HIV/HBV co-infected patients had a high baseline HBV viral load ( $\geq 20\,000$  IU/ml) in both countries: 43.3% in Zambia and 44.6% in Switzerland ([Table 1](#)). The proportion of patients with significant liver fibrosis increased with HBV viral load: from 3.7% in HBsAg-negative or HBsAg-positive with HBV viral load <20 IU/ml to 12.8% in those with an HBV viral load  $\geq 20\,000$  IU/ml in Zambia, and from 4.4% to 21.2% in Switzerland ([Figure 3](#)). In multivariable analyses, individuals with a high HBV viral load were more likely to have significant liver fibrosis compared to HBsAg-negative or HBsAg-positive patients with an undetectable HBV viral load: aOR 3.85 (95% CI 1.29–11.44) in Zambia and aOR 4.20 (95% CI 1.64–10.76) in Switzerland ([Supplementary Material](#), Table S1). Of note, there was no clear difference in the proportion of patients with significant liver fibrosis between HIV/HBV co-infected patients with moderate and those with high viral loads in Zambia ([Figure 3](#)). Among patients with high HBV viral loads, 72% in Zambia and 58% in Switzerland had normal aminotransferases and only one of these 47 patients had significant fibrosis. After exclusion of these potentially immune-tolerant patients, the



**Figure 2.** Risk factors for significant liver fibrosis (APRI  $\geq 1.5$ ) from multivariable logistic regression, by cohort.



**Figure 3.** Proportion of patients with significant fibrosis, by country and HBV replication status.

proportion of individuals with significant fibrosis among those with high viral loads increased from 13% to 36% in Zambia and from 21% to 50% in Switzerland.

#### 4. Discussion

In this cross-sectional study of HIV-infected, ART-naïve adults in Zambia and Switzerland, it was found that HBV co-infection was strongly associated with liver fibrosis. HIV/HBV co-infected patients were at least three times more likely to have significant fibrosis compared to HIV monoinfected individuals. This association was similar in Zambia and Switzerland despite differences in the natural history of HBV infection and the genetic background of the study populations, and seemed to be driven by HBV viral load. Liver cirrhosis was rare in Zambia but present in over 10% of HIV/HBV co-infected individuals in Switzerland. This analysis also showed differences in alcohol intake and the impact on liver disease between the two regions, underlining the need to better characterize alcohol consumption and its health-related effects in Sub-Saharan Africa.

Few studies have evaluated the impact of HBV co-infection on the development of liver fibrosis in HIV-infected individuals using non-invasive methods. The Multicenter AIDS Cohort Study (MACS) showed a strong association between viral hepatitis co-infection and significant liver fibrosis using the APRI score, but the number of HBV-infected patients analyzed was small.<sup>19</sup> In SSA, two studies based on transient elastography measurements showed conflicting results: Hawkins et al. reported a strong association between HBV co-infection and liver fibrosis in HIV-infected individuals in Nigeria, whereas Stabinski et al. found no such association in a large cohort in Uganda.<sup>4,23</sup> The present analysis of two large HIV cohorts provides further evidence in favour of a link between HBV co-infection and the development of liver fibrosis. Although non-invasive markers of liver fibrosis have mostly been validated and used in studies on HCV infection, they will increasingly be used in the management of HBV infection, especially in the context of improving coverage of ART in resource-limited settings. Recently, Stockdale et al. showed that the APRI score had a good negative predictive value for excluding cirrhosis and significant fibrosis among HIV/HBV co-infected individuals in West Africa, but had a poor overall diagnostic performance.<sup>24</sup> As APRI is now recommended by the WHO to evaluate treatment eligibility for chronic HBV infection in the absence of liver biopsy or transient elastography,<sup>13,14,25</sup> there is an urgent need for validation studies of this marker in other contexts, ideally in comparison with the results of liver biopsies.

The association between HBV infection and liver fibrosis was found to depend on the level of HBV viral replication. In both countries, the proportion of patients with significant liver fibrosis was similar in HBV-uninfected and HBV co-infected patients with a viral load <20 IU/ml, whereas the prevalence of liver disease was much higher in those with high viral loads. These results are in line with those of prospective studies on viral replication in HBV monoinfected individuals and the risk of liver cirrhosis and HCC.<sup>26,27</sup> HBV replication is influenced by the natural history of HBV infection: patients infected during early childhood are likely to undergo hepatitis B e antigen (HBeAg) seroconversion early in life and to remain in a non-replicating phase for many years, whereas those acquiring chronic HBV infection in adulthood often experience high-level replication, hepatic inflammation, and progressive development of liver fibrosis.<sup>5</sup> Compared to HIV/HBV co-infected patients in Switzerland, liver cirrhosis was less common among Zambians, despite what were likely longer durations of HBV infection and similar HBV viral loads at ART initiation. Host genetic factors could partially explain the lower prevalence of cirrhosis in Zambia, analogous to the protective effect of black ethnicity on the development of HCV-related complications.<sup>28</sup> Other potential explanations include differences in viral factors (HBV genotypes and HBeAg positivity), as well as environmental factors unaccounted for in the present analyses. For instance, insulin resistance, a known risk factor for the development of liver fibrosis and HCC, might have been more prevalent in the Swiss population.<sup>29</sup> Although the results of this study confirm previous evidence on the impact of replicating HBV infection on liver disease in treatment-naïve populations, it is not yet known to what extent HBV-active therapy reduces the excess liver-related morbidity seen in HIV/HBV co-infected patients.

Another important difference between patients in Zambia and Switzerland was the difference in the association between alcohol consumption and liver disease. At-risk alcohol consumption did not seem to be a strong risk factor for hepatic damage in Zambia, whereas there was a clear association with significant liver fibrosis in Switzerland. Due to the paucity of data published on alcohol consumption and related health consequences in HIV-infected individuals in SSA, it was difficult to evaluate the generalizability and robustness of these data. However, besides the potential explanations mentioned above, the nature of the alcohol assessment could have influenced the results. Self-reported alcohol intake is subject to several biases and socio-cultural differences between the two settings studied, making the comparison difficult. More research on alcohol-related and metabolic-induced liver complications is urgently needed to improve our understanding of liver disease progression in SSA, especially in HIV-infected populations, in which alcohol consumption is high.

This assessment of liver-related complications using detailed assessments of HBV virological determinants as well as other risk factors for liver disease, including alcohol consumption and HIV stage of disease, is a unique strength of this study. The impact of HCV co-infection on liver fibrosis could be excluded, as all patients were tested for HCV infection, including in the Zambian cohort. The association between HBV replication and liver fibrosis could be tested, as viral load measurements were available for >80% of the HBV co-infected participants. However, due to missing HBeAg data in a large sample of the patients, the influence of HBeAg positivity could not be evaluated. As the majority of adult patients with HBV infection in SSA are HBeAg-negative, these data could have explained the differences in the prevalence of liver cirrhosis between the two settings. Similarly, data on hepatitis delta infection, a well-known risk factor for liver fibrosis in HIV/HBV co-infected individuals, were not available. Another limitation of this study was the reliance on the APRI score to measure liver fibrosis and cirrhosis. As this test has not been properly validated in

HBV-infected populations in SSA, cut-offs generally used for HCV infection had to be applied. Although this score has a good negative predictive value to rule out liver cirrhosis (APRI <1.0), more data are needed from SSA to better define its accuracy, and results need to be compared with data from HBV mono-infected populations. To expand the results of this study, similar comparative analyses should be repeated in cohorts with access to more detailed data on liver-related events, including HCC and liver decompensation. Finally, it was not possible to determine when the co-infected participants acquired their HBV infection. Although it was assumed that most patients in Zambia were infected during early childhood and most in Switzerland during adulthood, individual-level data on the time of infection would have allowed the role of duration of infection to be better defined.

In conclusion, as HBV-active antiretroviral agents such as tenofovir become increasingly available, it is essential to improve our knowledge on the prevalence and main determinants of liver disease among those infected with HIV. These results show that the prevalence and determinants of HBV-related liver fibrosis in Zambia and Switzerland are largely comparable. Further research is needed to better understand the complex relationship between the duration of HBV infection, natural history, viral replication, and liver disease in different parts of the world.

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**Conflict of interest:** All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. No other disclosures are reported.

## Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.ijid.2016.08.028>.

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