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Long-term Hepatitis B and Liver Outcomes Among Adults Taking Tenofovir-Containing Antiretroviral Therapy for HBV/HIV Coinfection in Zambia

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Background. Long-term outcomes of tenofovir-containing antiretroviral therapy (ART) for hepatitis B virus (HBV)/human immunodeficiency virus (HIV) coinfection were evaluated in Zambia.

Methods. A prospective cohort of adults with HIV and hepatitis B surface antigen (HBsAg)-positivity was enrolled at ART initiation. On tenofovir-containing ART, we ascertained HBV viral load (VL) non-suppression, alanine aminotransferase (ALT) elevation, serologic end-points, progression of liver fibrosis based on elastography, and hepatocellular carcinoma (HCC) incidence. We also described a subgroup (low HBV VL and no/minimal fibrosis at baseline) that, under current international guidelines, would not have been treated in the absence of their HIV infection.

Results. Among 289 participants at ART start, median age was 34 years, 40.1% were women, median CD4 count was 191 cells/mm^3, 44.2% were hepatitis B e antigen-positive, and 28.4% had liver fibrosis/cirrhosis. Over median 5.91 years of ART, 13.6% developed HBV viral non-suppression, which was associated with advanced HIV disease. ALT elevation on ART was linked with HBV VL non-suppression. Regression of fibrosis and cirrhosis were common, progression to cirrhosis was absent, and no cases of HCC were ascertained. HBsAg seroclearance was 9.4% at 2 and 15.4% at 5 years, with higher rates among patients with low baseline HBV replication markers.

Conclusions. Reassuring long-term liver outcomes were ascertained during tenofovir-based ART for HBV/HIV coinfection in Zambia. Higher than expected HBsAg seroclearance during ART underscores the need to include people with HIV in HBV cure research.

Keywords. hepatitis B; HIV/AIDS; liver fibrosis; hepatocellular carcinoma; antiviral therapy.

Chronic hepatitis B virus (HBV) infection affects around 250 million individuals and causes up to 1 million deaths per year from cirrhosis and/or hepatocellular carcinoma (HCC) [1]. This includes 80 million with HBV in sub-Saharan Africa (sSA), a region where where HBV-related HCC occurs at a younger age than in other regions [2], and the virus intersects with the human immunodeficiency virus (HIV) epidemic [1]. To mitigate the increased risk of liver-related mortality with HBV/HIV coinfection versus HBV alone [3, 4], universal tenofovir-containing antiretroviral therapies (ART) are recommended for people with coinfection. However, in sSA, long-term data on HBV outcomes, including in people with HIV, are extremely limited. Existing analyses of coinfection treated with tenofovir-based ART in sSA had short durations of follow-up (usually 1–2 years) and small sample sizes [5–7].

Understanding the outcomes of HBV/HIV coinfection in sSA is globally relevant for several reasons. First, even under current tenofovir-based ART, all-cause mortality remains higher in HBV/HIV coinfection compared to HIV alone [5]. Universal treatment of coinfection also provides opportunities to understand the immunologic responses that underpin immune control of HBV [8]. Outcomes of HBV/HIV coinfection treatment in sSA may also inform hepatitis elimination strategies in low- and middle-income countries (LMICs). In addition to full implementation of highly effective HBV immunization, universal treatment of HBV monoinfection is increasingly debated in LMICs due to its operational simplicity, reducing cost of generic tenofovir-based therapies, and the high costs and laboratory capacity required for treatment eligibility [9].

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Investigators in Asia recently reported lower risk of HCC in HBV/HIV coinfection compared to HBV monoinfection, which was attributed to broader used of antiviral therapies [10].

In a well-characterized sentinel prospective HBV/HIV coinfection cohort in Zambia we investigated the long-term HBV outcomes of tenofovir-containing ART. We sought to analyze the burden and clinical significance of HBV DNA non-suppression during ART, evolution to HBV functional cure, and liver outcomes including fibrosis progression, based on transient elastography, and HCC. Finally, in a subgroup analysis, we explored hepatitis B surface antigen (HBsAg) seroclearance in patients with pre-therapy low HBV DNA and no/minimal liver fibrosis—a population that would not have qualified for therapy if not for their HIV infection.

METHODS

Cohort Description

Zambia has a robust, decentralized, national program that provides free access to HIV care for all people with or at risk for HIV. Among more than 30 facilities in Lusaka, at 2 large volume ones we established a prospective HBV/HIV coinfection cohort to investigate causes of liver disease [11]. For people with HIV, as a routine part of initial registration at an HIV clinic, HBsAg testing is performed using a rapid point-of-care (POC) assay. Inclusion criteria for the cohort were age ≥18 years, HIV-positive, HBsAg-positive, treatment-naïve, and initiating ART or had initiated in the previous month. The only exclusion criterion was HCV coinfection based on HCV RNA-positivity or anti-HCV-positivity with unknown HCV RNA. The target sample size was 400 participants, based on feasibility with available resources. All participants were eligible for ART, which was provided for free. From 2013 to 2019, the first-line regimen was fixed-dose combination of tenofovir disoproxil fumarate (TDF), lamivudine (3TC), and efavirenz. Starting in mid-2019, participants on first-line ART with an HIV RNA <1000 copies/mL were transitioned to fixed-dose combination TDF, 3TC, and dolutegravir. Written informed consent was obtained, and the study was approved by the ethics committees at University of Zambia (Lusaka, Zambia) and University of Alabama at Birmingham (Birmingham, USA).

Study Measurements

At enrollment, the World Health Organization (WHO) HIV clinical stage was assessed, and blood was collected for ALT, AST, platelets, CD4 count, HBV DNA (Roche COBAS Ampliprep/COBAS Taqman or Cepheid Xpert HBV), and HBeAg. HBsAg levels were measured in a subset. Alcohol use was assessed at baseline and yearly thereafter with the alcohol use disorders identification test-consumption (AUDIT-C) and dichotomized as unhealthy use (AUDIT-C > 3 for women, >4 for men) versus moderate use or abstinence. Transient elastography (TE) was performed (Fibroscan 402, Echosens, France) at enrollment and yearly on ART. Although not mandatory, fasting for several hours prior to TE [12] was routine as most measures occurred in the late morning. HCC screening using 6-monthly abdominal ultrasound was introduced for all participants starting in 2015 [13]. New lesions >1 cm on ultrasound were followed up with a 4-phase computed tomography (CT) scan. Follow-up cohort visits occurred every 6 months for up to 10 years. Every 6 months we repeated ALT, and every 12 months we did HIV RNA testing per local guidelines and repeated AST, platelets, CD4 count, HBV DNA, HBeAg (in those who were positive on prior assessment), and HBsAg. HIV RNA suppression was used as a marker of medication adherence. During therapy, we also re-assessed HBsAg status yearly using a rapid POC assay in the clinic, and if negative, a more sensitive (0.05 IU/mL) confirmatory assay (Access2Analyzer, Beckman Coulter, USA) was performed at a central laboratory.

Outcomes

Cohort outcomes were described including transfer out, withdrawal, loss to follow-up (LTFU), defined as >12 months without a study visit, and death, which was ascertained through report by a relative of the participant and/or during outreach after missed visits. For the current analysis, we focused on treatment outcomes among participants with at least 1 year of follow-up, excluded the remainder. HBV DNA outcomes were categorized as suppressed (<20 IU/mL), low level viremia (20–2000 IU/mL), or high-level viremia (>2000 IU/mL). We defined HBV DNA non-suppression as ≥2 episodes of HBV DNA viremia (low- or high-level) at ≥2 years on ART. ALT levels were categorized as <1, 1–2 or >2 times the upper limit of normal (ULN), with normal defined as <25 U/L for women and <35 U/L for men [14]. Median liver stiffness measurements (LSM) were categorized as normal (<7 kPa; equivalent to Metavir stage F0-1), significant fibrosis (7–11 kPa; Metavir F2-3), or cirrhosis (>11 kPa; Metavir F4), using thresholds proposed by the World Health Organization [15]. HBeAg and HBsAg loss were also described during ART, with HBsAg seroclearance based on the confirmatory assay.

Statistical Analysis

We defined baseline as the date of ART initiation. We described baseline sociodemographic and clinical characteristics of the analysis cohort, stratified by sex, using proportions for categorical variables and median plus interquartile range for continuous ones. The end of follow-up was the date of death, transfer, withdrawal, or exiting. For LTFU patients, their end of follow-up was their last study visit. Patients in ongoing follow-up were censored at their most recent visit prior to database closure on 20 February 2023.

At each year on ART, we estimated the proportion of individuals with low- (20–2000) moderate- (2000–200 000 IU/mL),

and high-level (>200 000) HBV DNA non-suppression. Among patients with HBV DNA non-suppression at ≥2 years on ART, we used multivariable logistic regression to identify factors independently associated with non-suppression including age, sex, WHO stage, baseline HBV DNA, and suboptimal treatment adherence, defined as any episode of HIV RNA non-suppression (≥60 copies/mL) at ≥2 years on ART. Likelihood *P* values <.05 were considered statistically significant. We described ALT normalization, and described trends in ALT elevation over time with the Jonckheere-Terpstra test for trend. We explored the associations of alcohol use and HBV DNA non-suppression with ALT elevation >2 ULN at ≥2 years on ART using χ^2 tests.

The incidence of HBeAg loss and HBsAg loss were calculated. Using a Cox proportional hazard model, we identified factors independently associated with HBsAg loss including age, sex, WHO stage, baseline ALT, baseline fibrosis, CD4 count at baseline and change to the last measure, HBeAg, HBV DNA, and ALT, change in CD4 from baseline to last measure, medication adherence, and HBV DNA non-suppression. We evaluated trends in the proportion of patients with liver fibrosis or cirrhosis over time on ART with the Jonckheere-Terpstra test. We described regression of liver disease in those with baseline significant fibrosis and cirrhosis and progression in those with no-minimal or significant fibrosis at baseline. As LSM can be influenced by factors other than fibrosis, regression and progression events were only ascertained when confirmed by a subsequent measure. We described the incidence of HCC based on confirmation of ultrasound findings by 4-phase CT.

In a subgroup analysis, we further described the outcomes of patients with pre-therapy HBV DNA <2000 IU/mL and normal liver stiffness. If not for their HIV coinfection, this group would have been deemed to be at low risk for liver disease progression and not eligible for HBV antiviral therapy [14]. Among them, we described HBV DNA suppression, liver disease progression, and HBsAg loss during ART.

Role of the Funding Source

The study funders had no role in the study design, collection, analysis, and interpretation of the data, writing of the paper, or the decision to submit the paper for publication.

RESULTS

From October 2013 to August 2017, 345 adults with HBV/HIV coinfection were enrolled. As of database closure, 43 died, 41 transferred out, 25 were lost to follow-up, and 16 withdrew. The mortality rate was 6.75 per 100 person-years in the first year on ART and 1.77 per 100 person-years thereafter. For 19 deaths, the cause was unknown. Among the rest, the leading causes were tuberculosis (7), gastroenteritis (3), and pneumonia (3). No deaths from cirrhosis or HCC were ascertained. For the remaining analysis, patients with <1 year of follow-up were excluded. Compared to those excluded, patients included in the analysis cohort were not statistically different in terms of age, sex, WHO clinical stage, baseline median LSM, or baseline CD4 count (all $P > .05$).

In the analysis cohort (n = 289), the average duration of follow-up was 5.91 years (interquartile range [IQR], 3.19–7.06), median age was 33 years (IQR, 19–62), and 116 (40.1%) were women. At ART initiation, 91 (44.2%) were HBeAg-positive, 109 (43.4%) had any degree of ALT elevation, median CD4 count was 191 cells/mm^3 (IQR, 92–347), and 102 (36.6%) were classified as WHO stage 3 or 4. HBV DNA was ≥2000 IU/mL for 133 (56.6%) participants. In a subgroup of 85, median HBsAg was 16 469 IU/mL (IQR, 3753–49 326). By elastography, 46 (20.7%) had significant fibrosis and 17 (7.7%) had cirrhosis at baseline. When comparing men and women, HBV parameters (HBeAg, HBV DNA, and HBsAg levels) were not significantly different. Compared to women, men were older, had lower CD4 counts, were more likely to have unhealthy alcohol use, smoking, ALT elevation, hepatic fibrosis/cirrhosis, and were less likely to be overweight or have obesity (all $P < .05$; Table 1).

During ART, 87.1% achieved HIV RNA suppression by 1 year, and CD4 counts increased. The median CD4 increase from baseline was 92 cells/mm^3 (IQR, 16–169) at 1 year and 114 (IQR, 10–241) at the last measure. HBV DNA suppression also increased, reaching 74.6% at 2 years, 83.1% at 3 years, and 90.2% at 5 years (Figure 1). In the 204 with sufficient data, HBV DNA non-suppression was ascertained in 29 (14.2%), including 7 with high-level (ie, >2000 IU/mL) non-suppression. Good medication adherence, based on HIV RNA suppression (<60 copies/mL), was present for 54.6% of those with HBV DNA non-suppression, compared to 80.0% in those with HBV DNA suppression. In multivariable analysis, only WHO HIV clinical stage 3 or 4 (adjusted odds ratio [AOR], 3.58; 95% confidence interval [CI], 1.25–10.27; *P*-value = .02) was significantly associated with HBV DNA non-suppression, but trends were seen for male sex, higher baseline HBV DNA, and suboptimal ART adherence (Table 2). Of the 29, 7 participants with non-suppression had prior suppression, and 13 of 21 (61.9%) participants who were re-assessed at later time points achieved suppression.

Among patients with baseline ALT elevation, it normalized for 54 of 80 (67.5%) at 1 year and 42 of 65 (64.6%) at 2 years on ART. The prevalence of ALT reduced over time on ART ($P = .005$ for trend). However, at 2–5 years on ART, approximately 30% had ALT elevation (Figure 2). ALT elevation that was 2 times ULN was more common in patients with HBV DNA non-suppression (28.2% vs 10.9%; $P = .005$) but similar between those with and without unhealthy alcohol use.

Among 101 HBeAg-positive patients, 90 had at least 1 repeat HBeAg test on ART. At 2 years on ART, 22 (24.4%) had lost

Table 1. Pre-treatment Characteristics of 289 Adults Who Underwent Long-term Tenofovir-Based ART for HBV/HIV Coinfection in Lusaka, Zambia, by sex

Characteristic	Overall	Men (n = 171)	Women (n = 118)	P^a
Age, y	33 (27–38)	34 (20–39)	30 (26–36)	<.001
Age				
18–29	97 (33.6)	41 (23.7)	56 (48.3)	<.001
30–39	130 (45.0)	90 (52.0)	40 (34.5)	
≥40	62 (21.4)	42 (24.3)	20 (17.2)	
WHO stage 3 or 4	102 (36.6)	71 (42.0)	31 (28.2)	.02
Active tuberculosis	22 (9.2)	16 (11.2)	6 (6.2)	.19
Body mass index, kg/m^2				
Underweight	87 (31.2)	59 (35.8)	28 (24.6)	<.001
Normal	153 (54.8)	97 (58.8)	56 (49.1)	
Overweight	28 (10.0)	4 (2.4)	24 (21.0)	
Obese	11(3.9)	5 (3.0)	6 (5.3)	
Alcohol use status				
Abstinence/moderate use	140 (50.5)	69 (41.2)	71 (65.1)	<.001
Unhealthy use	137 (49.5)	99 (58.9)	38 (34.9)	
Current smoker	55 (19.8)	49 (29.2)	6 (5.4)	<.001
ALT level, U/L	27 (18–43)	33 (21–44)	20 (14–33)	<.001
ALT level				
<ULN	142 (56.6)	80 (52.3)	62 (63.3)	.002
1–2 ULN	86 (34.3)	64 (41.8)	22 (22.4)	
>2 ULN	23 (9.2)	9 (5.9)	14 (14.3)	
HBV DNA level, IU/mL				
≤20	56 (23.8)	29 (20.4)	27 (29.0)	.27
21–1999	46 (19.6)	30 (21.1)	18 (17.2)	
2000–200 000	47 (20.0)	26 (18.3)	21 (22.6)	
>200 000	86 (36.6)	57 (40.1)	29 (31.2)	
HBeAg-positive	101 (46.8)	67 (50.8)	34 (40.5)	.14
CD4 count, cells/mm^3	191 (92–347)	167 (85–283)	247 (134–376)	.002
CD4 count, cells/mm^3				
<100	60 (24.2)	29 (19.5)	31 (31.3)	.03
100–350	121 (48.8)	72 (48.3)	49 (49.5)	
>350	67 (27.0)	48 (32.2)	19 (19.2)	
Liver stiffness, kPa				
<7.0 (no-min. fibrosis)	159 (71.6)	89 (63.1)	70 (86.4)	<.001
7.0–11.0 (sig. fibrosis)	46 (20.7)	36 (25.5)	10 (12.4)	
>11.0 (cirrhosis)	17 (7.7)	16 (11.3)	1 (1.2)	

All values are median (interquartile range) or number (%).

Abbreviations: ALT, alanine aminotransferase; HBeAg, hepatitis B e antigen; HBV, hepatitis B virus; HIV, human immunodeficiency virus; kPa, kilopascals; WHO, World Health Organization.

[a]Comparisons were made by sex using Wilcoxon rank-sum test for continuous values and χ^2 (or Fisher exact test if <5 patients) for categorical ones.

their HBeAg, and this increased to 30 (33.3%) by 5 years. During ART, HBsAg was re-assessed at least once in 267 patients and 46 experienced HBsAg seroclearance, based on having a negative test on a sensitive HBsAg assay. There were 58 additional patients who were HBsAg-negative on a rapid test and were either HBsAg-positive on the more sensitive assay (27), reverted back to rapid HBsAg-positive on a subsequent visit before a serological test could be done (25), or did not have the more sensitive assay (6). HBsAg seroclearance was confirmed in 25 (9.4%) participants by 2 years of ART and 44 (16.5%) by 5 years. Among the 46 with confirmed HBsAg seroclearance, 12 of 42 (28.6%) individuals tested also became anti-HBs-positive. In multivariable analysis, no factors assessed were significantly associated with HBsAg seroclearance (see Supplementary Table 1); however, there was a trend toward lower seroclearance with HBV DNA non-suppression (adjusted hazard ratio, 0.19; 95% CI, .26–1.36; $P = .10$). Among the 72 with sufficient data, HBsAg seroclearance was substantially higher with baseline HBsAg levels <1000 IU/mL (33.3% vs 9.5%; $P = .04$). In 8 of those with HBsAg seroclearance, baseline HBsAg levels ranged from 40 to 100 596 IU/mL. Among 42 patients with confirmed HBsAg loss who were re-assessed at a later visit, only 1 reverted back to HBsAg-positivity.

During ART, the prevalence of significant fibrosis and cirrhosis declined ($P < .001$ for trend; Figure 3). Among 46 with significant fibrosis at baseline, 37 (80.4%) declined to no-minimal disease, based on TE. No patient with significant fibrosis at baseline progressed to cirrhosis during follow-up. For the

17 with cirrhosis at baseline, 15 (88.2%) regressed to no-minimal or significant fibrosis during follow-up. Finally, among 163 with no-minimal disease at baseline, only 4 (2.4%) progressed to significant fibrosis and none progressed to cirrhosis. Over follow-up, participants had a 1178 HCC screening ultrasounds (median, 4.1 per participant), equating to <1 per year. Liver lesions were documented in 38 (3.2%) of ultrasounds; however, no cases of HCC were ascertained through further investigations.

Within the analysis cohort, 64 patients started ART in the setting of low HBV DNA and no/minimal fibrosis. Compared to the overall sample, they had similar demographics and slightly higher CD4 at baseline (median, 248 cells/mm^3). Over a median of 6.20 years on ART, only 1 patient (1.5%) developed HBV DNA non-suppression and none progressed to significant fibrosis/cirrhosis. In the 55 with sufficient data, HBsAg seroclearance occurred in 4 (7.3%) at 2 years and 10 (18.2%) at 5 years.

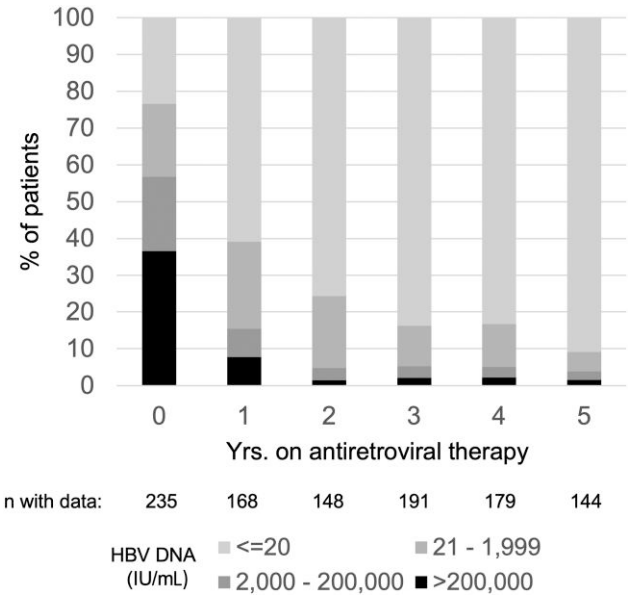

Figure 1. HBV DNA levels before and during tenofovir-based ART-treated HBV/HIV coinfection. Abbreviations: ART, antiretroviral therapy; HBV, hepatitis B virus; HIV, human immunodeficiency virus.

DISCUSSION

The majority of cases of HBV/HIV coinfection occur in sSA, a region where data on HBV outcomes are severely lacking. In a unique long-term prospective cohort the outcomes of HBV/HIV coinfection treated with tenofovir-containing ART were described. ART initiation led to high levels of HBV DNA suppression, reduced transaminase elevation, and reduction in liver stiffness in most patients. No cases of HCC on ART were ascertained over a median of 6 years of screening. The rate of HBsAg seroclearance was also higher than expected, including in patients with low pre-therapy HBV viremia, suggesting this is an immune-mediated phenomenon.

Rates of HBV DNA suppression were high; however, we documented a non-trivial frequency of HBV DNA non-suppression, which was driven by HIV-related and non-HIV-related factors. Using a rigorous definition, we observed non-suppression in 12.8% of patients, which is similar (13.5%) to a coinfection French cohort and a report from the Swiss HIV cohort study (27%) [16, 17]. In the French cohort, as well as one in North

Table 2. Factors Associated With HBV DNA Non-Suppression in ART-Treated HBV/HIV Coinfection in Zambia

Factor	Crude OR	*P*	Adjusted OR	*P*
Age, per year	1.00 (0.95–1.05)	.94		
Sex				
Female	Reference		Reference	
Male	2.71 (1.10–6.67)	.03	2.92 (0.85–10.01)	.09
Baseline WHO HIV stage				
1 or 2	Reference		Reference	
3 or 4	2.61 (1.14–5.95)	.02	3.58 (1.25–10.27)	.02
Baseline liver fibrosis stage				
None/minimal	Reference			
Significant or advanced fibrosis	1.77 (0.61–5.10)	.29		
Cirrhosis	2.03 (0.50–8.31)	.32		
Baseline HBV DNA, per $\log_{10}$ IU/mL	1.24 (1.06–1.45)	<.01	1.19 (0.99–1.43)	.07
Suboptimal adherence during ART				
No	Reference		Reference	
Yes	3.33 (1.32–8.44)	.01	2.72 (0.95–7.79)	.06

HBV DNA non-suppression was defined as 2 episodes of DNA level >20 IU/mL at 2 or more years of ART. Suboptimal adherence was based on HIV RNA >60 copies/mL at a visit at 2 or more years of ART. Liver fibrosis was based on transient elastography. Factors that were associated with the outcome at $P < .2$ in crude analysis were included in the adjusted model.

Abbreviations: ART, antiretroviral therapy; HBV, hepatitis B virus; HIV, human immunodeficiency virus; OR, odds ratio; WHO, World Health Organization.

America, HIV-related factors including lower nadir or time-updated CD4 count, predicted persistent DNA viremia (France) and delayed DNA suppression (North America), which supports our finding of advanced HIV (ie, WHO stage 3 or 4) as a risk factor for non-suppression [16, 18]. Suboptimal medication adherence was also associated with DNA non-suppression in our participants and those in the Swiss study [17]. Further supporting adherence as a mechanism for DNA non-suppression, the majority of our patients with non-suppression, and even more in the Swiss study, eventually suppressed with additional follow-up [17]. Building on these studies, we also observed that HBV DNA non-suppression was associated with ALT elevation and a trend toward reduced HBsAg loss. DNA non-suppression during antiviral therapy has been linked to liver disease progression in the French coinfection cohort and in data from people with HBV monoinfection [16, 19].

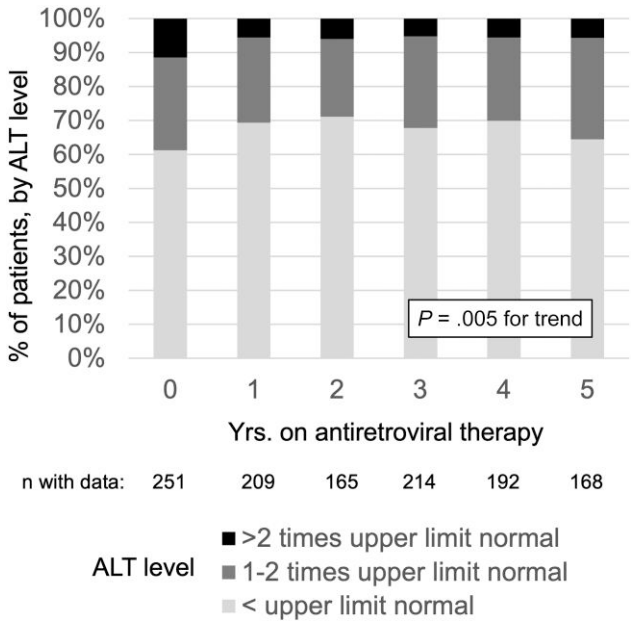

Figure 2. ALT elevation before and during antiretroviral therapy for HBV/HIV infection. Abbreviations: ALT, alanine aminotransferase; HBV, hepatitis B virus; HIV, human immunodeficiency virus.

Another important finding was the high rate of HBsAg seroclearance, higher than that typically observed in tenofovir-treated HBV monoinfection (0.5%–1% per year) [20]. Higher rates of HBsAg seroclearance were reported in smaller coinfection cohorts in Asia and sSA, as well as in HBV monoinfection trials where nucleosides were discontinued [21, 22]. Restoration and/or enhancement of HBV-specific immunity has been hypothesized as the mechanism for HBsAg clearance in people with HIV. This is supported by our finding of heightened HBsAg clearance in patients with low HBV DNA. Although the degree of global immunosuppression, based on CD4 count, is associated with HBV replication in people with HBV/HIV coinfection [23], we did not observe an association between baseline or change in CD4 on HBsAg seroclearance. Perhaps

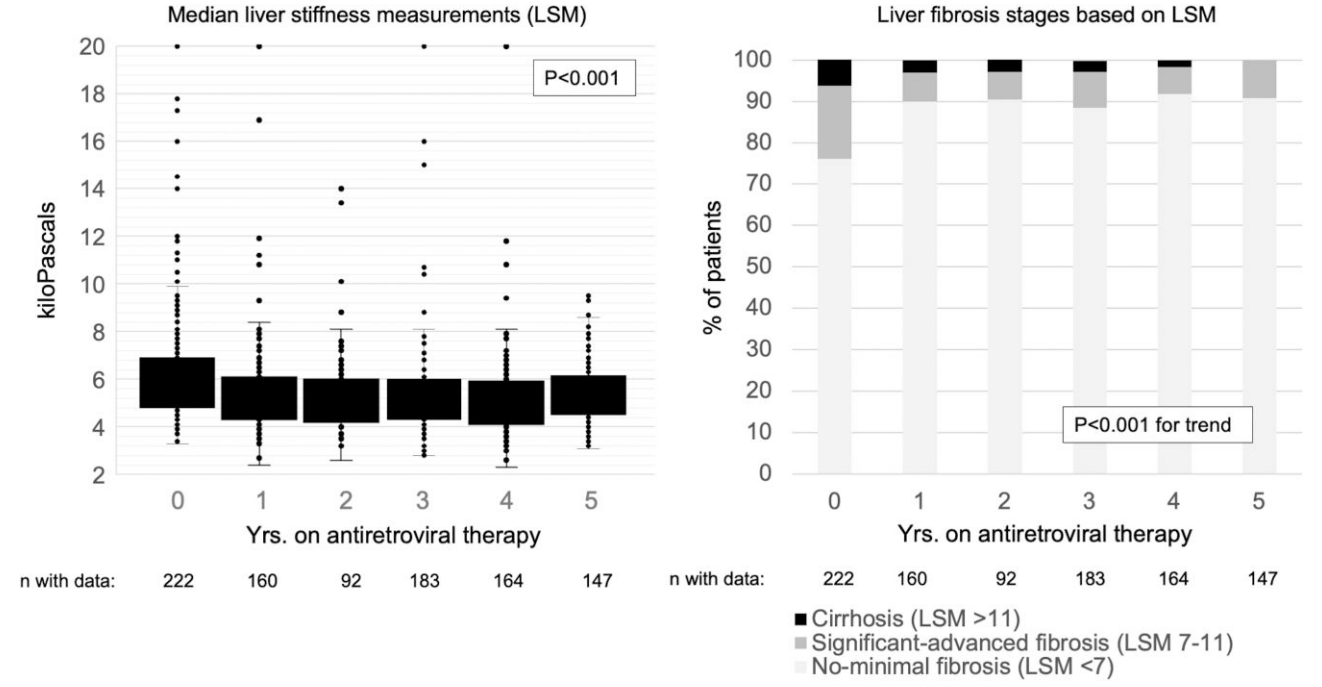

Figure 3. Elastography-based liver fibrosis before and during tenofovir-containing antiretroviral therapy for HBV/HIV infection in Zambia. Abbreviations: HBV, hepatitis B virus; HIV, human immunodeficiency virus.

intrahepatic HBV-related immunity is poorly reflected in peripheral markers like CD4 count. HBsAg seroclearance is an important endpoint of HBV monoinfection treatment as it reduces the risk of HCC [24]; however, the clinical significance of HBsAg seroclearance in people with HIV is assumed but not yet demonstrated. Whether HBsAg seroclearance would be sustained off tenofovir may become increasingly important with increased use of non-tenofovir-containing HIV treatments, including injectable long-acting agents [25].

Our data also show long-term liver outcomes of universal ART for HBV/HIV coinfection. Overall mortality, 6% in the first year, and 2% per year thereafter, was similar to or slightly higher than in the Temprano ANRS 12136 trial in Ivory Coast [5]. Long-term data on elastography in HBV/HIV coinfection built on studies of short-term changes, which likely reflect HIV-associated inflammation [6, 26]. Over an average of 6 years of follow-up, none of the deaths ascertained were liver-related and nearly all patients with significant fibrosis or cirrhosis, based on elastography, experienced regression of disease. In Temprano, only 2 of 12 deaths in people with coinfection were liver-related [5]. In our study, progressive liver disease during ART was exceedingly rare. Although liver biopsies were not performed, sustained decline in liver stiffness is a proxy of reduced fibrosis in people with chronic HBV infection [27]. The absence of HCC was reassuring, considering the annual risk, 0.1%–1.4% without and 0.9%–5.4% with cirrhosis, during NA therapy for HBV monoinfection reported in a meta-analysis that did not include African patients [28]. Although proxies of liver fibrosis improved overall, we observed a moderate prevalence of ALT elevation during long-term ART, which could be explained by HBV DNA non-suppression and unhealthy alcohol use. This underscores the need to screen for non-HBV-related causes of liver disease in people with chronic HBV.

Our data have implications for elimination of hepatitis B. First, they support current ART regimens used to treat millions of individuals worldwide with HBV/HIV coinfection. Our data provide further rationale for HBV DNA and HBsAg monitoring, and interventions, whether behavioral or pharmacologic, to address DNA non-suppression. Within the HBV cure agenda, high rates of HBsAg seroclearance make people with HIV/HBV coinfection important for future research [22]. Understanding immunological mechanisms for HBsAg loss in people with HIV could potentially inform immunotherapies in general and guide the use of novel antiviral and immunologic therapies in people with coinfection. Finally, we observed that patients with low HBV DNA and no/minimal fibrosis pretherapy achieved both biochemical and serological benefits as result of ART. This not only further validates the need for universal HBV therapy in HIV, but it may support the need to explore the benefits of earlier treatment initiation in HBV monoinfection. Expanding current guidelines for antiviral therapy in HBV monoinfection is a major point of discussion in East and Southern Africa, where providing tenofovir-based therapy is less costly and less complex than providing the recommended package of lab and radiology tests to determine treatment eligibility.

The major strength of this analysis was the unique population with HIV/HBV coinfection in sSA, and availability of long-term follow-up with yearly and rigorous measures of liver fibrosis, virological markers, and HCC screening. Because the cohort was nested within real-world HIV clinics in Zambia, the data also have broad external validity within East and Southern Africa where HBV/HIV coinfection is common. Finally, losses to follow-up were very low (~7%), considering the length of follow-up. Although inclusion of elastography was a significant strength, we acknowledge that the measure is not equivalent to liver biopsy and can be impacted by many factors other than HBV-related fibrosis. Thus, we may have over- or under-estimated the degree of change in liver fibrosis during ART. We also acknowledge that HIV viral load measures were less available than HBV DNA, limiting their use in multivariable analyses. Also, time to HBsAg loss in this analysis was inflated due to our two-step algorithm, which often resulted in 1–2 year delays between an initial negative rapid HBsAg test and a confirmatory assay. Many recorded deaths had an unknown cause, which is common in sSA; hence, we may have under-ascertained liver-related mortality.

In summary, in a sentinel HBV/HIV coinfection cohort in Zambia, long-term retention and adherence to tenofovir-based ART led to significant reduction in markers of liver disease, no cases of HCC, and seroclearance of HBsAg in 15.4% at 5 years.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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References

1. World Health Organization. Global hepatitis report. Geneva, Switzerland: WHO, **2017**.
2. Yang JD, Mohamed EA, Aziz AOA, et al. Characteristics, management, and outcomes of patients with hepatocellular carcinoma in Africa: a multicountry observational study from the Africa Liver Cancer Consortium. Lancet Gastroenterol Hepatol **2017**; 2:103–11.

3. Thio CL, Seaberg EC, Skolasky R, et al. HIV-1, hepatitis B virus, and risk of liver-related mortality in the Multicenter Cohort Study (MACS). Lancet **2002**; 360: 1921–6.
4. Nikolopoulos GK, Paraskevis D, Hatzitheodorou E, et al. Impact of hepatitis B virus infection on progression of AIDS and mortality in HIV-infected individuals: a cohort study and meta-analysis. Clin Infect Dis **2009**; 48:1763–71.
5. Kouamé G-M, Boyd A, Moh R, et al. Higher mortality despite early antiretroviral therapy in human immunodeficiency virus and hepatitis B virus (HBV)—coinfected patients with high HBV replication. Clin Infect Dis **2018**; 66:112–20.
6. Stockdale AJ, Phillips RO, Beloukas A, et al. Liver fibrosis by transient elastography and virologic outcomes after introduction of tenofovir in lamivudine-experienced adults with HIV and hepatitis B virus (HBV) co-infection in Ghana. Clin Infect Dis **2015**; 61:883–91.
7. Anderson M, Gaseitsiwe S, Moyo S, et al. Slow CD4+ T-cell recovery in human immunodeficiency virus/hepatitis B virus-coinfected patients initiating truvada-based combination antiretroviral therapy in Botswana. Open Forum Infect Dis **2016**; 3:ofw140.
8. Block TM, Alter H, Brown N, et al. Research priorities for the discovery of a cure for chronic hepatitis B: report of a workshop. Antiviral Res **2018**; 150:93–100.
9. Tordrup D, Hutin Y, Stenberg K, et al. Additional resource needs for viral hepatitis elimination through universal health coverage: projections in 67 low-income and middle-income countries, 2016–30. Lancet Global Health **2019**; 7:e1180–e8.
10. Lui G, Yip T, Yuen B, et al. HIV infection and the risk of hepatocellular carcinoma in patients with hepatitis B virus (HBV) co-infection: a propensity score-matched cohort study. ID Week; **2019**.
11. Vinikoor MJ, Mulenga L, Siyunda A, et al. Association between hepatitis B co-infection and elevated liver stiffness among HIV-infected adults in Lusaka, Zambia. Trop Med Int Health **2016**; 21:1435–41.
12. Lemoine M, Shimakawa Y, Njie R, et al. Food intake increases liver stiffness measurements and hampers reliable values in patients with chronic hepatitis B and healthy controls: the PROLIFICA experience in the Gambia. Aliment Pharmacol Ther **2014**; 39:188–96.
13. Riebensahm C, Chitundu H, Muula G, et al. Screening for hepatocellular carcinoma among adults with HIV/hepatitis B coinfection in Zambia: a pilot study. Int J Infect Dis **2022**; 116:391–6.
14. Terrault NA, Lok AS, McMahon BJ, et al. Update on prevention, diagnosis, and treatment of chronic hepatitis B: AASLD 2018 hepatitis B guidance. Hepatology **2018**; 67:1560–99.
15. World Health Organization. Guidelines for the prevention, care, and treatment of persons with chronic hepatitis B infection. Geneva, Switzerland: World Health Organization, **2015**.
16. Boyd A, Gozlan J, Maylin S, et al. Persistent viremia in human immunodeficiency virus/hepatitis B coinfected patients undergoing long-term tenofovir: virological and clinical implications. Hepatology **2014**; 60:497–507.
17. Hofmann E, Surial B, Boillat-Blanco N, et al. HBV replication during tenofovir therapy is frequent in HIV/HBV-coinfection. Clin Infect Dis **2023**; 76:730–3.
18. Kim HN, Rodriguez CV, Van Rompaey S, et al. Factors associated with delayed hepatitis B viral suppression on tenofovir among HBV-HIV coinfected patients in the CNICS cohort. J Acquir Immune Defic Syndr **2014**; 66:96.
19. Sun Y, Wu X, Zhou J, et al. Persistent low level of hepatitis B virus promotes fibrosis progression during therapy. Clin Gastroenterol Hepatol **2020**; 18:2582–91.e6.
20. Yeo YH, Ho HJ, Yang H-I, et al. Factors associated with rates of HBsAg seroclearance in adults with chronic HBV infection: a systematic review and meta-analysis. Gastroenterology **2019**; 156:635–646.e9.
21. Berg T, Simon K-G, Mauss S, et al. Long-term response after stopping tenofovir disoproxil fumarate in non-cirrhotic HBeAg-negative patients—FINITE study. J Hepatol **2017**; 67:918–24.
22. Audsley J, Avihingsanon A, Littlejohn M, et al. Long-term TDF-inclusive ART and progressive rates of HBsAg loss in HIV-HBV coinfection—lessons for functional HBV cure? J Acquir Immune Defic Syndr **2020**; 84:527–33.
23. Muula GK, Bosomprah S, Sinkala E, et al. HBV Viral replication markers and hepatic fibrosis in untreated chronic HBV infection with and without HIV coinfection in Zambia. AIDS **2023**; 37:2015–20.
24. Yip TC-F, Wong GL-H, Chan HL-Y, et al. HBsag seroclearance further reduces hepatocellular carcinoma risk after complete viral suppression with nucleos (t) ide analogues. J Hepatol **2019**; 70:361–70.
25. Thoueille P, Choong E, Cavassini M, Buclin T, Decosterd LA. Long-acting antiretrovirals: a new era for the management and prevention of HIV infection. J Antimicrob Chemother **2022**; 77:290–302.
26. Vinikoor MJ, Sinkala E, Chilengi R, et al. Impact of antiretroviral therapy on liver fibrosis among human immunodeficiency virus-infected adults with and without HBV coinfection in Zambia. Clin Infect Dis **2017**; 64:1343–9.
27. Kim BK, Fung J, Yuen M-F, Kim SU. Clinical application of liver stiffness measurement using transient elastography in chronic liver disease from longitudinal perspectives. World J Gastroenterol **2013**; 19:1890.
28. Papatheodoridis GV, Chan HL-Y, Hansen BE, Janssen HL, Lampertico P. Risk of hepatocellular carcinoma in chronic hepatitis B: assessment and modification with current antiviral therapy. J Hepatol **2015**; 62:956–67.