High rates of hepatitis B virus (HBV) functional cure among HIV/HBV coinfected Chinese adults on antiretroviral therapy

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Reports suggest that approximately 37.7 million people are infected with human immunodeficiency virus (HIV) worldwide,[1] and 10% to 28% of people living with HIV (PLWH) are coinfected with hepatitis B virus (HBV).[2] The routes of transmission shared by both HIV and HBV may explain the relatively high proportions of HIV/HBV coinfection,[3] which represent a significant challenge to global public health. In China, hepatitis B surface antigen (HBsAg) prevalence is estimated at 13.7% in PLWH.[4]

Compared to HBV mono-infected individuals, those coinfected with HIV may experience a faster progression of liver disease and an increased risk of developing advanced liver diseases such as cirrhosis or hepatocellular carcinoma (HCC).[5] Despite the widespread utilization of potent antiretroviral regimens with antiviral activities against both HBV and HIV, liver-related mortality remains the second most common cause of death among coinfected individuals.[6] In addition, despite the early introduction of antiretroviral therapy (ART), HIV/HBV coinfected individuals with high HBV replication profiles continue to have a higher mortality risk.[7] HBsAg clearance/loss with or without development of hepatitis B surface antibody (anti-HBs) is regarded as a "functional cure" for HBV mono-infection.[8] Functional cure decreases the risk of liver disease progression and development of HCC.[8,9] In short, this is the ultimate treatment target for HIV/HBV coinfected individuals.

Although HIV inhibits the host immune response which becomes vulnerable to chronic HBV infection, functional cure in HIV/HBV coinfected individuals treated with tenofovir disoproxil fumarate (TDF)-based ART and immunological recovery seems to be more achievable than in those with HBV mono-infection.[7] Recent studies indicate that cumulative HBsAg loss rates varied between 10% and 18% in developed countries after long-term HBV-active ART.[10-13] Thus far, however, HBsAg loss and its determinants are rarely studied in China, particularly in individuals coinfected with HIV/HBV receiving long-term ART. In this retrospective study, we investigated HBsAg loss and the factors associated with HBV functional cure in a Chinese HIV/HBV cohort with a median follow-up of at least 5 years.

This study was conducted in compliance with the *Declaration of Helsinki*. Ethical approval was obtained from the Human Medical Ethics Committee of Tianjin Second People's Hospital (No. 2022-06). Written informed consent was provided by each recruited participant.

This non-interventional, retrospective study examined a cohort of HIV/HBV coinfected patients treated at Tianjin Second People's Hospital, between January 2010 and March 2021. In this cohort study, patients who met the following inclusion criteria were enrolled: (1) ≥18 years old, (2) HIV-positive, (3) chronic HBV-positive (HBsAg positive for at least 6 months), and (4) ≥ 12 months of stable anti-HBV-ART containing TDF or tenofovir alafenamide (TAF) in combination with lamivudine (3TC) or emtricitabine (2',3'-dideoxy-5-fluoro-3'-thiacytidine [FTC]). Exclusion criteria were hepatitis C and D infection, death, inadequate data, and loss to follow-up.

At study enrollment and each subsequent visit, clinical and laboratory data were collected. Alanine aminotransferase (ALT), hemoglobin, platelets, HBsAg, anti-HBs, hepatitis B e antigen (HBeAg), hepatitis B e antibody (anti-HBe), HBV deoxyribonucleic acid (DNA), HIV ribonucleic acid

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(RNA), and cluster of differentiation 4 (CD4) cells count were measured every 3 to 12 months. Demographic information was taken from medical records.

Participants (with at least one HBV serology test) who have been monitored for at least one year were included in our study. Elevated ALT was defined as >40 U/L. Significant fibrosis was defined as fibrosis-4 score >3.25. $CD4^+$ T-cell gain was defined as CD4 count increase 1 year after treatment initiation.[12] HBV functional cure was defined as serum HBsAg seroclearance with or without anti-HBs positivity, and undetectable serum HBV DNA.[14]

The chi-squared test, Fisher's exact test, and Mann-Whitney *U* test were used for statistical analysis. Logistic regression models were used to identify the factors associated with HBV functional cure. A $P < 0.05$ was considered statistically significant. All analyses were performed using SPSS version 26.0 for Windows (SPSS, Chicago, IL, USA).

Participants' clinical and demographic features were categorized depending on their HBsAg seroclearance status. The details were presented in [Supplementary Table 1, http://links.lww.com/CM9/B376]. The 240 patients had a median age of 41 years (Q_1–Q_3: 35–52 years), and 229 (95.4%) were males. The predominant transmission route of infection was sexual intercourse (homosexual [149, 62.1%] and heterosexual [61, 25.4%]). Moreover, vertical HBV transmission was self-reported by 59 (24.6%) patients. The median CD4 count and, HIV RNA was 245 cells/L (Q_1–Q_3: 109–361 cells/L) and 38,636 copies/mL (Q_1–Q_3: 12,975–91,333 copies/mL), respectively. Ninety-nine (41.3%) patients were HBeAg positive, and 157 (65.4%) were HBV DNA positive. The baseline ALT was elevated in 58 (24.2%) patients. Significant fibrosis was seen in 22 (9.2%) of the individuals.

Overall, 240 HIV/HBV coinfected individuals were followed up for a median of 5.4 (Q_1–Q_3: 2.5–7.5) years. Of note, 11.3% (27/240) achieved our definition of HBV functional cure (HBsAg loss). Subsequent investigations revealed that 19 (19/27, 70.4%) were positive for anti-HBs. When comparing patients with HBsAg loss to those with HBsAg persistence, we noted a statistically significant difference in age ($P = 0.006$), HIV risk factor ($P = 0.026$), vertical transmission of HBV ($P = 0.015$), duration of ART ($P = 0.017$), and CD4 gain ($P = 0.009$) [Supplementary Table 1, http://links.lww.com/CM9/B376].

Multivariable regression analysis showed that vertical transmission of HBV (adjusted odds ratio [aOR], 23.37; 95% confidence interval [CI]: 1.57–347.24; $P = 0.022$), duration on ART (aOR, 1.22; 95% CI: 1.04–1.44; $P = 0.016$), and $CD4^+$ T-cell gain (aOR, 1.01; 95%CI: 1.00–1.01; $P = 0.005$) were associated with increased odds of HBsAg seroclearance. HBeAg positive at baseline was associated with decreased odds of HBsAg seroclearance (aOR, 0.26; 95%CI: 0.09–0.75; $P = 0.012$) [Table 1].

This Chinese cohort of HIV/HBV coinfected patients on TDF-/TAF-containing ART shows 11.3% of HBsAg seroclearance during a median follow-up of 5.4 years. The longer duration of ART, higher increases in CD4 count, and HBeAg positive at baseline were more likely to achieve HBsAg seroclearance.

The higher incidence of HBsAg loss might possibly be attributed to the relatively long-time follow-up. In comparison, the Zambian cohort was followed up for just 2 years (10% of HBsAg loss), while the American and

Table 1: Factors associated with HBsAg seroclearance.

	Univariable		Multivariable	
Variables	**OR (95% CI)**	***P* values**	**aOR (95% CI)**	***P* values**
Male	0.78 (0.09–6.35)	0.817	0.99 (0.09–11.15)	0.991
Age	1.05 (1.02–1.09)	0.005	1.04 (0.99–1.09)	0.065
HIV risk factor				
Sexual transmission	Ref	Ref	Ref	Ref
No sexual transmission	0.24 (0.03–1.87)	0.174	0.16 (0.02–1.45)	0.102
Vertical transmission of HBV	9.73 (1.29–73.34)	0.027	23.37 (1.57–347.24)	0.022
Baseline $CD4^+$ T-cell				
<200 cells/μL	Ref	Ref	Ref	Ref
200–499 cells/μL	0.68 (0.29–1.59)	0.375	0.64 (0.24–1.72)	0.377
≥500 cells/μL	0.99 (0.26–3.81)	0.991	1.28 (0.26–6.26)	0.759
Elevated baseline ALT*	1.13 (0.43–2.95)	0.802	1.42 (0.45–4.47)	0.549
Duration of ART	1.20 (1.04–1.38)	0.010	1.22 (1.04–1.44)	0.016
HBV DNA positive at baseline	1.35 (0.59–3.05)	0.476	2.86 (0.96–8.49)	0.058
HBeAg positive at baseline	0.52 (0.23–1.17)	0.113	0.26 (0.09–0.75)	0.012
Significant liver fibrosis†	0.38 (0.13–1.14)	0.083	0.53 (0.13–2.22)	0.388
$CD4^+$ T-cell gain‡	1.00 (1.00–1.01)	0.040	1.01 (1.00–1.01)	0.005

* Defined as >50 U/L for men and >40 U/L for women. † Based on FIB-4 score >3.25. ‡ Defined as $CD4^+$ T-cell count increase at 1 year after treatment. ALT: Alanine aminotransferase; aOR: Adjusted odds ratio; ART: Antiretroviral therapy; CI: Confidence interval; DNA: Deoxyribonucleic acid; FIB-4: Fibrosis 4; HBeAg: Hepatitis B e antigen; HBsAg: Hepatitis B surface antigen; HBV: Hepatitis B virus; HIV: Human immunodeficiency virus; OR: Odds ratio; Ref: Reference.

German cohorts were observed for 7.3 (10% of HBsAg loss) and 11 years (18% of HBsAg loss),[10-12] respectively. The median time to HBsAg loss in our study was 6.7 years, indicating that longer durations of HBV-active ART may lead to higher rates of HBsAg loss in HIV/HBV coinfection.

Notably, the increase in CD4 count one year after ART initiation significantly influenced HBsAg seroclearance rates. Upon ART initiation, the suppressed immune system starts to recover, hence boosting the likelihood of HBsAg clearance in coinfected individuals. It seems that immunological restoration has a significant influence on HBsAg removal. Our results show that the baseline CD4 count is not associated with HBsAg-seroclearance, which contradicts previous reports. Indeed, the negative effects of low baseline CD4 count on HBsAg seroclearance have been established in previous studies.[10,12] Thus, further investigations with a larger sample size are needed to confirm our observations.

Vertical transmission of HBV, which represents 24.6% of our coinfected cohort, is linked to a reduced likelihood of clearing HBsAg. In comparison to Western countries, HBV in China is transmitted early in life either perinatally or horizontally in infancy.[15] Thus, individuals may have been infected with HBV before becoming infected with HIV. Consequently, they seldom achieve functional cure despite being treated with modern ART.[16] As such, our findings reflect that the timing of HBV acquisition especially the longer duration of HBV infection does not favor functional cure in coinfected adults.

This study has several limitations. Firstly, due to our study design, some data are unavoidably missing. Secondarily, since study visits spanned from three months to a year, the median time to HBsAg loss or seroconversion may have been overstated. Moreover, the present findings need to be further validated in a larger-scale study.

In conclusion, HIV/HBV coinfected individuals receiving long-term TDF-/TAF-based ART in Tianjin (China) displayed a high percentage of HBV functional cure. Further studies are required to understand how immune recovery in HIV infection impacts HBV control, which could be relevant to new therapies for HBV functional cure.

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Conflicts of interest

None.

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