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*Clinical Infectious Diseases*

MAJOR ARTICLE

# Kinetics and Predictors of Hepatitis B Surface Antigen (HBsAg) Loss After Commencing Hepatitis B Virus (HBV)–Active Antiretroviral Therapy in the Setting of HIV and Chronic HBV Coinfection

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***Background.*** An effective therapeutic strategy for hepatis B virus (HBV) cure remains an urgent unmet need. We aimed to define the incidence, kinetics, and predictors of hepatitis B surface antigen (HBsAg) loss in people with HIV and HBV (PWH-HBV) following HBV-active antiretroviral therapy (ART) in PWH-HBV in Asia.

***Methods.*** 97 PWH-HBV commencing HBV-active ART were recruited prospectively in Thailand (n = 94) and Malaysia (n = 3), then followed for 24 months. Time to HBV serology change was calculated. Univariate associations between baseline characteristics and HBsAg loss were examined using the Mann-Whitney or chi-square tests. Multivariable analysis was undertaken using Cox regression.

***Results.*** Twenty-one individuals (22%) lost HBsAg during follow-up (11.7 per 100 person-years), 14 of whom gained anti-HBs. Twenty-two of 61 (36.1%) individuals who were hepatitis B "e" antigen (HBeAg) positive at baseline lost HBeAg over the study, 15 of whom gained anti-HBe. Most individuals lost HBsAg and HBeAg by the month 12 study visit (81% and 63.6%, respectively), with median times of 5.8 and 12.0 months to HBsAg and HBeAg loss, respectively. Univariate analysis showed baseline characteristics associated with HBsAg loss were higher alanine aminotransferase (ALT; $P = .005$), tenofovir alafenamide (TAF)–containing ART regimen ($P = .025$), younger age ($P = .040$), lower liver stiffness ($P = .010$), and quantitative HBsAg < $\log_{10}$ 2.0 IU/mL ($P = .001$). All 5 factors remained significant in a Cox regression analysis that adjusted for baseline CD4 count.

***Conclusions.*** High HBsAg loss rates occur in PWH and HBV early after commencing ART. Our study suggests that TAF-containing ART regimens may be preferable as first-line therapy in HIV-HBV coinfection.

**Keywords.** HIV-HBV coinfection; HBsAg loss; antiretroviral therapy; treatment initiation; tenofovir alafenamide.

In 2019 it was estimated that there were 254 million people with chronic hepatitis B (CHB) [1]. Effective antiviral treatment of hepatitis B virus (HBV) with nucleos(t)ide reverse transcriptase inhibitors (NRTIs) is available, but NRTI treatment is lifelong in most individuals, expensive, and associated with some toxicity. An effective therapeutic strategy to achieve a sustained functional cure for HBV (defined as loss of HB surface antigen [HBsAg] with or without acquisition of antibodies to HBsAg [anti-HBs]) remains an urgent unmet need.

Over 37 million people worldwide have human immunodeficiency virus (HIV) and approximately 7% (~2.7 million) are also coinfected with HBV [2]. Chronic hepatitis B prevalence in people with HIV (PWH) varies geographically, with CHB median prevalence estimates in PWH in Asia of 5%–8% [3].

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It has been shown previously that, following the initiation of HBV-active antiretroviral therapy (ART) in HIV-HBV coinfection, HBsAg loss rates approach 19% in the first 2 years of treatment [4, 5], significantly higher than seen following the initiation of NRTI in CHB (~1% per year) [6]. These earlier cohorts included people with low CD4 counts and more advanced HIV. While there are virological and immunological differences between PWH and HBV (PWH-HBV) and those with CHB alone, this initial high rate of HBsAg loss in PWH-HBV may have lessons for HBV functional cure. We established a prospective cohort of PWH-HBV starting HBV-active ART to confirm high HBsAg loss rates and describe the kinetics and predictors of HBsAg loss. We also examined levels of HBsAg complexed with anti-HBs (HBsAg-IC). Co-existing HBsAg and anti-HBs in the blood of individuals with CHB infection has been well documented [7, 8] but poorly characterized.

## METHODS

### Study Participants

HIV- and HBV-treatment–naive PWH-HBV (n = 97) initiating HBV-active ART were recruited prospectively in Thailand (HIV Netherlands Australia Thailand Research Collaboration [HIV-NAT]; Thai Red Cross AIDS Research Centre, Bangkok; n = 94) and Malaysia (Universiti Malaya Medical Centre [UMMC], Kuala Lumpur; n = 3) between August 2018 and March 2020. Written informed consent was obtained from all participants prior to enrollment and before any study-related procedures. The study was approved in Thailand (Institutional Review Board, Faculty of Medicine, Chulalongkorn University, Bangkok; study HIV-NAT 250) and Malaysia (UMMC Medical Research Ethics Committee study 2017929-5606). Study participants were selected by review of patient lists attending upcoming clinics at each site for potential participants who might meet the study inclusion criteria, who were then approached about participating in the study. Participants attended the clinic for their study visits. Detection of HIV antibodies and detectable HBsAg/HBV DNA on 2 occasions at least 6 months apart or HBsAg-positive with the absence of immunoglobulin M (IgM) antibodies to HBV core at screening (to confirm chronic HBV) were inclusion criteria. People with antibodies to hepatitis C or hepatitis delta virus were excluded. Participants were followed for 24 months, with study visits at baseline, month 3 and month 6, then every 6 months to 24 months.

Clinical and laboratory data were collected at all study visits. Laboratory measurements included alanine aminotransferase (ALT), aspartate aminotransferase (AST), full blood cell count, hepatitis B "e" antigen (HBeAg), HBe antibody (anti-HBe), quantitative (q) HBsAg, quantitative hepatitis B surface antibody (anti-HBs), hepatitis C virus (HCV) antibody, hepatitis delta antibody, HIV RNA, and CD4 count. Full details are in the study protocol (Supplementary Data). Study data were collected and managed using REDCap electronic data capture tools hosted at The University of Melbourne.

### Viral Quantification

HBV DNA quantification was performed at each site, using either Abbott Realtime M2000 HBV or Roche COBAS AmpliPrep/COBAS Taqman HBV V2.0, in accordance with the manufacturers' instructions. For categorical data analysis, HBV DNA was classified as detectable (≥20 IU/mL) or undetectable (<20 IU/mL), and HBV DNA was also analyzed as a continuous variable.

HIV RNA quantification was performed at each site, using either Abbott Realtime HIV or Roche COBAS Taqman HIV V2.0, in accordance with the manufacturers' instructions. For categorical data analysis, HIV RNA was classified as detectable (≥40 copies/mL) or undetectable (<40 copies/mL). HIV RNA was also analyzed as a continuous variable.

### HBV Serology

Quantitative HBsAg was measured using the Cobas HBsAgII quant II assay on the Cobas e411 analyzer (Roche Diagnostics) in accordance with manufacturer's instructions. The lower limit of detection for the assay was 0.05 IU/mL. Quantitative HBsAg was analyzed as a continuous and categorical variable.

Anti-HBs, HBeAg, and anti-HBe assays were performed on the Liaison XL (DiaSorin Ltd) in accordance with the manufacturer's instructions. Anti-HBs quantification was measured using the Liaison XL Murex Anti-HBs chemiluminescent immunoassay (CLIA), with an assay range of 3–1000 mIU/mL. The cutoff value that discriminated between the presence and absence of anti-HBs at levels consistent with immunity against HBV infection was 10 mIU/mL. HBeAg quantification was measured using the Liaison XL HBeAg CLIA, with a linear range of 0.1–120 Paul Ehrlich Institute Unit/mL.

### HBs Immune Complexes

HBsAg-IC were quantified as previously described [9 ]. Briefly, this combined an established method for HBsAg-antiHBs immune complex isolation with a commercial assay (Cobas HBsAgII quant II assay, as described previously) for HBsAg quantification within pelleted immune complexes.

### ALT Flares

We defined ALT flare as an increase in ALT greater than 2 times the upper limit of normal (ULN) from normal ALT levels, or an increase in ALT greater than 2 times baseline ALT level. The ULN was in accordance with the local pathology laboratories' reference ranges (Supplementary Data).



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### Statistical Analysis

Associations between baseline characteristics and HBsAg loss were examined at the univariable level using the Mann-Whitney test for continuous variables and the chi-square test for categorical variables. Statistically significant associations at the univariable level were included in multivariable model using Cox regression, with baseline CD4 cell count included in the model as a possible confounder. A survival curve was constructed as part of the Cox analysis. In all analyses, $P < .05$ was considered significant. For analysis, loss to follow-up and death were classified as HBsAg positive at study end. In the Cox regression model, a listwise deletion approach was used to handle missing data. Analyses were completed using IBM SPSS Statistics software (version 29.0.0.0; IBM Corporation, Armonk, NY, USA). Graphs were prepared using GraphPad Prism for Windows (version 10.2.3; GraphPad Software, Boston, MA, USA).

## RESULTS

### Study Cohort

Ninety-seven participants were eligible for the study (Figure 1). The cohort was predominantly male (92%), HBeAg positive (63%), with a median CD4 T-cell count of 240 cells/mm$^3$ (interquartile range [IQR]: 131–250 cells/mm$^3$), and a median age of 32 years (Table 1). The known duration of being HIV positive was a median of 10 days, with 87% enrolled within 40 days of HIV diagnosis, although the date of diagnosis likely does not reflect the date of HIV acquisition. The median HBV DNA was 6.7 $\log_{10}$ IU/mL and median ALT was 31.5 U/L. Month 24 follow-up was completed for 89 of 97 (92%) participants (Figure 1). Total follow-up for the cohort was 183.5 person-years (PY).

A total of 20 participants in the cohort (20.6%) received a tenofovir alafenamide (TAF)–containing ART regimen, with 18 on TAF throughout the study. One participant ceased TAF at month 18. The other switched to TAF after losing HBsAg on a tenofovir disoproxil fumarate (TDF)–containing regimen at month 16, and so was not classified as being on TAF prior to HBsAg loss. Full ART details are described in Table 1.

### HBV Serology Changes

Over the first 2 years of HBV-active ART, 21 of 97 participants (22%) lost HBsAg, or 11.7 per 100 PY. Fourteen of 97 participants (14%) additionally seroconverted (anti-HBs gain), or 67% (14/21) of those who lost HBsAg. Most HBsAg loss (17/21, 81%) was observed by the month 12 study visit, with a median time to HBsAg loss of 5.8 months (Figure 2). Thirty-six percent (22/61) of HBeAg-positive participants lost HBeAg, or 12.1 per 100 PY. Sixteen of 61 participants (26.2%) seroconverted (anti-HBe gain), or 72.3% (16/22) of those who lost HBeAg. Most HBeAg loss was observed by the month 12 study visit (14/22, 63.6%), with a median time to HBeAg loss of 12.0 months. Fourteen of 15 participants who were HBeAg positive at study entry and lost HBsAg during follow-up, also lost HBeAg.

By study end, half of the total cohort (51.1%) experienced at least a 1.0 $\log_{10}$ decrease in qHBsAg. The median decrease was 6.4 $\log_{10}$ for those with HBsAg loss and 0.6 $\log_{10}$ for those who remained HBsAg positive (Figure 3). Nineteen of 97 participants had baseline qHBsAg of less than 3.0 $\log_{10}$, of whom 7 (37%) lost HBsAg, with 5 participants losing HBsAg by month 3, 1 participant by month 6, and the other participant by month 12 (Supplementary Figure 1). HBsAg loss by month 3 was only observed in participants with baseline qHBsAg of less than 3.0 $\log_{10}$. Fourteen of 78 (18%) of the participants with baseline qHBsAg of 3.0 $\log_{10}$ or greater lost HBsAg during the study, and this proportion was not significantly different from those who lost HBsAg with a baseline qHBsAg of less than 3.0 $\log_{10}$ ($P = .07$).

The median time to HBsAg seroconversion was 12.5 months. Three participants gained protective levels (>10 mIU/mL) of quantitative anti-HBs by month 3 and each had a baseline qHBsAg of less than 3.0 $\log_{10}$. Quantitative anti-HBs levels fluctuated over time, with the greatest fluctuations observed during the first 12 months (Supplementary Figure 2).

### Associations With HBsAg Loss and Seroconversion

A range of baseline clinical parameters were examined for univariate association with HBsAg loss (Table 2). Higher baseline ALT, lower liver stiffness (kPa), younger age, and a TAF-containing ART regimen were significantly associated with HBsAg loss in this cohort.

While baseline qHBsAg as a continuous variable was not associated with HBsAg loss ($P = .55$) (Table 2), the median decline in qHBsAg by month 24 in those who lost HBsAg was significantly greater than in those who remained HBsAg positive ($\log_{10}$ 6.4 and $\log_{10}$ 0.61, respectively; $P < .001$). Quantitative HBsAg of less than $\log_{10}$ 2.0 IU/mL was also associated with HBsAg loss ($P = .01$) (Table 2).

Cox regression was undertaken to examine HBsAg loss in a multivariable model (Table 2) and included baseline factors that were significant at the univariable level (age, ALT, liver stiffness [kPa], qHBsAg <2 $\log_{10}$ IU/mL, and TAF-containing ART) and baseline CD4 count as a potential confounder. The Cox regression model was statistically significant: $\chi^2(6) = 62.06$, $P < .001$. Baseline CD4 count was the only factor that did not contribute significantly ($P = .091$) to the model. The odds ratio (OR) for TAF-containing ART was 4.30 (95% CI: 1.507–12.261), for ALT was 1.03 (95% CI: 1.017–1.044), for liver stiffness was .438 (95% CI: .275–.697), for baseline qHBsAg less than 2 $\log_{10}$ IU/mL was 201.563 (95% CI: 29.220–1390.401), and for age was .900 (95% CI: .844–.960). So, for each increase of 1 U/L in ALT there was a 2.7% increase in

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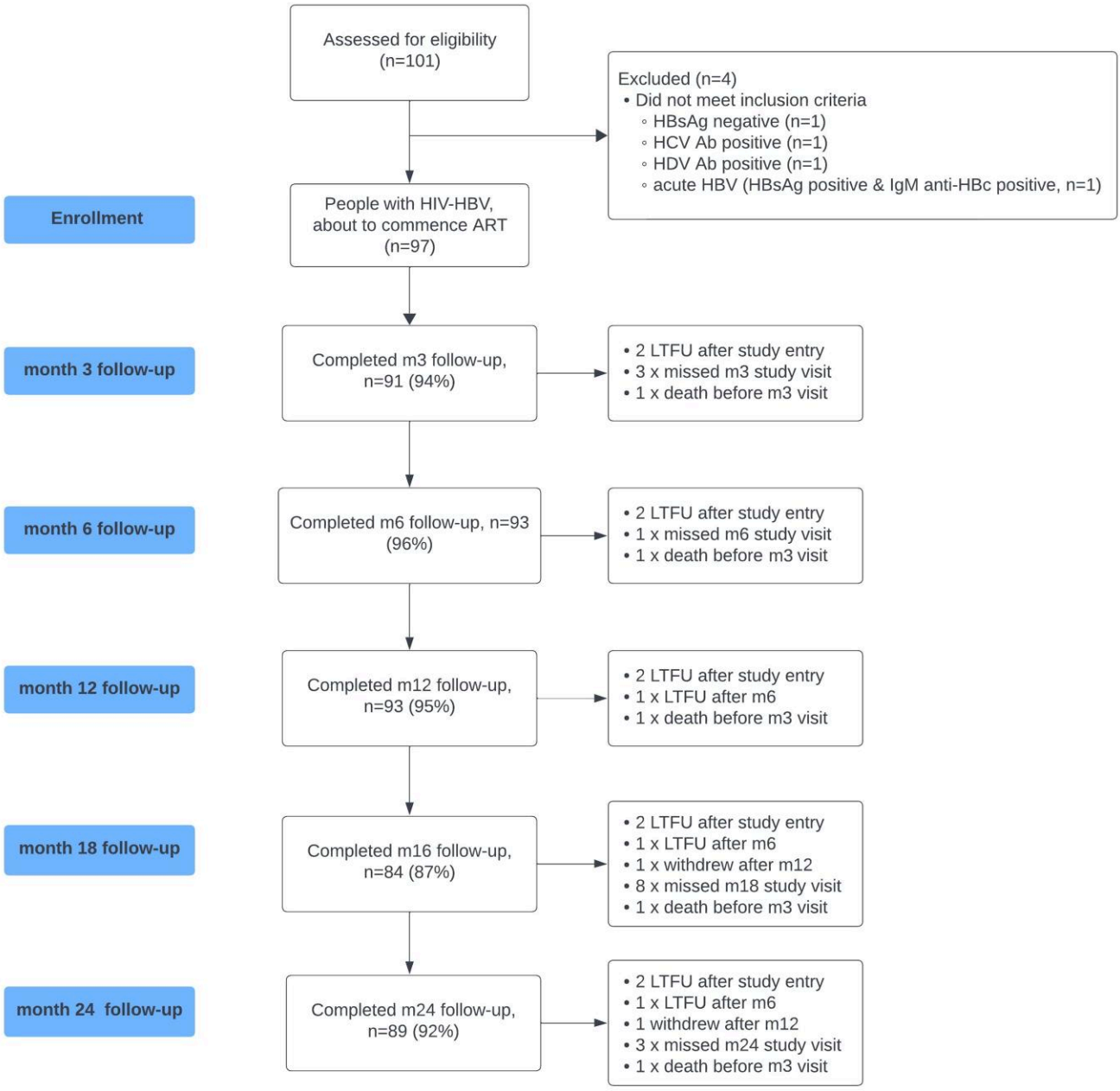


**Figure 1.** STROBE cohort flow diagram. Abbreviations: Ab, antibody; anti-HBc, Hepatitis B core antibody; ART, antiretroviral therapy; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCV, hepatitis C virus; HDV, hepatitis D virus; HIV-HBV, human immunodeficiency virus-hepatitis B virus coinfection; IgM, immunoglobulin M; LTFU, lost to follow-up; m, month; STROBE, Strengthening the Reporting of Observational Studies in Epidemiology.

the odds of losing HBsAg, for each 1-kPa increase in liver stiffness there was a 56.2% decrease in the odds of losing HBsAg, and for each increase in age of 1 year there was a 10% decrease in the odds of losing HBsAg.

We further examined the role of ALT over time in HBsAg loss (Supplementary Figure 3). Three participants with HBsAg loss had ALT levels more than 2 times the ULN at baseline, and another 7 participants had at least 1 follow-up visit with ALT levels more than 2 times the baseline level, for a total of 10 of 21 (47.6%) participants losing HBsAg following or with an increase in ALT (Supplementary Figure 4).

Baseline total HBsAg-IC was not associated with HBsAg loss. However, the total HBsAg-IC at baseline of those with an ALT flare (as defined previously) and who lost HBsAg was significantly higher than in those who lost HBsAg without flare (Mann-Whitney $P < .001$; median: 13.5 and 0.00 IU/ml, respectively).

The baseline clinical parameters examined for univariate association with HBsAg loss were examined for association with



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**Table 1. Cohort at Baseline and Month 24**

| Characteristic | Number (% or IQR) | |
|---|---|---|
| | Baseline (n = 97) | Month 24 (n = 89)[a] |
| Age, y | 32 (26, 39) | … |
| Site of recruitment, Thailand/Malaysia, n (%) | 94 (96.9)/3 (3.1) | … |
| Sex, M/F, n (%) | 89 (91.8)/8 (8.2) | … |
| Duration known HIV positive, d | 10 (6, 16) | … |
| HBV genotype (Gt), n (%) | | |
| Gt B | 5 (5.2) | … |
| Gt C | 68 (70.1) | … |
| Gt D | 1 (1.0) | … |
| Gt G | 6 (6.2) | … |
| Not done (insufficient level of HBV DNA) | 17 (17.5) | … |
| HBV DNA ($log_{10}$ IU/mL) | 6.67 (2.97, 7.98) | 1.30 (1.00, 1.40) |
| HBV DNA positive (>40 copies/mL), n (%) | 88 (90.70) | 24 (27.0) |
| HIV RNA, $log_{10}$ copies/mL | 4.47 (3.92, 4.97) | 1.60 (1.30, 1.60) |
| HIV RNA positive (>40 copies/mL), n (%) | 88.0 (90.7) | 5 (5.2) |
| ART regimen, n (%) | | |
| TDF/FTC/EFV | 56 (57.7) | 50 (51.5) |
| BIC/FTC/TAF | 19 (19.6) | 20 (20.6) |
| TDF/FTC/DTG | 18 (18.6) | 19 (19.6) |
| TDF/LMV/DTG | 2 (2.1) | 4 (4.1) |
| TAF/FTC/EVG/COBI | 1 (1.0) | … |
| TDF/FTC/RPV | 1 (1.0) | 2 (2.1) |
| TDF/FTC/LPV/RTV | … | 1 (1.0) |
| DTG/FTC/TAF | … | 1 (1.0) |
| Quantitative (q) HBsAg, $log_{10}$ IU/mL | 4.12 (3.31, 4.92) | 2.5 (0.10, 3.80) |
| qHBsAg ($log_{10}$ IU/mL) <3.0, n (%) | 19 (19.6) | 35 (50.7)[b] |
| qHBsAg ($log_{10}$ IU/mL) <2.0, n (%) | 8 (8.2) | 16 (22.5)[b] |
| HBeAg positive, n (%) | 61 (62.9) | 34 (36.6) |
| Transient elastography, kPa | 5.7 (4.6, 7.2) | 5.0 (4.3, 6.1) |
| CD4 T-cell count, total, cells/$mm^3$ | 240 (121, 350) | 457 (355, 620) |
| Nadir CD4 T-cell count, total, cells/$mm^3$ | 226 (139, 328) | … |
| ALT, U/L | 32 (20, 54) | 29 (23, 42) |
| ALT 2× ULN at BL, yes/no, n (%) | 8/88 (8.3/91.7) | … |
| HBsAg-IC, IU/mL | 2.60 | … |

Values are median (25th, 75th percentile) unless otherwise stated.

Abbreviations: ALT, alanine aminotransferase; ART, antiretroviral therapy; BIC, bictegravir; BL, baseline; COBI, cobicistat; DNA, deoxyribonucleic acid; DTG, dolutegravir; EVG, elvitegravir; F, female; FTC, emtricitabine; Gt, genotype; HBV, hepatitis B virus; HIV, human immunodeficiency virus; HBeAg, hepatitis B "e" antigen; HBsAg, hepatitis B surface antigen; HBsAg-IC, HBsAg complexed with anti-HBs; HBV, hepatitis B virus; HIV, human immunodeficiency virus; IQR, interquartile range; kPa, kilo pascal; LMV, lamivudine; LPV, lopinavir; M, male; q, quantitative; RPV, rilpivirine; RTV, ritonavir; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate; U/L, units per litre; ULN, upper limit of normal.

[a]Three participants lost to follow-up, 1 death (unrelated to study), 1 withdrawn, 3 missed month 24 visit.

[b]n = 71; also excludes those with HBsAg loss by month 24.

HBsAg seroconversion (Supplementary Table 2). This analysis compared those with HBsAg seroconversion (n = 14) with those who remained HBsAg positive throughout the study (and excluded HBsAg loss alone [n = 7]). Higher baseline ALT, lower liver stiffness, and a TAF-containing ART regimen were significantly associated with HBsAg seroconversion in this cohort (Supplementary Table 2).

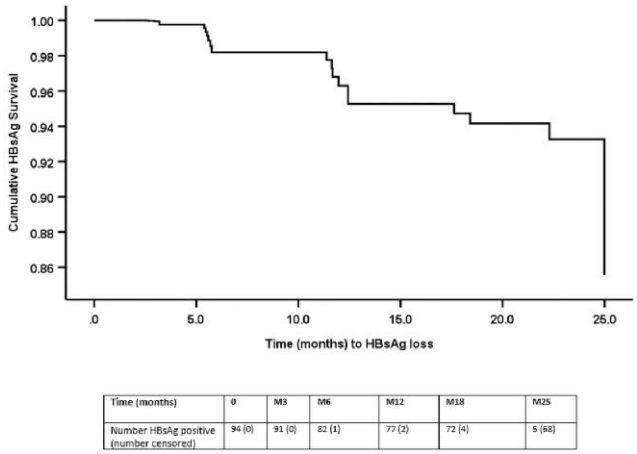


**Figure 2.** Cox regression survival function at mean of covariates, duration (months) to HBsAg loss. Covariates included baseline ALT, liver stiffness, CD4 cell count, age, TAF-containing ART regimen, and qHBsAg < $log_{10}$ 2.0 IU/mL. Numbers shown in the table represent HBsAg-positive participants at each time point. Abbreviations: ART, antiretroviral therapy; HBsAg, hepatitis B surface antigen; M, month; qHBsAg, quantitative hepatitis B surface antigen; TAF, tenofovir alafenamide.

### Associations With HBeAg Loss and Seroconversion

The same clinical parameters (excluding HBeAg status) that were examined for univariate association in HBsAg loss and seroconversion were also analyzed for association with HBeAg loss and seroconversion. This analysis was conducted in the 61 participants who were HBeAg positive at baseline (Supplementary Table 1). There were no significant associations with HBeAg loss, although a TAF-containing ART regimen approached statistical significance for HBeAg loss ($P = .05$). There were no statistically significant associations with HBe seroconversion, including a TAF-containing ART regimen ($P = .064$).

## DISCUSSION

HBsAg loss is now a major endpoint in HBV cure studies. While recognizing immunological and virological differences between PWH and people with HBV alone, the initial high rates of HBsAg loss in PWH-HBV commencing HBV-active ART make this a useful population to gain potential insights into the mechanisms underlying this phenomenon and to contribute to possible HBV cure strategies. In PWH-HBV who initiate HBV-active ART, we demonstrated that HBsAg loss was common and most HBsAg loss occurred by the month 12 study visit. In a Cox regression model, this was associated with higher ALT, receiving a TAF-containing ART regimen compared with

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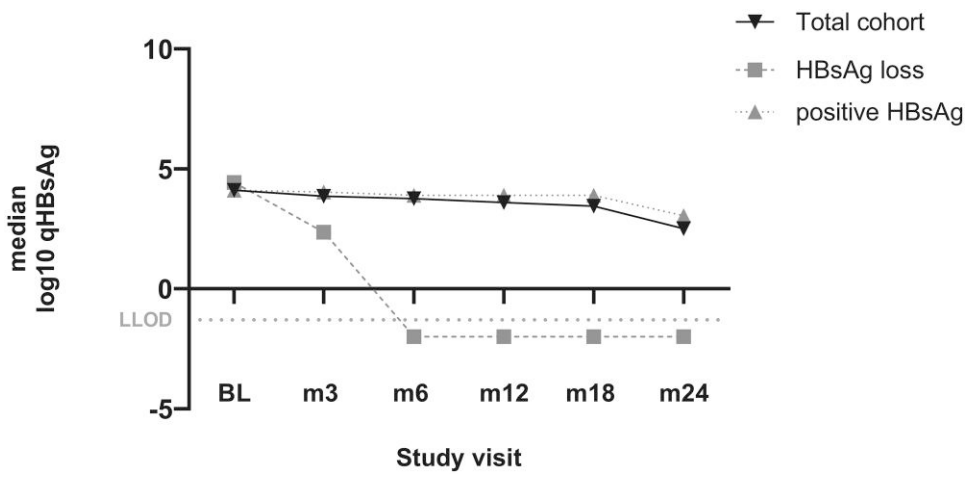


**Figure 3.** Median change in quantitative (q) HBsAg over the study. Abbreviations: BL, baseline; HBsAg, hepatitis B surface antigen; m, month.

**Table 2. Statistical Associations With HBsAg Loss**

| | | HBsAg Loss, Univariate Analysis (Median Value or (%)) | | HBsAg Loss, Cox Regression Model | | | |
|---|---|---|---|---|---|---|---|
| Baseline Factor | *P* | HBsAg Loss (n = 21) | HBsAg Positive (n = 76) | B | *P* | Exp (B) | 95% CI for Exp (B) |
| Alanine aminotransferase (ALT), U/L | **.005** | 48 | 28 (n = 75) | 0.030 | <.001 | 1.030 | 1.017–1.044 |
| Liver fibrosis (transient elastography), kPa | **.010** | 4.9 | 6.0 (n = 75) | −0.825 | <.001 | .438 | .275–.697 |
| TAF-containing ART regimen, yes/no, n (%) | **.025** | 8/13 (38.1/61.9) | 12/64 (15.8/84.2) | 1.458 | .006 | 4.229 | 1.507–12.261 |
| Total CD4 cells/mm$^3$ | .078 | 300 | 223 | 0.002 | .091 | 1.002 | 1.000–1.005 |
| Age, y | **.04** | 28.0 | 32.5 | −0.105 | .001 | .900 | .844–.960 |
| Sex, M/F, n (%) | .512 | 20/1 (95.2/4.8) | 69/7 (90.8/9.2) | … | | … | … |
| Known duration HIV positive, d | .923 | 10 | 10 | … | | … | … |
| HBV DNA, $\log_{10}$ IU/mL | .489 | 7.01 | 6.63 (n = 75) | … | | … | … |
| HIV RNA, $\log_{10}$ copies/mL | .355 | 4.19 | 4.59 (n = 67) | … | | … | … |
| qHBsAg, IU/mL | .546 | 4.44 | 4.11 | … | | … | … |
| qHBsAg ($\log_{10}$ IU/mL <2.0), yes/no, n (%) | **.011** | 5/16 (23.8/76.2) | 3/73 (3.9/96.1) | 5.306 | <.001 | 201.563 | 29.220–1390.401 |
| HBeAg positive, yes/no, n (%) | .301 | 15/6 (71.4/28.6)[a] | 46/30 (60.5/39.5) | … | | … | … |
| Aspartate aminotransferase (AST), U/L | .088 | 37.5 (n = 20) | 26.5 (n = 66) | … | | … | … |
| Alkaline phosphatase (ALP), U/L | .414 | 78.0 (n = 15) | 72.0 (n = 56) | … | | … | … |
| HBsAg-IC, IU/mL | .810 | 2.87 (n = 20) | 2.55 (n = 74) | … | | … | … |

*p* values < 0.05 are highlighted in bold text.

Baseline factors that were significant at the univariate level were included in the Cox regression model, along with baseline CD4 count as a potential confounder.

Abbreviations: ART, antiretroviral therapy; B, estimated coefficient; CI, confidence interval; DNA, deoxyribonucleic acid; Exp (B), exponential value of B, or odds ratio (predicted change in odds for a unit increase in the predictor); F, female; HBeAg, hepatitis B "e" antigen; HBsAg, hepatitis B surface antigen; HBsAg-IC, HBsAg complexed with anti-HBs; HBV, hepatitis B virus; HIV, human immunodeficiency virus; M, male; qHBsAg, quantitative hepatitis B surface antigen; TAF, tenofovir alafenamide.

[a]1 HBeAg equivocal at baseline, designated as HBeAg negative for analysis.

a TDF-containing regimen, baseline qHBsAg less than 2 $\log_{10}$ IU/mL, and lower liver stiffness at baseline.

In our study, HBsAg loss was observed in 22% of the cohort, or 11.7 per 100 PY over the first 2 years of HBV-active ART. This is in concordance with HBsAg loss observed in other cohorts of PWH-HBV, which was up to 19% [4, 5], although rates as low as 4% have been reported [10]. Some cohort studies of PWH-HBV with longer follow-up observed a decline in HBsAg loss rate by 3–5 years of treatment [11–13]. A recent review examining HBsAg loss in PWH-HBV on HBV-active ART [14] reported median HBsAg loss rates in PWH-HBV following HBV-active ART of 2.39 per 100 PY (0.6–10.46), compared with 0.37 per 100 PY (0–1.06) in patients with treated CHB. The higher rate of HBsAg loss observed in our cohort compared with prior studies of PWH-HBV may also be due to the heterogeneity of other studies, with many cohorts being treatment experienced, as well as the use of different HBV-active agents, different participant ethnicities, and likely different HBV genotypes.



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We found an association between the magnitude of decline in qHBsAg over the study and HBsAg loss by month 24, although baseline qHBsAg as a continuous measure was not statistically different between those who lost HBsAg and those who remained HBsAg positive. However, baseline qHBsAg of less than 100 IU/mL was associated with subsequent HBsAg loss. Baseline qHBsAg in this cohort was comparable to that reported in other studies of PWH-HBV, ranging from 3.6 to 4.9 [5, 13, 15, 16]. A greater decline in qHBsAg over time has been previously reported as being associated with HBsAg loss in PWH-HBV [5, 17], although this may be associated with baseline HBeAg status [17]. An association between lower baseline qHBsAg and HBsAg loss has been reported previously in smaller cohorts of PWH-HBV [15, 17], but in 1 study this was only observed in those who were HBeAg negative at baseline [17]. Lower baseline qHBsAg has also been associated with HBsAg loss in CHB monoinfection by meta-analysis [18].

We identified baseline ALT, age, liver stiffness, baseline qHBsAg less than 100 IU/mL, and receiving a TAF-inclusive ART regimen as being associated with HBsAg loss in a multivariable model. Baseline CD4 cell count was not significant in the Cox regression model. Low baseline CD4 count and accelerated increase in CD4 cell count have been associated with HBsAg, but this is not consistent across studies [14]. While CD4 cell count change is a surrogate marker of immune restoration, it may be that specific CD4 cell phenotypes are linked more closely with immune control or exhaustion. Younger age has previously been associated with immune reconstitution–induced inflammatory syndrome hepatic flare prior to HBsAg loss in a retrospective study of PWH-HBV in Japan [16]. Elevated ALT is often a marker of intrahepatic inflammation, and therefore a surrogate marker of a primed inflammatory response [19–23]. ALT levels are lower in PWH-HBV, even in the setting of liver disease [24]; however, a strong association was still observed in this cohort between ALT and HBsAg loss. Elevated ALT following ART initiation has been reported previously as being associated with HBsAg loss and may be related to immune restoration disease [16, 25, 26].

The association of lower liver stiffness with HBsAg loss was somewhat unexpected. Increased ALT can result in overestimation of fibrosis staging [27], so our finding of an association between both lower liver stiffness and higher ALT with HBsAg loss appears counterintuitive. However, the median liver stiffness of participants with and without HBsAg loss was 7.6 and 7.8 kPa, respectively, which is well below published cutoffs for advanced fibrosis in PWH-HBV [28, 29]. Based on the ≥F2 cutoff (5.9 kPa) in Miailhes et al [28], participants with HBsAg loss had mild fibrosis (4.9 kPa) and those without HBsAg loss were borderline for mild fibrosis (6.0 kPa). Therefore, the difference in liver stiffness by kPa, while statistically significant, may not be clinically significant.

Tenofovir disoproxil fumarate has been the backbone of therapy in PWH-HBV for many years due to its dual activity against both viruses and high barrier to HBV resistance [30, 31]. Tenofovir alafenamide is a more plasma-stable prodrug of TDF, which allows for dosing at approximately 10% of the TDF dose [32]. Initial studies examining TAF in PWH-HBV involved participants on TDF being switched to a TAF-based regimen. The first published switch study reported HBsAg loss in 4.2% and HBsAg seroconversion in 2.9% over 48 weeks of treatment [33]. Subsequent studies in PWH-HBV reported HBsAg loss on TAF between 0.0% and 8.7% [34–38]. The combined results from 2 phase 3 TAF switch studies in people with CHB followed by 3 years of open-label TAF reported an HBsAg loss of 1.2% or less and seroconversion of 1% [39], suggesting that TAF compared with TDF was no different in achieving HBsAg in people with CHB.

Results from the first randomized, phase 3 trial [Bictegravir, emtricitabine, and tenofovir alafenamide versus dolutegravir, emtricitabine, and tenofovir disoproxil fumarate for initial treatment of HIV-1 and hepatitis B coinfection (ALLIANCE)] of an HBV-active regimen including TAF in treatment-naive PWH-HBV have been recently published [40]. Seventeen percent (42/243) of participants in ALLIANCE were co-enrolled in our study. In the ALLIANCE cohort (followed for 96 weeks), total HBsAg loss (18.3%) was comparable to our study (22%) but seroconversion was higher in our cohort (14% vs 7%). For HBeAg, overall loss (28.3% and 36%) and seroconversion (23.5% and 26.2%) was similar. While both cohorts were treatment naive, predominantly Asian, male, and young, the variation in HBsAg seroconversion may be due to other differences between the studies or cohorts. Our study was observational, and undetectable HBV DNA was not an exclusion, whereas ALLIANCE required plasma HBV DNA of at least 2000 IU/mL. However, HBV DNA was not associated with HBsAg loss in our study. The ALLIANCE cohort had more participants with non-Asian ethnicity (20% and 0%, respectively), fewer female participants (4% and 8%), and no participants with HBV genotype G (0% and 6%) compared with our cohort.

Higher ALT, lower liver stiffness, and a TAF-containing regimen were also significantly associated with HBsAg seroconversion in our study. This is not surprising as two-thirds of those who lost HBsAg also seroconverted during the study.

HBsAg-IC can be detected by sensitive immunoassays, although not by current diagnostic assays. We hypothesized that baseline levels of HBsAg-IC would be higher in those who went on to lose HBsAg, as initials levels of anti-HBs would be undetectable diagnostically in the excess of HBsAg. The presence of anti-HBs in HBsAg-IC may signal the ability to mount HBV-specific immune responses [8]. In this study we quantified baseline HBsAg-IC and, while this was not associated with HBsAg loss, we observed that baseline HBsAg-IC was significantly higher in those who lost HBsAg with ALT flare



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compared with those who lost HBsAg without ALT flare. We have previously reported an association between HBsAg-IC and ALT flare peaks/rise prior to HBsAg loss in HBV monoinfection [9]. The drivers for the association are unknown, and may include cytotoxic T-cell–mediated hepatocyte killing, or anti-HBs opsonization of infected hepatocytes [9].

We did not identify any predictive baseline characteristics for HBeAg loss, although a TAF-containing ART regimen approached significance ($P = .05$). HBeAg positivity rate was similar to other studies of PWH-HBV previously reported, ranging from 52% to 67% [5, 12, 15–17, 25], although lower rates between 10% and 21% HBeAg positivity have been observed in treatment-experienced [10, 41] and sub-Saharan African [12, 13] cohorts. There were no associations with HBe seroconversion. The recent ALLIANCE study, however, reported significantly higher HBeAg loss and HBe seroconversion in those who received TAF [40]. This is likely due to the lower number of HBeAg participants receiving TAF in our cohort (16/61 [26%]) compared with ALLIANCE (34/90 [38%]).

Strengths of this study included prospective follow-up, recruitment of treatment-naive participants, exclusion of HCV and hepatitis delta, use of highly potent HBV-active ART, a large sample size, and low loss to follow-up. The study, however, did have some limitations. As we did not exclude baseline low HBV DNA, we were unable to determine HBV genotype in 17% of participants. Additionally, participants with low baseline HBV DNA or qHBsAg may have been in the process of losing HBsAg without treatment. However, neither baseline HBV DNA nor qHBsAg were associated with HBsAg loss in this cohort. We did not collect the date of first known HBsAg diagnosis, so are unable to examine duration of HBV infection.

In summary, we observed high rates of HBsAg loss in PWH-HBV initiating HBV-active ART. Our observation that most HBsAg loss occurs within 12 months of initiating ART directs the optimal timing for future investigations into HBsAg-loss immunological drivers. Our study suggests that TAF-containing ART regimens may be preferable as first-line therapy in HIV-HBV coinfection.

## 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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All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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