Received: 29 March 2020 | Revised: 8 August 2020 | Accepted: 25 September 2020

DOI: 10.1111/liv.14684

BRIEF DEFINITIVE REPORT

Liver INTERNATIONAL WILEY

Obstacles to HBV functional cure: Late presentation in HIV and its impact on HBV seroconversion in HIV/HBV coinfection

Kathrin van Bremen[1,2] | Christian Hoffmann[3] | Stefan Mauss[4] | Thomas Lutz[5] | Patrick Ingiliz[6] | Christoph D. Spinner[2,7] | Stefan Scholten[8] | Carolynne Schwarze-Zander[1,2] | Florian Berger[4] | Sven Breitschwerdt[1] | Stephan Schneeweiss[8] | Fabian Busch[1] | Jan-Christian Wasmuth[1,2] | Gerd Fätkenheuer[2,9] | Clara Lehmann[2,9] | Jürgen K. Rockstroh[1,2] | Christoph Boesecke[1,2]

[1]Bonn University Hospital, Bonn, Germany

[2]German Centre for Infection Research (DZIF), Bonn-Cologne, Germany

[3]ICH Study Center, Hamburg, Germany

[4]Center for HIV and Hepatogastroenterology, Düsseldorf, Germany

[5]Infektiologikum, Frankfurt/Main, Germany

[6]zibp, Berlin, Germany

[7]School of Medicine, Technical University of Munich, Munchen, Germany

[8]Praxis Hohenstaufenring, Cologne, Germany

[9]Cologne University Hospital, Cologne, Germany

Correspondence
Dr. Kathrin van Bremen, Department of Medicine I, Bonn University Hospital, Venusberg-Campus 1, 53127 Bonn, Germany.
Email: kathrin.vanbremen@ukbonn.de

Funding information
This study is funded by NEATID, German Centre for Infection Research (DZIF) and Deutsche Leberstiftung.

Handling Editor: Pietro Lampertico

[Correction added on 24 October 2020, after first online publication: Projekt Deal funding statement has been added.]

Abstract

Several cohorts have shown that long-term tenofovir-containing combination antiretroviral therapy (cART) leads to higher HBsAg seroclearance rates in HIV/HBV coinfected patients vs HBV-monoinfected patients under tenofovir disoproxil fumarate (TDF)-based therapy. We have analysed data on determinants of HBsAg loss in a retrospective multicentric cohort of 359 HIV/HBV coinfected patients. Median CD4 T-cell count at baseline was 359/ul (321-404), CDC stage was C in 20% (n = 70). Most patients (68%) were ART-naïve when TDF- or tenofovir alafenamide (TAF)-containing cART was initiated (baseline). After a median follow-up of 11 years HBsAg loss had occurred in 66/359 (18%) patients. However, patients with stage CDC C ($P \leq .001$), lower CD4 gain ($P = .043$) and not receiving TDF/FTC ($P = .008$) were less likely to lose HBsAg. Long-term TDF-containing cART appears to achieve higher rates of HBsAg seroclearance compared to published data for HBV monoinfected subjects. However, late presentation for HIV and poor immune recovery significantly impair HBV seroconversion rates.

KEYWORDS

HBsAg loss, HIV/HBV coinfection, immune reconstitution, late presentation, TDF

This work was presented in part at the Conference on Retroviruses and Opportunistic Infections 2017 and 2019 (CROI 2017 and 2019) in Seattle, USA as poster and oral presentations (Abstracts 580 and 627).

1 | INTRODUCTION

Chronic hepatitis B (HBV) is still a common coinfection in HIV-infected individuals, with 6% of patients in Germany suffering from HIV/HBV coinfection.[1] Because of the mutual negative interference of HIV and HBV, individuals with both diseases are at increased risk for rapid progression to liver fibrosis and cirrhosis leading to a higher mortality in co-infected patients.[2] Therefore, viral suppression of HBV with TDF-containing combination antiretroviral therapy (cART), which has proven to be a long-acting and effective therapy without any documented development of resistance against HBV to date, is most important and recommended throughout all guidelines.[3,4] Since HBsAg loss or seroconversion to anti-HBs-Ab is regarded as stable remission of HBV infection or a "functional cure", loss of HBsAg is the ultimate therapeutic goal in HIV/HBV coinfected patients.

HBV seroconversion occurs in around 95% of immunocompetent individuals undergoing acute HBV infection.[5] In HIV-infected subjects however, risk of developing chronic hepatitis B is six times higher, most likely as a consequence of HIV-associated immunodeficiency.[6] Several cohorts have shown that successful long-term TDF-containing cART leads to higher HBsAg seroclearance rates of 5%-15% in HIV/HBV coinfected patients compared to HBV monoinfected patients.[7,8] Immunoreconstitution under antiretroviral therapy therefore, may impact HBV seroconversion rates. Data on determinants of HBsAg loss remains sparse.

In this study, we evaluated factors associated with HBV seroconversion under HBV active ART in a large German multi-center cohort with a median follow-up of at least 10 years.

2 | METHODS

The study was designed as a non-interventional retrospective cohort, taking place at seven German HIV centres. The aim was to assess the rates of HBV seroconversion, defined as HBsAg loss. All HIV/HBV coinfected patients receiving HBV-active cART containing TDF or TAF were enrolled. TDF was dosed at 300mg daily, TAF at 25mg with nucleoside reverse transcriptase inhibitors/non-nucleoside reverse transcriptase inhibitors (NRTI/NNRTI) based regimens, respectively, 10mg when using boosted protease inhibitor-based ART. Baseline was defined as the beginning of HBV-active containing cART either with TDF or TAF. In addition to collection of pseudonymized demographic data, HBsAg, HBeAg and HBV DNA were measured. The applied assay was based on local standard, mainly Abbott Diagnostics ARCHITECT platform was used for measurements of HBsAg and HBeAg, serum HBV DNA was mainly quantified using Abbott RealTime PCR. CD4 count was assessed by flow cytometry. CD4 T-cell gain was measured as continuous variable.

2.1 | Statistical analysis

Fisher's exact, chi-square and Mann-Whitney U test were used for statistical analysis. The study was conducted according to the declaration of Helsinki.

3 | RESULTS

3.1 | Baseline characteristics

Baseline characteristics are shown in Table 1. Overall, 359 patients with a median age of 41 years (IQR 41-43) were included. 91% (n = 325) of the patients were male. 82% (n = 296) were of Caucasian, 14% (n = 51) of African and 3% (n = 12) of Asian descent. Main routes of HIV transmission were MSM (74%; n = 264), origin from high prevalence country (9%; n = 34) and heterosexual intercourse (9%; n = 30). The CDC stage at HIV diagnosis was A in 46% (n = 159), followed by B in 34% (n = 118) and C in 20% (n = 70). Median CD4 T-cell nadir was 251/ul (range 211-296) and median CD4 T-cell count at baseline was 359/ul (321-404).

In total, 66% (n = 218) were ART-naive when TDF- or TAF-containing cART was initiated. In 138 cases with an available pre-treatment ART-history, 68 (49%) had been treated with lamivudine in the past as part of their ART.

TABLE 1 Baseline Characteristics (n = 359)

Demographic characteristics	
Age (years)	41 (41-43)
Male gender, n (%)	325 (91%)
Ethnicity	
Caucasian	296 (82%)
African	51 (14%)
Asian	12 (3%)
HIV-related characteristics	
Main transmission risk	
MSM	264 (74%)
Origin from high-prevalence country	34 (9%)
Heterosexual intercourse	30 (9%)
CDC stage (n = 347)	
A	159 (46%)
B	118 (34%)
C	70 (20%)
CD4-nadir (cells/µl)	251 (211-296)
CD4 at baseline (cells/µl)	359 (321-404)
HBV-ART regimen (n = 329)	
TDF/FTC	240 (73%)
ART naïve	218 (66%)
TDF/3TC	59 (18%)
TAF/FTC	9 (3%)
Treatment regimen (n = 329)	
2 NRTI + PI/r	146 (44%)
2 NRTI + 1 NNRTI	134 (41%)
2 NRTI + INSTI	32 (10%)
HBV characteristics	
HBV-DNA positive	210/233 (90%)
HBeAg positive	111/159 (59%)

Of these, 90% (n = 61) were later switched to TDF (baseline). Moreover, 59% (n = 111) of the patients were HBeAg positive and 90% (n = 210) were HBV-DNA positive (limit of detection < 10 IU/ml). Data on HBV genotype (GT) was only available in 2% (n = 8, among them 5 with GT A, one each with GT C, D and G).

At baseline, cART contained in 73% (n = 240) TDF/FTC, in 18% (n = 59) TDF/3TC and in 3% (n = 9) TAF/FTC. During follow-up 53% (n = 107) were switched to TAF. Third HIV agent was in 43% (n = 146) a boosted protease inhibitor, in 41% (n = 134) a NNRTI and in 10% (n = 32) an integrase strand transfer inhibitor (INSTI).

3.2 | Follow-up characteristics

Median follow-up was 11 years (10-12). Median CD4 gain was 188/μl (130-229/μl). Overall, HBsAg loss occurred in 66/359 (18%) patients. Median time to HBsAg loss was 41 months (33-60). 24% (n = 24) HBeAg positive respectively 13% (n = 9) of the HBeAg negative participants lost HBsAg. There was no correlation between HBsAg loss and gender (P = .551), age (P = .307), ethnicity (P = .269), CD4 cell count (P = .639), CD4 nadir (P = .364), HbeAg (P = .712), ART class (P = .818) or switch to TAF (P = .267).

However, patients with stage CDC C (P < .001), lower CD4 gain (P = .043) and not receiving TDF/FTC (P = .008) were less likely to lose HBsAg.

4 | DISCUSSION

This real-life cohort of HIV/HBV coinfected patients on TDF-containing cART presents novel data on determinants of HBsAg seroclearance defined as HBsAg loss. Our rate of 18% HBsAg loss appears to be higher than those found in smaller coinfection cohorts from Thailand/Australia, the Netherlands and France. In these, HBsAg loss rates of approximately 8% had been reported.[7,8] These differences may be in part explained by differences in ethnicity. At least two studies in monoinfected patients have reported on higher rates associated with caucasian ethnicity, compared to Asian ethnicity.[9,10] This may be because of different host factors like Human Leukocyte Antigen polymorphisms which have an impact on HBV persistence, seroclearance and progression in HBV monoinfected individuals. Concerning HIV/HBV coinfected individuals Gantner et al recently attributed African ethnicity a better prognosis of achieving HBV functional cure.[11] Data from Jain et al found Hispanic origin and AIDS diagnosis at baseline being favourable for clearing HBsAg.[12] In our cohort ethnicity remained without any impact on clearing HbsAg, the difference is that our cohort was predominantly Caucasian while the cohort from Jain et al consisted mainly of African participants and the cohort of Gantner et al also consisted of 31% African participants.

The underlying HBV genotype may also have an impact on HBsAg seroclearance. However, data on HBV genotype and seroclearance in HIV/HBV coinfected patients is scarce. Because of the few documented genotypes in our cohort we cannot provide valuable data on the outcome of the different HBV genotypes.

Our higher rate of HBsAg loss might also be because of the fact of the so far longest period of follow-up. The Thai cohort had a follow-up of only 24 months, the Dutch cohort 6 years and the French cohort 10 years respectively. The median time to HBsAg loss in our cohort was 41 months, showing that with longer duration of HBV-active ART, higher rates of HBsAg loss in HIV/HBV coinfection can be achieved. This was also shown by Gantner et al After HBsAg loss, 71% of our patients developed Anti-HBs which shows that full seroclearance is likely to develop.

Age and gender had no impact on occurrence of HBsAg loss in our study. As in other cohorts from France and the Netherlands, mostly young MSM at about 40 years were affected by HIV/HBV coinfection in our cohort. The high rate is most likely caused by the risky sexual behaviour in this group, and demonstrates that there has still to be done more effort on preventing HIV/HBV coinfection especially with emphasizing necessary vaccination against hepatitis B (and A). The young age and the absence of comorbidities such as diabetes mellitius or hypertension might have had an impact on better viral control.

The actual EACS guidelines recommend to initiate a cART containing TDF or TAF in each HIV/HBV coinfected individual irrespective of the CD4 T-cell count.[13] We found no impact of the third agent with HBsAg loss, which underlines the fact that mainly TDF and immune reconstitution are important for viral suppression in coinfected individuals. Moreover, there was no difference concerning the incidence of HBsAg loss when comparing TDF or TAF containing regimens. The equal efficiency has already been described in monoinfected patients.[14] TAF is thought to deliver the active metabolite tenofovir disphosphate more efficiently than TDF to the hepatic cells with the additional favourable effect of improved renal and bone safety. Moreover, there have not been reported resistance mutation using TAF in monoinfected patients, which though has to be further investigated in long-term follow-up studies.

Of note, CD4 T-cell gain had an impact on the rates of HBsAg loss. After initiation of cART the immune system begins to reconstitute and therefore the chance of clearing HBsAg is increasing in HIV/HBV coinfected individuals when cART includes TDF. This has also been shown by Kosi et al and Piroth et al[15,16] In contrast, the rate of HBsAg seroclearance in monoinfected patients is lower with a pooled annual rate of 1.02%.[17] Therefore, immune reconstitution seems to have a strong impact on HBsAg loss. While absolute CD4 T-cell count as well as CD4 T-cell nadir did not correlate with HBsAg loss, CD4 T-cell gain correlated with loss of HBsAg demonstrating that individuals with lower CD4 gain and therefore possible impaired immune reconstitution were less likely to resolve HBsAg. The cohorts from the Netherlands and France also found an increased CD4 T-cell gain in patients who lost HBsAg. In contrast, data of a HIV/HBV-coinfected cohort from Zambia showed an overall loss of HBsAg in 10% of participating patients and CD4 T-cell counts < 350 μl being predictive of HBsAg loss. Moreover, the majority of patients with HBsAg loss had a CD4 T-cell count < 200/μl showing a higher incidence of advanced immune deficiency, the prevalence of AIDS defining diseases were not reported.[18] The impact of low CD4 T-cell count on HBsAg seroclearance was also observed in a recent cohort from Texas, which showed that patients with AIDS and therefore corresponding lower CD4 count were more likely to clear HBsAg.[12] The impact of CD4 T-cell gain was not presented in those cohorts. It seems that

even with generally lower baseline CD4 T-cell counts the occurrence of immune reconstitution itself is the main effect on clearing HBsAg.

Our study has some limitations inherent from its retrospective nature. Several medical records were partly incomplete because of lost to follow-up individuals. Another factor is the non-standardized measurement of HBsAg based upon the treating physicians. Moreover, the data of ART-adherence is lacking. However, this study represents real-life data on a large cohort with the so far longest follow-up time.

Taken together, ART-induced immune reconstitution may enable patients, who potentially would have cleared HBV in the first place if there had not been HIV-associated immunodeficiency, to achieve HBsAg seroclearance. In our cohort patients with CDC C stage had a lower chance for HBsAg seroclearance. This might be because of poorer immune reconstitution as well as concomitant active AIDS defining diseases which might also impede proper immune reconstitution.

Thus, initiation of TDF containing cART leads to immune reconstitution which itself improves clearing of chronic HBV infection in addition to the high antiviral effect of TDF on HBV. Taken together this might explain the higher rates of HBsAg seroclearance in coinfected individuals in contrast with HBV monoinfection.

In conclusion, highly effective cART containing TDF leading to immune reconstitution and additional HBV suppression is the ultimate therapeutic tool regarding HBsAg loss even in patients with late presentation.

ACKNOWLEDGEMENTS

We extend our grateful thanks to all study participants. Open access funding enabled and organized by Projekt DEAL.

CONFLICT OF INTEREST

CB has received honoraria for consulting or educational lectures from abbvie, BMS, Gilead, MSD and ViiV. SM has received honoraria for consulting or educational lectures from abbvie, Gilead, Janssen, MSD and ViiV. PI has received honoraria for consulting or educational lectures from abbvie, BMS, Gilead, MSD, Janssen and ViiV. PI has received a GILEAD research grant (NoCo). CDS has received honoraria for consulting or educational lectures from abbvie, BMS, Gilead, Hexal, Janssen, MSD and ViiV. JKR has received honoraria for consulting or educational lectures from abbvie, Bionor, BMS, Gilead, Hexal, Janssen, MSD, Roche and ViiV. GF has received honoraria for consulting or educational lectures from Biogen, Gilead, Janssen, Merck-Serono, MSD, Pfizer, Roche, Sanofi, Shionogi, ViiV, Akademie für Infektionsmedizin and Med Update. The other authors have no conflict of interest to declare.

ORCID

Kathrin van Bremen https://orcid.org/0000-0002-6701-1084
Patrick Ingiliz https://orcid.org/0000-0001-7218-4548
Christoph D. Spinner https://orcid.org/0000-0002-3875-5367

REFERENCES

1. Konopnicki D, Mocroft A, de Wit S, et al. Hepatitis B and HIV: prevalence, AIDS progression, response to highly active antiretroviral therapy and increased mortality in the EuroSIDA cohort. *AIDS*. 2005;19(6):593-601.
2. 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(9349):1921-1926.
3. de Vries–Sluijs TEMS, Reijnders JGP, Hansen BE, et al. Long-term therapy with tenofovir is effective for patients co-infected with human immunodeficiency virus and hepatitis B virus. *Gastroenterology*. 2010;139(6):1934-1941.
4. Thibault V, Stitou H, Desire N, Valantin M-A, Tubiana R, Katlama C. Six-year follow-up of hepatitis B surface antigen concentrations in tenofovir disoproxil fumarate treated HIV-HBV-coinfected patients. *Antivir Ther (Lond)*. 2011;16(2):199-205.
5. Liaw Y-F, Chu C-M. Hepatitis B virus infection. *Lancet*. 2009;373(9663):582-592.
6. Bodsworth NJ, Cooper DA, Donovan B. The influence of human immunodeficiency virus type 1 infection on the development of the hepatitis B virus carrier state. *J Infect Dis*. 1991;163(5):1138-1140.
7. Zoutendijk R, Zaaijer HL, de Vries-Sluijs T, et al. Hepatitis B surface antigen declines and clearance during long-term tenofovir therapy in patients coinfected with HBV and HIV. *J Infect Dis*. 2012;206(6):974-980.
8. Audsley J, Bent SJ, Littlejohn M, et al. Effects of long-term tenofovir-based combination antiretroviral therapy in HIV-hepatitis B virus coinfection on persistent hepatitis B virus viremia and the role of hepatitis B virus quasispecies diversity. *AIDS*. 2016;30(10):1597-1606.
9. van Hees S, Chi H, Hansen B, et al. Caucasian Ethnicity, but Not Treatment Cessation is Associated with HBsAg Loss Following Nucleos(t)ide Analogue-Induced HBeAg Seroconversion. *Viruses*. 2019;11(8):687.
10. Nguyen LH, Hoang J, Nguyen NH, et al. Ethnic differences in incidence of hepatitis B surface antigen seroclearance in a real-life multicenter clinical cohort of 4737 patients with chronic hepatitis B infection. *Aliment Pharmacol Ther*. 2016;44(4):390-399.
11. Gantner P, Cotte L, Allavena C, et al. Higher rates of HBsAg clearance with tenofovir-containing therapy in HBV/HIV co-infection. *PLoS One*. 2019;14(4):e0215464.
12. Jain MK, Parisot P, Go G, et al.Hepatitis B cure in HIV patients is more likely in Hispanics and those with AIDS. 26th Conference on Retroviruses and Opportunistic Infections, March 04–07, 2019, Seattle, abstract 0624.
13. European AIDS Clinical Society. Guidelines Version 9.1; 2018 [cited June 10th 2019]. http://www.eacsociety.org/files/2018_guidelines-9.1-english.pdf
14. Agarwal K, Brunetto M, Seto WK, et al. 96 weeks treatment of tenofovir alafenamide vs. tenofovir disoproxil fumarate for hepatitis B virus infection. *J Hepatol*. 2018;68(4):672-681.
15. Piroth L, Pol S, Lacombe K, et al. Management and treatment of chronic hepatitis B virus infection in HIV positive and negative patients: the EPIB 2008 study. *J Hepatol*. 2010;53(6):1006-1012.
16. Kosi L, Reiberger T, Payer BA, et al. Five-year on-treatment efficacy of lamivudine-, tenofovir- and tenofovir + emtricitabine-based HAART in HBV-HIV-coinfected patients. *J Viral Hepat*. 2012;19(11):801-810.
17. 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(3):635-646.e9.
18. Chihota BV, Wandeler G, Chilengi R, et al.High rates of HBV functional cure among HIV/HBV-coinfected patients on ART in Zambia. 26th Conference on Retroviruses and Opportunistic Infections, March 04–07, 2019, Seattle, abstract 0625.

How to cite this article: van Bremen K, Hoffmann C, Mauss S, et al. Obstacles to HBV functional cure: Late presentation in HIV and its impact on HBV seroconversion in HIV/HBV coinfection. *Liver Int*. 2020;40:2978–2981. https://doi.org/10.1111/liv.14684