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ORIGINAL ARTICLE

# Increasing hepatitis B vaccination coverage and decreasing hepatitis B co-infection prevalence among people with HIV-1 in Germany, 1996–2019. Results from a cohort study primarily in men who have sex with men

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## Abstract

**Objectives:** Viral hepatitis co-infection among people living with HIV is known to accelerate the progression of liver disease and AIDS. An increased prevalence and incidence of hepatitis B virus (HBV) infection among people living with HIV demands continuous monitoring to adapt targeted prevention strategies to reach the global goals of eliminating viral hepatitis as a public health threat.

**Methods:** We determined the prevalence and incidence of HBV for the years 1996–2019 from yearly blood sample testing and questionnaire reports among people living with HIV belonging to a nationwide, multicentre observational, prospective cohort study.

**Results:** Among this study population of 3479 participants, the majority (87%) indicated that being men who have sex with men (MSM) was their likely HIV transmission route; 51% were recruited from Berlin. HBV prevalence for acute/chronic and resolved infections decreased from 4.1% and 45% in 1996–1999 to 1.3% and 16% in 2019, respectively. Simultaneously, participants with a serological status indicating HBV vaccination increased from 25% in 1996–1999 to 69% in 2019. Among vaccinated participants with relevant information ($n = 1135$), 38% received their first HBV vaccination after HIV infection. The HBV incidence rate in 565 eligible participants decreased from 6.9/100 person-years in 2004–2007 to 0.45/100 person-years in 2015.

**Conclusion:** Increasing vaccination coverage because of a general HBV vaccination recommendation and catch-up vaccination efforts among risk groups decreased HBV infection prevalence over time among this study population of people living with HIV, primarily MSM and from Berlin. Despite this success, the prevalence and incidence of HBV remains higher than in the general

population in Germany. This emphasizes the need for continued HBV prevention by promoting HBV vaccination and HBV screening at regular intervals based on the individual risk behaviour.

**KEYWORDS**

Germany, hepatitis B virus, HIV, incidence, prevalence

## INTRODUCTION

Liver disease from chronic infection with hepatitis B or C virus (HBV, HCV) leads to high morbidity and mortality with viral hepatitis deaths from acute infection, cirrhosis, and liver cancer. Liver disease is described as the seventh leading cause of deaths worldwide in 2013 [1]. Among those, HBV and HCV account for 96% of viral hepatitis-related mortality. Therefore, the World Health Organization (WHO) has set global goals for eliminating viral hepatitis as a public health threat by 2030 [2]. Despite a low prevalence of HBV and HCV in Germany, vulnerable populations in particular remain affected [3, 4]. To meet the WHO goals, the German Federal Ministry of Health published the "Integrated Strategy for HIV, Hepatitis B and C and Other Sexually Transmitted Infections" in 2016 [5].

Transmission of HBV occurs mainly through permucosal transmission and through blood and blood products. In Germany, sexual transmission was stated as the likely route for 28% of mandatory notified (acute and chronic) cases in 2019 with relevant information available [4]. Injecting drug use was the third most common route of transmission, at 20%. A highly effective vaccine for the prevention of HBV infection has been available since 1982. In 1994, the German Standing Committee for Vaccination recommended vaccination for neonates and catch-up vaccination until the age of 18 years. People with an increased risk for HBV infection, such as patients with immunosuppression or people with increased behavioural exposure risk (i.e. injecting drug users, men who have sex with men [MSM], people in prison) have been further recommended for vaccination since 1995 [6].

In the general population, only 5%–10% of adults infected with HBV develop a chronic infection. Among immune-compromised people, infection progresses chronically in 30%–90% [7]. However, chronic infection with HBV can be treated using nucleoside reverse transcriptase inhibitors (NRTIs) such as tenofovir, which are also used as part of the NRTI-based antiretroviral therapy (ART) for HIV-1 [8]. Therefore, patients receiving an HBV-active ART for their HIV infection have been shown to be protected against HBV infections [9, 10]. This becomes especially important for patients lacking a sufficient immune response after HBV vaccination. Nevertheless, despite hepatitis B surface antibody (anti-HBs) detection after treatment, patients persistently carry so-called covalently closed circular DNA, which could lead to reactivation of infection in times of immune suppression [11].

Although the incidence of notifiable HBV cases among the general population in Germany in 2019 is 0.01/100 person-years (PYs) [4], Jansen et al. reported an incidence of 3.2/100 PYs among MSM living with HIV and participating in the HIV-1 Seroconverter Cohort for the time period 2008–2012 [12]. A scoping review on the prevalence of HBV, HCV, and hepatitis D in Germany reported a seroprevalence ranging from 0.3% to 1.6% for hepatitis B surface antigen (HBsAg) among the general population and of 4.5% for people living with HIV [13].

The aim of this analysis is to define the magnitude of HBV co-infection and HBV vaccination coverage in people living with HIV in Germany to continuously adjust screening and prevention strategies as needed and assess current progress towards the global viral hepatitis elimination goals.

## METHODS

### Study population, design and sample collection

The study population was people living with HIV in Germany and participating in the HIV-1 Seroconverter Study, a nationwide, multicentre, long-term observational, prospective cohort study. A total of 63 study centres located across Germany recruited patients with a known or reliably estimated date of HIV-1 seroconversion defined as:

1. detectable HIV-1 RNA or p24 antigen combined with a negative or indeterminate enzyme-linked immunosorbent assay result or
2. reactive HIV-1 enzyme-linked immunosorbent assay combined with a negative/indeterminate immunoblot result with confirmation of complete seroconversion within 6 months or
3. a documented HIV seroconversion with at most a 3-year interval between the last negative and the first confirmed positive HIV antibody test.

Among this study population, the majority was male with MSM contact as the likely route of HIV transmission, came from Berlin, and had an early diagnosed infection, so they tended to be better medically supervised. Methodological details of the study have been published elsewhere [14–17].

The study period was from 15 June 1996 until 31 December 2019. We analysed HBV incidence, prevalence, and vaccination coverage in 4-year time periods for the years 1996–1999, 2000–2003, and 2004–2007, because of the small study population during these years, and in yearly periods for the years 2008–2019.

## Sampling procedure

Additional inclusion criteria to the HIV-1 Seroconverter Study criteria were applied for this analysis. At least one record of HBV testing—irrespective of the test result—needed to be available to estimate the prevalence of HBV co-infection. Participants had to be seronegative at baseline with at least one additional record of HBV testing, irrespective of results, to be included in the HBV incidence calculation.

Laboratory results from plasma samples (tested by MVZ Labor Krone [Bad Salzuflen] or the Department of Infectious Diseases at the Robert Koch Institute) and results documented via a standardized questionnaire completed by the attending physician or study nurse were included. Sociodemographic and further details on each participant's vaccination status (vaccination date, number of doses, antibody titre) were sourced from the questionnaire responses.

## Laboratory analysis HBV

From the beginning of the study until June 2012, all plasma samples were tested to determine HBV infection status (see testing procedure in Table 1). Between July 2012 and October 2016, only the last sample received for each study participant was tested. All samples received from study participants who tested positive on their last sample or reported HBV positivity in their questionnaire between July 2012 and October 2016 were tested. No HBV laboratory testing was performed in the time period 2017–2019, but questionnaire responses were available.

The selected samples were tested with the ARCHITECT anti-hepatitis B core antigen (HBc) assay (Abbott) or the Monolisa anti-HBc PLUS EIA (BIO-RAD), the ARCHITECT anti-HBs assay (Abbott) or the Monolisa anti-HBs PLUS EIA (BIO-RAD), the ARCHITECT HBsAg Qualitative II (Abbott), or the Monolisa HBsAg ULTRA EIA (BIO-RAD) when analysed at the Department of Infectious Diseases. When tested at Labor Krone, the samples were tested with ARCHITECT anti-HBc II (Abbott), ARCHITECT anti-HBs (Abbott), ARCHITECT HBsAg Qualitative II (Abbott), and ARCHITECT HBsAg Qualitative II Confirmatory (Abbott). For any molecular verification, the Aptima HBV Quant Assay (HOLOGIC) was used.

Based on results from laboratory tests and questionnaires, participants with negative HBsAg but positive anti-HBc test results were considered positive for a resolved HBV infection. Participants with a positive HBsAg test result were considered to have an acute/chronic HBV infection. Participants with positive anti-HBs but negative anti-HBc and HBsAg test results were considered HBV vaccinated.

Questionnaire responses on the date and number of vaccine doses received were used to assess whether HBV vaccination was conducted before or after HIV seroconversion.

## Statistical analysis

We used descriptive statistics (STATA 14) to determine the baseline sociodemographic and clinical characteristics of the study participants.

HBV prevalence and vaccination status were calculated in 4-year time periods (1997–2007) or per year (2008–2019) as the respective proportion of participants

**TABLE 1** Criteria for HBV laboratory testing for anti-HBc, anti-HBs, HBsAg, HBV-PCR confirmation test by time period.

| Test | 1997–12/2007 | 01/2008–06/2012 | 07/2012–10/2016 | 11/2016–12/2019 |
|---|---|---|---|---|
| Anti-HBc | All samples | All samples | Selected samples | No HBV laboratory testing (but questionnaire reported results are available) |
| Anti-HBs | Anti-HBc positive samples | All samples | Selected samples | |
| HBsAg | All samples | All samples | Selected samples | |
| HBV-PCR | - | If results are unclear | If results are unclear | |
| HBsAg confirmation | - | - | If results are HBs-Ag positive only | |

Abbreviations: HBc, hepatitis B core; HBs, hepatitis B surface; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; PCR, polymerase chain reaction.

with an acute/chronic or resolved HBV infection or HBV vaccination among all study participants with HBV test results for this year/time period. Study centres are supposed to send in yearly questionnaires and blood samples for their participating patients. However, this yearly interval is not always realized, so we applied the following procedure to determine the HBV status per year/time period. Participants were included in the study from their first to their last result (see Figure 1), that is, the first/last visit with a blood sample collected or questionnaire completed, respectively. If test results were missing for the observed time period, the previous result was considered to persist (see Figure 1; participant B, year B). If participants had more than one result in the same observation period, possibly even one indicating an acute/chronic infection and one a resolved infection, priority for analysis was given to the test result indicating an acute/chronic infection (see Figure 1; participant C, year B). If followed by an observation period without new results, the latest result was considered to persist, despite this prioritization (see Figure 1; participant C, year C). The same methodology was used for analysis of HCV infection prevalence and incidence among the same study population and time period [18].

Since the date of HBV transmission was unknown, HBV incidence was calculated assuming that the date of an incident HBV infection was the mid-point between the dates of the last available negative test result and the first HBV-positive test result, irrespective of whether test results indicated an acute, chronic, or resolved infection. The person-time contributed per participant was calculated from the first negative test result until the calculated date of HBV infection or the date of the last negative test result in the database. Incidence rates were reported per 100 PYs. HBV infection reactivations were not considered for this incidence analysis.

Factors potentially associated with prevalent HIV–HBV co-infection (age, sex, region of origin, and likely route of HIV transmission) were analysed using univariable and multivariable regression analysis and risk ratio for measure of association. We used a binomial regression model for HBV prevalence and a Poisson regression model for HBV incidence.

## Data protection and ethics

The study protocol was first approved by the ethics committee of the Charité University Medicine Berlin (EA2/105/05) in 2005 and was amended in 2013 and 2021 (EA2/024/21). Participants provided written informed consent for study participation.

# RESULTS

## Study population

By 31 December 2019, a total of 3479 participants of the German HIV-1 Seroconverter Study with an HBV test result were included in this analysis. They contributed a total of 14830 follow-up PYs; the median follow-up time was 4.3 years (range 0–21). A median of three (range 1–23) test results were received.

Sociodemographic characteristics among included study participants are summarized in Table 2. The majority of participants were male (95% [$n = 3292$]) and reported MSM contact as their likely HIV-transmission route (87% [$n = 3020$]). Most participants were aged 25–34 years (44% [$n = 1540$]) at the time of HIV seroconversion and were from Germany (84% [$n = 2919$]). The majority of participants were recruited from Berlin (51% [$n = 1764$]), followed by North-Rhine Westphalia (14% [$n = 481$]).

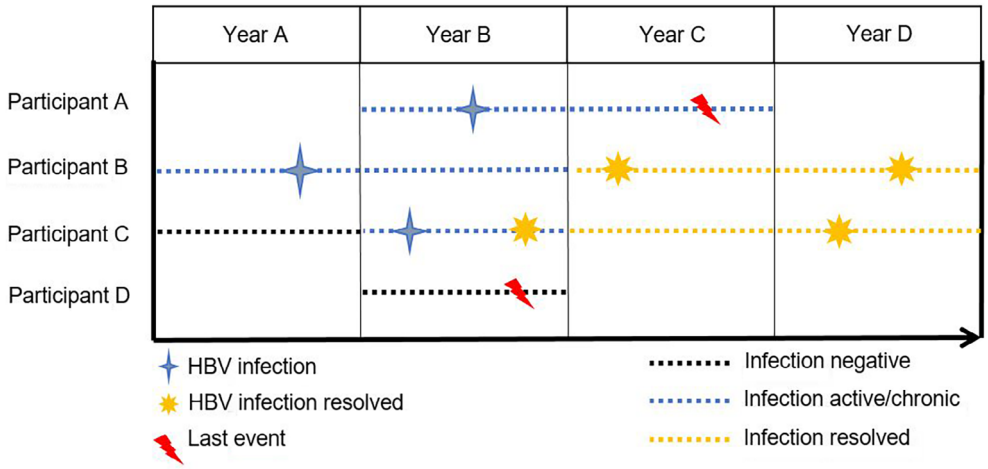


FIGURE 1 Demonstration of prevalence calculation based on different potential testing results. HBV, hepatitis B virus.

**TABLE 2** Sociodemographic characteristics of study participants.

| Characteristics | | *n* (%) |
|---|---|---|
| Total | | 3479 (100) |
| Sex | Male | 3292 (95) |
| | Female | 185 (5.3) |
| | Unknown | 2 (0.1) |
| Age | <25 | 538 (16) |
| | 25–34 | 1540 (44) |
| | 35–44 | 929 (27) |
| | 45–54 | 356 (10) |
| | ≥55 | 109 (3.1) |
| | Unknown | 7 (0.2) |
| Risk of transmission | MSM | 3020 (87) |
| | Heterosexual | 267 (7.7) |
| | High-prevalence country | 56 (1.6) |
| | IDU | 50 (1.4) |
| | Occupational risk | 14 (0.4) |
| | Unknown | 72 (2.1) |
| Region of origin | Germany | 2919 (84) |
| | Europe (without Germany) | 329 (9.5) |
| | America | 96 (2.8) |
| | Africa | 84 (2.4) |
| | Asia | 41 (1.2) |
| | Other | 8 (0.2) |
| | Unknown | 2 (0.1) |
| Federal state | Baden-Württemberg | 242 (7.0) |
| | Bavaria | 225 (6.5) |
| | Berlin | 1764 (51) |
| | Brandenburg | 144 (4.1) |
| | Bremen | 9 (0.3) |
| | Hamburg | 153 (4.4) |
| | Hesse | 54 (1.6) |
| | Mecklenburg-West Pomerania | 27 (0.8) |
| | Lower Saxony | 90 (2.6) |
| | North Rhine-Westphalia | 481 (14) |
| | Rhineland Palatinate | 88 (2.5) |
| | Saarland | -- |
| | Saxony | 143 (4.1) |
| | Saxony-Anhalt | 20 (0.6) |
| | Schleswig Holstein | 19 (0.6) |
| | Thuringia | 17 (0.5) |

Abbreviations: IDU, injecting drug use; MSM, men who have sex with men.

## HBV prevalence

The cumulative prevalence of HBV, defined as HBV positivity irrespective of an acute/chronic or resolved infection, among the 3479 study participants during the study period from 1996–2019 was 30% ($n = 1032$; 95% confidence interval [CI] 28–31).

The prevalence of resolved HBV infections decreased steadily from 52% in 1996–1999 to 16% in 2019 (Figure 2). The prevalence of acute/chronic infections was 3.9% (95% CI 3.3–4.6) during the total time period and also decreased from 4.1% (95% CI 2.0–8.5) in 1996–1999 to 1.3% (95% CI 0.6–2.8) in 2019, although not as steadily as the prevalence of resolved HBV infections. Calculated per year/time period, the overall infection prevalence decreased and the proportion of participants with a serological status indicating HBV vaccination increased. During the total time period 1996–2019, vaccination was indicated for 54% ($n = 1855$; 95% CI 52–55) of study participants. The proportion of participants with HBV vaccination increased from 25% (95% CI 19–33) in 1996–1999 to 69% (95% CI 65–73) in 2019. The proportion of participants with HBV-negative test results increased to 24% (95% CI 22–27) in 2008 and decreased to 14% (95% CI 11–17) in 2019 in favour of participants with HBV vaccination.

We used multivariable regression analysis to evaluate the risk of ever having an HBV infection (active/chronic or resolved) compared with being HBV negative. Participants with HBV vaccination were excluded, as we assumed they are no longer susceptible to HBV infection. The results showed that female study participants had a lower risk than male study participants, and participants aged <25 years had a lower risk than those aged 25–34 years (Table 3). Participants aged ≥35 years had an increased risk of ever having had an HBV infection, with increasing adjusted risk ratios per 10-year age group. Compared with heterosexual study participants, all other indicated risks for HIV infection (MSM, injecting drug use, occupational exposure, and coming from a country with high prevalence) were associated with an increased risk for ever having had an HBV infection. In addition, participants from an Asian country had a greater risk for HBV infection than those from Germany.

## HBV incidence

A total of 565 of 3479 study participants were eligible for HBV incidence analysis, contributing a total of 2287.5

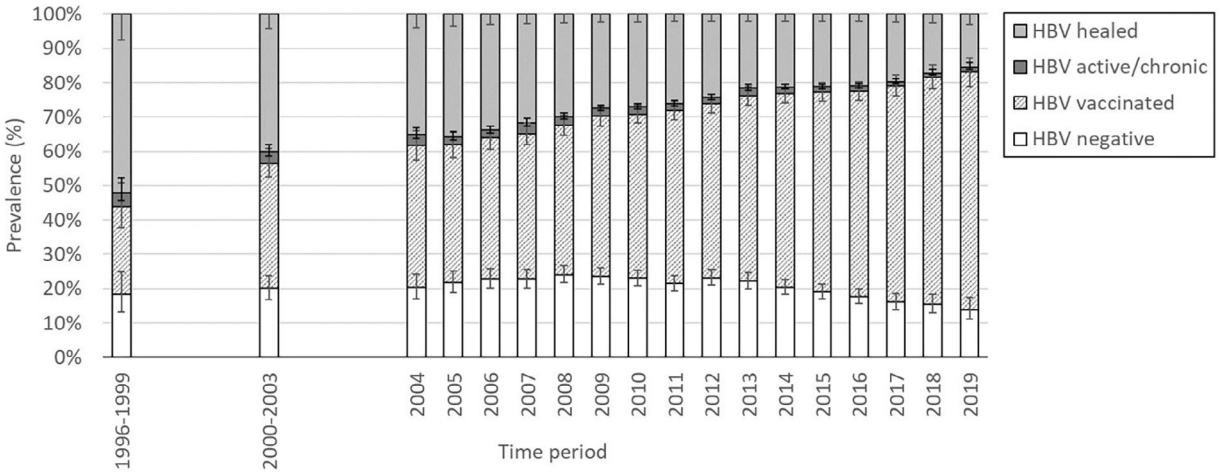


**FIGURE 2** Prevalence for acute/chronic or resolved hepatitis B virus (HBV) infections and HBV vaccination by time period (1996–2019).

**TABLE 3** Results of the multivariable Poisson regression analysis assessing the risk of gender, age, the likely cause of HIV transmission, and region of origin as factors associated with the prevalence of acute/chronic or resolved hepatitis B virus infection.

| Characteristics | | aRR | 95% CI | *p*-value |
|---|---|---|---|---|
| Sex | Male | Ref. | | |
| | Female | **0.72** | **0.56–0.91** | **0.007** |
| Age | <25 | **0.80** | **0.68–0.95** | **0.010** |
| | 25–34 | Ref. | | |
| | 35–44 | **1.20** | **1.10–1.31** | **<0.001** |
| | 45–54 | **1.29** | **1.16–1.43** | **<0.001** |
| | ≥55 | **1.34** | **1.15–1.57** | **<0.001** |
| Risk of transmission | MSM | **1.97** | **1.50–2.58** | **<0.001** |
| | Heterosexual | Ref. | | |
| | High-prevalence country | **3.35** | **2.15–5.23** | **<0.001** |
| | IDU | **2.98** | **2.22–4.00** | **<0.001** |
| | Occupational risk | **2.57** | **1.42–4.66** | **0.002** |
| | Unknown | 1.50 | 0.96–2.34 | 0.072 |
| Region of origin | Germany | Ref. | | |
| | Europe (without DE) | 1.07 | 0.95–1.21 | 0.295 |
| | America | 1.15 | 0.97–1.37 | 0.104 |
| | Africa | 0.91 | 0.65–1.27 | 0.568 |
| | Asia | **1.45** | **1.15–1.82** | **0.002** |
| | Other | 0.88 | 0.43–1.78 | 0.720 |
| | Unknown | 0.84 | 0.21–3.35 | 0.800 |

Abbreviations: aRR, adjusted risk ratio; CI, confidence interval; DE, Germany; IDU, injecting drug use; MSM, men who have sex with men.

PYs. The other study participants either had only one HBV test result or were already HBV positive when entering the study. The HBV incidence calculated for the overall time period from 1996–2019 was 2.2/100 PYs (95% CI 1.7–2.9; 51 HBV infections). HBV incidence was highest in 2004–2007, with 6.9/100 PYs (95% CI 4.4–12; 20 HBV infections; 291 PYs) and decreased in the following years, not steadily but enough to significantly lower incidence rates in 2013–2015 (Figure 3). However, it is important to note that these incidence rates are based on few observations and infections; for example, only one HBV infection and 222 PYs in 2015 or two HBV

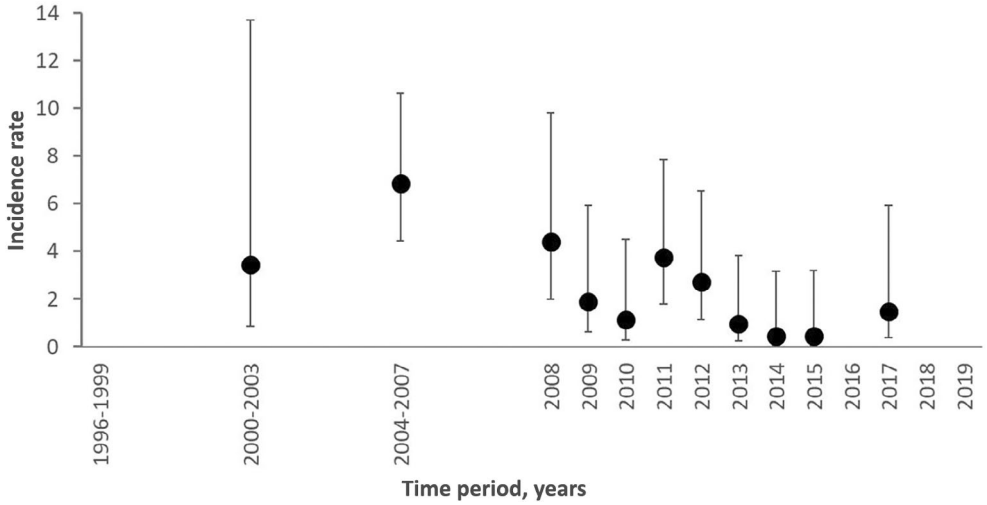


**FIGURE 3** Hepatitis B virus incidence rate per 100 person-years among eligible study participants ($n = 565$) by time period (1996–2019).

**TABLE 4** Person-years, number of failures, and incidence rate per 100 person-years with corresponding 95% confidence intervals per time period/year.

| Time period | PYs | No. of failures | Incidence rate (per 100 PYs) | 95% CI |
|---|---|---|---|---|
| 1996–1999 | 9.29 | 0 | - | - |
| 2000–2003 | 58.32 | 2 | 3.43 | 0.86–13.71 |
| 2004–2007 | 291.05 | 20 | 6.87 | 4.43–10.65 |
| 2008 | 135.89 | 6 | 4.42 | 1.98–9.83 |
| 2009 | 156.9 | 3 | 1.91 | 0.62–5.93 |
| 2010 | 177.72 | 2 | 1.13 | 0.28–4.50 |
| 2011 | 186.57 | 7 | 3.75 | 1.79–7.87 |
| 2012 | 183.25 | 5 | 2.73 | 1.14–6.56 |
| 2013 | 209.89 | 2 | 0.95 | 0.24–3.81 |
| 2014 | 224.47 | 1 | 0.45 | 0.06–3.16 |
| 2015 | 221.81 | 1 | 0.45 | 0.06–3.20 |
| 2016 | 178.77 | 0 | - | - |
| 2017 | 135.12 | 2 | 1.48 | 0.37–5.92 |
| 2018 | 97.87 | 0 | - | - |
| 2019 | 20.58 | 0 | - | - |

Abbreviations: CI, confidence interval; PYs, person-years.

infections and 135 PYs in 2017. No HBV infections were observed in 2016, 2018, and 2019 (Table 4).

## HBV vaccination status

The vaccination status of study participants for the respective time period based on test results is shown in Figure 2. In addition, we used the study questionnaire results for the number of vaccine doses and date of vaccination to further define vaccination status. Based on testing results, 1976 of 3479 (57%) study participants had an indication of being vaccinated. The questionnaire entries indicated vaccination coverage in 1534 of the 3479 (44%) study participants, with an agreement of 80% (Cohen's kappa 0.52; "moderate agreement"). The median number of vaccine doses received was three (range 1–20). Information on the date of vaccination was available for 1135 study participants, of whom 38% (95% CI 35%–41%; $n = 292$) had received their first reported HBV vaccination after their HIV infection.

## Influence of HIV therapy on HBV infection

Among all study participants susceptible to HBV infection who had also received treatment including tenofovir ($n = 326$), three (1%) had an incident HBV infection. One of these participants had two documented test results indicating HBV vaccination. For another seven study participants (2%), the incident HBV infection and tenofovir-including therapy was indicated for the time period between two visits. Therefore, we could not determine the order of infection and treatment initiation.

Among study participants susceptible to HBV infection and receiving emtricitabine- or lamivudine-containing HIV ART ($n = 141$), three (2%) had an incident HBV infection while receiving treatment. One additional participant (1%) had an incident HBV infection and an indication of treatment initiation between two test results.

## DISCUSSION

Our findings are an important update and overview over time of the HBV prevalence and incidence among people living with HIV. This is needed to monitor Germany's progress towards the elimination of HBV. Throughout the study period from 1996–2019, we observed a high prevalence (3.7%) of ever having had an HBV infection. In comparison, an HBV prevalence of 0.3%–1.6% was reported among the general population in a scoping review that included studies covering 1996–2016 [13], resulting in a 2.3- to 12-fold increased HBV prevalence among the people living with HIV in this study. However, it is important to note that this study population is not fully representative of people living with HIV in Germany, since this study population is primarily male (95%), was recruited in Berlin (51%), and reported MSM contact as their likely risk for HIV transmission (87%). In comparison, the proportion of new HIV infections in 2019 with MSM contact as the likely route of HIV transmission was estimated at 61.5%; of those, about 13.6% were notified from Berlin [19]. It is also important to consider that this is a cohort of people with known or well-defined dates of HIV seroconversion, so we can assume that the participants are likely to be aware of health risks taken and were medically supervised at least after participating in this cohort. Participants were therefore likely to have received an HBV vaccination recommendation (according to the HIV treatment guidelines [20]) and further health information based on their HIV transmission risk. This might result in an underestimation of HBV infection prevalence and incidence and an overestimation of HBV vaccination rates compared with people living with HIV with similar risk behaviour who may not be aware of their HIV status or be diagnosed later.

With regards to the data sources to determine HBV prevalence over time and especially in the most recent time periods, it is important to keep in mind that, despite an overall good agreement between the laboratory and questionnaire-reported test results, no further laboratory testing was performed in 2017–2019. In addition, follow-up visits may still be pending for some participants, so the analysis is based on fewer test results and fewer participants. This could have an influence on the robustness of prevalence and incidence estimates for this time period.

The results show an increasing proportion of study participants with HBV vaccination and therefore protection from HBV infection over time. Simultaneously, the proportion of participants with active/chronic and resolved infections decreased, and the HBV incidence shows some evidence of a potential decrease (although in this case only based on a few participants eligible for incidence analysis and thus resulting in wide CIs, as mentioned). The growing proportion of study participants with HBV vaccination could already be part of the birth cohort that was vaccinated during their childhood. Since the recommendation of HBV vaccination for neonates in 1994, vaccination coverage has drastically increased [21]. It may also reflect the success of including particular risk groups in the recommendations for catch-up vaccination and continuously promoting vaccination efforts, for example among MSM [6, 12]. This is supported by the finding that 38% of participants had their first report of HBV vaccination after being diagnosed with an HIV infection. Interestingly, the proportion of study participants without HBV vaccination and HBV infection remained relatively stable over time. Assuming continuous risk behaviour, which had already led to HIV transmission and therefore also a risk for HBV infection, this may be because the HIV treatment is suppressing HBV infection [10]. Overall, further analyses regarding HBV vaccination were limited by the incomplete additional information available from the questionnaires. This also probably explains the higher vaccination coverage calculated based on the testing results compared with the coverage calculated based on the questionnaire reports, resulting in the "moderate" agreement between the respective vaccination status drawn from these two sources. Although it is difficult to define risk factors for HBV infection among this study population based on the allocation to risk groups assumed from their route of HIV transmission, the risk factors associated with an HBV-prevalent infection found in this analysis were coming from a high-prevalence country, injecting drug use, having an occupational risk, or being MSM. These risk factors are commonly known routes of transmission for HBV infection [4]. Study participants aged 25–34 years had a lower risk for HBV-prevalent infection than did those aged ≥35 years. This result is expected: the cumulative number of risk events increases with time, so prevalence increases with age. Further contributing to this may be the above-mentioned birth cohort effect of vaccinated study participants.

Pre-exposure prophylaxis (PrEP) for HIV has been covered by statutory health insurances in Germany since September 2019. It is unlikely that the introduction of PrEP will mean an increase in HBV infections, as has been discussed for other sexually transmitted infections [22] or an increase in HCV among MSM without HIV accessing PrEP [23]. In a nationwide evaluation of PrEP use in Germany, almost 80% of PrEP users had antibodies against HBsAg and therefore were protected against HBV. New HBV infections occurred rarely in the study: 0.039/100 PYs [24]. In the analysis presented here, the increasing proportion of vaccinated study participants and the effect of HIV therapy with NRTIs such as tenofovir are likely to protect from HBV transmission [9, 10],

and the latter is supported by our findings. Only 1% of HBV-susceptible study participants receiving tenofovir and 2% of participants receiving emtricitabine or lamivudine had an incident HBV infection during the study period.

The analysis of HBV incidence suffered from the low number of participants who were susceptible to HBV infection and therefore eligible for the incidence analysis. Despite the observed decrease, the incidence rate of 2.2 infections per 100 PYs, calculated for the overall observation period from 1996–2019, is considerably higher than the incidence of 0.01 infections per 100 PYs among the general population estimated based on the mandatory disease notification for 2019 [4].

## CONCLUSION

This analysis shows a continuously decreasing prevalence of acute/chronic and resolved HBV infection and, in part, HBV infection incidence among people living with HIV from 1996–2019. At the same time, the proportion of participants with HBV vaccination has increased, reaching a vaccination coverage of 69% in 2019. This shows the great success of vaccination efforts, which are resulting in greater protection of people at increased risk for infection. However, 14% remained unvaccinated and susceptible to HBV, so efforts should be continued with intensified catch-up of HBV vaccination among people in risk populations. Nevertheless, the prevalence and incidence of HBV among this study population remain considerably higher than in the general population in Germany. This supports the necessity of regular screening for HBV and other relevant infections such as HCV and *Treponema pallidum* at HIV diagnosis and thereafter, depending on the individual risk behaviour, as currently recommended [25]. Similar screening recommendations with partially shorter screening intervals were decided for MSM using PrEP [26]. Distribution of harm-reduction material is recommended among certain high-risk groups, such as networks of MSM consuming stimulating drugs. This should be supported by a test and (if indicated) treat strategy to reduce HBV infections.

### AUTHOR CONTRIBUTIONS

AK: Conceptualization, formal analysis, methodology, visualization, writing – original draft. DS: conceptualization, methodology, project administration, supervision, writing – review and editing. CK: Conceptualization, data curation, methodology, writing – review and editing. KM: Conceptualization, data curation, project administration, writing – review and editing. NB: Conceptualization, funding acquisition, project administration, writing – review and editing. DM and CT: Data curation, writing – review and editing. VB: Funding acquisition, writing – review and editing. BGB: Conceptualization, funding acquisition, methodology, project administration, supervision, writing – review and editing. Study group: Data curation.

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## CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest.

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