



Dynamics of anti-HBS antibody decay in vaccinated people living with HIV/AIDS: a long-lasting response

Alice Tomio

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**PERSISTANCE DES ANTICORPS ANTI-HBS
POST-VACCINAUX CHEZ LES PERSONNES VIVANTS AVEC
LE VIH : UNE RÉPONSE DE LONGUE DURÉE**

THÈSE
PRÉSENTÉE POUR L'OBTENTION DU TITRE DE DOCTEUR EN MÉDECINE
DIPLOME D'ÉTAT

Alice TOMIO

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Supplementary figure 1: Proportion of patients with anti-HBs antibody titer >100 mUI/mL over time

Supplementary figure 2: Proportion of patients with anti-HBs antibody titer >10 mUI/mL over time

ABBREVIATIONS

AIDS: Acquired immune deficiency syndrome

cART: combined antiretroviral therapy

CMV: cytomegalovirus

DNA: deoxyribonucleic acid

HBcAb: Anti-HBc antibody

HBsAb: Anti-HBs antibody

HBeAg: HBe antigen

HBsAg: HBs antigen

HB: Hepatitis B

HBV: Hepatitis B virus

HBC: Hepatitis C virus

HCC: hepatocellular carcinoma

HIV: Human immunodeficiency virus

HSC: hepatic stellate cells

IQR: interquartile range

mIU/mL: milli-international units per millilitre

OBI: occult HBV infection

PLWHA: People living with HIV/AIDS

PVVIH : Personnes vivant avec le VIH

SD: standard deviation

RÉSUMÉ

Introduction

Il est recommandé que les PVVIH soient immunisées contre le virus de l'hépatite B. Un rappel vaccinal doit être réalisé en cas de décroissance du taux plasmatique d'anticorps anti-HBs sous le seuil de protection (10 mUI/mL). La vitesse de décroissance de ce taux est mal connue.

Méthodes

Nous avons inclus toutes les PVVIH adultes suivies dans notre centre qui avaient eu entre 2001 et 2018 au moins 2 déterminations du taux d'anticorps anti-HBs, dont la 1^{ère} >10 mUI/mL, et non séparées par un rappel vaccinal. Nous avons analysé la vitesse de décroissance au cours du temps sur le 1^{er} couple de valeur analysable pour chaque PVVIH, puis pour l'ensemble de tous les couples de valeurs successives. Nous avons enfin réalisé une analyse de Kaplan-Meier pour déterminer les cinétiques de passage à moins de 100 et 10 mUI/mL.

Résultats

887 couples de valeurs successives étaient analysables chez 287 patients. La décroissance moyenne et médiane du taux d'anticorps anti-HBs était de $2,6 \pm 10$ et de 0,29 [-0,02 ; 1,9] mUI/mL par mois, respectivement. Cette diminution représentait $0,7 \pm 3\%$ (moyenne) ou 0,6% (médiane) [0,1 ; 1,8] par mois du titre initial. Il n'y avait pas d'association entre la vitesse de décroissance du taux d'anticorps anti-HBs et le nadir de lymphocytes T CD4, l'âge au 1^{er} taux d'anticorps, le genre, ou le statut sérologique pour le CMV. La décroissance en valeur absolue du taux d'anticorps était corrélée avec le taux d'anticorps initial ($\rho=0.198$, $p<0,0001$), mais pas la valeur relative. L'analyse des 130 patients avec un taux d'anticorps anti-HBs >100 mUI/mL montrait que la médiane d'atteinte d'un taux d'anticorps <100 mUI/mL était de 102 mois, et n'était pas atteinte pour celles dont le taux était >500 mUI/mL.

Conclusion

La diminution du taux d'anticorps anti-HBs est lente chez les PVVIH vaccinés contre l'hépatite B. Une surveillance tous les 3 à 4 ans apparaît suffisante pour guider les rappels vaccinaux, voire à plus large intervalle en cas de taux >500 mUI/ml.

ABSTRACT

Background

Hepatitis B virus vaccination is recommended for people living with HIV/AIDS (PLWHA); we aimed to investigate anti-hepatitis B surface antibody (HBsAb) persistence over time.

Design

Retrospective monocentric study of anti-HBs antibodies in PLWHA.

Methods

We included PLWHA with at least two measurements of HBsAb between 2001 and 2018, excluding subjects positive for anti-HBc antibody or HBs antigen. We analyzed variations between two successive measurements if the first was >10 mUI/mL, unless HBV vaccination was performed between measurements, or if the increase between two dates was >100 mUI/mL (suggesting unrecorded vaccination).

Results

We analyzed 887 pairs of successive titrations in 287 patients. The interval between samples was <10 months for 23.9%, 10-14 months for 43.6%, 15-27 months for 18.3%, and >27 months for 14.2%. Mean and median monthly decreases in anti-HBs titer were 2.6 ± 10 mUI/mL and 0.29 mUI/ml, respectively. This monthly decay represents $0.7 \pm 3\%$ (mean) or 0.6% (median) of the initial titer. Antibody decay was not associated with CD4+ T cell nadir, age, gender, or cytomegalovirus serostatus. The absolute value of monthly decay was positively correlated with the initial antibody titer, unlike the relative value. In 169 patients with HBsAb titer of >100 mUI/mL, median time to titer of <100 mUI/mL was 80 months for those with an initial HBsAb titer between 100-500 mUI/mL; this level was not reached for most of those with >500 mUI/mL.

Conclusions

In vaccinated PLWHA, anti-HBs antibody titer decrease is low. It may be not necessary to measure it more than every 3-4 years, and even longer intervals in those with titer >500 mUI/mL.

Key words

Anti-HBs antibodies; Hepatitis B vaccine; PLWHA; Hepatitis B; Protection

INTRODUCTION

1. Hepatitis B and Human immunodeficiency virus infection

1.1 Epidemiology

Hepatitis B (HB) and Human immunodeficiency virus (HIV) infection are worldwide epidemics. The World Health Organization estimated that 40 million people were living with HIV/AIDS in the world in 2019, and that 257 million people had hepatitis B virus (HBV) chronic infection (with positive HBs antigen [HBsAg]) in 2016, mostly in sub-Saharan Africa and Asia (Figure 1). In 2019, 690,000 people died of HIV-related illness worldwide; in 2015, HB resulted in an estimated 887,000 deaths, mostly from cirrhosis and hepatocellular carcinoma (HCC) (1–4). In France, 153,400 people live with HIV and the HBsAg carriage is estimated at 0.65 percent in the general population, resulting in 280,000 people living with chronic HB infection, and 1,500 HBV-related death per year (5–7).

HBV and HIV infection are closely connected. PLWHA are at higher risk to be infected by HBV than the general population due to their common modes of transmission (both are vertically, parenterally and sexually transmitted). Ten percent of people living with HIV/AIDS (PLWHA) worldwide are chronically infected with HBV, corresponding to 2 to 4 million of people (figure 1 bis); 7.1 % of the European PLWHA is affected (8–11). Liver diseases have become one of the most frequent causes of non-AIDS mortality in PLWHA, including those related to hepatotropic viruses such as HBV (12,13).

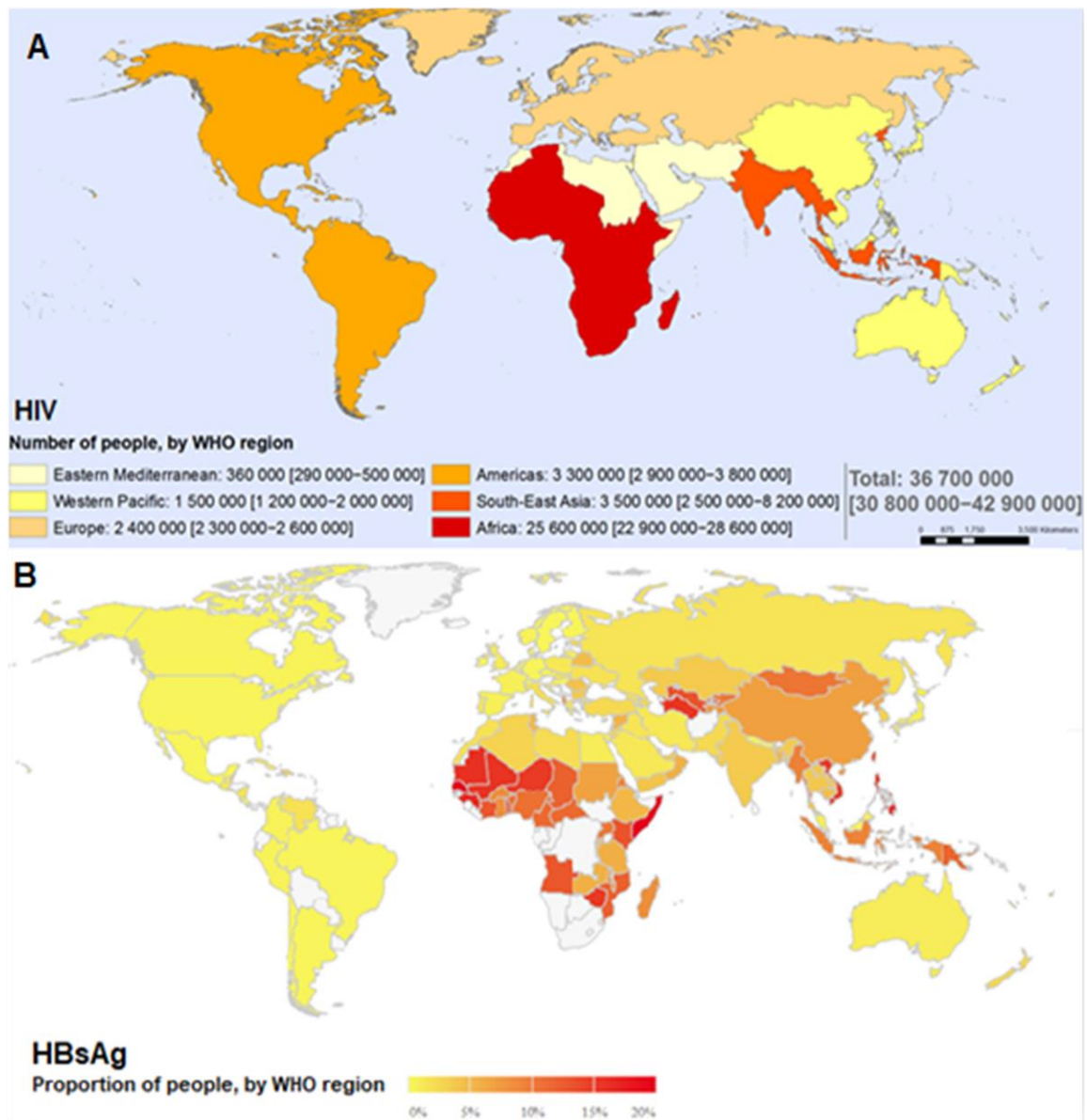


Figure 1: (A) Estimation of people living with HIV, and (B) with chronic hepatitis B infection (with positive HBsAg) worldwide in 2016, by Polaris Observatory Collaborators (data Source: World Health Organization 2017) (14) (modified figure)

1.2 Hepatitis B virus infection

Hepatitis B virus infects, replicates and assembles in hepatocytes, resulting in lifelong infection (15). The initial HBV infection can vary to asymptomatic acute infection to fulminant hepatitis.

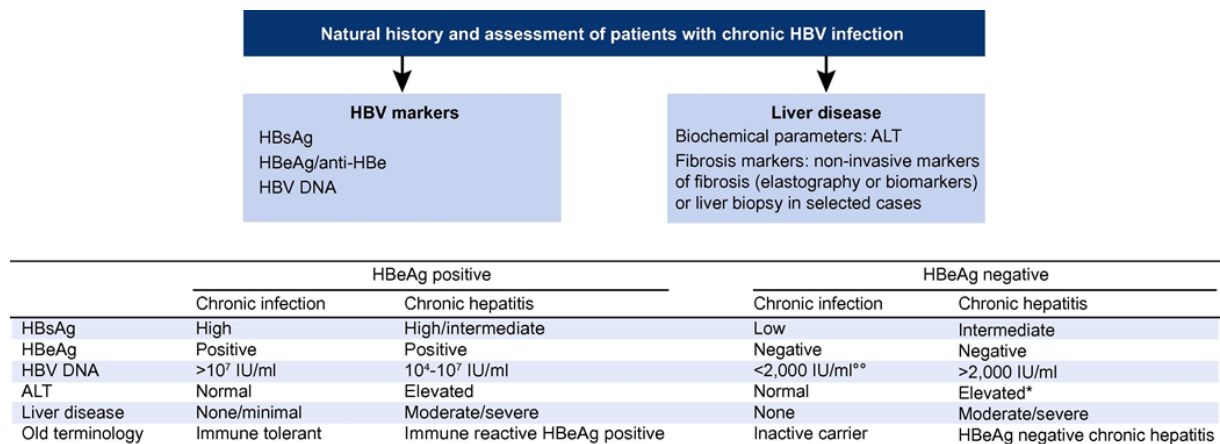
HBV can establish a persistent infection. Indeed, HBV can manipulate initial innate immune responses by blocking recruitment of natural killer cells and macrophages, decreasing cytokines secretion (interferon- γ , tumour necrosis factor, IL-6, IL-8 and IL-1 β) from Kupffer cells, and blocking retinoic-acid inducible gene I protein and Toll-like receptor-signalling within the hepatocyte (16). HBV can suppress Toll-like-receptor-mediated innate immune responses, and therefore the activation of pro-inflammatory cytokines in hepatocytes (17). HBsAg can inhibit IFN- α production in plasmacytoid dendritic cells through TNF- α and IL-10 induction in monocytes (18).

Both the innate and adaptive immune systems are involved in the resolution of acute HBV infections. HBV clearance involves a coordinated adaptive CD4 $^{+}$ and CD8 $^{+}$ T cell reaction, inducing a cytolytic dependent and independent antiviral effect through expression of antiviral cytokines. HBV-specific neutralizing antibodies produced by B cells can prevent HBV spread (19,20).

Acute HBV infection can become chronic, in particular when T cell function is impaired. Chronic HBV infection is defined as detectable HbsAg in the blood for longer than 6 months. Its spectrum varies to inactive carrier state (HbeAg negative chronic infection) to chronic hepatitis, cirrhosis, hepatic decompensation, hepatocarcinoma (HCC), extrahepatic manifestation, and is a prominent cause of death worldwide (Figure 2) (21).

In HBV infection, HCC may develop even in the absence of liver cirrhosis. HBV oncogenicity may be partly related to its capacity to integrate the host genome,

inducing genomic instability and direct insertional mutagenesis of cancer-related genes (22).



*Persistently or intermittently.

^{°°}HBV DNA levels can be between 2,000 and 20,000 IU/ml in some patients without signs of chronic hepatitis

Figure 2: Natural history and assessment of patients with chronic HBV infection based upon HBV and liver disease markers, by the European Association for the Study of the Liver (21).

HBV reactivation is defined as the increase in HBV replication (high plasmatic HBV DNA and positive HbsAg) in a patient with anterior inactive (HbeAg negative chronic infection, negative or low plasmatic HBV DNA) or resolved (positive HbsAb and HbcAb, and negative HbsAg) HBV infection. Residual HBV is controlled by cellular and humoral immune responses, and viremia can re-emerge spontaneously or more typically triggered by an immunosuppressive setting (therapy or disease). Reactivation can be silent and transient, but often causes a flare of disease (23).

Occult HBV infection (OBI) refers to patients with negative AgHBs, but persistent viral replication either in the liver (as covalently closed circular DNA), and/or in the serum (as fluctuant low plasmatic HVB DNA), with the consequence of increased integration of HBV DNA. HBcAb is usually positive in OBI. OBI has been associated with increased progression of hepatic fibrosis, ESLD, HCC, and possible HBV reactivation (24–27).

HBV course depends on the interplay between viral replication and the host immune response. HBV disease is mostly immune-mediated, and not due to viral cytopathic effect toward hepatocytes. The host immune response against HBV chronic infection is responsible for liver inflammation and fibrosis (28).

1.3 HIV impact on HBV natural history

1.3.1 Pathogenesis

Paradoxically, HBV related liver damage, which is an immune-mediated process, is worsened by HIV-immune alterations. In HBV-infected PLWHA, liver injury arises from HIV-induced immune suppression due to CD4+ T-cell depletion, systemic immune activation, increased lymphocyte and hepatocyte apoptosis, oxidative stress, inflammation, impaired immune responses, promotion of infection of hepatic stellate cells (HSC) and Kupffer cells, and microbial translocation (29,30) (Figure 3).

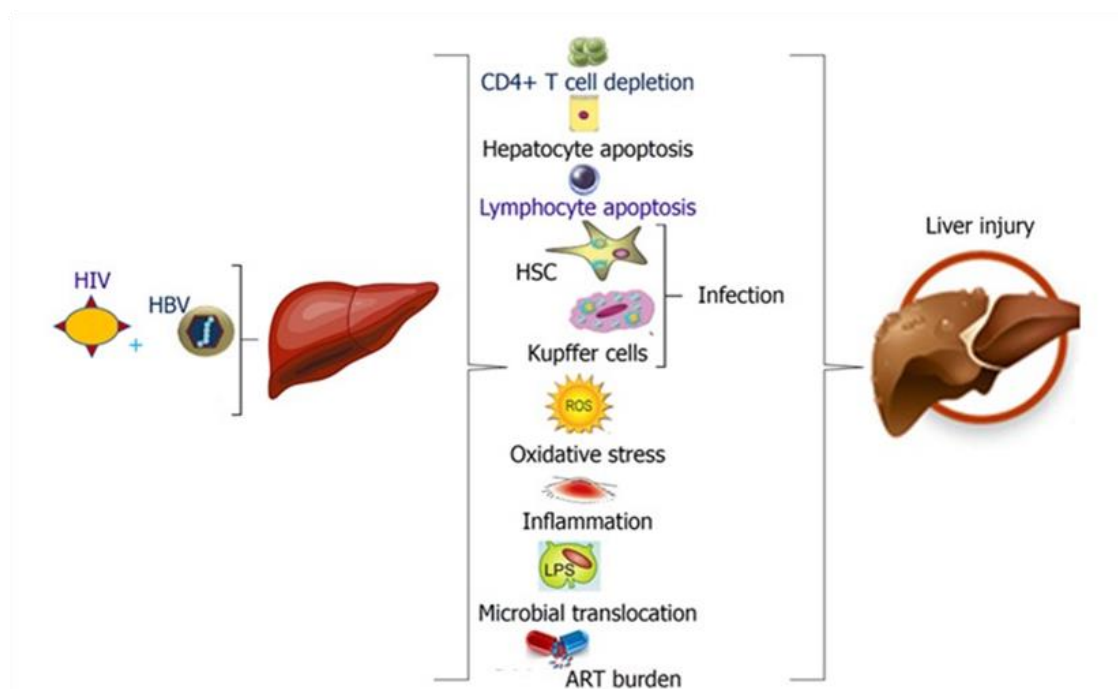


Figure 3: Mechanisms of human immunodeficiency virus (HIV) / Hepatitis B virus (HBV) co-infection induced liver injury, by Ganesan M et al (29) (modified figure).

Both HBV and HIV infect hepatocytes in which they interact (Figure 4). However, only HIV infects HSC (perisinusoidal pericytes involved in liver fibrosis), Kupffer cells (liver macrophages), CD4⁺ lymphocytes and macrophages, disrupting innate and adaptative immunity in the liver. HIV can also impair the integrity of the gastrointestinal tract leading to increased microbial translocation and elevated levels of lipopolysaccharide in the portal and systemic circulation. Lipopolysaccharide can activate Kupffer cells and HSC, leading to increased intrahepatic inflammation and fibrosis. In HBV infection, liver disease can also be mediated by migration from the blood to the liver of HBV specific and non-HBV specific T cells, CXCR6⁺ NK cells (by chemokines CXCL10 and CXCL16) and monocytes (by chemokine CCL2) (31).

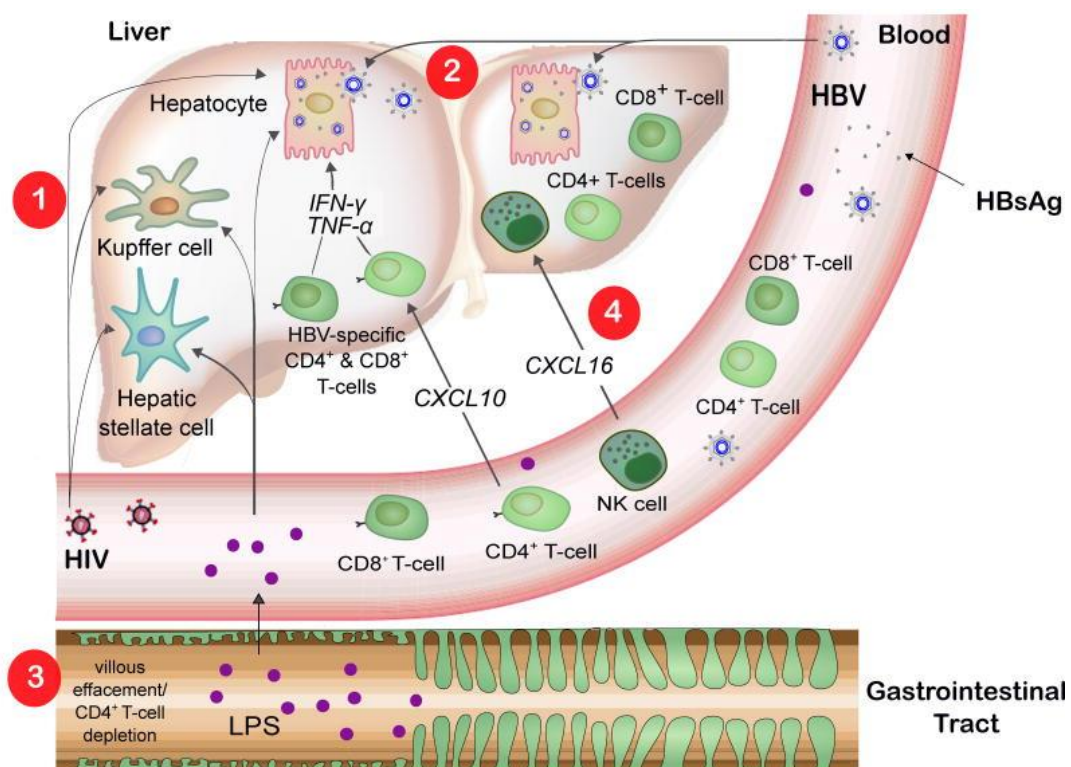


Figure 4: Effects of HIV and HBV on the liver and circulating HBV-specific immune cells, by Singh and al. (31)

HIV infection of immune cells (such as CD4+ T-lymphocytes, macrophages, Kupffer cells) disrupts both innate and adaptive immunity, weakening anti-HBV immune response in the liver (32). Hence, HIV-induced immunosuppression increases HBV antigen titers, leading to hepatitis aggravation. HIV-infected cells release proteins responsible for activation of cell metabolism trans-activator of transcription, viral turnover, attachment of virus to cell surface, and induction of cell death (gp120). Those proteins are captured by hepatocytes, which may accelerate HBV-induced fibrosis and HCC.

1.3.2 Coinfection morbidity and mortality

HBV-infected PLWHA have an increased risk of developing chronic HBV infection, HBV reactivation, occult HBV infection (OBI), have higher level of HBV replication, and have less frequently a spontaneous clearance of HBeAg. The risk of HB infection and reactivation may be associated with lower CD4 cells counts in PLWHA (33–37).

HBV course depends on the age at HIV infection; HBV chronically persists in 25 percent of those co-infected with HIV in adulthood and in 50 to 90 percent of those exposed to HIV at birth or in early childhood (38).

HB progresses faster and is responsible for higher liver-related morbidity and mortality in co-infected PLWHA than in HBV mono-infected patients. HBV-infected PLWHA have an increased risk of progression to liver fibrosis, cirrhosis, end-stage liver disease, hepatocellular carcinoma, and death (33,36,39–43). Increased liver disease progression may be associated with lower CD4 T cell count, heavy alcohol use, hepatitis D coinfection, non-black/non-Hispanic ethnics, and diabetes among HBV-infected PLWHA (44,45). Higher liver-related mortality rate may be worsened by lower

nadir CD4 T-cells count, hepatitis D coinfection and alcohol abuse in this population (12,36,39,44).

Fatal acute liver failures occurring after initiation of cART have been reported, potentially due to HBV-related immune reconstitution inflammatory syndrome (46). HB may as well increase risk of drug induced liver injury in PLWHA, which complicate the treatment of HIV infection (47,48).

Whereas HIV infection worsen the HB course, it is controversial whether chronic hepatitis B affects the natural history of HIV or not. HBV does not seem to impact HIV progression, more precisely on CD4 depletion, HIV load suppression, progression to AIDS or AIDS mortality (8,49–51). Those results are contested, particularly on HBV potential impact on impaired CD4 cells recovery during cART (52–54).

2. Hepatitis B Vaccine

Despite progress in the last decades, chronic HB management is still complex and requires long-term therapy, given the low annual rate of HBsAg seroclearance (55). HBV-infected PLWHA mostly require life-long treatment to suppress both viruses, in particular a cART regimen containing tenofovir (21). Therefore, HBV primary prevention is crucial, and vaccination is its main pillar.

In 1963, the USA geneticist Baruch Blumberg discovered the HBsAg, initially called the "Australia Antigen". In 1976, in Tours, France, Philippe Maupas developed the first Human plasma-derived HBV vaccine. In 1986, the first recombinant HBV vaccine produced by genetic engineering was marketed, providing a major tool in HBV infection prevention worldwide. Since 1992, the World Health Organization has recommended the universal HBV vaccination in new-borns, and promulgated the objective of eliminating HBV hepatitis as a major public health threat (90% diagnosed and 80% treated) in 2030 (56,57).

Nowadays, safe and efficient recombinant HB vaccines are used worldwide.

Regarding single-antigen vaccines (monovalent), the most commonly used are yeast-derived vaccines, which are produced by cloning the HBV S gene in yeast cells and thus include not glycosylated recombinant viral surface HBsAg particles (eg, Recombinax HB, Engerix-B®, HBVAXPRO®, and Heplisav-B®). Mammalian cell-derived vaccines also contain pre-S epitopes (eg, Genhevac B Pasteur®, AG-3 Hepacare®, and Bio-Hep-B®).

Hepatitis B vaccine can also be combined with hepatitis A vaccine (e.g., Twinrix®, GlaxoSmithKline), or with diphtheria, tetanus, pertussis, *Haemophilus influenzae* and poliovirus vaccines (eg, Vaxelis®, Hexyon®, Infanrix Hexa®, Pediarix®).

HBV vaccination has proven to be safe and efficient to prevent HBV infection, chronic carriage, clinical disease and transmission (58–60). Beside new-borns, HBV vaccination should therefore be provided to not immune patients exposed, as well as patients with higher risk of poor outcome (61,62). Accordingly, it is widely recommended to immunize PLWHA against HBV (63). The vaccination strategy in PLWHA (e.g., in France) is different from the general population, as double doses are used (40 µg HBs antigen (HBsAg)) and a supplementary injection (4 instead of 3) is performed (64,65).

After completion of vaccination, the protective HBsAb threshold of ≥ 10 mUI/mL is well proven in healthy individuals (66,67), and is also considered clinically protective in PLWHA (68,69).

In an observational study (70), 46/409 (11,2%) military PLWHA with a HBsAb titer lower than 10 mIU/mL developed an acute HBV infection, whereas only 11/217 (5.1 %) PLWHA with a HBsAb titer equal or superior to 10 IU/L developed an acute HBV infection. Moreover, of those affected by acute HBV infection, 16 of 46 (34.7%) with HBsAb titer lower than 10 mUI/mL developed HBV chronic infection, while none of the 11 patients with a HBsAb titer equal or superior to 10 mUI/mL developed HBV chronic infection.

The recombinant HB vaccines have a response rate higher than 90 percent in most healthy individuals. Post-vaccination response should be assessed in individuals with

high exposure (for example healthcare workers), as well as those who are less likely to respond to vaccination (62). The vaccination response rate indeed may be slightly lower in obese patients, smokers, men; and more significantly lower in elderly, patients with diabetes, cirrhosis, coeliac disease, chronic renal failure, on chronic haemodialysis, and immunocompromised patients, including organ transplant recipients and AIDS patients (71–73). As PLWHA may have impaired immune response (particularly in case of CD4 T cell lymphopenia, or in case of detectable HIV viral load (54,74–76)), it is recommended to assess their initial immune response to HBV vaccination by measuring the HBsAb levels 1 to 2 months after the HBV vaccine series (77–79).

The immunological mechanisms of HBV vaccine induced long-term protection are complex, and combines humoral and cellular responses through memory B and T cell (80,81). In vaccinated healthy individuals, even if HBsAb titer declines below 10 mIU/mL, memory B lymphocytes able to produce HBsAb persist, attested by rapid rise in HBsAb titer after a booster (82). In vaccinated healthy individuals, HBV-specific T-cells memory (measured on the basis of HBsAg-specific TNF- α , IL-10, or IL-6 production) persists at least for 32 years, even in case of loss of HBsAb (83).

Bauer and al. (80) proved that vaccinees without detectable HBsAb titer still have immunologic T cell memory. Indeed, they isolated vaccine-induced HBsAg-specific T cells of both effector and memory phenotype CD4⁺/CD45RA⁺ and CD4⁺/CD45RO⁺ T cells, respectively; moreover, when stimulated them with HBsAg and tested for IFN-gamma and IL-5-secretion by enzyme-linked immunospot assays (Elispot), these cells proved to be functional.

A meta-analysis has reported that HBV vaccine protection persists for at least two decades in the great majority of immunocompetent adequately vaccinated individuals (84). In healthy healthcare workers, the higher the peak of HBsAb levels following vaccination, the longer it usually takes for HBsAb to decline below 10 mIU/mL (85). After neonatal vaccination, the protection against chronic HB persists even if the HBsAb level declines below 10 mIU/mL after 30 years (86). Booster doses are therefore not necessary in immunocompetent subjects who have received an adequate full primary vaccine series, even if the HBsAb titer declines below 10 mIU/mL, since they appear to be protected by memory B and T cells (84,87,88)

However, regarding immunocompromised patients, a booster dose should be considered based on serological monitoring. As a more profound decay of HBsAb levels has been reported in PLWHA at month 42 or 43 after vaccination in adults (89,90), or after 10 years in children (91), regular monitoring of HBsAb levels is generally recommended to assess the potential need for revaccination. Under 10 mIU/mL, patients should be informed of HBV infection risk and booster doses should be considered (68,87).

The long-term dynamics of waning HBsAb have been scarcely explored in vaccinated PLWHA. We conducted a retrospective study to evaluate the persistence of HBsAb in a population of PLWHA vaccinated against HBV over the last two decades.

METHODS

Patients

Grenoble-Alpes University Hospital is a tertiary center with a cohort of 580 PLWHA in 2000 and 1,000 in 2018. We retrospectively included all non-HBV-infected PLWHA with an initial response to HBV vaccination (defined as HBsAb levels of >10 mUI/ml) and at least one consecutive measurement of HBsAb in the 2001-2018 period. HBV-infected patients (positive HBsAg and/or anti-HBc antibodies) were excluded.

Data collection

HBV serologies were performed using Abbott AxSYM or Architect immunoassay systems. Demographic and clinical variables of interest were collected: gender, age, cytomegalovirus (CMV) serological status, CD4 at the first HBsAb measurement, CD4+ T cell nadir, and date of HBV vaccination if available.

Statistical analysis

We analyzed the variations in each pair of successive HBsAb measurements, excluding pairs in which the first measurement was <10 mUI/mL, or if HBV vaccination was reported between the two dates. Moreover, if the rise between two successive measurements was >100 mUI/mL, suggesting unreported HBV vaccination, the pair was excluded from the analysis.

We first analyzed all the HBsAb variations between the 2 first available dates for all included patients. We then analyzed all the pairs of successive measurements, compiling data for patients with between two and seven measurements. We were then

able to compute the variation in HBsAb levels by unit of time. We calculated the mean with standard deviation (SD) and the median with interquartile range (IQR 25-75).

The comparison of two groups of the same quantitative variable was performed using the Mann-Whitney test. The correlation between quantitative variables was assessed using the Spearman test. Kaplan-Meier analysis was carried out to explore the long-term persistence of seroprotection after HBV vaccination. The log-rank test was applied to explore the association of this persistence with various patient characteristics.

A p-value of <0.05 was considered statistically significant.

Ethics

This study was conducted in accordance with the French legislation on the retrospective use of healthcare data and validated by the Clinical Research Direction of Grenoble-Alpes University Hospital. All patients formally accepted the anonymous use of their medical data for research purposes. No additional sample or sample volume was drawn for this study.

RESULTS

Patients

We identified 287 PLWHA negative for HBsAg and HBcAb with at least one pair of HBsAb measurements. Overall, 70.6% of PLWHA were men, and mean age at the time of their first HBV serology was 40.6 ± 11 years. Mean CD4+ T cell count at HIV diagnosis was $615 \pm 275/\text{mm}^3$, and mean CD4+ T cell nadir was $488 \pm 225/\text{mm}^3$ (Table 1).

Overall, 66, 59, 43, 53, 34, and 32 patients had one, two, three, four, five, and six pairs of successive measurements analyzed, respectively.

	Patients (n=287)
Age (years), mean (SD)	40.6 ± 11
Male, n (%)	203 (70.6)
CD4+ T cell nadir, mean (SD)	488 ± 225
CD4+ T cell count at HIV diagnosis, mean (SD)	615 ± 275
Negative cytomegalovirus serology, n* (%) (* determined in 225 patients)	35 (15)

Table 1: Characteristics of the study population

HBsAb dynamics from the analyse of the 1st pair of HBsAb testing

We first analyzed the dynamics of HBsAb level using only two values per patients: the first measured value above 10 mUI/mL, and the first subsequent value if there was no vaccination in the interval. The median interval was 13.8 months [IQR:11;22]. The median initial HBsAb value was 132 mUI/mL [IQR: 37;614]; at this time, 21.0% patients had a value of ≥ 1000 mUI/mL. The median second HBsAb value was 95 mUI/mL [IQR: 31;369]. The mean monthly decrease in HBsAb was 2.8 ± 7 mUI/mL, and the median was 0.3 mUI/mL [IQR: 0;2]. When expressing this decrease as a proportion of the first HBsAb titer, the mean monthly anti-HBsAb decrease was $0.7 \pm 7\%$. This decline did not differ according to gender, age ($>$ or <40 years) at the first antibody titer, CMV serostatus, or CD4+ T cell nadir ($>$ or $<200/\text{mm}^3$, $>$ or $<500/\text{mm}^3$).

When categorizing the intervals between the two measurements by classes, we observed a gradual loss of HBsAb over time: for example, a median decrease of 4 mUI/ml [IQR: -1;23] for measurements separated by 11 to 14 months, and 1.2 mUI/ml [IQR: 0;44] for measurements separated by 22 to 34 months (Figure 5).

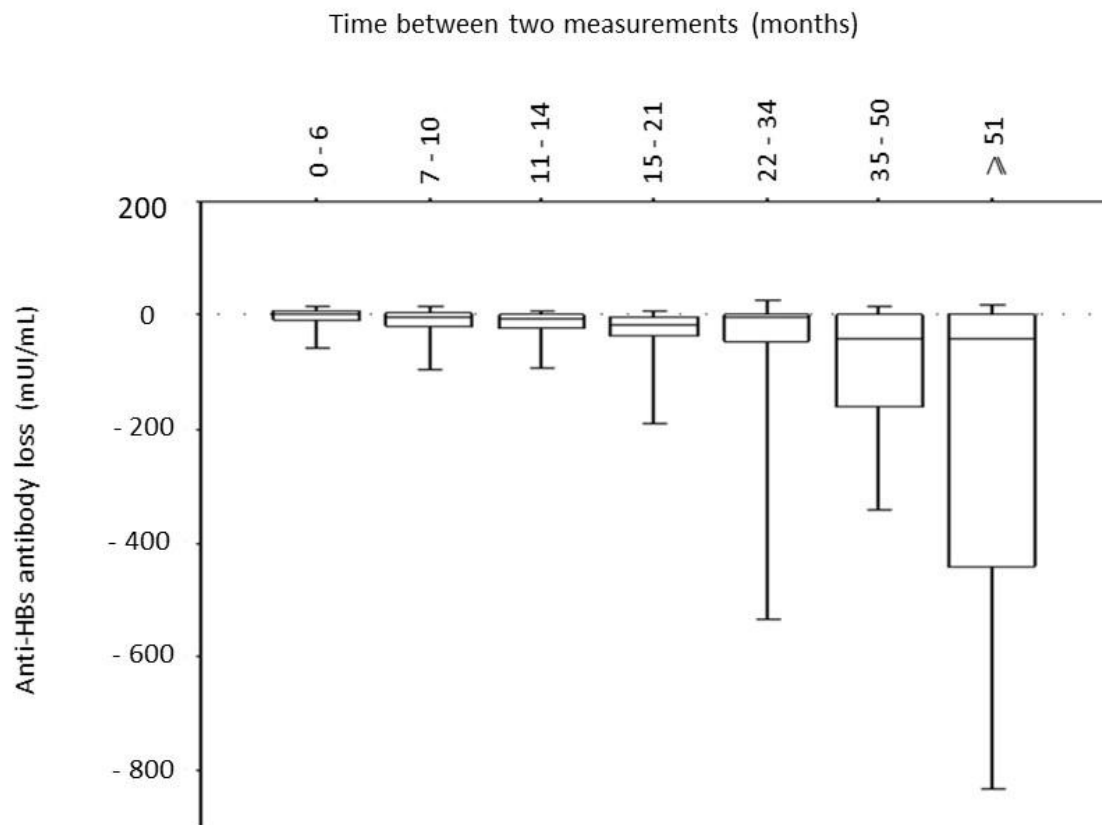


Figure 5: Variations in anti-HBs antibody levels according to the time between the first two measurements

HBsAb dynamics from the analyze of all pairs of measurements

We then analyzed all the successive measurements in 287 patients, i.e., the 887 pairs for which the first measurement was >10 mUI/mL, no anti-HBV vaccine was recorded between the two dates, and no increase of >100 mUI/mL was observed (which may reflect unrecorded vaccination) (Figure 6).

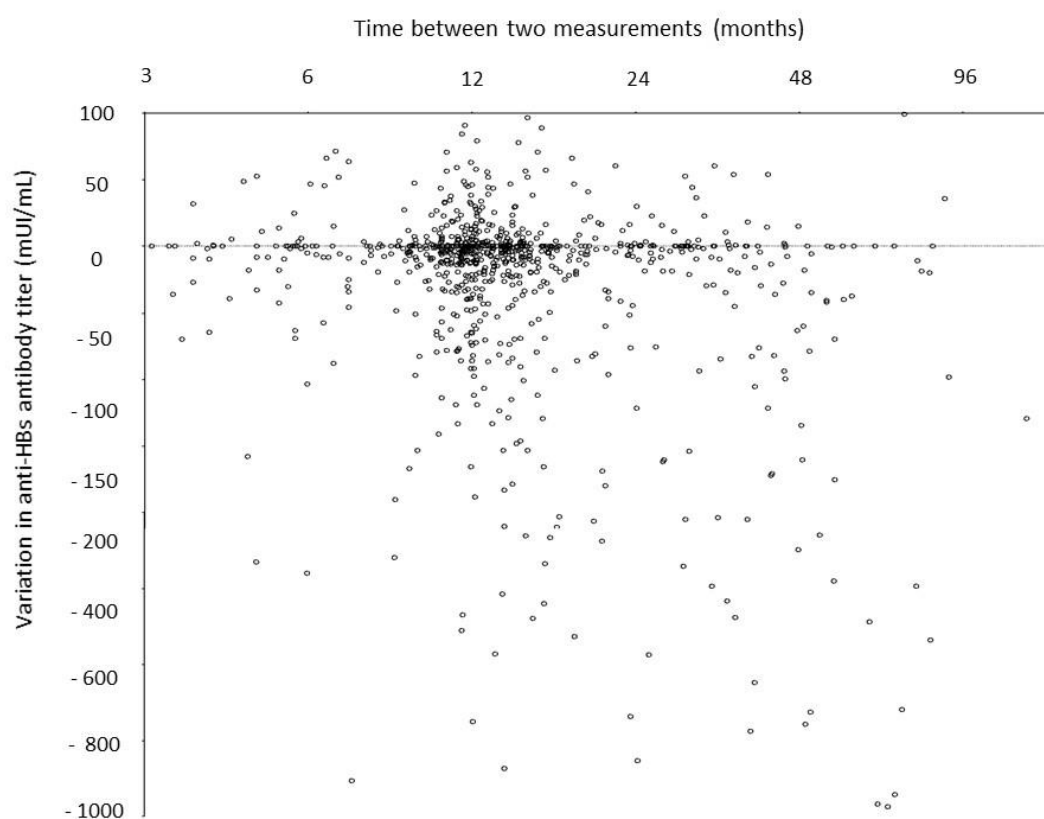


Figure 6: Variations in anti-HBs antibody levels over time (logarithmic scale)

When categorizing the intervals between the two measurements by classes, we observed a loss of HBsAb over time: for example, the decrease was 3.6 mUI/mL [IQR: -2;22] for measurements separated by 11 to 14 months, and 28 mUI/mL [IQR: 0;101] for measurements separated by 35 to 50 months (Figure 7).

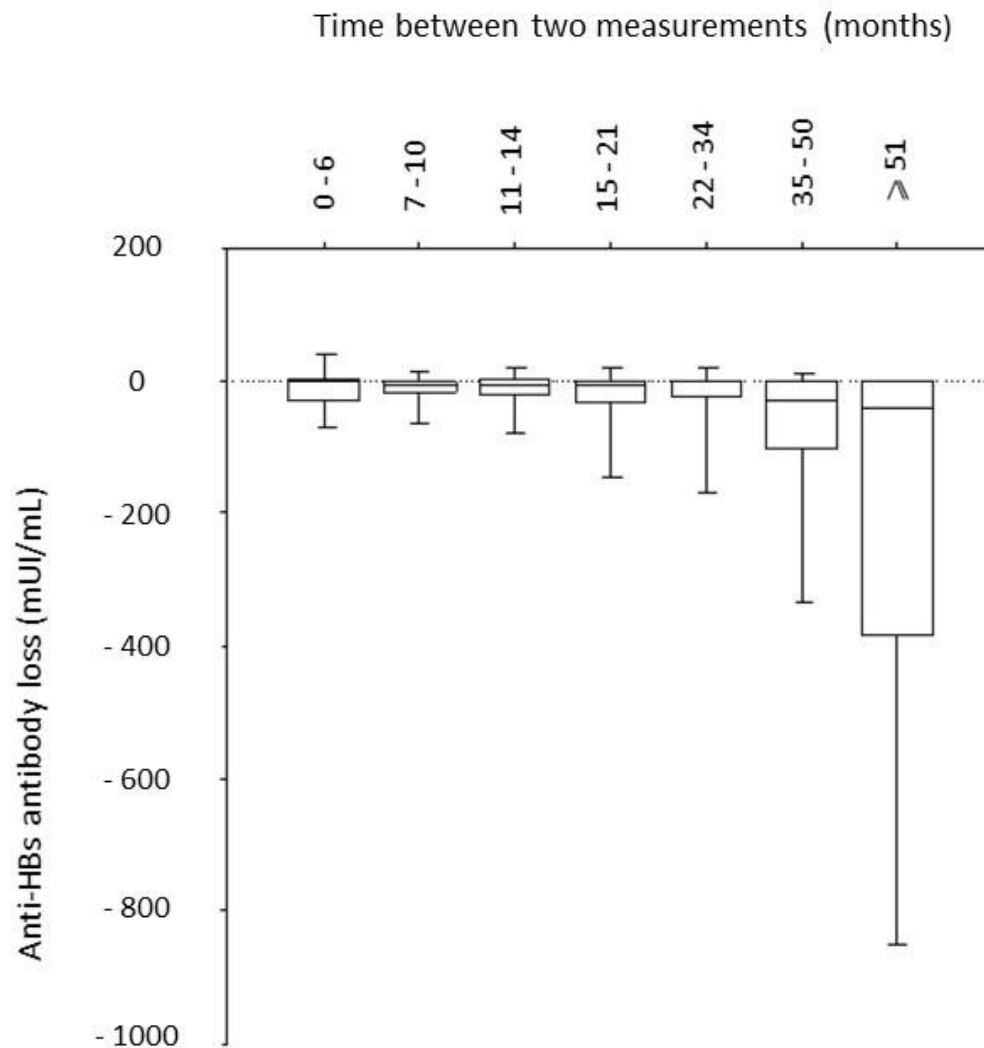


Figure 7: Variations in anti-HBs antibody titers according to the time between the two measurements (all pairs)

The mean monthly HBsAb decrease was 2.6 ± 10 UI/mL, and the median HBsAb decrease was 0.3 mUI/mL [IQR: 0;2]. When expressing this decrease as a proportion of the first HBsAb titer, the mean monthly decrease was $0.7 \pm 3\%$. HBsAb loss did not

differ according to gender, age (> or <40 years) at the first antibody titer, CMV serostatus, or CD4+ T cell nadir (> or <200/mm³, > or <500/mm³). The absolute value of the monthly decay was positively correlated with the initial antibody titer (Rho=0,198, p <0,0001), unlike the relative value.

Time to reach HBsAb <100 mUI/mL

In the Kaplan-Meier analysis of 169 patients with one HBsAb titer of >100 mUI/mL and at least one consecutive measurement (median follow-up: 40 months), the median time to reach an HBsAb value of <100 mUI/mL was 102 months. In particular, the median time was 80 months for patients with an initial titer between 100 and 500 mUI/mL. The majority of PLWHA with an initial HBsAb titer of >500 mUI/mL never reached the lower limit of 100 mUI/mL (Figure 8a). No differences were observed according to gender, age (> or <40 years) at the first measure, CMV serostatus, or CD4+ T cell nadir (> or <200/mm³, > or <500/mm³).

Time to reach HBsAb <10 mUI/mL

Similarly, in the Kaplan-Meier analysis of 287 patients with at least one HBsAb titer of >10 mUI/mL and at least one consecutive measurement not separated by vaccination (median follow-up: 38 months), the median time to a titer of <10 mUI/mL was 150 months. In particular, it was 102 months for PLWHA with a first measurement of <100 mUI/mL, while it was not reached for those with an initial measurement of ≥100 mUI/mL; in the latter group, no patient reached a value of <10 mUI/mL after 96 months (Figure 8b). Again, there was no difference according to gender, age (> or <40 years) at the first measure, CMV serostatus, CD4+ T cell nadir (> or <200/mm³, > or <500/mm³), or gender.

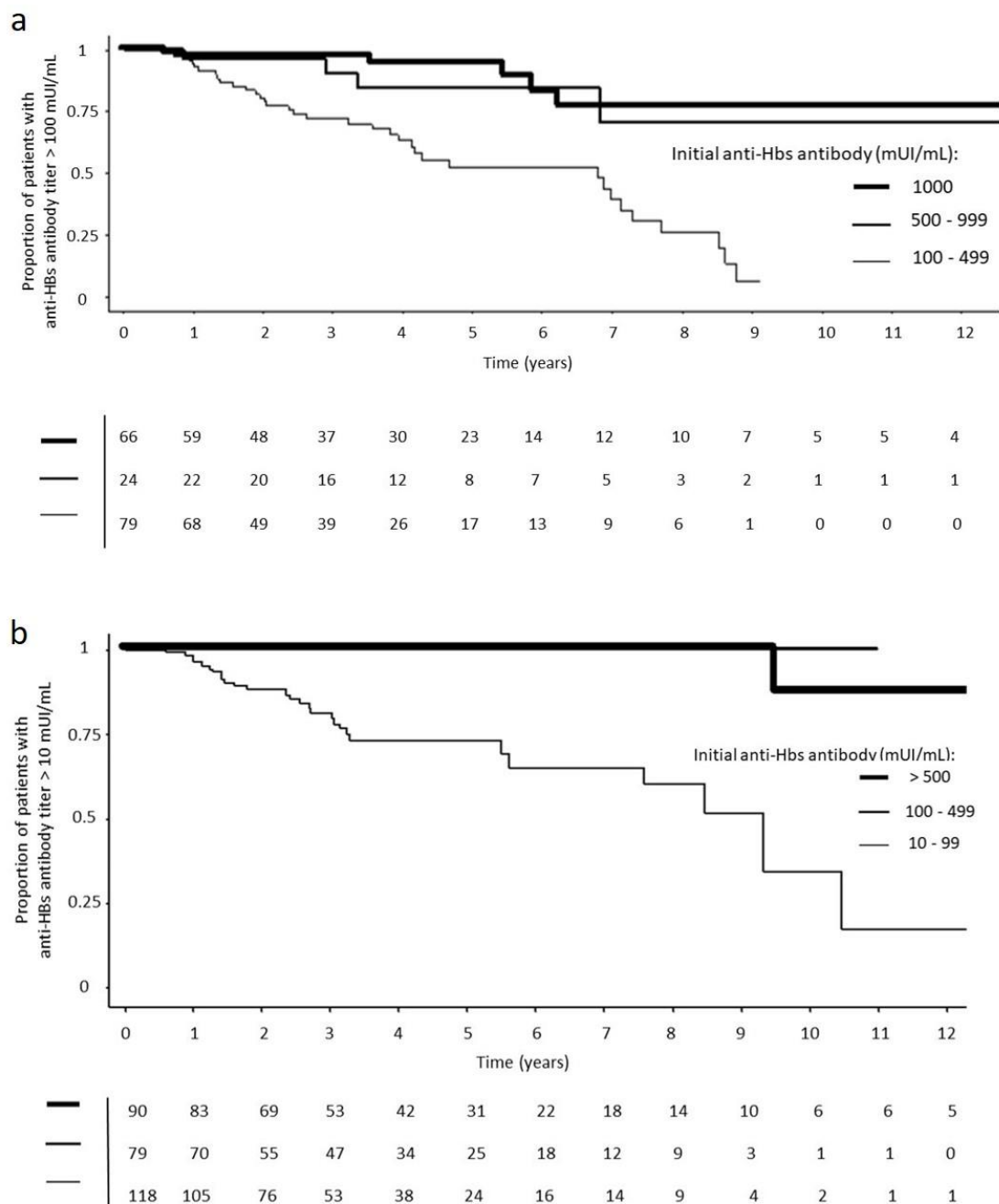


Figure 8:

a) Proportion of patients with anti-HBs antibody titer of >100 mUI/mL over time according to the initial anti-HBs antibody titer.

b) Proportion of patients with anti-HBs antibody titer of >10 mUI/mL over time according to the initial anti-HBs antibody titer

DISCUSSION

We aimed to determine the dynamics of HBsAb waning in vaccinated PLWHA. Our study highlighted the long-lasting HBV seroprotection in this population. More precisely, we observed that protective HBsAb level lasted for several years, and for even longer periods in those with an initial HBsAb level of >500 mUI/mL.

The absolute value of monthly decay was positively correlated with the initial HBsAb level, unlike the relative value. This is consistent with the results of a retrospective study (92) in which the durability of protective HBsAb levels was significantly related to the HBsAb levels after the initial immunization procedure. The authors of this study also observed that HBsAb levels of >100 mUI/mL were associated with long-lasting seroprotection in PLWHA; more precisely, the mean time for the loss of an effective HBsAb titer was 3.7 years for patients with an initial HBsAb titer between 100 and 1000 mUI/mL, and 4.4 years for those with a HBsAb titer of >1000 mUI/mL. These results and our own are also in line with another study in which HBsAb levels of >100 mUI/mL were associated with long-lasting seroprotection in PLWHA (93).

A 2014 meta-analysis of twelve studies highlighted the short-term immunity against HBV in PLWHA, with less than half of primary responders maintaining protective antibodies 2 years after vaccination (94). Some authors still recommend annual check-ups of anti-HBs levels in vaccinated PLWHA at risk of HBV exposure (77,95), whereas other data suggest an interval of 5 years (96). This divergence of results could be partly explained by the differences in the studied populations (particularly the degree of CD4+ lymphopenia) and the HBV vaccination modalities (schedule, dose, etc.), which have evolved in the past few years. Previous studies clearly observed that the initial immune response to HBV vaccination was associated with antiretroviral therapy, control of HIV replication (21-27), and frequently, high CD4+ T cell counts (98,99,103).

In an Italian retrospective study of 60 HIV responders vaccinated with a 20 mg dose HBV vaccination schedule, the persistence of HBV seroprotection was associated with female sex and time-updated CD4 cells count, but not with high HBsAb levels after the completion of the vaccination schedule (96).

Contrary to these previous reports, we did not observe a significant association between the slope of HBsAb decay and the nadir of CD4 cells, age at the first antibody test, gender, or CMV serostatus. This may be related with the fact that the median CD4 T cell nadir of our study population was high, reflecting the fact that few patients were diagnosed with severe immune dysfunction as observed in AIDS. Our results however suggest that the HBV vaccine should be offered to all PLWHA, even those with a low nadir of CD4+ T cells. A retrospective study of the US Military HIV Natural History Study cohort found that the vaccinal response is even better if made prior to HIV infection (104). Nevertheless, even for those vaccinated in the neonatal period, HBV immunity of PLWHA can still wane, and some authors suggest revaccination (105).

The immunological mechanisms of the long-term protection induced by the HBV vaccine are complex, combining humoral and cellular responses through memory B and T cells (80). In our study, the analysis of HBsAb levels focused on the humoral response. We did not assess the possibility of de novo HBV infection by monitoring HBsAg and HBcAb at each measurement. The protective HBsAb threshold of 10 mIU/mL is well proven in non-PLWHA (66,67) and is also considered clinically protective in PLWHA (68).

The major limitation of our study is the lack of complete data regarding HBV vaccinations. Indeed, we retrospectively collected these data from clinical files, and the HBV vaccination date was not always reported. However, we took into account potential cases of unrecorded vaccination by excluding from the analysis the values

showing an increase of >100 mIU/mL in HBsAb levels between two successive measurements. For some patients, we were unable to retrieve the vaccine schedule details and determine whether vaccination occurred before or after HIV seroconversion, which can impact the immune response.

It may also be relevant to study the seroprotection in HBV vaccinated PLWHA with negative HBsAg, negative HBsAb, and positive HBcAb (reflecting a prior HBV infection). These patients may have lost their HBsAb over time, or have an occult HBV infection. In this second possibility, some experts consider that those patients should receive HBV vaccine, since it is susceptible to induce a protective response (21,78). The immune response against HBV vaccine was weak in a multicenter prospective cohort of PLWHIV with isolated anti-HBc, suggesting the potential benefit of a reinforced vaccine schedule (106). The immune response was short-lived in one and two years follow up of HBV vaccinated PLWHA with isolated anti-HBc cohorts (107,108). Nevertheless, at our knowledge, there is no data about the long-term decay of anti-HBs population in HBV vaccinated PLWHA with negative HBsAg and positive HBcAb.

Finally, other methods of preventing HBV infections should not be overlooked, especially avoiding risky behavior (eg, unprotected sex, sharing contaminated materials as needles, toothbrush or razor with chronic hepatitis B infected household members or sexual partner), prevention of mother to child transmission, and HBV immunoglobulin in case of exposure.

The slow and progressive decline of anti-HBsAb levels in vaccinated PLWHA suggests that the monitoring of the anti-HBs response to vaccination should take place no more than every 3 to 4 years and even longer for the patients with anti-HBs levels over 500 mIU/mL at their first measurement post-vaccination. Further investigations are needed to better evaluate the factors associated with the long-term persistence of HBV seroprotection in vaccinated PLWHA.

CONCLUSION

THÈSE SOUTENUE PAR : TOMIO ALICE

TITRE : PERSISTANCE DES ANTICORPS ANTI-HBS POST-VACCINAUX CHEZ LES PERSONNES VIVANTS AVEC LE VIH : UNE RÉPONSE DE LONGUE DURÉE

CONCLUSION :

Il est recommandé que les personnes vivant avec le VIH (PVVIH) soient immunisées contre le virus de l'hépatite B. Un rappel vaccinal doit être réalisé en cas de décroissance du taux plasmatique d'anticorps anti-HBs sous le seuil de protection (10 mUI/mL); cependant la vitesse de décroissance de ce taux est mal connue.

Nous avons inclus toutes les PVVIH adultes suivies dans notre centre qui avaient eu entre 2001 et 2018 au moins 2 déterminations du taux d'anticorps anti-HBs, dont la 1ère >10 mUI/mL, et non séparées par un rappel vaccinal. Nous avons analysé la vitesse de décroissance au cours du temps sur le 1er couple de valeur analysable pour chaque PVVIH, puis pour l'ensemble de tous les couples de valeurs successives. Une analyse de Kaplan-Meier a secondairement été conduite pour déterminer les cinétiques de passage à moins de 100 et 10 mUI/mL.

Sur les 287 patients inclus, 887 couples de valeurs successives étaient analysables. La décroissance moyenne et médiane du taux d'anticorps anti-HBs était de $2,6 \pm 10$ et de 0,29 [-0,02 ; 1,9] mUI/mL par mois, respectivement. Cette diminution représentait $0,7 \pm 3\%$ (moyenne) ou 0,6% (médiane) [0,1 ; 1,8] par mois du titre initial. Il n'y avait pas d'association entre la vitesse de décroissance du taux d'anticorps anti-HBs et le nadir de lymphocytes T CD4, l'âge au 1er taux d'anticorps, le genre, ou le statut sérologique pour le CMV. La décroissance en valeur absolue du taux d'anticorps était corrélée avec le taux d'anticorps initial ($\rho=0.198$, $p<0,0001$), mais pas la valeur relative. L'analyse des 130 patients avec un taux d'anticorps anti-HBs >100 mUI/mL montrait que la médiane d'atteinte d'un taux d'anticorps <100 mUI/mL était de 102 mois, et n'était pas atteinte pour celles dont le taux était >500 UI/mL.

Bien que nos données sur les modalités de vaccination soient partielles, la diminution du taux d'anticorps anti-HBs est lente chez les PVVIH vaccinés contre l'hépatite B. Ces résultats suggèrent qu'une surveillance tous les 3 à 4 ans est suffisante pour guider les rappels vaccinaux, voire à plus large intervalle en cas de taux >500 mUI/mL.

VU ET PERMIS D'IMPRIMER

Grenoble, le 07/05/2021

LE DOYEN

Pr Patrice Morand



LE PRÉSIDENT DE LA THÈSE

Pr Patrice Morand

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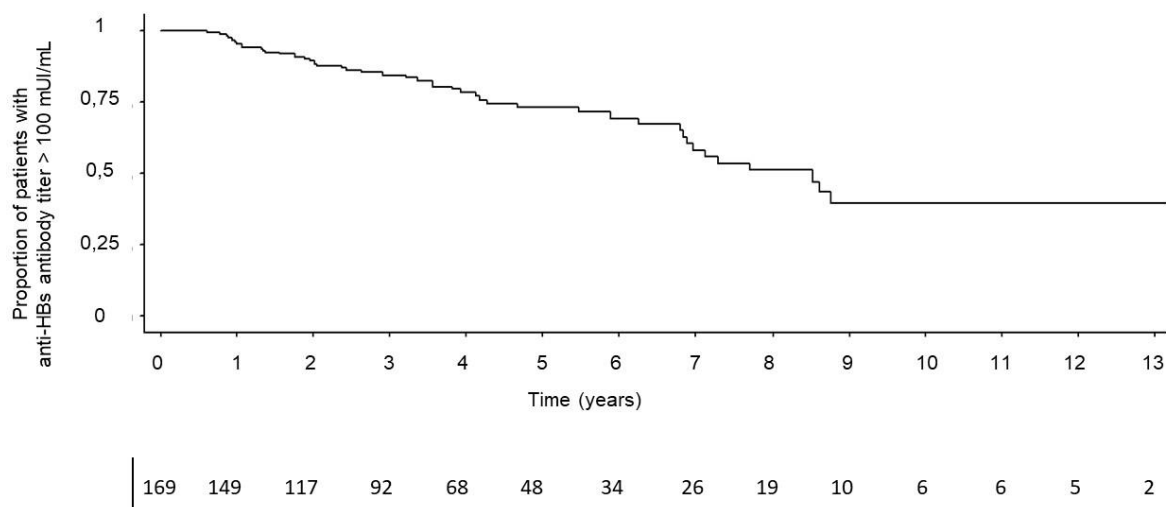
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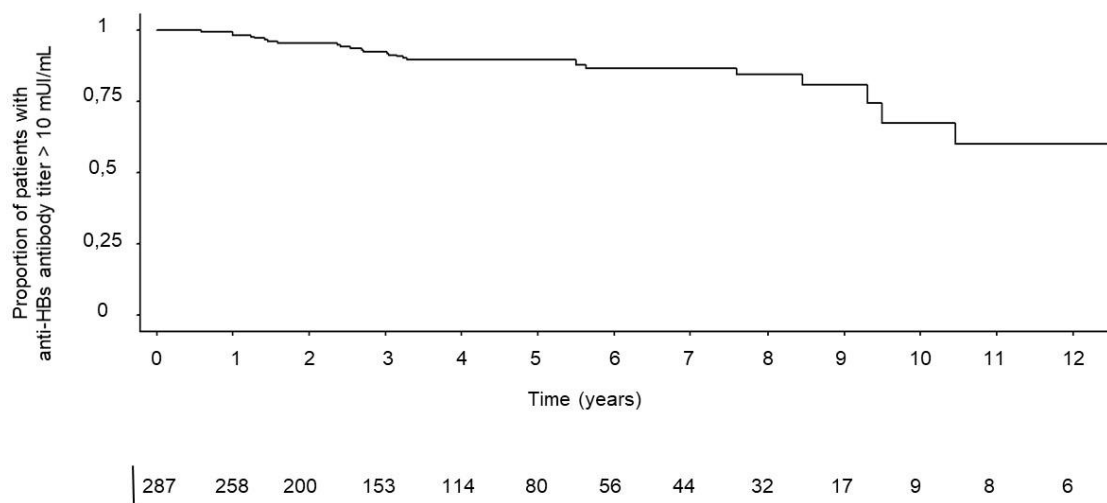
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ANNEXES



Supplementary figure 1: Proportion of patients with anti-HBs antibody titer of >100 mIU/mL over time



Supplementary figure 2: Proportion of patients with anti-HBs antibody titer of >10 mIU/mL over time

*L*e serment d'Hippocrate

Texte revu par l'Ordre des médecins en 2012

“ **Au moment d'être admis(e) à exercer la médecine, je promets et je jure d'être fidèle aux lois de l'honneur et de la probité.**

Mon premier souci sera de rétablir, de préserver ou de promouvoir la santé dans tous ses éléments, physiques et mentaux, individuels et sociaux.

Je respecterai toutes les personnes, leur autonomie et leur volonté, sans aucune discrimination selon leur état ou leurs convictions. J'interviendrai pour les protéger si elles sont affaiblies, vulnérables ou menacées dans leur intégrité ou leur dignité. Même sous la contrainte, je ne ferai pas usage de mes connaissances contre les lois de l'humanité.

J'informerai les patients des décisions envisagées, de leurs raisons et de leurs conséquences.

Je ne tromperai jamais leur confiance et n'exploiterai pas le pouvoir hérité des circonstances pour forcer les consciences.

Je donnerai mes soins à l'indigent et à quiconque me les demandera. Je ne me laisserai pas influencer par la soif du gain ou la recherche de la gloire.

Admis(e) dans l'intimité des personnes, je tairai les secrets qui me seront confiés. Reçu(e) à l'intérieur des maisons, je respecterai les secrets des foyers et ma conduite ne servira pas à corrompre les mœurs.

Je ferai tout pour soulager les souffrances. Je ne prolongerai pas abusivement les agonies. Je ne provoquerai jamais la mort délibérément.

Je préserverai l'indépendance nécessaire à l'accomplissement de ma mission. Je n'entreprendrai rien qui dépasse mes compétences. Je les entretiendrai et les perfectionnerai pour assurer au mieux les services qui me seront demandés.

J'apporterai mon aide à mes confrères ainsi qu'à leurs familles dans l'adversité. Que les hommes et mes confrères m'accordent leur estime si je suis fidèle à mes promesses ; que je sois déshonoré(e) et méprisé(e) si j'y manque.

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