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Quantification of Hepatitis B Surface Antigen: Is there a Role in HIV-Hepatitis B Virus Coinfection?

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Abstract

Hepatitis B surface antigen (HBsAg) level plays an important role in conjunction with other markers such as hepatitis B envelope antigen (HBeAg) and hepatitis B virus (HBV) deoxyribonucleic acid levels to predict disease activity in chronic Hepatitis B (CHB). Quantification of HBsAg is useful in differentiating carriers from active hepatitis in HBeAg negative patients, and current guidelines recommend monitoring of pegylated interferon alpha treatment in CHB infection. However, there are only few studies about the role of quantitative HBsAg (qHBsAg) monitoring in HIV-HBV coinfected patients. Studies have shown that tenofovir based antiretroviral therapy regimen leads to a very slow decline in HBsAg levels and a predicted time of 10-42 years to lose the HBsAg, in majority of patients. Rapid drop in HBsAg levels and gain in CD4 within the 1st year of treatment and low baseline HBsAg level are associated with faster seroconversion. The reported rate of HBsAg loss in this population is < 15%. In this review, we discuss utility of qHBsAg in monitoring disease activity and treatment in HIV-HBV coinfected population. **(AIDS Rev. 2019;21:175-183)**

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Key words

Hepatitis B surface antigen quantification. HIV-hepatitis B virus coinfection. HIV. Hepatitis B.

Introduction

In the era of highly active antiretroviral therapy (ART), the incidence of HIV-related deaths has decreased by 45% between 2000 and 2018 according to the recent World Health Organization (WHO) data[1]. Hepatic disease has been one of the leading causes of non-HIV related mortality[2,3]. HIV and hepatitis B virus (HBV) coinfected patients have a higher risk of liver-related mortality compared to HIV or HBV infection alone[4]. HBsAg is produced from covalently closed circular form of HBV deoxyribonucleic acid (DNA) (covalently closed circular DNA [cccDNA]) as well as integrated HBV DNA[5]. Successful eradication of HBV infection remains a challenge due to persistence of cccDNA in the nucleus of hepatocytes. The current knowledge on cccDNA is limited, and available therapies for HBV infection do not target the eradication of cccDNA[6,7]. Studies have shown that serum hepatitis B surface antigen (HBsAg) levels correspond to the activity of the

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intrahepatic HBV DNA[8,9]. Various clinical studies have assessed the levels of HBsAg in different phases of chronic hepatitis B (CHB) infection, and it has proved to be a useful marker in predicting disease activity. HBsAg loss along with absence of HBV DNA with or without HBsAg seroconversion is considered as functional cure and is not attainable in most patients treated with nucleos(t)ide analog (NA) therapy[10,11]. In this review, we will discuss the potential role of quantification of HBsAg in HIV-HBV coinfected patients.

Epidemiology of HIV-HBV coinfection

According to the recent WHO data, approximately 37.9 million people were HIV infected in 2018, and the global prevalence of HBV infection in HIV infected people was 7.4%[1]. In the United States (U.S.), approximately 10% patients with HIV are coinfected with HBV[12]. Roughly 71% (1.96 million) of HIV-HBV coinfected people live in sub-Saharan Africa[13]. In high prevalence regions (i.e. Asia and sub-Saharan Africa), HBV is acquired in infancy through perinatal transmission and at a young age and has a high likelihood to progress to chronic HBV infection[14]. In Western Europe and U.S., HBV infections are acquired more commonly during adulthood through sexual contact, injection drug use, and occupational exposure and are less likely to progress to chronic phase. Accordingly, the prevalence in the U.S. and Western Europe is between 7 and 9% and is highest among men who have sex with men and/or intravenous drug users (IVDU)[15,16].

Natural course of HBV infection in HIV

HBV-specific T cell responses play an important role in the destruction of HBV-infected hepatocytes. HIV-induced impairment of CD4+ T cells impairs host ability to mount an effective T-cell response resulting in an unchecked replication of HBV virus, leading to persistent HBV infection. This is supported by the fact that HIV-infected people are more likely to progress to chronic phase after acute hepatitis B infection and people with higher CD4+ T-cell counts are more likely to clear HBsAg[17]. In a study by Colin et al., the prevalence of HBV DNA levels and cirrhosis was higher in HIV-HBV coinfected individuals as compared to those who are HIV negative[18]. Moreover, coinfected individuals have higher prevalence, and slower clearance of hepatitis B envelope antigen (HBeAg) compared to HIV-negative people. HIV-HBV coinfection was associated with a 14-fold increase in mortality compared to those without HBV in a multicenter cohort study. The increased mortality was attributable to lower CD4 counts[4]. In addition, reappearance of HBsAg after serological clearance has also been reported in HIV-HBV coinfected patients more often than in HBV monoinfected patients[19].

HBV virologic life cycle and HBsAg

The cccDNA produced by the HBV during infection is present in the nucleus and serves as a template for transcription of viral ribonucleic acid (RNA) and proteins. cccDNA is stable and has a long half-life which makes it persistent and difficult to cure. It can lead to the reactivation of HBV infection after clearance of HBsAg. An accurate measure of cccDNA would require a liver biopsy. HBsAg is the principal envelope protein of the HBV and exists in three sizes – small, medium, and large. HBsAg is generated from either cccDNA or integrated DNA. Although integrated DNA cannot produce a replication-competent virion, it has been found to be an important source of HBsAg production[5]. The surface antigen proteins generate infectious virions as well as non-infectious subviral particles (SVP). These non-infectious SVPs exist in spherical and filamentous forms and are usually present in excess amounts in the serum of infected patients (Fig. 1). They may play a role in suppressing humoral immunity. It is thought to block the generation of antibodies to HBsAg, hence reducing the chances of HBsAg seroconversion and leading to persistence of infection[11,20].

There are four widely available commercial assays for the detection of quantitative HBsAg (qHBsAg). They include the Architect HBsAg assay (Abbott Diagnostics), the Elecsys HBsAg II assay (Roche diagnostics), the DiaSorin Liaison XL assays, and the highly sensitive Lumipulse HBsAg HQ assay[21]. These commercially available assays for quantification of HBsAg cannot differentiate between the infectious and non-infectious forms of HBsAg[11]. Table 1 describes and compares the four commercially available assays. Discrepancies in the results between different assays have been reported due to the presence of HBsAg mutants; hence, they must be interpreted carefully[22].

Definitions of HBV cure

The functional cure is considered when there is loss of HBsAg and suppression of HBV DNA with or without HBsAg seroconversion. The virological cure is considered when cccDNA can be eradicated. Although functional cure can be attained in a very small subset of

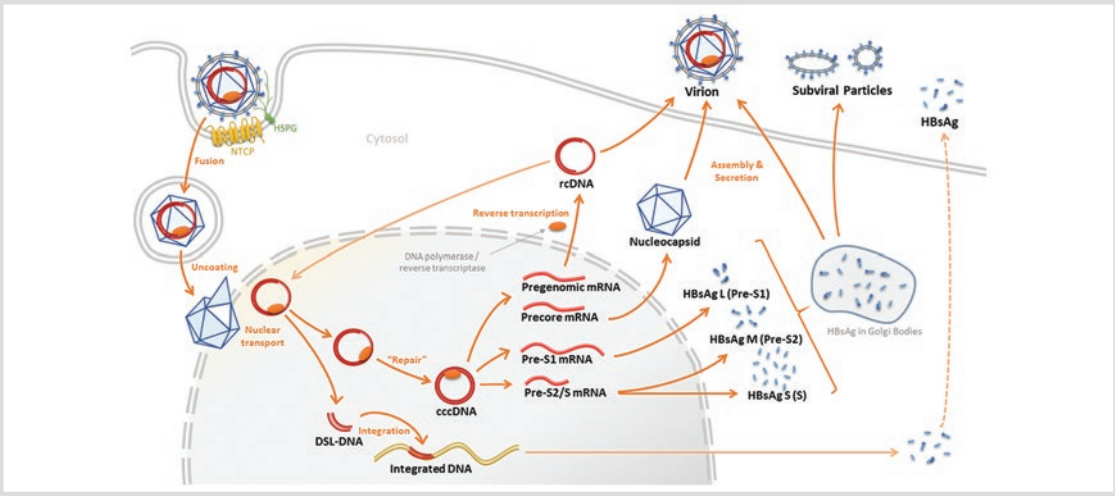

Figure 1. *Hepatitis B surface antigen (HBsAg) has three components: small-HBsAg (S-HBsAg), middle-HBsAg (M-HBsAg) and large-HBsAg (L-HBsAg). Low-affinity binding by the S-HBsAg to heparan sulfate proteoglycan, followed by high-affinity attachment by the L-HBsAg to the sodium taurocholate cotransporting polypeptide receptors on the hepatocyte cell membrane allows fusion subsequent entry of the virus into the cell. The viral genetic material within a nucleocapsid in the form of a relaxed circular deoxyribonucleic acid (rcDNA) is transported and released into the nucleus. The viral polymerase/reverse transcriptase enzyme converts this rcDNA to the covalently closed circular DNA, which acts as a transcription template for the various viral ribonucleic acids needed for replication. The surface proteins (L-HBsAg, M-HBsAg, and S-HBsAg) can form non-infectious subviral particles through the Golgi body pathway. Some of the intra-nuclear double-stranded linear DNA (DSL-DNA) can integrate into the host genome which can also produce HBsAg.*

Table 1. Characteristics of commercially available quantitative HBsAg assays

Assay characteristics	Architect HBsAg assay (Abbott diagnostics)[60]	Roche diagnostics HBsAg II assay[61]	DiaSorin Liaison XL assay[62]	Lumipulse HQ[63]
Principle of assay	Two-step chemiluminescent microparticle immunoassay	Automated electrochemiluminescence immunoassay	Direct two-step sandwich chemiluminescence assay	Automated chemiluminescent enzyme immunoassay instrument
Assay range (IU/mL)	0.05-250	0.05-130	0.030-150	0.005-150
Analytical sensitivity (IU/mL)	0.05	0.05	0.03	0.005
Capture antibodies	Monoclonal	Monoclonal	Monoclonal	Monoclonal
Conjugate antibodies	Polyclonal	Monoclonal+Polyclonal	Monoclonal	Monoclonal

HBsAg: hepatitis B surface antigen

infected patients with current therapies, virologic cure is currently not achievable[23].

Phases of chronic HBV infection

HBV causes chronic infection over the years and goes through several phases during the course of infection. Chronic HBV infection can be divided into four phases: HBeAg positive immunotolerant phase and immunoactive phase and HBeAg negative inactive disease and immunoreactive phase[24]. HBeAg positive CHB infection phase, usually occurs after perinatal infection and is characterized by high viral replication and low inflammation, with high HBV DNA levels and HBsAg levels >100,000 IU/mL[25,26].

Over years, it can progress to the next phase with active hepatitis leading to inflammation and necrosis. Infections acquired in adulthood progress to this immune active phase faster. A patient with chronic HBV can transition between these phases multiple times in life.

Occult HBV infection is characterized by the presence of HBV DNA in the absence of detectable serum HBsAg. The prevalence in HIV positive individuals varies between 1% in U.S. and 15% in South Africa[27]. HIV and immunosuppression are some predisposing risk factors for occult HBV and may cause reactivation and flares. It may have further clinical implications in blood transfusion and organ transplant recipients[28].

qHBsAg in chronic HBV infection

HBeAg negative patients may present as inactive carriers, who have a low risk of progression to cirrhosis and hepatocellular carcinoma (HCC) or may progress to chronic active infection. HBV viral loads and alanine transaminase levels are important markers to identify active hepatitis in HBeAg negative patients; however, their fluctuating levels can make distinguishing inactive and active challenging. HBsAg levels may be helpful in differentiating hepatitis from inactive carriers in HBeAg negative patients[10].

In a Taiwanese cohort with genotypes B and C from the REVEAL-HBV study, a single time measurement of HBsAg level <1000 IU/mL and HBV DNA <2000 IU/mL had sensitivity 71%, specificity 85%, positive predictive value 83%, negative predictive value 74%, and an overall diagnostic accuracy of 78% in distinguishing inactive carriers from active CHB[29]. In another cohort of genotype D patients, using similar cutoffs, higher sensitivity (91%), specificity (95%), and diagnostic accuracy (94%) were reported[30]. In HBeAg negative CHB patients with baseline HBV DNA<2000 IU/ml, a baseline HBsAg level of <10 IU/ml was a strong predictor of HBsAg loss in future[31]. The cumulative risk for cirrhosis was 4.8%, 8.8%, and 16.2%, and HCC was 1.4%, 4.5%, and 9.2% in patients with HBsAg levels <100, 100-1000, and >1000 IU/mL, respectively[32]. In patients on treatment with NAs, >1 $\log_{10}$ IU/mL drop/year in HBsAg levels is associated with seroclearance[25]. Thus, qHBsAg levels can be useful in identifying patients with active hepatitis and starting therapy.

HBsAg quantification is also useful to monitor response to treatment with Peg-interferon (IFN) alpha and is recommended for monitoring by the European Association for the Study of the Liver and AASLD guidelines. In HBeAg positive patients, HBsAg levels >20,000 IU/mL or no response after 12 weeks of treatment are associated with low rates of seroconversion and are used as an indicator to stop therapy. Similarly, in HBeAg negative patients with genotype D, no decrease in HBsAg level along with < 2 $\log_{10}$ decreases in HBV DNA is a predictor of poor response and used as a marker to stop treatment[21,26].

Comparison of HBsAg levels in HIV-HBV coinfection and HBV monoinfection

Immune status plays an important role in the pathogenicity of HBV; hence, HIV infection influences the course of CHB infection. In a study by Jaroszewicz et al., HBsAg levels were higher in HIV-HBV coinfected individuals compared to HBV alone (4.29 vs. 3.94 $\log_{10}$ IU/mL, p = 0.016)[33]. HBsAg levels were at least 1 $\log_{10}$ IU/mL higher in patients with CD4 count of <200 cells/µL as compared to those with higher counts (4.30 vs. 3.31 $\log_{10}$ IU/mL, p = 0.001). The highest HBsAg levels were seen in those with advanced AIDS (Centers for Disease Control and Prevention Stage C). They were also higher in HBeAg positive patients. The HBsAg levels were 1 $\log_{10}$ IU/mL lower in treated patients as compared to untreated, but the difference was significant only in HBeAg positive patients[33]. In a Ukrainian cohort study by Moroz et al., HBsAg levels were higher in coinfected patients as compared to monoinfected, in all phases of CHB infection – HBeAg positive, immune active, and HBeAg negative inactive as well as reactivation phase[34].

qHBsAg as a predictor of seroclearance in HIV-HBV coinfection

There are various factors that impact the HBsAg levels in coinfected patients, which includes immune restoration and treatment. There are few studies in literature that have assessed the kinetics and role of HBsAg levels in predicting serological conversion in HIV-HBV coinfection.

The rate of loss of HBsAg has been < 15% in various studies with HIV-HBV coinfected patients (Table 2). High rates of HBeAg loss, ranging from 36 to 48%, have been reported[35-37]. Studies have shown that a decline of > 1 $\log_{10}$ IU/mL HBsAg at 1 year was predictive of seroclearance[36]. In a study by Strassl et al., baseline HBsAg level of < 100 IU/mL in HBeAg negative patients had 100% sensitivity and 83% specificity in predicting HBsAg loss[36].

In a sub-Saharan study by Boyd et al., a drop of 1 $\log_{10}$ IU/mL of HBsAg at 1 year had 95% specificity

Table 2. Summary of studies on quantitative HBsAg levels in HIV-HBV coinfected patients

Study/Year/Number of patients	Reference	Population characteristics			Follow up duration (months)	Results
		HBV genotype (most common)	HIV suppression and ART	Median CD4 cell count/mL		
Strassl et al. 2014 Vienna retrospective study (n = 59)	36	A, D, and mixed A/G	93% on TDF/FTC based regimen	310	First sample tested after 16 months of ART	**In HBeAg positive** – Baseline lower CD4, higher HBsAg level and HBV DNA – 15% had HBsAg loss – Decline in HBsAg of 1 log IU/ml/year predicts earlier loss **In HBeAg negative** – 13.6% had HBsAg loss – Baseline HBsAg level of < 100 IU/ml has 100% sensitivity and 83% specificity in predicting HBsAg loss
Zoutendijk et al. 2012 Dutch multicenter cohort study (n = 104)	37	A	TDF based regimen for 6 months	288	57	**In HBeAg positive:** – 8% HBsAg loss – 2 log IU/ml drop of HBsAg at 6 months predictive of seroclearance – Rise in CD4 count at 6 and 12 months correlated with HBsAg decline **In HBeAg negative** – Had 0.6 log IU/ml drop in 6 years – 8% with HBsAg loss
Maylin et al. 2012 France multicenter cohort study (n = 143)	35	A and G	76% with HIV VL suppressed at 1 year	461	30	**In HBeAg positive** – Change in HBsAg level was faster in patients with CD4 >350 cells/μL – 4% had HBsAg loss, and 75% of them had level less than 400 IU/ml
Matthews et al. 2013 Thailand prospective study (n = 47)	39	C	100% suppression during follow up TDF, 3TC or FTC based until 48 weeks, TDF based after	Nadir 48	42	– 13% had HBsAg loss – HBsAg drop of >0.5 log IU/ml at 12 week and > 1 log IU/ml drop at 24 weeks had sensitivity of 100% and specificity 43-84% to predict HBsAg loss
Boyd et al. 2015 France prospective study (n = 290)	41	A, followed by D, G, and E	Most patients switched to TDF + 3TC/FTC based regimen	400 (268-554)	88	– 5.9% patients lost HBsAg at median 4.6 years, but three reverted back, and 64% seroconverted. – Higher decline in qHBsAg during the first 3 years in patients who underwent HBsAg loss.

(Continues)

Table 2. Summary of studies on quantitative HBsAg levels in HIV-HBV coinfected patients *(Continued)*

Study/Year/Number of patients	Reference	Population characteristics			Follow up duration (months)	Results
		HBV genotype (most common)	HIV suppression and ART	Median CD4 cell count/mL		
Boyd et al. 2016 Abidjan, Côte d'Ivoire observational study (n = 161)	38	E	Either TDF or 3TC based regimen 29% with CD4 guided interruption and 36% with 2 months interruptions	312 (220-430)	36	– 6.2% had HBsAg clearance – Baseline HBsAg level of < 100 IU/ml or < 10 IU/ml at 12 months were 90% sensitive and 100% specific in predicting seroclearance – Decline > 1 log IU/ml at 12 months had 95% specificity and 65% sensitivity in predicting clearance – Lower baseline qHBsAg levels, and greater 12-months changes in CD4 + cell count and qHBsAg levels were significantly associated with clearance in both HBeAg positive and negative patients

TDF: tenofovir disoproxil fumarate; 3TC: lamivudine; FTC: emtricitabine; VL: viral load; ART: antiretroviral therapy; HBsAg: hepatitis B surface antigen, HBV: hepatitis B virus.

and 65% sensitivity in predicting clearance[38]. Faster decline in HBsAg levels has been associated with HBsAg seroclearance[37]. In a Thai cohort study, a > 1 $\log_{10}$ IU/mL drop in HBsAg level at 6 months had 100% sensitivity and 84% specificity in predicting seroclearance[39]. For the patients who had a steady decline in HBsAg level, predicted time to clearance varied from 10 to 42 years[37,40]. In the French cohort study, 64% patients who lost HBsAg developed anti-HBs antibodies. Three patients (17.6%) who had unstable HBsAg levels reverted back to being HBsAg positive after 1.3-3.7 years, and one of them had liver-related morbidity[41]. Another study from Brazil showed a 50% HBsAg reappearance rate in coinfected patients who had HBsAg loss[42].

The above studies show that a baseline low level of HBsAg and faster rate of qHBsAg decline during the 1st year of treatment are good predictors of future HBsAg loss.

HBsAg levels in hepatitis delta infection

Hepatitis delta virus (HDV) is an incomplete single-stranded RNA virus that requires viral envelope of HBV to complete virion assembly and secretion. Hence, HDV infection always occurs in association with HBV infection. About 15-20 million people are infected with HDV worldwide, which is approximately 5% of chronically HBV infected people[43]. Progression of liver fibrosis is faster and mortality from cirrhosis and HCC is higher in HDV as compared to HBV or HCV infection[44]. At present, only Peg IFN alpha has been approved for the treatment of HDV infection for patients with elevated HDV RNA and ALT levels[21]. The ideal goal of HDV treatment is eradication of both HBV and HDV. Many studies have shown that HDV RNA and HBsAg levels are useful markers to assess response to therapy with Peg IFN alpha[45,46]. In the study by Niro et al., HBsAg kinetics were assessed in 62 patients with HDV treated with IFN alpha. HBsAg level <1000 IU/ml and a decrease of at least 0.105 log from baseline were associated with HDV clearance. These values can be used as a marker to interrupt therapy and avoid unnecessary treatment[46]. These studies show that HBsAg along with HDV RNA is useful in predicting response to treatment and will remain an important tool in studying new treatment drugs.

Factors that affect HBsAg and its seroclearance

Several studies on HIV-HBV coinfection have shown that faster immune restoration, represented by a higher

increase in CD4 count in short time have a greater decline in qHBsAg. Baseline CD4 cell count > 350 cells/μL and increase in absolute CD4 cell count by 100 cells/μL in the 1st year were associated with greater qHBsAg decline[35,37,47]. Mitsumoto et al. reported three patients who experienced liver failure due to hepatitis B related immune reconstitution inflammatory syndrome. These patients had greater decline in qHBsAg compared to patients who did not have liver failure, and decline was remarkable at the time of liver failure. The patient who experienced liver failure had lower nadir CD4 counts and greater increase in CD4 count of 119 cells/μL compared to 64 cells/μL in patients without liver failure after 8 weeks of treatment initiation[48]. Higher rate of HBsAg loss has been reported in patients who have early hepatic failure characterized by ALT elevation > 5 × upper limit of normal within first 12 weeks of therapy[49]. One study from France reported a significant association of HBsAg loss with baseline advanced HIV (Stage C), while another study from New York reported higher rate of HBsAg loss in patients with a baseline CD4 cell count >500 cells/μL[50,51].

In a study by Tuaillon et al., patients with optimal adherence to ART and sustained HIV viral load suppression had 0.38 $\log_{10}$ IU/mL/year decline in HBsAg compared to patients who had suboptimal adherence with HIV virologic failure who had 0.15 $\log_{10}$ IU/mL/year decline[40]. In another study which published data with 6 years follow-up of HIV-HBV coinfected patients, who were on tenofovir based ART and had HIV viral load suppressed as well as undetectable HBV DNA, the HBsAg levels were variable with a steady decrease in only 39% patients[52]. In a prospective cohort study, Peg IFN alpha was added to TDF containing regimen in patients for 1 year and compared to TDF regimen alone. The rates of decline of HBsAg and HBeAg were faster during the year of treatment, but there was no difference in the two groups after 1 year or in HBsAg clearance[53].

HBV can have mutations in HBsAg, basal core promoter and precore proteins, and anti-drug resistance mutations. HBsAg mutations that can impair the HBsAg secretion decrease its levels and can affect the sensitivity of the commercial HBsAg assays leading to false-negative results[54]. A study in HIV-positive individuals with occult HBV infection showed that the mutations in "a" determinant region of HBV led to decreased HBsAg levels[55]. In a study by Lacombe et al., an increase in incidence of polymerase and surface antigen gene mutations was observed in HIV-HBV coinfection, but no significant liver-related complications occurred[56]. Another study in West African patients with HIV-HBV coinfection, the absence of G1896A mutation in precore protein was associated with increase in HBsAg loss[57]. Thus, HBsAg levels must be interpreted carefully since they can be false negative in patients with mutations.

Conclusion and recommendations

The course of HBV infection in HIV is dynamic due to the interplay with the immune system. There is increased progression to cirrhosis and liver-related mortality in HIV-HBV coinfected patients. HBsAg level plays an important role in conjunction with other markers such as HBeAg and HBV DNA levels to predict disease activity in CHB. At present, the guidelines recommend the use of HBsAg levels in monitoring Peg IFN therapy. qHBsAg levels have been shown to be useful in distinguishing inactive carriers from active hepatitis in HBeAg negative patients and thus help in risk stratification and impact decision of starting treatment.

In patients with HIV-HBV infection, the utility of qHBsAg remains unclear, since lifelong therapy is warranted due to HIV infection. HBV DNA remains a significant marker to assess response to therapy with NA in coinfected patients. qHBsAg cannot substitute HBV DNA since it measures active replication[58]. The studies in HIV-HBV population so far have revealed that lower baseline qHBsAg, steep decline during the 1st year of treatment, and rapid gain in CD4 within 1 year of treatment initiation have been associated with HBsAg loss. However, the results of these studies do not alter the treatment of coinfected patients. It might be useful in patients who need tenofovir sparing regimens; however, there are not enough studies to suggest appropriate endpoints for stopping NA therapy. Unlike HBV monoinfected patients, the utility of qHBsAg in HIV-HBV coinfected patients remains limited. With the currently available evidence in HIV-HBV coinfected patients, the utility of regular monitoring of HBsAg levels in clinical practice at this time remains limited; hence, routine clinical use of qHBsAg cannot be recommended at this time.

Prospective studies with long-term monitoring of HBsAg levels to predict the risk of cirrhosis and HCC are needed since there is higher liver-related mortality in this population.

Several new drugs for HBV treatment are in development include HBV entry inhibitor, core inhibitors, cccDNA inhibitors, capsid inhibitors, HBsAg release blockers, RNA interference molecules, as well as host

targeting agents[59]. Since qHBsAg fairly correlates with the replicative activity of cccDNA, trials being conducted evaluating the efficacy of these agents utilizes decline in HBsAg as their primary endpoint. It would be reasonable to monitor the levels every 3-6 months; however, the best interval in monitoring HBsAg response will not be known until an HBV agent able to induce functional cure is found. Nonetheless, qHBsAg remains an indispensable tool in assessing the treatment response in new drug trials and has potential for clinical use in future when better treatment options will be available.

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