

Possible association of *HLA-DP* polymorphism and antiretroviral therapy with hepatitis B virus clearance in an HIV-infected Vietnamese population

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Abstract: There is little evidence regarding the association between hepatitis B virus (HBV) chronicity and *HLA-DP* among the HIV-infected Vietnamese population. To study this, we conducted a cross-sectional analysis and a prospective study involving an HIV-infected Vietnamese cohort. The association between HBV chronicity and *HLA-DP* single nucleotide polymorphisms (SNPs) of rs3077 and rs9277535 among Vietnamese patients with previous HBV exposure was first evaluated. In addition, treatment-naïve patients with chronic HBV infection were followed between 2012 and 2017 for HBV clearance after the initiation of antiretroviral therapy (ART). A total of 820 subjects with previous HBV exposure were included in the cross-sectional study. Among them, 147 (17.9 %) had chronic HBV infection, and 673 (82.1 %) achieved HBV clearance. The proportions of minor allele homozygotes of rs3077 and rs9277535 were 10.9 % and 15.2 % ($p = 0.481$) and 4.1 % and 11.7 % ($p = 0.003$), respectively. Multivariate analysis showed that rs9277535 minor homozygote was a significant protective factor against chronic HBV infection (odds ratio [OR], 0.271; 95 % confidence interval [CI]; 0.114-0.642, $p = 0.001$). Further, none of the 43 patients in the prospective study, who received ART possessed the rs9277535 minor homozygote. The average follow-up period was 4.8 years, and 10 subjects (23.3 %, 4.9 %/person-years) achieved HBV clearance. Univariate analysis revealed that the SNPs were not significantly associated with HBV clearance. In conclusion, our study confirmed that the rs9277535 minor allele homozygote was significantly associated with HBV clearance among HIV-infected Vietnamese patients.

Keywords: hepatitis B virus, HIV, *HLA-DP*, Vietnamese

Introduction

Hepatitis B virus (HBV) infection is a global public health threat, with more than 240 million carriers worldwide (1). Chronic HBV infection (*i.e.*, positive for hepatitis B surface antigen [HBsAg] for at least six months) is highly endemic in Asia, where its prevalence is more than 8 % in some countries (2). The estimated prevalence of chronic HBV infection in Vietnam is over 8 % in the general adult population (1) and reaches up to 15 % in people who use drugs or female sex workers (3). More than 70 % of new hepatocellular carcinomas (HCCs) diagnosed globally were reported from Asia, where chronic HBV infection is one of the major causes of HCC (4).

Although the mechanisms that contribute to HBV chronicity and clearance are not fully understood, various factors including those related to the virus and host and other extrinsic elements are considered important.

Considering host-related factors, age at which infection occurred was strongly and inversely related to the risk of chronicity. Ninety percent of perinatally acquired HBV infections develop into chronic HBV infections (5); 20-50% of children between the age of one and five years old (6), and less than 5% of adults develop chronic HBV infections (7). Previous genome-wide association studies (GWAS) identified relationships between *HLA-DP/DQ* polymorphisms (*HLA-DP* rs3077, rs9277535, *HLA-DQ* rs2856718, rs7453920) and HBV clearance (8,9). These findings were confirmed among various ethnic groups, including the Japanese, Han Chinese, Korean, Thai, and Saudi Arabian populations (10-12).

Additionally, HBV and HIV infections are commonly diagnosed in the same patient because both these viruses share similar routes of transmission. Unlike HBV mono-infected patients, all HIV/HBV co-infected patients should be treated to suppress both viruses regardless of HBV DNA level or degree of liver damage (13).

The preferred regimen for HIV infection includes a combination of lamivudine (3TC) or emtricitabine (FTC) plus tenofovir disoproxil fumarate (TDF) or tenofovir alafenamide (TAF), which acts strongly against HBV. These therapies suppress HBV and HIV viral loads and prevent the development of hepatic complications (14); however, HBsAg antigen clearance is rarely achieved. The relationship between HBsAg clearance and *HLA-DP* single nucleotide polymorphisms (SNPs) among people living with HIV remains to be elucidated. Thus, we evaluated the relationship between HLA and HBsAg clearance among a Vietnamese population living with HIV in a cross-sectional study. Further, we evaluated the relationship between HLA and response to treatment using a TDF/3TC-based regimen in a longitudinal study in Vietnam.

Patients and Methods

Study design

We performed a cross-sectional study and a prospective, observational study on a single-center cohort of Vietnamese HIV-infected individuals to evaluate the relationship between *HLA-DP* SNPs and HBsAg clearance. This cohort was established in 2007 at the National Hospital for Tropical Disease (NHTD) in Hanoi, one of the largest outpatient clinics for HIV-infected patients in Vietnam. The population of this cohort comprised Vietnamese HIV-infected patients aged > 18 years who were referred to the NHTD.

In the cross-sectional study, to analyze the relationship between *HLA-DP* and HBsAg clearance, all the participants enrolled in the cohort until May 2016 were evaluated for their HBV status, including HBsAg, hepatitis B surface antibody (HBsAb), hepatitis core antigen (HBcAg), and hepatitis C antibody (HCVAb) at the time of recruitment. Those who tested positive for HBcAb were regarded as subjects with previous HBV exposure and were included in the present study. These subjects were evaluated for their *HLA-DP* and other factors including liver enzyme, administration of antiretroviral therapy (ART), and immune status to analyze the relationship between HBV chronicity and factors including *HLA-DQ*.

In the prospective study, ART-naive subjects with chronic HBV infection were included and followed for HBV clearance after initiation of ART between October 2012 and October 2019. In addition to the testing of factors mentioned in the cross-sectional study, HBe antigen (HBeAg) and HBV DNA were measured every six months; HBV genotype and HBV drug resistance were measured at baseline. The association between HBV clearance, antiretroviral treatment, and other factors, including *HLA-DP*, were prospectively evaluated. The definition of HBV clearance was defined as HBs Ag conversion from positive to negative, namely,

HBs Ag clearance.

Measurements

Clinical and laboratory data included demographic variables (age and sex), history of ART, CD4+ cell count (cell/mm³, measured by flow cytometry), plasma HIV RNA (copies/mL, measured by the Roche COBAS TaqMan HIV monitor assay), serum aspartate aminotransferase (AST, U/L), and alanine aminotransferase (ALT, U/L). As serological markers of HBV, HBsAg (IU/mL) and HBeAg (signal to cut-off ratio, S/CO) were measured using a chemiluminescent enzyme immunoassay (CELIA). HBV DNA was measured using real-time polymerase chain reaction (PCR). For the genotyping assay of HBV, eight genotypes (A to H) were determined genetically using the PCR-invader method (structure-specific 5' nuclease-based method). To evaluate *HLA-DP* SNPs, two SNPs at the 3' untranslated region of *HLA-DPA1* and *HLA-DPB1* gene, namely, rs3077 and rs9277535 were selected because in previous studies these SNPs were identified as having a strong correlation with HBV chronicity (8,15). TaqMan SNP Genotyping Assays (Thermo Fisher Scientific, MA, USA) were used to determine the rs3077 and rs9277535 genotypes.

Statistical analysis

In the cross-sectional study, characteristics were compared between HBsAg-positive and HBsAg-negative patient groups using the Student's *t*-test for continuous variables and either the χ^2 test or Fisher's exact test for categorical variables. In the prospective study, the time from baseline to HBV clearance was analyzed using Cox proportional hazards regression analysis to estimate the impact of *HLA-DP* SNPs and other factors on the incidence of HBV clearance. Variables significantly associated with HBsAg clearance in the univariate analysis ($p < 0.05$) were entered into the multivariate analysis. Statistical significance was defined as a two-sided p value < 0.05. All statistical analyses were performed using SPSS software, version 23.0 (IBM Corp., Armonk, N.Y., USA).

The study was approved by the Human Research Ethics Committee of NCGM (NCGM-A-000238-00) and NHTD (IORG 0006480). All the study participants provided written informed consent for the use and publication of their clinical and laboratory data. This study was conducted in accordance with the principles of the Declaration of Helsinki.

Results

Since October 2007, 1,820 patients were registered for the cohort; 1,441 were enrolled and underwent follow-up in May 2016. Of them, 820 were positive for HBcAb and

were included in the cross-sectional study. Table 1 shows the basic demographics of patients with and without HBsAg positivity at the time of enrollment. Of the 820 study subjects, 147 (17.9%) had chronic HBV infection, and 673 (82.1%) achieved HBV clearance. The average age of patients with and without chronic HBV infection was 34.5 and 35.2 years, respectively ($p = 0.343$). The proportion of females was 28.5% and 31.6% in both these groups, respectively ($p = 0.223$). The average serum AST and ALT levels in these groups were 36.6 and 41.0 U/L ($p = 0.099$) and 42.4 and 47.1 U/L ($p = 0.192$), respectively. The average CD4+ cell count, indicating HIV infection status of these groups was 277.3 and 263.5 (cell/mm³), respectively. The proportion of patients with HIV RNA < 200 copies/mL and the proportion of patients who underwent ART in the two groups were 68.7 % and 73.0 % ($p = 0.391$) and 78.2 % and 84.8 % ($p = 0.049$), respectively. The proportion of patients positive for HCVAb was 42.1 % and 27.3 % ($p = 0.254$), respectively. *HLA-DP* polymorphism signified by the proportions of minor allele homozygotes of rs3077 (AA) and rs9277535 (AA) were 10.9% and 15.2% ($p = 0.481$)

and 4.1% and 11.7% ($p = 0.003$), respectively.

In univariate analysis, SNP rs9277535 was significantly associated with HBsAg clearance and the administration of ART and SNP rs3077 was marginally associated with HBsAg clearance (Table 2). These three factors were entered into the multivariate analysis and the rs9277535 minor homozygote was identified as a significant protective factor against chronic HBV infection (odds ratio [OR]: 0.271, 95 % confidence interval [CI]; 0.114-0.642, $p = 0.001$), and the administration of ART was marginally associated with HBsAg clearance (OR, 0.646; 95 % CI, 0.411-1.014; $p = 0.057$).

A prospective study was also conducted to evaluate HBsAg clearance followed by HIV/HBV treatment with TDF/3TC among treatment-naïve patients with HIV and chronic HBV coinfection. During the study period, 43 patients were included in this prospective study, and ART was initiated. Baseline characteristics are shown in Table 3. The mean age was 34.7 years, and 32.6% (14/43) were women. While 42 of the patients (97.7%) were administered ART containing TDF/3TC, the remaining

Table 1. Baseline characteristics of Vietnamese patients according to HBsAg status in the cross-sectional study

Variables	Overall (n = 820)	HBsAg Positive (n = 147)	HBsAg Negative (n = 673)	p value
Age, years	35.1 ± 8.56	34.5 ± 7.79	35.2 ± 8.71	0.343
Female, n (%)	252 (30.7)	39 (26.5)	213 (31.6)	0.223
HCVAb (+), n (%)*	360 (46.3)	61 (42.1)	299 (47.3)	0.254
Asparate aminotransferase, U/L	41.0 ± 35.0	36.6 ± 20.5	41.9 ± 37.3	0.099
Alanine aminotransferase, U/L	46.3 ± 40.2	42.4 ± 28.3	47.1 ± 42.4	0.192
CD4+ cell count, cell/μL	266.0 ± 176.0	277.3 ± 170.7	263.5 ± 177.1	0.391
HIV RNA < 200 copies/ml, n (%)	592 (72.2)	101 (68.7)	491 (73.0)	0.298
Use of ART, n (%)	686 (83.7)	115 (78.2)	571 (84.8)	0.049
SNPs (rs3077) minor allele homozygote, n (%)	118 (14.4)	16 (10.9)	102 (15.2)	0.481
SNPs (rs3077) heterozygote	325 (39.6)	53 (36.0)	272 (40.4)	0.327
SNPs (rs3077) major allele homozygote, n (%)	377 (46.0)	78 (53.1)	299 (44.4)	0.057
SNPs (rs9277535) minor allele homozygote, n (%)	85 (10.4)	6 (4.1)	79 (11.7)	0.003
SNPs (rs9277535) heterozygote, n (%)	338 (41.2)	54 (36.7)	284 (42.2)	0.223
SNPs (rs9277535) major allele homozygote, n (%)	397 (48.4)	87 (59.2)	310 (46.1)	0.004

Data are expressed as mean ± SD or n (%). HBsAg, hepatitis B surface antigen; HCVAb, hepatitis C virus antibody; ART, antiretroviral therapy; SNP, single nucleotide polymorphism. *There are missing values.

Table 2. Evaluation of factors associated with HBsAg clearance using univariate and multivariate analyses

Variables	Univariate analysis		Multivariate analysis		
	OR	95% CI	OR	95% CI	p value
Age	0.990	0.968 – 1.011			
Female sex	0.780	0.522 – 1.164			
HCVAb (+), n (%)*	0.809	0.562 – 1.165			
Asparate aminotransferase, U/L	1.001	0.998 – 1.004			
Alanine aminotransferase, U/L	1.000	0.998 – 1.003			
CD4+ cell count, cell/μL	1.000	0.999 – 1.001			
HIV RNA < 50 copies/mL, n (%)	0.814	0.552 – 1.200			
Administration of ART	0.642	0.411 – 1.002	0.646	0.411 – 1.014	0.057
SNPs (rs3077) minor allele homozygote	0.601	0.336 – 1.077	0.889	0.467 – 1.690	0.719
SNPs (rs9277535) minor allele homozygote	0.271	0.114 – 0.642	0.296	0.118 – 0.743	0.010

OR, odds ratio; CI, confidence interval HBsAg, hepatitis B surface antigen; HCVAb, hepatitis C virus antibody; ART, antiretroviral therapy; SNP, single nucleotide polymorphism. *There are missing values.

one subject received ART containing only 3TC as an effective agent against HBV. Ten (23.3 %) subjects were positive for HBeAg. HBV DNA was undetectable in nine (20.9%) patients. Among the 35 subjects with successful genotype analysis, genotype B was the most prevalent (29/35, 23 for genotype Ba and two for genotype B, subtype not determined), followed by genotype C (7/35). HBV resistance to entecavir was observed in 6.5% (2/31) of the patients. Twelve (27.9%) subjects were HCV-positive. None of them possessed the *HLA-*

DP rs9277535 minor homozygote, which was identified as a protective factor for chronic HBV infection in the cross-sectional study. The *HLA-DP* rs3077 minor allele homozygote was observed in four (9.3%) subjects.

These 43 subjects were followed until October 2019 (average follow-up period 4.8 years). Of them, 10 (23.3%, 4.9%/person-years) achieved HBsAg clearance. Of 10 with HBeAg positive at the baseline, among whom one (10%, 1.94%/person-years) subject achieved HBeAg clearance. Although the sample size was quite limited, we attempted to identify factors associated with HBsAg clearance, including *HLA-DP* (Table 4). In univariate analysis, the SNPs were not significantly associated with HBsAg clearance, while the inverse association of HBV DNA with HBsAg clearance was statistically significant.

Table 3. Baseline characteristics of treatment-naïve HIV-infected Vietnamese patients in the prospective study

Variables	Overall (n = 43)
Age, years	34.7 ± 9.6
Female, n (%)	14 (32.6)
HCVAb (+), n (%) [*]	12 (27.9)
Aspartate aminotransferase, U/L	41.2 ± 21.6
Alanine aminotransferase, U/L	39.0 ± 23.1
CD4+ cell count, cell/μL	280.2 ± 161.6
HIV RNA load, copies/mL	143,593.6 ± 327,525.7
HBsAg,	5,503 ± 13,015.9
HBeAg positive, n (%)	10 (23.3%)
HBV DNA	4.5 ± 3.2
HBV genotype, n (%) [*]	Genotype B, 29 (82.9) Genotype C, 7 (20) Mix of B and C, 1 (2.9)
HBV drug resistance, n (%) [*]	2 (6.5)
SNPs (rs3077)	
Minor allele homozygote	3 (7.0)
Heterozygote	21 (48.8)
Major allele homozygote	19 (44.2)
SNPs (rs9277535)	
Minor allele homozygote	0 (0)
Heterozygote	18 (41.9)
Major allele homozygote	25 (58.1)

Data are expressed as mean ± SD or n (%). HBsAg, hepatitis B surface antigen; HCVAb, hepatitis C virus antibody; HBsAg, hepatitis B surface antigen; HBeAg, hepatitis E surface antigen; SNPs, single nucleotide polymorphisms. ^{*}There are missing values.

Discussion

In our cross-sectional study, we found that HBV clearance was associated not only with *HLA-DP* rs9277535 minor homozygote, but also with ART among HIV-infected Vietnamese patients. To the best of our knowledge, this is the first study to illustrate these associations among HIV-infected Vietnamese individuals. However, our attempt to elucidate the causative relationship between HBV clearance and *HLA-DP* among the HIV-infected Vietnamese patients who received ART in the prospective study was unsuccessful. This was because these subjects did not possess the *HLA-DP* rs9277535 minor homozygote, probably on account of the allele's protective nature against HBV chronicity. Our cross-sectional and prospective studies showed that there was no relationship between rs3077 minor allele homozygote and HBV clearance; this finding corresponds to that of a previous study conducted in Taiwan (16). Although it may be roughly speculated that the irrelevance of rs3077 could be because of the

Table 4. Factors associated with HBsAg clearance in the prospective study estimated by univariate analysis

Variables	Univariate analysis		
	HR	95% CI	p value
Age, years	1.002	0.940 – 1.068	0.958
Female, n (%)	0.772	0.199 – 2.998	0.709
HCVAb (+) [*]	0.685	0.142 – 3.309	0.638
Aspartate aminotransferase, U/L	0.962	0.916 – 1.009	0.112
Alanine aminotransferase, U/L	0.976	0.936 – 1.018	0.253
CD4+ cell count, cell/μL	1.001	0.997 – 1.006	0.587
HIV RNA load, copies/mL	1.000	1.000 – 1.000	0.840
HBsAg	1.000	0.999 – 1.000	0.162
HBeAg positive	0.030	0.000 – 10.885	0.243
HBV DNA	0.764	0.616 – 0.949	0.015
HBV genotype [#]	0.027	0.000 – 231.5	0.435
HBV drug resistance [#]	1.000	0.000 – 46,237.8	1.000
SNPs (rs3077) minor allele homozygote	0.046	0.000 – 1,132,461.3	0.723
SNPs (rs9277535) heterozygote	0.271	0.034 – 2.172	0.219

[#]10 patients cleared HBsAg after initiation of ART among 43 patients with chronic HBV infection in this prospective phase (see Table 3). HR, hazard ratio; CI, confidence interval; HBsAg, hepatitis B surface antigen; HCVAb, hepatitis C virus antibody; HBsAg, hepatitis B surface antigen; HBeAg, hepatitis E surface antigen; SNPs, single nucleotide polymorphisms; ART, antiretroviral therapy. ^{*}There are missing values.

Vietnamese ethnicity of the study group, considering the relatively close ethnicity between our study group and that of the Taiwanese study group, further research is warranted.

Previous study findings show that the rate of HBsAg clearance after initiation of different therapeutic strategies among HIV/HBV co-infected individuals varied between 1.7% and 2.6%/person-years; this was lower than the value of 4.9%/person-years determined in the current study (17-19). This result may be attributed to the relatively longer follow-up period in our study. In addition to TDF containing ART, higher CD4+ T cell counts have been identified in previous studies (20,21). Our findings in the prospective study indicate that no factors are associated with HBsAg clearance; this may be attributed to the small sample size. Nevertheless, a recent study revealed that immune reconstitution-induced inflammatory syndrome (IRIS) after ART was associated with HBsAg loss in HIV/HBV co-infected individuals (22). Although IRIS was not assessed in our study, the relationship between IRIS and *HLA-DP* is of interest and requires further investigation, given the hypothesis that IRIS is induced by HBV-specific cytotoxic CD8+ T cells, which could be related to *HLA-DP*. The study lacked subjects with rs9277535 minor allele, one of the key factors, in the prospective study, resulting in inability to evaluate exact impact of *HLA-DP* on HBsAg clearance. Further prospective studies with larger sample size are required for sound analysis, given a possible protective effect of this factor on HBV clearance.

This study has several limitations. First, the time and mode of HBV transmission were unknown in most cases in this study; thereby, resulting in difficulty in estimating whether HBsAg clearance was achieved before or after acquisition of HIV among the subjects who tested negative for HBsAg and positive for HBcAb. This information would have been especially useful in the cross-sectional study where 83.7% of the participants received ART at the time of enrollment into the cohort. However, the finding in the cross-sectional study that identified ART as a factor associated with HBsAg clearance suggest that most subjects achieved HBsAg clearance after HIV acquisition. Second, while we evaluated the association of only two *HLA-DP* SNPs, *i.e.*, rs3077 and rs9277535 with HBV clearance, more recent studies analyzed multiple HLA polymorphism alleles using a GWAS. This might have been one of the causes for negative outcomes in the prospective study, in addition to the small sample size and the absence of *HLA-DP* rs9277535 minor homozygote in the subjects, which was the main focus of the study; this precludes a sound analysis such as Mendelian randomization. The impact of HLP-DP genotypes on HBV clearance in this special population needs to be evaluated in a further study.

In conclusion, the present study showed that the *HLA-DP* minor allele rs9277535 homozygote and ART

were significantly and marginally associated with HBsAg clearance, respectively, among HIV-infected Vietnamese individuals in the cross-sectional study. Nevertheless, further prospective studies with larger sample size are warranted to confirm the causative relationship.

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References

- Schweitzer A, Horn J, Mikolajczyk RT, Krause G, Ott JJ. Estimations of worldwide prevalence of chronic hepatitis B virus infection: a systematic review of data published between 1965 and 2013. *Lancet*. 2015; 386:1546-1555.
- Ott JJ, Stevens GA, Groeger J, Wiersma ST. Global epidemiology of hepatitis B virus infection: new estimates of age-specific HBsAg seroprevalence and endemicity. *Vaccine*. 2012; 30:2212-2219.
- Nguyen VT. Hepatitis B infection in Vietnam: current issues and future challenges. *Asia Pac J Public Health*. 2012; 24:361-373.
- Ashtari S, Pourhoseingholi MA, Sharifian A, Zali MR. Hepatocellular carcinoma in Asia: prevention strategy and planning. *World J Hepatol*. 2015; 7:1708-1717.
- Stevens CE, Beasley RP, Tsui J, Lee WC. Vertical transmission of hepatitis B antigen in Taiwan. *N Engl J Med*. 1975; 292:771-774.
- Tassopoulos NC, Papaevangelou GJ, Sjogren MH, Roumeliotou-karayannis A, Gerin JL, Purcell RH. Natural history of acute hepatitis B surface antigen-positive hepatitis in Greek adults. *Gastroenterology*. 1987; 92:1844-1850.
- Wasley A, Grytdal S, Gallagher K; Centers for Disease Control and Prevention (CDC). Surveillance for acute viral hepatitis--United States, 2006. *MMWR Surveill Summ*. 2008; 57:1-24.
- Kamatani Y, Wattanapokayakit S, Ochi H, *et al*. A genome-wide association study identifies variants in the *HLA-DP* locus associated with chronic hepatitis B in Asians. *Nat Genet*. 2009; 41:591-595.
- Mbarek H, Ochi H, Urabe Y, Kumar V, Kubo M, Hosono

- N, Takahashi A, Kamatani Y, Miki D, Abe H, Tsunoda T, Kamatani N, Chayama K, Nakamura Y, Matsuda K. A genome-wide association study of chronic hepatitis B identified novel risk locus in a Japanese population. *Hum Mol Genet.* 2011; 20:3884-3892.
10. Guo X, Zhang Y, Li J, Ma J, Wei Z, Tan W, O'Brien SJ. Strong influence of human leukocyte antigen (HLA)-DP gene variants on development of persistent chronic hepatitis B virus carriers in the Han Chinese population. *Hepatology.* 2011; 53:422-428.
 11. Nishida N, Tokunaga K, Mizokami M. Genome-wide association study reveals host genetic factors for liver diseases. *J Clin Transl Hepatol.* 2013; 1:45-50.
 12. Al-Qahtani AA, Al-Anazi MR, Abdo AA, Sanai FM, Al-Hamoudi W, Alswat KA, Al-Ashgar HI, Khalaf NZ, Eldali AM, Viswan NA, Al-Ahdal MN. Association between HLA variations and chronic hepatitis B virus infection in Saudi Arabian patients. *PLoS One.* 2014; 9:e80445.
 13. Saag MS, Benson CA, Gandhi RT, *et al.* Antiretroviral drugs for treatment and prevention of HIV infection in adults: 2018 Recommendations of the International Antiviral Society-USA Panel. *JAMA.* 2018; 320:379-396.
 14. Price H, Dunn D, Pillay D, Bani-Sadr F, de Vries-Sluijs T, Jain MK, Kuzushita N, Mauss S, Núñez M, Nüesch R, Peters M, Reiberger T, Stephan C, Tan L, Gilson R. Suppression of HBV by tenofovir in HBV/HIV coinfecting patients: a systematic review and meta-analysis. *PLoS One.* 2013; 8:e68152.
 15. Liao Y, Cai B, Li Y, Chen J, Tao C, Huang H, Wang L. Association of *HLA-DP/DQ* and *STAT4* polymorphisms with HBV infection outcomes and a mini meta-analysis. *PLoS One.* 2014; 9:e111677.
 16. Cheng HR, Liu CJ, Tseng TC, Su TH, Yang HI, Chen CJ, Kao JH. Host genetic factors affecting spontaneous HBsAg seroclearance in chronic hepatitis B patients. *PLoS One* 2013; 8:e53008.
 17. Toscano AL, Correa MC. Evolution of hepatitis B serological markers in HIV coinfecting patients: a case study. *Rev Saude Publica.* 2017; 51:24.
 18. Boyd A, Canini L, Gozlan J, Lascoux-Combe C, Miaillhes P, Fonquernie L, Girard PM, Lacombe K. Development of anti-hepatitis B surface (HBs) antibodies after HBs antigen loss in HIV-hepatitis B virus co-infected patients. *J Clin Virol.* 2017; 95: 55-60.
 19. Martin-Carbonero L, Teixeira T, Poveda E, Plaza Z, Vispo E, González-Lahoz J, Soriano V. Clinical and virological outcomes in HIV-infected patients with chronic hepatitis B on long-term nucleos(t)ide analogues. *AIDS.* 2011; 25:73-79.
 20. Arendt E, Jaroszewicz J, Rockstroh J, Meyer-Olson D, Zacher BJ, Mederacke I, Manns MP, Wedemeyer H, Cornberg M, Wurstthorn K. Improved immune status corresponds with long-term decline of quantitative serum hepatitis B surface antigen in HBV/HIV co-infected patients. *Viral Immunol.* 2012; 25:442-447.
 21. Gantner P, Cotte L, Allavena C, Bani-Sadr F, Huleux T, Duvivier C, Valantin MA, Jacomet C, Joly V, Chéret A, Pugliese P, Delobel P, Cabié A, Rey D; Dat'AIDS Study Group. Higher rates of HBsAg clearance with tenofovir-containing therapy in HBV/HIV co-infection. *PLoS One.* 2019; 14: e0215464.
 22. Yoshikawa S, Yoshio S, Yoshida Y, *et al.* Impact of immune reconstitution-induced hepatic flare on HBsAg loss in HBV/HIV-1-coinfected patients. *J Infect Dis.* 2021; 223:2080-2089.
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