


ORIGINAL ARTICLE

# Prevalence of hepatitis B e antigenemia in Bahraini hepatitis B patients: A retrospective, single-center study

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## Key words

Bahrain, comorbidities, hepatitis B, hepatitis B e antigen, hepatocellular carcinoma, laboratory, liver transplant, radiology.

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## Abstract

**Background and Aim:** Hepatitis B e (HBe) antigen (HBeAg) is commonly encountered among hepatitis B patients and is indicative of active infection. There is a lack of data in the literature about the prevalence of HBeAg among hepatitis B patients in Bahrain and its impact on the disease. The aims of this study were to investigate the prevalence of HBeAg among a sample of hepatitis B patients in Bahrain and to analyze their associated laboratory profile, radiological characteristics, comorbidities, and complications.

**Methods:** This was a retrospective record-review study conducted on patients' records at Salmaniya Medical Complex hospital in Bahrain during the period of 2011–2016. All records of hepatitis B patients who had HBeAg tests performed were included in this study.

**Results:** Of 323 patients recruited, 18.9% had positive HBeAg. The prevalence of anti-HBe antibodies and hepatitis B core immunoglobulin G (HBc IgG) differed significantly between patients with positive and negative HBeAg ( $P < 0.001$ ,  $P = 0.026$ , respectively). Alanine transferase and gamma-glutamyl transferase were significantly higher among patients with positive HBeAg ( $P = 0.017$ ,  $P = 0.016$ , respectively). There was no significant difference with regard to the prevalence of hepatitis C virus, human immunodeficiency virus, hepatocellular carcinoma, or liver transplantation between HBe-positive and -negative patients ( $P \geq 0.05$ ).

**Conclusion:** HBeAg is prevalent among hepatitis B patients in Bahrain and is associated with a significantly different laboratory profile.

## Introduction

Hepatitis B e antigen (HBeAg) is one of the small polypeptides detected in the sera of patients with hepatitis B virus (HBV).<sup>1,2</sup> It is detected shortly after the appearance of hepatitis B surface (HBs) antigens, rising rapidly during the early stage of infection and swift viral replication.<sup>1</sup> Thus, the existence of HBeAg in patients' sera correlates with the degree of infectivity of the HBV and with the number of infectious virions.<sup>1</sup> In many studies, the HBeAg level in patients' sera also correlates with the existence of hepatitis B core (HBc) antigens in hepatocytes. After the infection quietens, the level of HBeAg declines gradually until it becomes undetectable during the recovery of acute hepatitis B infection. Meanwhile, hepatitis B e (HBe) antibodies increase and remain positive for several years after resolution of the acute hepatitis.<sup>1</sup>

Evaluation of the state of HBeAg positivity in hepatitis B patients is an essential indicator for infectivity and the viral replication state.<sup>3,4</sup> From a patient perspective, it provides information about the development of anti-HBe immunity, a turning point in

the battle between HBV and its host, and can be used to monitor response to treatment. The mode of transmission and the clinical course of HBV infection can also be determined by the length of the HBeAg-positive phase.<sup>4</sup> In addition, HBeAg status is incorporated in management guidelines internationally,<sup>3,5</sup> where it directs treatment choices and decisions to discontinue treatment.<sup>6</sup> Knowing the infectivity of patients with HBV can also help plan further measures for disease control because the primary mode of transmission is person to person, either through vertical or horizontal transmission.<sup>7</sup> In Bahrain, 61% of infections were estimated to be due to dental procedures and surgical operations, followed by blood transfusions (24%).<sup>8</sup>

In Bahrain, the prevalence of HBV infection was reported to be 0.58%, with the number increasing over the past few years.<sup>8</sup> The most common HBV genotypes reported among this population are genotypes D (61%) and A (10%).<sup>9</sup> Epidemiological data relating to HBeAg in any population would provide important data about the infectivity of the disease and the importance of disease control.<sup>1</sup> To the best of our knowledge, there is

**Table 1** Demographic data among the studied groups ( $n = 323$ )

	Hepatitis B e antigen (HBeAg) positive ( $n = 61$ , 18.9%)	HBeAg negative ( $n = 262$ , 81.1%)	Statistical test	<i>P</i> -value
Age				
M (SD)	45.3 (15.9)	46.33 (14.3)	$t = 0.5$	0.620
(Min, Max)	(16, 82)	(19, 88)		
Gender				
Male	36 (59.0)	191 (59.1)	$\chi^2 = 0$	0.984

Values are number and (%) unless otherwise is specified.

$\chi^2$ : Chi-square test;  $t$ : Independent  $t$ -test.

a lack of data in the literature about the prevalence of HBeAg positivity among hepatitis B patients in Bahrain.

## Objectives

The aims of this research were to study the prevalence of HBeAg among hepatitis B patients in Bahrain and to study the impact of the existence of these antigens on the laboratory profile; radiological characteristics; and hepatitis complications, such as cirrhosis, hepatocellular carcinoma (HCC), or liver transplantation.

## Methods

This was a record-review study conducted in Salmaniya Medical Complex (SMC) in Bahrain during the period 2011–2016. Bahrain has a universal health-care system, and the government provides free health care to Bahraini citizens and subsidized health care for non-Bahrainis. The SMC hospital is the main public hospital in the country and is considered a tertiary hospital that serves the whole nation, a population of 1.7 million as of 2020. The SMC hospital has all specialties available and receives referrals from other government hospitals, private hospitals, and health centers (including primary care) scattered all over the country. The hospital is considered the main center for the treatment of hepatitis B as all treatments are available, and therefore, it receives referrals for patients with hepatitis.

The records that were eligible for inclusion in this study were only those of hepatitis B patients who had undergone HBeAg testing. Demographic data were collected from all records (e.g. age and gender). Laboratory data included HBeAg, anti-HBe antibodies (anti-HBe Ab), HBs antigen (HBsAg), HBe immunoglobulin M (HBe IgM), HBe immunoglobulin G (HBe IgG), HBV DNA level, hepatitis C virus (HCV), human immunodeficiency virus (HIV), alanine transferase (ALT), alkaline phosphatase (ALP), gamma-glutamyl transferase (GGT), bilirubin, albumin, urea, and creatinine. Data from hepatic imaging were also gathered. Details on comorbidities were recorded,

which included diabetes mellitus, hypertension, hyperlipidemia, HCV, liver or renal transplant, HIV, hypothyroidism, lymphoma, inflammatory bowel disease (IBD), and solid organ cancer.

All data were fed into the computer and analyzed using the Statistical Package for Social Science (SPSS) software, version 23.0 (IBM, Armonk, NY, USA).<sup>10</sup> Categorical variables were presented as frequencies and percentages. Continuous variables were presented as means  $\pm$  SDs. Chi square, Fisher's exact, and student-independent  $t$  tests were used for comparison of means between patients with positive and patients with negative HBeAg depending on the normality of variables. The comparison between the two groups was made in regard to the demographic data, the lab profile, the radiological characteristics, the associated comorbidities, and the associated complications. Statistical analysis was performed at the 0.05 level of significance.

## Results

Of 323 hepatitis B patients recruited, 18.9% ( $n = 61$ ) had positive HBeAg. The mean age of patients did not differ between the HBeAg-positive ( $45.3 \pm 15.9$  years) and the HBeAg-negative ( $46.3 \pm 14.5$ ) groups ( $P = 0.62$ ). Males constituted 59% of the whole sample (Table 1). Most of the HBe-positive group (86.9%) had an HBV DNA level of less than  $10^4$  IU/mL. For the HBe-negative patients, 86.6% had HBV DNA levels below 2000 IU/mL (Table 2).

Upon comparison of the virology profile between patients with positive and negative HBeAg, HBs antigens and HBV DNA positivity were not significantly different among the two groups ( $P = 0.97$ ). Patients who were HBeAg positive had higher loads of HBV DNA than HBeAg-negative patients, although the difference was not statistically significant ( $P = 0.09$ ). Anti-HBe Ab were not detected in any of the HBeAg-positive group, but they were detected in 84.4% of the HBeAg-negative group ( $P < 0.001$ ). HBe immunoglobulins were also significantly different between the two groups. HBe IgM was significantly higher

**Table 2** Distribution of hepatitis B virus DNA (measured in IU/mL) among the studied groups ( $n = 323$ )

Hepatitis B e antigen (HBeAg) status	HBeAg +ve			HBeAg -ve	
	< $10^4$	$10^4$ to $10^7$	> $10^7$	<2000	>2000
Hepatitis B virus (HBV) DNA					
<i>n</i>	53	3	5	226	35
(%)	(86.9)	(4.9)	(8.2)	(86.6)	(13.4)

**Table 3** The virology profile among the studies groups ( $n = 3232$ )

	Hepatitis B e antigen (HBeAg) positive ( $n = 61, 18.9\%$ )		HBeAg negative ( $n = 262, 81.1\%$ )		Statistical test	<i>P</i> -value
Anti-hepatitis B e antibodies						
+ve	0	0.0	221	(84.4)	$\chi^2 = 162.94$	<0.001
Hepatitis B surface antigen						
+ve	54	(88.5)	232	(88.5)	FET	0.996
Hepatitis B core (HBc) immunoglobulin M						
+ve	4	(6.6)	3	(1.1)	$\chi^2 = 0.00$	0.026
HBc Big						
+ve	59	(96.7)	262	(100.0)	$\chi^2 = 0.00$	0.035
Hepatitis B virus (HBV) DNA						
Detected	37	(60.7)	196	(60.9)	$\chi^2 = 0.00$	0.970
HBV DNA <sup>†</sup>						
M (SD)	7.7 (4.6)		6.4 (2.5)		$t = 1.73$	0.092
(Min, Max)	(3.5, 18.7)		(2.7, 18.2)			

<sup>†</sup>DNA level among 37 HBeAg-positive and 196 HBeAg-negative cases only; in logarithmic scale.

Values are number and (%) unless otherwise is specified.

$\chi^2$ , Chi-square test; FET, Fisher's Exact test; *t*, independent *t*-test.

among patients with positive HBeAg (6.6% vs 1.1% in patients with negative HBeAg) ( $P = 0.026$ ), while HBc IgG were significantly lower (96.7% of HBe-positive patients vs 100% of HBe-negative patients) ( $P = 0.035$ ) (Table 3).

On evaluation of the laboratory profile of the studied groups, a higher percentage of patients with positive HBeAg (54.1%) had ALT levels higher than 33 U/L in comparison to patients with negative HBeAg ( $P = 0.017$ ). The percentage of patients with levels of GGT above 55 U/L was significantly higher among the HBeAg-positive patients (32.8% vs 18.7%) ( $P = 0.016$ ). Levels of ALP, bilirubin, albumin, urea, and creatinine were not significantly different between the two studied groups ( $P = 0.784$ ,  $P = 788$ ,  $P = 0.261$ ,  $0.767$ , and  $P = 0.096$ , respectively) (Table 4).

The prevalence of comorbidities, HCV, HIV, cirrhosis on abdominal imaging, HCC and liver transplantation was not different between patients with positive and patients with negative HBeAg (Table 5).

Of note, 44.3% of patients with positive HBeAg were on antiviral medications, whereas only 33.6% of HBeAg-negative patients were on treatment. Entecavir was the most common antiviral drug used in both groups (prescribed to 81.5% and 27.9% of HBeAg-positive and -negative groups, respectively). Tenofovir was prescribed to 18.5% and 5.3% of HBeAg-positive and -negative groups, respectively. Tacrolimus was prescribed to a single patient with negative HBeAg (Table 5).

## Discussion

Hepatitis B affects about 0.5% of the population in Bahrain, and the prevalence has reportedly been increasing in recent years.<sup>8</sup> Hepatitis B infection is a serious hepatic condition associated with considerable complications such as liver cirrhosis, hepatic failure, or HCC.<sup>11</sup> Early and adequate treatment of the condition not only reduces such complications but also prevents the transmission of infection to other members in the community.<sup>7</sup>

HBeAg is one of the secretory proteins formed from the hepatitis B precore protein and is therefore considered a marker of disease infectivity and viral replication state.<sup>2</sup> Assessment of HBeAg positivity helps in the monitoring of disease activity and is also an indicator for the rate of transmission of the infection to contacts and/or health-care workers.<sup>7</sup>

To the best of our knowledge, there is a lack of data from previously published literature studies about the state of HBeAg among hepatitis B patients in Bahrain. The results of our study revealed that HBeAg-positive status is prevalent among patients with hepatitis B infection. Almost one-fifth of the hepatitis B patients in our study had positive HBeAg, indicating their high infectivity and high viral replication. This level is higher than the prevalence reported in other studies.<sup>12</sup> This is of important consideration because it reflects that the rates of transmission of infection are expected to be high, and better measures should be adapted to reduce the disease infectivity. It also highlights a potential rise in the incidence of cirrhosis and HCC. The average age of HBeAg-positive patients in our sample was 45 years, which indicates worse outcomes as later seroconversion is linked to complications like liver cirrhosis.<sup>7</sup> Patients with cirrhosis, active hepatitis, or older than 40 years of age at the time of HBeAg seroconversion are also at significantly higher risk for HCC development.<sup>13</sup>

Moreover, less than one-fifth of hepatitis B patients with positive HBeAg, and only one-third of patients with negative HBeAg in Bahrain are on antiviral therapy. We did not collect data on time of diagnosis, previous treatment, or length of current treatment, and we cannot comment on the significance of this. A network meta-analysis suggested that telbivudine treatment followed by tenofovir therapy resulted in higher HBeAg seroconversion rates than other treatments, although its use may be limited by a high resistance rate.<sup>14</sup> Most patients in our cohort were receiving entecavir, which is a recommended first-line drug, but long-term use may reduce HBeAg seroconversion compared with the spontaneous HBeAg seroconversion rate.<sup>14</sup>

**Table 4** Laboratory profile among the studied groups (*n* = 323)

	Hepatitis B e antigen (HBeAg) positive ( <i>n</i> = 61, 18.9%)	HBeAg negative ( <i>n</i> = 262, 81.1%)	Statistical test	<i>P</i> -value
Alanine transferase				
≥33 U/L	33 (54.1)	131 (40.6)	$\chi^2 = 5.72$	0.017
M (SD)	106 (324.2)	69.1 (354.2)	<i>t</i> = 0.74	0.45
(Min, Max)	(7, 2429)	(8, 5126)		
Alkaline phosphatase				
M (SD)	94.8 (68.6)	91.5 (85)	<i>t</i> = 0.27	0.78
(Min, Max)	(7, 407)	(8, 960)		
Gamma-glutamyl transferase				
>55 U/L	20 (32.8)	49 (18.7)	$\chi^2 = 5.84$	0.016
M (SD)	89.9 (172.2)	53.6 (83.8)	<i>t</i> = 1.59	0.117
(Min, Max)	(6, 989)	(6, 555)		
Total Bilirubin (T.BIL) <sup>†</sup>				
<5 μmol/L	1 (1.6)	11 (4.2)	$\chi^2_{\text{lin}} = 0.07$	0.788
5–21 μmol/L	50 (82.0)	204 (78.5)		
>21 μmol/L	10 (16.4)	45 (17.3)		
M (SD)	31.1 (75.1)	18.4 (36.8)	<i>t</i> = 1.29	0.201
(Min, Max)	(3, 464)	(2, 366)		
Albumin <sup>‡</sup>				
<35 g/L	10 (16.4)	25 (9.7)	$\chi^2_{\text{lin}} = 1.27$	0.261
35–52 g/L	50 (82.0)	234 (90.3)		
>52 g/L	1 (1.6)	0 (0.0)		
M (SD)	40.7 (8.3)	41 (5.5)	<i>t</i> = 0.28	0.782
(Min, Max)	(12, 69)	(16, 52)		
Urea				
<3.2 mmol/L	8 (13.1)	17 (6.5)	$\chi^2_{\text{lin}} = 0.09$	0.767
3.2–8.2 mmol/L	43 (70.5)	224 (85.5)		
>8.2 mmol/L	10 (16.4)	21 (8.0)		
M (SD)	6.6 (5.7)	5.4 (2.5)	<i>t</i> = 1.54	0.127
(Min, Max)	(1.5, 36)	(1.8, 22.8)		
Creatinine				
Low	2 (3.3)	18 (6.9)	$\chi^2_{\text{lin}} = 2.77$	0.096
Normal	41 (67.2)	189 (72.1)		
High	18 (29.5)	55 (21.0)		
M (SD)	97.4 (127.9)	79.9 (50.1)	<i>t</i> = 1.05	0.297
(Min, Max)	(37, 1039)	(32, 665)		

<sup>†</sup>T.Bil was available for all HBeAg +ve cases and for 260 HBeAg +ve cases.

<sup>‡</sup>Albumin was available for all HBeAg +ve cases and 259 HBeAg +ve cases.

Values are number and (%) unless otherwise is specified.

$\chi^2$ , Chi-square test;  $\chi^2_{\text{lin}}$ , ordinal Chi-square test; *t*, independent *t*-test.

In this study, HBeAg were positively correlated with laboratory tests indicative of activity. Patients with positive HBeAg had significantly higher levels of ALT, GGT, and HBe IgM. Although we did not detect a statistically significant association between HBeAg positivity and HBV DNA load, data from previous studies reported that the presence of HBeAg was also associated with high levels of HBV DNA and high rates of infection transmission.<sup>1,4</sup> High viral replication and disease activity results in more hepatocellular damage and subsequent high levels of liver enzymes, and this explains our findings that hepatitis B patients with positive HBeAg had higher ALT and GGT levels.<sup>15,16</sup>

While HBeAg's existence is indicative of high viral replication and high infectivity status, it was not associated—in the

studied sample—with any increase in the prevalence of hepatitis complications such as cirrhosis, HCC, or the need for transplantation. In contrast to our results, Hou *et al.* reported in their study of 428 patients with HBV infection that patients with positive HBeAg had higher rates of complications such as liver cirrhosis, hepatic encephalopathy, and liver failure.<sup>17</sup> The differences encountered in our sample may be related to the different characteristics of the patients recruited.

Of the 262 patients with negative HBeAg, 84.4% had anti-HBe Ab. The levels of HBeAg decline with the recovery of the acute infection, and seroconversion to HBe Ab takes place.<sup>3,4</sup> The appearance of HBe Ab often reflects the beginning of remission of active infection.<sup>18</sup> In our sample, none of the patients with positive HBeAg had HBe Ab detected, indicating that the

**Table 5** Comorbidities and complications among the studied groups

	Hepatitis B e antigen (HBeAg) positive (n = 61, 18.9%)	HBeAg negative (n = 262, 81.1%)	Statistical test	P-value
Comorbidity				
Yes	10 (16.4)	31 (11.8)	$\chi^2 = 0.93$	0.335
Hepatitis C virus				
>55 U/L	5 (8.2)	14 (5.3)	FET	0.373
Human immunodeficiency virus				
Positive	1 (1.6)	1 (0.4)	FET	0.343
Imaging				
Post Tx Normal	1 (1.6)	3 (1.1)	MC	0.764
Normal	37 (60.7)	154 (58.8)		
Abnormal	23 (37.7)	105 (40.1)		
Hepatocellular carcinoma				
Positive	1 (1.6)	5 (1.9)	FET	1.000
Transplant				
Yes	5 (8.2)	13 (5.0)	FET	0.351
On medication				
Yes	27 (44.3)	88 (33.6)	$\chi^2 = 2.46$	0.117
Type of medication <sup>†</sup>				
Entecavtr	22 (81.5)	73 (27.9)	MC	1.000
Tenofovtr	5 (18.5)	14 (5.3)		
Tacrolimus	0 (0.0)	1 (0.4)		

<sup>†</sup>Only among cases on medications.

Values are number and (%) unless otherwise is specified.

$\chi^2$ , Chi-square test; FET, Fisher's exact test; MCT, Monte Carlo correct Chi-square test.

patients had not entered the recovery stage yet. This is significant at a population level as well because it indicates that these patients would still be infectious for a considerable time, increasing the risk of transmission. Health-care staff and patient education on the high infectivity of patients with HBV in Bahrain is, therefore, important in preventing further HBV infections.<sup>7</sup>

In this study, we also evaluated the association of other viruses with HBV infection in Bahrain. The prevalence of HIV among hepatitis B patients in our study was 0.4–1.6%, which is less than what was reported in the meta-analysis published by Roos *et al.* in 2010, which reported a prevalence ranging from 4.1 to 26.8%.<sup>19</sup> Hepatitis C coinfection in our sample ranged from 5.3 to 8.2%, which is also less than what was reported (9–30%).<sup>20–22</sup> There was no association between the existence of HBeAg and other viruses such as HCV or HIV.

One of the main strengths of this study is that it is the first study to report the prevalence of HBeAg among hepatitis B patients in Bahrain and to describe correlations with laboratory and clinical profiles. The main limitation, however, is that it was a retrospective record-review study that lacked the longitudinal follow up to assess the actual impact of HBeAg on a long-term basis. The study is also based on a single institution, and even though the hospital is the largest one in the country, the findings may not be representative of the whole country as no cases from other governmental or private health facilities were included. This is compounded by the small number of identified cases.

## Conclusion

HBeAg positivity is highly prevalent among hepatitis B patients in Bahrain, and it is associated with high liver enzymes and high

viral replication. However, patients with positive HBe do not appear to be at a significantly higher risk for hepatitis complications (such as cirrhosis or HCC) or liver transplantation.

## Declaration of conflict of interest

The authors declare that there are no competing interests.

## REFERENCES

- 1 Thompson AJV, Nguyen T, Iser D *et al.* Serum hepatitis B surface antigen and hepatitis B e antigen titers: disease phase influences correlation with viral load and intrahepatic hepatitis B virus markers. *Hepatology*. 2010; **51**: 1933–44.
- 2 Malmström S, Larsson SB, Hannoun C, Lindh M, Hepatitis B. Viral DNA decline at loss of HBeAg is mainly explained by reduced cccDNA load—down-regulated transcription of PgRNA has limited impact. *PLoS One*. 2012; **7**: e36349.
- 3 Santantonio P, Agarwal K, Berg T *et al.* EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection. *J Hepatol*. 2017; **67**: 370–98.
- 4 Kramvis A, Kostaki EG, Hatzakis A, Paraskevis D. Immunomodulatory function of HBeAg related to short-sighted evolution, transmissibility, and clinical manifestation of hepatitis B virus. *Front. Microbiol*. 2018; **9**: 2521.
- 5 Santantonio TA, Fasano M. Chronic hepatitis B: advances in treatment. *World J. Hepatol*. 2014; **6**: 284–92.
- 6 Pavlovic V, Yang L, Chan HLY *et al.* Peginterferon alfa-2a (40 kD) stopping rules in chronic hepatitis B: a systematic review and meta-analysis of individual participant data. *Antivir. Ther*. 2019; **24**: 133–40.
- 7 Tripathi N, Mousa OY. Hepatitis B [Updated 2020 Jun 18]. In: *StatPearls [Internet]*. Treasure Island (FL): StatPearls Publishing;

2020. Accessed 6 Jan 2021. Available from <https://www.ncbi.nlm.nih.gov/books/NBK555945/>.
- 8 Janahi EM. Prevalence and risk factors of hepatitis B virus infection in Bahrain, 2000 through 2010. *PLoS One*. 2014; **9**: e87599.
  - 9 Janahi EM, Ilyas Z, Al-Othman S *et al.* Hepatitis B virus genotypes in the Kingdom of Bahrain: prevalence, gender distribution and impact on hepatic biomarkers. *Medicina (Kaunas)*. 2019; **55**: 622.
  - 10 Wagner WE. *Using IBM® SPSS® Statistics for Research Methods and Social Science Statistics*, Fourth edn. Thousand Oaks, Calif: SAGE Publications, Inc.; 2013.
  - 11 Flichman D. Hepatitis B virus. In: *Chronic Liver Disease: From Molecular Biology to Therapy*. New York: Nova Biomedical; 2017; 149–67.
  - 12 Tan M, Bhadoria AS, Cui F *et al.* Estimating the proportion of people with chronic hepatitis B virus infection eligible for hepatitis B antiviral treatment worldwide: a systematic review and meta-analysis. *Lancet Gastroenterol. Hepatol*. 2020; **0**: 106–19.
  - 13 Zhou TC, Lai X, Feng MH, Tang Y, Zhang L, Wei J. Systematic review and meta-analysis: development of hepatocellular carcinoma in chronic hepatitis B patients with hepatitis e antigen seroconversion. *J. Viral Hepat.* 2018; **25**: 1172–9.
  - 14 Xing T, Xu H, Cao L, Ye M. HBeAg seroconversion in HBeAg-positive chronic hepatitis B patients receiving long-term nucleos(t)ide analog treatment: a systematic review and network meta-analysis. *PLoS One*. 2017; **12**: e0169444.
  - 15 Hadziyannis SJ. Natural history of chronic hepatitis B in Euro-Mediterranean and African Countries. *J. Hepatol*. 2011; **55**: 183–91.
  - 16 Matthews GV, Ali RJ, Avihingsanon A *et al.* Quantitative HBsAg and HBeAg predict hepatitis B seroconversion after initiation of HAART in HIV-HBV coinfecting individuals. *PLoS One*. 2013; **8**: e61297.
  - 17 Hou F, Qi X, Zhang Y *et al.* Association of hepatitis B e antigen and DNA viral load with severity of liver dysfunction and in-hospital outcomes in hepatitis B-related liver cirrhosis. *AME Med. J.* 2017; **2**: 145–5.
  - 18 Plotkin S, Leuridan E, Van Damme P. Hepatitis b and the need for a booster dose. *Clin. Infect. Dis.* 2011; **53**: 68–75.
  - 19 Barth RE, Huijgen Q, Taljaard J, Hoepelman AIM. Hepatitis B/C and HIV in sub-Saharan Africa: an association between highly prevalent infectious diseases. A systematic review and meta-analysis. *Int. J. Infect. Dis.* 2010; **14**: e1024–31.
  - 20 Mavilia MG, Wu GY. HBV-HCV coinfection: viral interactions, management, and viral reactivation. *J. Clin. Transl. Hepatol*. 2018; **6**: 1–10.
  - 21 Te HS, Jensen DM. Epidemiology of hepatitis B and C viruses: a global overview. *Clin. Liver Dis.* 2010; **14**: 1–21.
  - 22 Mysore KR, Leung DH. Hepatitis B and C. *Clin. Liver Dis.* 2018; **22**: 703–22.