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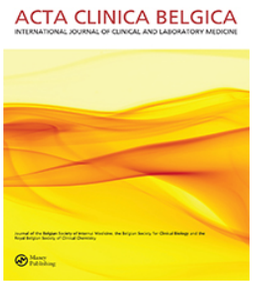

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Epidemiology and clinical management of HIV-HBV coinfected patients in a large AIDS Reference Center in Belgium

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ABSTRACT

Objectives: Human immunodeficiency virus (HIV) and hepatitis B virus (HBV) are both worldwide health concerns with similar routes of transmission and no curative treatment to date. Coinfection is associated with increased morbidity and mortality. We aim to provide epidemiological data about HIV-HBV coinfected patients and asses if management of patients following European recommendation (EACS) was achieved in a large AIDS Reference Center in Belgium.

Methods: Retrospective review of the HIV database of Saint-Pierre University Hospital in Brussels (Belgium) focusing on HIV-HBV coinfected patients in active follow-up. We classified patients in six serological profiles: (A) patients with active chronic HBV infection (HBsAg positive and HBeAg positive), (B) patients with persistent chronic HBV infection (HBsAg positive and HBeAg negative), (C) patients with isolated core antibody (isolated anti-HBc positive), (D) patients with resolved HBV infection (anti-HBc positive and anti-HBs positive), (E) vaccinated patients (anti-HBs positive), and (F) patients with all above markers negative. Chronic HBV infection (cHBV) was defined by two positive hepatitis B surface antigens (AgHBs positive) with at least 6-month intervals and chronic HBeAg positive group by a positive AgHBe (Ag HBe positive). We reviewed individual files of HIV-HBV chronically coinfected patients to assess if European recommendations in terms of HBV coinfection management were adequately followed in our center.

Results: Among 2601 HIV-infected patients in active follow-up, 98 (3.8%) were chronically infected with HBV. Median age of chronically coinfected patients was 46 years with male predominance and heterosexual Africans representing the majority. Among the chronically coinfected patients, 33.7% were HBeAg positive carriers. Mean HBV DNA and ALT/AST were significantly higher in the chronic HBeAg positive (cHBeAg positive) patients compared to chronic HBeAg negative patients (cHBeAg negative). Nearly 95% of the cHBV patients were treated with two anti-HBV drugs (99% for the cHBeAg positive group), with 79% having Tenofovir (TDF) in their antiretroviral treatment history. 8% were screened for hepatitis D virus (HDV) antibodies. Liver fibrosis, upper endoscopy and alpha-foetoprotein were assessed at least once in the last 5 years in 32%, 31% and 32% of cHBV patients respectively. cHBeAg positive patients were not significantly monitored closer except for liver fibrosis assessment in 52% ($p < 0.0017$).

Conclusion: The prevalence of cHBV coinfection in the Saint-Pierre HIV cohort is lower than in neighboring European countries. Hepatic monitoring should be reinforced in our cHBV and cHBeAg positive patients because of higher risk of progression to cirrhosis progression and hepatocellular carcinoma.

KEYWORDS
Hepatitis; HIV/AIDS; HIV-HBV coinfection; infectious diseases; epidemiology

Introduction

Human immunodeficiency virus (HIV) and hepatitis B virus (HBV) are both worldwide health concerns, with no curative treatment to date. According to World Health Organization (WHO), 36.7 million subjects are infected with HIV and an estimated 400 million live with HBV. Around 620 000 patients die annually from cirrhosis and hepatocellular carcinoma (HCC) making chronic HBV (cHBV) one of the leading causes of liver-related mortality worldwide [1,2]. The prevalence of HBV varies geographically with high endemicity in Asia and Africa and low endemicity in the United States, Canada, Australia and Europe. In highly endemic regions, transmission occurs mainly by mother-to-child transmission and through close contact within households, traditional habits and medical procedures, while in low endemic regions, it occurs mainly through sexual contact and IV drug use [1,3,4]. HBV and HIV share similar routes of transmission and coinfection with both viruses is thus common in regions where both are endemic. It is estimated that 3 to 6 million HIV-infected people live with cHBV [3]. Coinfected patients are more likely to develop cirrhosis and HCC compared to mono-infected patients with either virus and consequently are at risk for higher liver-related morbidity and mortality. It is estimated that HIV-HBV coinfected patients are 17 times more likely to die from liver-related causes compared to those mono-infected with HBV [5]. Therefore determination of HBV status is crucial

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for HIV-infected patients care and stratifying HBV disease more accurately could offer better therapeutic options in the near future. The main target of treating HBV infection is to clear the HBV surface antigen with anti-HBV surface antibody seroconversion which is achieved in only few cases. If seroconversion is not possible, the target should be long-term suppression of HBV replication to delay progression towards hepatic fibrosis by reducing liver inflammation. In Europe, few studies have addressed and described coinfection with HBV among HIV patients. It is estimated that in this region, less than 10% of HIV-infected patients are chronically infected with HBV [4,6]. To our knowledge, there is no recent study on the HIV-HBV coinfected population in Belgium. We aim to provide epidemiological data, including prevalence, on HIV-HBV coinfection and to assess adequacy of management of these patients in a large AIDS Reference Center in Belgium.

Materials and methods

We performed a cohort study of the HIV database of Saint-Pierre University Hospital Brussels, Belgium focusing on HIV-HBV coinfected patients. We choose to focus on patients in active follow-up (defined as attending at least one consultation at the HIV reference center during the last year) to be able to evaluate if management of patients following European recommendation (EACS) was achieved which recommend that HBV coinfected persons with high risk for HCC (including replicating HBV infection) should be screened at 6-month intervals with hepatic ultrasound, that a routine esophageal screening be done at the time of diagnosis (and at 3–4 years interval if portal hypertension is not present initially), that anti-HBc positive and HBsAg negative patients should be screened for HBV-DNA to rule out occult HBV infection and that all HBsAg positive persons should be screened for hepatitis delta antibodies and hepatitis A antibodies [7]. HBV coinfected patients should be treated in the early stages by Antiretroviral Therapy (ART) with a Tenofovir (TDF)-based strategy to reduce liver fibrosis progression. cHBV infection was defined by two positive hepatitis B surface antigen tests (HBsAg positive) at at least 6-month intervals and chronic HBeAg positive group by a positive HBeAg (HBeAg positive and HBsAg positive). HBV serological profiles were stratified into (A) patients with chronic HBeAg positive infection (HBsAg positive and HBeAg positive),(B) patients with chronic HBeAg infection (HBsAg positive and HBeAg negative),(C) patients with isolated core antibody (isolated anti-HBc positive), (D) patients with resolved HBV infection (anti-HBc positive and anti-HBs positive), (E) vaccinated patients (anti-HBs positive), and (F) patients with all above markers negative (see Table A1). Hepatitis C virus (HCV) coinfection was defined by positive HCV IgG independently from HCV PCR results. We reviewed every individual file of HIV-HBV coinfected patients and collected data about HBV treatment, abdominal ultrasound, liver biopsy, fibrotest, fibroscan, alpha-fetoprotein, and esophageal exam in the past 5 years (screened at least once in the past 5 years), as well as hepatitis D virus (HDV) and hepatitis A virus (HAV) antibodies.

Ethics approval for this study was obtained from the Ethics Committee of Saint-Pierre University Hospital.

Statistical analyses

Simple descriptive statistics were used for summarized characteristics of using median and interquartile (IQRs) ranges for continuous data, frequencies and percentages for categorical data. Statistical tests were performed with the Mann–Whitney U test if the data were continuous and Chi-square test if the data were categorical. All reported *p*-values are two-sided. We used logistic regression to refine the conclusion of univariate analyzes.

Analyses were produced using SAS statistical software (version 9.4; SAS Institute, Cary, NC, USA).

Results

The Brussels Saint-Pierre cohort currently includes 3010 patients, from which 2601 were in active follow-up in the Saint-Pierre HIV cohort in April 2017 when this analysis was performed. HBV serological profiles are summarized in Table A1 and their caracteristics in Table A2 . Ninety-eight patients (3.8%) were chronically coinfected with HBV. They represent the main group at risk. Among them were 33 (1.3%) HBeAg positive and 65 (2.5%) HBeAg negative. Two hundred and seventy four (10.5%) had positive isolated anti-HBc, 656 (25.2%) were vaccinated for HBV, 844 (32.5%) had resolved HBV infection, and 729 (28%) were negative for all markers. In the cHBV group, as in the total cohort, patients were predominantly male (>60%). There was no significant difference in the median age of the coinfected group compared to the total cohort (46 [IQR: 25–75%: 38–55]. There were significantly more Africans: 63% (62/98) in the coinfected cohort versus the total cohort: 46% (1385/3010) ($p < 0.0005$). We found no difference in sexual orientation: 28% (27/98) in the coinfected cohort versus the total cohort: 36% (1105/3010) ($p > 0.07$). We found no difference either in AIDS history in both populations: 18% (17/98) in the coinfected cohort versus the total cohort: 20% (591/3010) ($p = 0.6$).

When comparing chronic HBeAg positive ($n = 33$) and chronic HBeAg negative ($n = 65$) patients, there were significantly more homosexual/bisexual men in the cHBeAg positive group: 52% (17/33) versus 15% (10/65) in the HBeAg negative group ($p < 0.001$), and

significantly more Africans in the cHBeAg negative group: 78% (11/65) versus 33% (11/33) in the cHBeAg positive. There were significantly more HCV IgG positive patients in the cHBeAg positive group: 22% (7/32) versus 3% (2/65) in the cHBeAg positive group ($p < 0.0027$). The cHBeAg ± group had a higher median HBV viral load of 2×10^5 units [IRQ: 19600-205 × 10^5], than the cHBeAg negative group before starting treatment (median HBV viral load = 222 units []IQR: 80-9940). ALT and AST at the start of antiretroviral treatment were significantly (two times) higher in the cHBeAg ± group compared to the cHBeAg negative group (ALT: $p < 0.0001$; AST: $p < 0.0005$).

As expected HBV-HIV coinfected were more often treated with antivirals active against both viruses, with 84% (82/98), 78.6% (77/98) and 39% (38/98) of coinfected patients on Emtricitabine (FTC), TDF, or Lamivudine (LAM), respectively. Nearly 95% (93/98) of the cHBV patients were treated with two anti-HBV drugs, rising to 99% (32/33) in the cHBeAg positive group.

Among cHBV patients, 8% (8/98) were screened for hepatitis delta antibodies and 74% (72/98) were screened for hepatitis A IgG. All patients were screened for HCV. In our 2601 cohort patients, 10.5% (274/2601) of them are positive for isolated anti-HBc. Among the isolated positive anti-HBc patients, 3% (8/274) were screened for HBV-DNA to detect potential occult HBV infection.

Among the HIV-HBV coinfected patients, 14.3% (14/98) had at least one abdominal ultrasound per year in the last 5 years and 4.21% (4/98) had an abdominal ultrasound every 6 months in the last 5 years. Liver fibrosis was assessed by biopsy/fibrotest/fibroscan at least once in the past 5 years in 33% (32/98) of patients with alpha-foetoprotein measured in one third of patients at least once. We compared the implementation of European recommendations in terms of follow-up between the cHBeAg positive group and the cHBeAg negative group and we didn't find a significant difference in the abdominal ultrasound screening, in the screening of hepatitis delta antibodies, in the screening of hepatitis A antibodies and esophageal exam. However, more than half of the cHBeAg ± group was assessed for liver fibrosis ($p < 0.0017$). An alpha-foetoprotein test was performed at least once in 36.4% (12/33) of the cHBeAg positive group versus 27.7% (18/65) in the cHBeAg negative group. Only 3 out of the 98 patients were cirrhotic.

Discussion

Epidemiological data on HIV-HBV coinfection are scarce in Europe and few data are available on this population in Belgium: we report here on the epidemiological data and asses if management of patients following European recommendation (EACS) was achieved from Saint-Pierre HIV cohort. We classified HIV patients in six HBV serological profiles to have a better assessment of our HIV cohort; we differentiated our chronic coinfected HIV-HBV patients in two separate groups (Chronic HBeAG positive and the Chronic HbeAG negative group) [8]. We found a prevalence of HIV-cHBV coinfection of 3.8% which is close to the one reported in low endemic regions such as Canada and the United States [2,9]. In Europe, Konopnicki et al. (2005) analyzed 72 European HIV centers and estimated the prevalence of HBV coinfection at 9% in the EuroSIDA cohort. In France, a neighboring country to Belgium with similar HIV epidemiology, the prevalence of HIV-HBV coinfection was evaluated at 7% [12]. Our prevalence of HIV-HBV coinfection is lower. This could be related to a lower percentage of IVDU and a higher proportion of migrants in the HIV population in our country. Moreover, our strict definition of HBV infection (positive hepatitis B surface antigen (HbsAg positive) twice at at least 6-month intervals) could also participate to this low prevalence [2,9–11]. On the other hand, HBV coinfection may have been underestimated because of occult HBV patients who are HBV-DNA positive, but hepatitis B surface antigen negative patients [13]. For example in Sicily, Italy and in the Netherlands the prevalence of occult hepatitis B infection is estimated at 5.9 and at 4.7%, respectively, which is not negligible [8,14].

The majority of our HIV-HBV coinfected patients were heterosexual African males which is a reflection of our HIV epidemiology. In areas with low HBV endemicity, HIV and HBV are mainly acquired through sexual transmission or injecting drug use [1,2]. In our study, the main mode of HIV acquisition is heterosexual while in the EuroSIDA cohort, it was mainly through homosexual/bisexual transmission [10,11]. We found a significantly higher prevalence of homosexual/bisexual patients in the chronic HbeAg positive group and the chronic HbeAg negative group had significantly more Africans. HCV coinfection reached 10% with highest rate found in the chronic HbeAg positive group (24%) which can be explained by the shared route of transmission with HIV and HBV.

HbeAg is a secretory protein, an indicator of active viral replication and infectivity. It is usually associated with higher levels of HBV DNA and is useful in evaluating patients who need antiviral therapy and closer monitoring [15]. High levels of HBV DNA are however not always associated with higher levels of ALT/AST (immune tolerant phase). In our cohort, HBV viral load was significantly higher ($p < 0.001$) in the cHBeAg positive group with a median of 2×10^5 units/µL, and with significantly higher levels of ALT/AST. Higher serum levels of HBV DNA are associated with an increased risk for progression to cirrhosis and HCC.

The cHBeAg positive patients present thus higher risk for cirrhosis and HCC than the other serological groups [16].

Nearly 95% of the cHBV patients were treated with two anti-HBV drugs with 79% having TDF in their antiretroviral treatment history. Among cHBeAg positive group patients 99% had anti-HBV double therapy with TDF and FTC or 3TC.

TDF is indeed a strong anti-HBV nucleotide analog reverse-transcriptase inhibitor recommended in all patients with chronic positive HbeAg especially in cases with elevated HBV viral load. TDF has recently been replaced by tenofovir alafenamide (TAF) which reduces the impact on bone mineralization and renal function as demonstrated by several parameters during clinical studies. TAF-based treatment can hence target a broader population of patients at risk for bone and renal diseases and adolescents who haven't reached maximum bone mass [17].

We have also evaluated the level of adherence to guidelines on monitoring of HBV-infected patients in our practice. It appears that implementation of these recommendations is far from optimal, with the exception of screening for HAV antibodies for which three in four patients in the HIV-HBV coinfected patients were tested. Screening for hepatitis delta is low. In a recent epidemiological study by Ho et al, the prevalence of HBV-HDV coinfection in Belgium was estimated to 3.7–5.5% in HIV negative patients [18]. In Europe, the prevalence of anti-HDV in HIV patients being chronic HBsAg carriers was estimated at 14.5%. In our coinfected patients, only 8% were screened for hepatitis delta antibodies and among them 12.5% were positive for hepatitis delta antibodies. Chronic Delta hepatitis (CDH) is a form of chronic viral hepatitis with a progressive and accelerated course compared to cHBV mono-infection and may lead to cirrhosis within 2 years in 10–15% of patients. It is therefore essential to screen all HBsAg patients for hepatitis delta antibodies [7,19,20].

Isolated anti-HBc was detected in 10.5% of the cohort, which is a low prevalence suggesting the necessity to improve testing of this group. They represent either occult cHBV infection with undetectable levels of HbsAg and detectable HBV DNA, or resolved HBV infection with loss of hepatitis B surface antibody (anti-HBs) or a false-positive test result (cross reaction with suppressing HBV replication and HbsAg production in patients coinfected with HCV and HBV) [21–23]. The proportion of HCV IgG-positive patients was indeed high in the isolated anti-HBc group (16.42%). The low prevalence of HBV-DNA screening in the isolated anti-HBc group (3% (8/274)) to rule out occult HBV infection can be explained by the fact that it is an expensive test that is not part of the Belgium reimbursement strategy and that a high proportion of these patients on TDF −3TC for their HIV, preventing a reliable result of the HVB viral charge. It should also be noted that untested patients for HBV-DNA have normal ALT-AST, if not they get tested.

Individuals without cirrhosis but with chronic hepatitis B infection have a high risk for the development of HCC. HBV is thought to be the most carcinogenic trigger as the DNA of the virus integrates with host genome. It is the most common cause of HCC in the East, but is rarely seen in the Western world especially with better control of viral replication using nucleotide and nucleoside inhibitors. Guidelines thus recommend that the HCC screening by hepatic ultrasound be carried out on a semiannual basis. Only one third of our HIV-HBV coinfected patients had a liver fibrosis assessment or an alpha-protein test. Less than 5% of patients had a hepatic ultrasound every 6 months. However, it was three times higher if we considered a hepatic ultrasound per year.

Of note, almost one third of our HIV cohort had negative HBV markers and are thus candidate for HBV vaccination. This proportion could be overestimated given the fact that the vaccine does not produce a humoral immune response in 5–10% of immunocompetent patients, a number increasing with chronic diseases and immunosuppressed status. Around 96.13% of mono-infected HIV positive patients were on cART anti-HBV treatment, which provide them a kind of preexposure prophylaxis against HBV.

Our study has several limitations. It is a monocentric study with a specific demographic landscape consisting of a large migrant population that decreases the generalizability of our data. Its retrospective nature limits the data available on liver-related complications. We chose to select patients that were on active follow-up to audit recent (5 years) clinical management – this study design did not allow to analyze outcome data.

Our study has also strengths: the size of the cohort of 2601 patients in active follow-up represents the biggest HIV cohort in Belgium. Few in Europe have used a strict definition of the AgHBs carriers like we have in our study and we differentiated our chronic coinfected HIV-HBV patients in cHBeAg positive and cHBeAg negative groups to audit their management more accurately.

In summary, the prevalence of HBV coinfection in the Saint-Pierre HIV cohort is lower than in neighboring European countries, probably due to its HIV epidemiology. Priority in resources allocation for monitoring and treatment must be given to the chronic HBeAg positive group and the triple-infected patients as they are more at risk of cirrhosis progression and HCC.

Disclosure statement

No potential conflict of interest was reported by the authors.

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Appendix

Table A1. HBV serological profiles.

	Ag HBs	Ag HBe	Ac HBs	Ac HBc
(A) Chronic HBeAg +	+	+	−/+	−/+
(B) Chronic HBeAg −	+	−	−/+	−/+
(C) Isolated anti-HBc	−	−	−	+
(D) Vaccinated	−	−	+	−
(E) Resolved HBV	−	−	+	+
(F) Negative HBV markers	−	−	−	−

Table A2. Characteristics of patients in the cohort according to their HBV serological profile (n= 2601).

N (%)	cHBeAg+ n=33	cHBeAg− n=65	Isolated anti-HBc n=274	Vaccinated n=656	Resolved HBV n=844	Negative HBV markers n=729	All patients n=2601
Age	47	46	49	43	50	47	48
[IQR: 25–75%]	(40–53)	(37–55)	(41–56)	(34–51.5)	(42–57)	(38–55)	(39–55)
Male	26(78.8)	34 (52.3)	144(52.6)	455(69.4)	501(59.4)	417(57.2)	1577(60.6)
Caucasian	19(57.6)	13 (20.0)	82(29.9)	408(62.2)	330(39.1)	403(55.3)	1378(53)
African	11(33.3)	51 (78.5)	186(67.9)	218(33.2)	472(55.9)	286(39.2)	1223(47)
Heterosexual	11(33.3)	41(63.1)	183(66.8)	268(40.9)	480(56.9)	429(58.9)	1696(65.2)
MSM	18(54.6)	10(15.4)	49(17.9)	322(49.1)	287(34.0)	219(30.0)	905(34.8)
IVDA	1(3.0)	2(3.1)	26(9.5)	8 (1.2)	17(2.0)	11(1.5)	65(2.5)
History of AIDS	7(21.2)	10(15.4)	80(29.2)	81(12.4)	196(23.2)	152(20.9)	526(20.2)
HCV antibody-positive [n (%)]	8(24.2)	2(3.1)	45(16.4)	37(5.6)	70(8.3)	31(4.3)	**193(7.4)**
HAV antibody-positive [n (%)]	19(59.3)	44(67.7)	214(77.8)	480(73.3)	616(73.0)	461(63.2)	**1834(70.5)**
Nadir CD4 count:	15(45.5)	26(40.0)	132(48.2)	173(26.4)	355(42.2)	311(42.7)	998(38.4)
<200/µl	30(90.9)	58(92.0)	230(87.1)	589(91.7)	702(87.5)	588(85.7)	2197(84.5
Last HIV VL: ≤50							

MSM: Men having Sex with Men
IVDA: Intravenous drug abuse;
VL: viral load,
AIDS: acquired immune deficiency syndrome