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Hepatitis B prevalence and influence on HIV treatment outcome and mortality in the Chilean AIDS Cohort

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SUMMARY

Objectives: To analyze the prevalence of hepatitis B virus (HBV) co-infection and its influence on mortality and treatment outcome within a large AIDS cohort in Chile.
Methods: Clinical and epidemiological data from the Chilean AIDS Cohort were retrospectively analyzed. Adult patients tested for hepatitis B surface antigen (HBsAg) during the time period of October 2001 to October 2007 were included.
Results: Of 5115 cohort patients, 1907 met the inclusion criteria. The prevalence of HBV co-infection was 8.4%. Overall mortality rates were 2.15 and 1.77 per 100 person-years for HBsAg-positive and HBsAg-negative HIV patients, respectively, with a mortality rate ratio of 1.22 (95% confidence interval 0.58–2.54). Kaplan–Meier survival and Cox regression analysis did not show significant differences between the groups. Virological and immunological responses to antiretroviral therapy (ART) were not influenced by HBsAg status, but in co-infected patients, initial ART was more frequently changed.
Conclusions: The prevalence of hepatitis B co-infection was 8.4%, indicating a markedly elevated hepatitis B risk compared to the general population in Chile. Neither treatment outcome nor overall mortality was influenced by hepatitis B co-infection. Still, patients with hepatitis B co-infection had less stable ART regimens, which might be related to a higher risk of hepatotoxic drug effects.

1. Introduction

Antiretroviral therapy (ART) has increased life expectancy and quality of life of HIV-infected individuals by suppressing viral replication. In this setting, co-morbidities such as chronic viral infections are gaining importance in the management of HIV.

Hepatitis B is a frequent co-infection with a similar mode of transmission and has been recognized as a challenge worldwide.[1] About 10% of all HIV-positive patients are co-infected with the hepatitis B virus (HBV).[2] Factors influencing the prevalence of this co-infection include the predominant mode of HIV transmission and the prevalence of HBV in the population of the country, which ranges between 0.1% and 20% worldwide.[3] Chile belongs to the low endemic countries. Recent data from the Chilean Ministry of Health show a prevalence of only 0.15% chronic HBV in the general population.[4] In Chile as much as 84% of HBVs belong to genotype F,[5] which has been associated with higher mortality and incidence of hepatocellular carcinoma.[6] There are very few epidemiological data on HBV/HIV co-infection in Chile. A publication by Pérez et al. reported a prevalence of 6.1% of hepatitis B surface antigen (HBsAg) carriers among 311 HIV patients in a private HIV center in Santiago.[7]

There are still many uncertainties about the clinical relevance of viral co-infection with HBV and HIV and the influence of ART. In the pre-ART era, some studies described a faster progression to AIDS[8] and reduced survival for co-infected patients.[9] Others did not find any impact on the progression of HIV infection.[10,11] Later studies under ART showed conflicting results regarding mortality and AIDS progression. The majority of studies showed a higher liver-related mortality associated with HBV co-infection for HIV patients under ART,[12–14] while virological or immunological response to ART did not seem to be influenced.[15–20]

Regarding discordant responses to ART, i.e., an adequate virological without immunological response, or vice versa, the situation in HBV co-infected patients is unclear. This phenomenon is associated with a worse clinical outcome regarding mortality and AIDS-defining events.[21–24] Well-known risk factors for discordant responses include age, low CD4+ cell count nadir, high

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HIV viral load, concomitant immunosuppressive therapies, specific ART combinations, and adherence problems.[24–27] A small series from Spain did not find an association with hepatitis C co-infection,[28] while HBV co-infection as a risk factor for discordant treatment outcome has not been investigated so far. Remarkably, most of the studies mentioned above were performed in industrialized countries, while data from low- or middle-income countries, with their limited diagnostic and treatment options for both hepatitis B and HIV, are scarce.

In this study, data from the Chilean AIDS Cohort, a national joint project that follows clinical information and treatment data of HIV patients receiving ART within the Chilean public health system,[29] were used to retrospectively analyze the prevalence of HBV co-infection in Chile, as well as the possible influence of HBV co-infection on mortality and the virological and immunological treatment response, including discordant response, after 12 months of ART.

2. Methods

The Chilean AIDS Cohort Study Group founded the Chilean Cohort in 2001. During the study period, this project prospectively recorded patient data from 29 of the 32 public HIV centers. Patients were included if they were at least 18 years old and eligible for the initiation of ART according to the Chilean HIV/AIDS guidelines. During our study period, ART was recommended for patients with symptomatic HIV infection (Centers for Disease Control and Prevention (CDC) stage B/C), or for asymptomatic patients with CD4+ counts of <200 cells/μl.[30] All patients included in this database were ART-naive at entry and were followed-up twice yearly using standardized forms, which included demographic and clinical data as well as laboratory examinations.

Our study analyzed data from October 2001 to October 2007. Of all patients who were added to the database during this period, only those who had at least one test result for HBsAg were included in the study. Assays were performed at local laboratories and therefore derived from different manufacturers. HIV patients were categorized as hepatitis B co-infected if they had at least one positive result for HBsAg testing (HBsAg-positive). HIV patients with only negative results for HBsAg served as a control group (HBsAg-negative). Mortality data were analyzed and survival times were calculated for HBsAg-positive and HBsAg-negative patient groups.

Of the included patients, only those who provided a complete set of CD4+ cell counts and plasma viral load (VL) at baseline (0–6 weeks) and at follow-up after 6–18 months, were included in the analysis of treatment response. If more than one CD4+ cell count or VL was recorded at follow-up, the value closest to 12 months was taken for the analysis. Virological response was defined as a VL <500 copies/ml, and immunological response as an increase of CD4+ cells >100 cells/μl from baseline to the time of follow-up. According to these laboratory values, patients were categorized into four different groups of treatment outcome: virological and immunological response (VL+/CD4+), immunological response only (VL−/CD+), virological response only (VL+/CD4−), and no response (VL−/CD4−). CD4+ cell counts were determined by standard flow cytometry methodology; for VL the NucliSENS HIV-1 assay (bioMérieux, Durham NC, USA) with a detection limit of 80 copies/ml was used.

The statistical analysis was performed using PASW Statistics (PASW Statistics Version 18.0, IBM, New York, USA). Continuous variables were presented as means with a standard deviation (SD) and compared between the groups with the Student's *t*-test. Categorical data were presented as counts and percentages, and the Chi-square test was used to look at differences between groups. Mortality rates show the overall mortality over 100 person-years at risk with 95% confidence intervals (95% CI). Information about survival was censored at the last available entry that was recorded for each individual patient, or at the day of a fatal event. Kaplan–Meier survival curves were used to graph survival time. Cox regression models were used to investigate the association of potential risk factors with overall mortality. The covariates, sex, age at beginning of ART (<40 vs. >40 years), baseline CD4+ cell count (<100 vs. >100 cells/μl), and baseline VL (<100 000 vs. >100 000 copies/ml) were entered simultaneously into the model. The selection of covariates is based on their prior identification as substantial risk factors for mortality in the literature.

The corresponding ethics committee approved the project of the Chilean AIDS Cohort and waived informed consent requirements. All patient data were handled anonymously. Unique non-identifiable codes were used for each patient.

3. Results

Our study cohort consisted of 5115 ART-naive HIV patients, of whom 1907 (37.3%) provided HBsAg test results and were included in the study. Of these, 161 patients were HBsAg-positive, resulting in a prevalence of 8.4% HBV/HIV co-infection. Among all studied patients, 1435 (75.2%) provided a full set of immunological and virological data and were included in the treatment response analysis (Figure 1).

As shown in Table 1, significantly more patients in the HBsAg-positive group were found to be male (96.9% vs. 83.7%, $p < 0.01$). The route of transmission was predominantly homosexual in both groups, with a significantly higher percentage in the HBsAg-positive patients ($p < 0.01$). There was no intravenous drug use reported in either group. Serological testing for syphilis (VDRL, venereal disease research laboratory test) was more frequently positive in the HBsAg-positive patients (20.5% vs. 14.9%); this difference did not reach statistical significance. Most patients presented in CDC categories A and C. Groups did not differ by their baseline CDC classification, or show significant differences in the spectrum of opportunistic infections at baseline. Opportunistic infections with the highest frequencies were oral candidiasis and *Pneumocystis jirovecii* infection.

At 2.15 (95% CI 0.7–3.7) per 100 person-years, the mortality rate of the HBsAg-positive group was higher than that of the HBsAg-negative group with 1.77 (95% CI 1.3–2.2) per 100 person-years; this difference, resulting in a mortality rate ratio of 1.22 (95% CI 0.58–2.54), was not statistically significant. Further analysis by

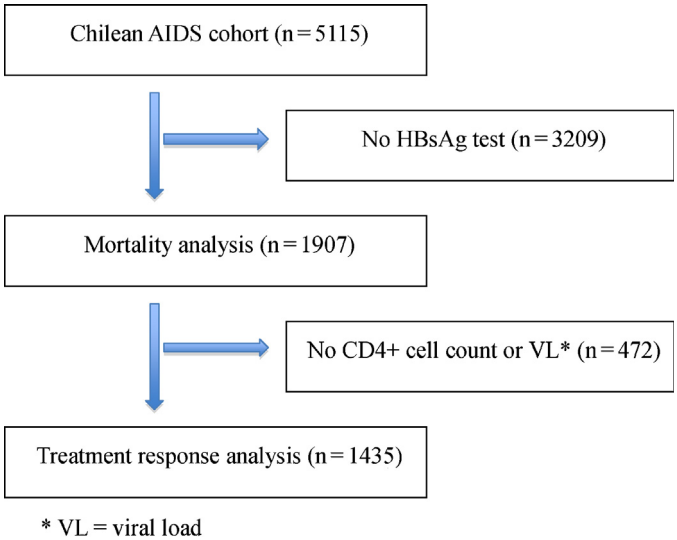

Figure 1. Flow chart: patient numbers for subgroup analysis and patient numbers for drop out (HBsAg, hepatitis B surface antigen; VL, viral load).

Table 1
Characteristics of patients of the Chilean AIDS Cohort, grouped by hepatitis B co-infection (HBsAg-positive and HBsAg-negative)

Characteristic[a]	All subjects ($n = 1907$)	HBsAg-positive ($n = 161$)	HBsAg-negative ($n = 1746$)	p-Value
Age at start of ART, mean (SD)	37.2 (9.9)	36.8 (9.5)	37.2 (9.9)	0.62
Male sex, *n* (%)	1617 (84.8)	156 (96.9)	1461 (83.7)	<0.01[b]
Person-years of follow-up time/patient (mean, SD)	2.12 (1.45)	2.30 (1.58)	2.10 (1.43)	0.08
VDRL once positive, *n* (%)	293 (15.4)	33 (20.5)	260 (14.9)	0.06
Hepatitis C, *n* (%)	26 (1.4)	3 (1.9)	23 (1.3)	0.57
Route of transmission, *n* (%)				
Homosexual	990 (61.5)	105 (79.5)	885 (59.8)	<0.01[b]
Heterosexual	563 (35.0)	24 (18.2)	539 (36.4)	<0.01[b]
Intravenous drug users	0	0	0	
Other	57 (3.5)	3 (2.3)	56 (3.8)	0.35
No data	297 (15.6)	31 (19.3)	266 (15.2)	0.18
Baseline CDC classification, *n* (%)				
Class A	617 (32.9)	49 (30.8)	568 (33.1)	0.59
Class B	504 (26.9)	39 (24.5)	465 (27.1)	0.51
Class C	755 (40.2)	71 (44.7)	684 (39.8)	0.22
No data	31 (1.6)	2 (1.2)	29 (1.7)	0.69
Baseline opportunistic infections, *n* (%)				
Pneumocystis	306 (16.0)	27 (16.8)	279 (16.0)	0.79
Tuberculosis	120 (6.3)	7 (4.3)	113 (6.5)	0.29
CMV infection	10 (5.2)	0 (0)	10 (5.7)	0.34
Oral Candida	467 (24.5)	38 (23.6)	429 (24.6)	0.78
Others	332 (17.4)	34 (21.1)	298 (17.1)	0.19
No opportunistic infection	672 (32.2)	55 (34.2)	617 (35.3)	0.77

ART, antiretroviral therapy; CDC, Centers for Disease Control and Prevention; CMV, cytomegalovirus; HBsAg, hepatitis B surface antigen; SD, standard deviation; VDRL, venereal disease research laboratory test.
[a] Continuous variables of the groups (HBsAg-positive, HBsAg-negative) were compared with the Student's *t*-test, categorical variables by Chi-square test.
[b] Significant differences.

Kaplan–Meier did not reveal significant differences between survival times of HBsAg-positive and HBsAg-negative patients (Figure 2). Cox regression analysis including the covariates sex, age at beginning of ART (<40 vs. >40 years), baseline CD4+ cells count (<100 vs. >100 cells/μl), and baseline VL (<100 000 vs. >100 000 copies/ml) did not change the estimates significantly.

Treatment response data are presented in Table 2. Baseline immunological data did not show any significant differences between the HBsAg-positive and HBsAg-negative patients, with a mean baseline CD4+ cell count of 138 (SD 112) cells/μl and 125 (SD 96) cells/μl, respectively. Severe immunosuppression at baseline with CD4+ cell counts <100 cells/μl was observed in 53.4% of HBsAg-positive and 58.5% of HBsAg-negative patients. Baseline VL >100 000 copies/ml was detected in 69.5% of HBsAg-positive patients and 63.7% of HBsAg-negative patients. Analysis of immunological and virological treatment response rates after 12 months of ART did not reveal significant differences between the two groups. The mean increase in CD4+ cell count was +154 (SD 128) cell/μl for the HBsAg-positive patient group and +162 (SD 139) cells/μl for the HBsAg-negative patient group. Analysis of discordant response revealed no significant differences in the distribution of HBsAg-positive and HBsAg-negative patients within the four treatment response groups.

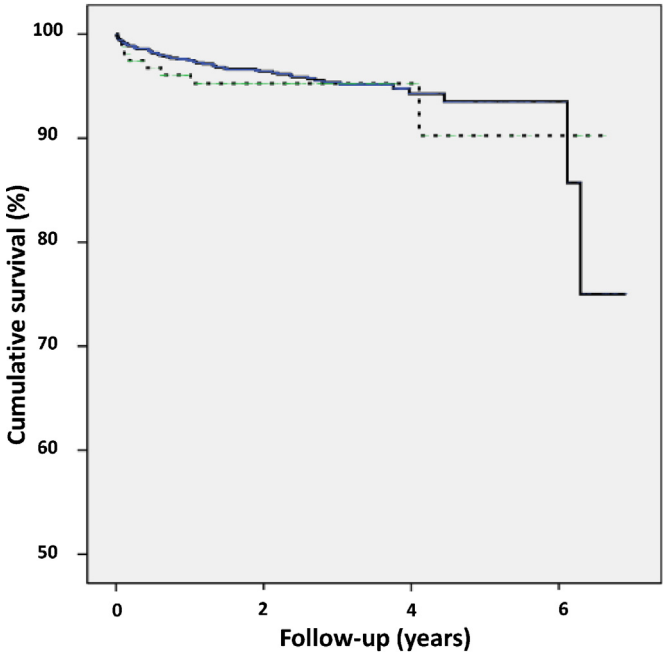

Figure 2. Kaplan–Meier survival curves for the Chilean AIDS Cohort ($n = 1907$), grouped by HBsAg-positive (dotted line) and HBsAg-negative (solid line) patients.

The use of selected ART drugs in the study population is summarized in Table 3. Lamivudine was prescribed in 98.7% of HIV therapies and there was no difference between the HBV co-infected and not co-infected patients. Only seven patients received tenofovir during the study period; among these were significantly more hepatitis B co-infected patients ($p < 0.01$). The use of nevirapine and efavirenz did not differ between groups. One ($p < 0.01$) or more than two treatment changes ($p < 0.05$) were recorded significantly more frequently in the HBV co-infected group.

4. Discussion

Most epidemiological studies on HBV/HIV co-infection describe populations in industrialized countries in Europe and North America, whereas the situation in Latin America is less well studied. Our study provides the first information on hepatitis B co-infection within the Chilean AIDS Cohort, which includes public HIV care centers of the country. Epidemiological information on the prevalence of HBV/HIV co-infection in Chile is limited. Our data show a prevalence of 8.4% (95% CI 7.3–9.8%), indicating that the burden of HBV co-infection might have been underestimated in a previous study, which described a prevalence of 6.1% (95% CI 3.8–9.5%).[7] Furthermore, our study highlights that HIV patients have a more than 50-fold increased risk of HBV infection compared to the general population in Chile. Until now, an HBV vaccine has not

Table 2
Treatment response after 12 months of ART, grouped by hepatitis B co-infection (HBsAg-positive and HBsAg-negative)

	All subjects (n = 1435)	HBsAg-positive (n = 118)	HBsAg-negative (n = 1317)	p-Value
Baseline parameters[a]				
CD4+ cells/μl, mean (SD)	125 (97)	138 (112)	125 (96)	0.15
CD4+ <100 cells/μl, n (%)	833 (58.0)	63 (53.4)	770 (58.5)	0.28
Viral load, copies/ml, mean (SD)	343 213 (797 037)	329 079 (475 808)	344 488 (819 976)	0.85
Viral load >100 000 copies/ml, n (%)	921 (64.2)	82 (69.5)	839 (63.7)	0.21
Response after 12 month of ART[a]				
Increase of CD4 cells/μl, mean (SD)	162 (139)	154 (128)	162 (139)	0.53
Viral load <400 copies/ml, n (%)	1186 (82.6)	95 (80.5)	1091 (82.8)	0.52
CD4+ increase >100 cells/μl, n (%)	960 (66.9)	76 (64.4)	884 (67.1)	0.55
Virological + immunological success[b], n (%) VL+/CD4+	852 (59.4)	69 (58.5)	783 (59.5)	0.84
Immunological success only[b], n (%) VL−/CD4+	108 (7.5)	7 (5.9)	101 (7.7)	0.49
Virological success only[b], n (%) VL+/CD4−	334 (23.3)	26 (22.0)	308 (23.4)	0.74
No response[b], n (%) VL−/CD4−	141 (9.8)	16 (13.6)	125 (9.5)	0.15

ART, antiretroviral therapy; HBsAg, hepatitis B surface antigen; SD, standard deviation; VL, viral load.
[a] Continuous variables of the groups (HBsAg-positive, HBsAg-negative) were compared with the Student's t-test, categorical variables by Chi-square test.
[b] Virological treatment success was defined as plasma VL <400 copies/ml after 12 month of therapy. Immunological treatment success was defined as an increase in CD4+ cells of 100/μl or more after 12 months of therapy.

been offered routinely to HIV patients attending the Chilean public health system. Our data indicate that this policy should be revised and vaccination strategies should be discussed.

The epidemiology of HBV/HIV co-infection is complex and not completely understood, but co-infection rates depend on the prevalence of HBV in the general population,[2,14] the dominant routes of HIV infection,[31] and the coverage of HBV immunization.[32] In our study population, co-infection was mainly associated with sexual transmission in homosexual men, confirming the existing data.[33,34] Our study and previous analysis of the Chilean AIDS Cohort showed that intravenous drug use, a known risk factor for co-infection,[31] is virtually absent in Chile. Surprisingly, this did not lead to a significantly lower rate of co-infection in comparison to European HIV cohorts with a much higher rate of intravenous drug use. In Denmark, for example, a prevalence of 6.1% HBV co-infection was found in the national HIV cohort reporting intravenous drug use in 9.7% of patients.[18] The influence of a high background prevalence within the general population on HBV/HIV co-infection also seems complex. An HIV cohort from Thailand with 82% heterosexual transmission and 1% intravenous drug use reported HBV co-infection in 8.7% of patients, although the prevalence of chronic HBV in blood donors in Thailand is estimated at 2.6%,[35] which is 17-times higher than in Chile.[4]

In South America, the Amazon basin is an area of high endemicity of hepatitis B,[36] whereas other regions have a low rate of hepatitis B infection. Comprehensive data on HBV/HIV co-infection in South America are lacking. In Brazil, for example, marked geographical differences with rates ranging from 3% to 24% have been reported.[37] Most other reports from South America have lacked a broad population base and have mostly focused on subgroups of HIV-infected patients. In Peru, a prevalence of 9.5% HBsAg was published for HIV-positive men who have sex with men.[38] In a Colombian study, only patients positive for antibodies to the hepatitis B core antigen (anti-HBc) were tested for HBsAg, resulting in a prevalence of 2.1%.[34] Data from Argentina that were taken as a part of the EuroSIDA multicenter study, showed a relatively high prevalence of 17.8% HBsAg positivity,[39] in accordance with older data.[40] This high prevalence was mainly attributed to intravenous drug use. A more recent study from 2010 found only 3.3% HBsAg-positives in a series of 593 HIV-positive patients in Buenos Aires. The authors state that political changes have led to a decrease in injecting drug use, resulting in a lower HBV/HIV prevalence since 1999.[41] The lack of comprehensive data and the heterogeneity of the existing evidence show a need for further studies on HBV co-infection in South America.

The influence of HBV co-infection on the mortality of HIV patients is a controversial subject. Large studies such as EuroSIDA found a significantly higher mortality for HBV co-infected in comparison to not co-infected HIV patients (3.7 vs. 2.6 per 100 person-years). This difference was mostly due to liver-related

Table 3
Selected antiretroviral drugs in the study population, grouped by hepatitis B co-infection (HBsAg-positive and HBsAg-negative). Groups (HBsAg-positive and HBsAg-negative) were compared with the Chi-square test.

	All subjects (n = 1907)	HBsAg-positive (n = 161)	HBsAg-negative (n = 1746)	p-Value
Drugs, n (%)				
Tenofovir[a]	7 (0.4)	4 (2.5)	3 (0.2)	<0.01[b]
Lamivudine	1882 (98.7)	157 (97.5)	1725 (98.8)	0.17
Efavirenz	1451 (76.1)	122 (75.8)	1329 (76.1)	0.92
Nevirapine	317 (16.6)	18 (11.2)	299 (17.1)	0.05[b]
Changes of therapy, n (%)				
1	592 (31.0)	65 (40.4)	527 (30.2)	<0.01[b]
2	197 (10.3)	22 (13.7)	175 (10.0)	0.14
>2	62 (3.3)	10 (6.2)	52 (3.0)	<0.05[b]

HBsAg, hepatitis B surface antigen.
[a] Tenofovir was not widely available in Chile during the study period.
[b] Significant differences.

mortality (0.7 vs. 0.2 per 100 person-years).[39] Another large HIV cohort from Denmark also found significantly higher mortality rates for HBsAg-positive compared to HBsAg-negative patients, 3.9 and 2.5 per 100 person-years, respectively.[18] The Multicenter AIDS Cohort Study (MACS), which includes male HIV patients in the USA, did not confirm this finding,[12] although in accordance with other studies, liver-related deaths were more frequent in co-infected patients.[14] In our study, we were not able to find an influence of HBsAg carrier status on survival. HBsAg-positive patients had a mortality rate of 2.15 (95% CI 0.7–3.7) per 100 person-years compared to 1.77 (95% CI 1.3–2.2) in the HBsAg-negative group, resulting in a mortality rate ratio of 1.22 (95% CI 0.58–2.54). A possible reason for these differences is that our cohort, as with the MACS study group, did not include intravenous drug users. Additionally, the distribution of hepatitis B genotypes might influence survival rates in different cohorts. Still, this cannot explain the above-mentioned differences, since in Chile genotype F is predominant and this genotype is associated with a higher mortality compared to genotypes A and D, which occur more frequently in Europe and North America.[5,6]

Low CD4 cell counts are considered a risk factor for liver-related mortality for HBV/HIV co-infected patients as well as for overall mortality in HIV patients regardless of their HBV status.[12,42] The EuroSIDA study found a lower mean baseline CD4+ cell count in the HBV co-infected HIV patients compared to the HBV-negative HIV patients (232 cells/μl vs. 275 cells/μl).[39] In contrast, the baseline mean CD4+ cell counts of our cohort were slightly higher in hepatitis B co-infected patients (138 cells/μl vs. 125 cells/μl), which is in accordance with other studies.[12,43] We integrated baseline CD4+ cell counts into our regression model and results remained unchanged. No influence of CD4+ cell counts on mortality was found in our data.

Another important factor in HBV co-infection is the increased risk of severe hepatotoxic side effects caused by antiretroviral drugs.[44,45] In our database, liver enzymes were not documented on a regular basis, thus hepatotoxicity could not be analyzed. However, we noticed significantly more ART changes in the HBV co-infected group, and hepatotoxic drug effects could have been one important reason for changing ART.

HBV/HIV co-infection is an important factor for the selection of an antiretroviral regimen. The Chilean public health system provides ART drugs free of charge, but the choice of drugs is predetermined by national guidelines. At the time of data collection, the standard treatment regimen consisted of a backbone of lamivudine and zidovudine combined with efavirenz or nevirapine. Therefore almost all our patients (98.7%) received lamivudine, without significant differences between study groups. Monotherapy with lamivudine in HBV-infected patients can lead to resistance in about 20% of cases per year. Nevertheless, an inter-cohort analysis of HBsAg-positive HIV patients found a reduced liver-related mortality associated with lamivudine use in combination therapies.[46] The high coverage of lamivudine in our study could have led to a decrease in mortality in the HBV co-infected patients, diminishing the difference between the two groups. Although tenofovir was used significantly more often in the HBV co-infected group, its overall use was negligible (seven of 1907 patients), since it was not widely available in the public health system of Chile until 2010.

After a period of 12 months of ART, we did not find a significant impact of HBV co-infection on immunological or virological treatment response in our cohort of treatment-naive patients. This is in accordance with data of the international HIV-NAT cohort after 48 weeks of treatment.[17] In contrast to our findings, a Taiwanese study described a significantly higher rate of virological failure in the HBV/HIV co-infected group.[19] The authors argue that a higher incidence of hepatitis and frequent treatment interruptions might explain this influence on virological response. Still, this study was performed in a population with a high HBV prevalence, resulting in a much higher HBV/HIV co-infection rate of 21.7% than in our study. Various other studies have reported findings in accordance with those of our study and did not show a negative influence of HBV co-infection on the virological treatment outcome.[16,17,20]

Our study also aimed to analyze the potential influence of HBV co-infection on the incidence of discordant treatment response to ART. Such an association has been suggested for cytomegalovirus (CMV),[47] supporting the hypothesis that viral co-infections might interfere with CD4+ cell recovery. However, hepatitis C co-infection did not show an association with discordant response in the multivariate logistic regression model of Moore and co-workers.[26] To our knowledge, HBV has never been investigated as a risk factor in this context. Our data could not support the hypothesis that an association between HBV co-infection and discordant treatment response is relevant.

A limitation of our study was that HBsAg testing was not available for all patients in the Chilean AIDS Cohort, since this test was not performed as part of the routine at all HIV centers, selection bias cannot be excluded. Nevertheless, baseline characteristics of the 1907 patients included did not differ from those of the entire cohort of 5115 patients described in an earlier publication.[48] One important factor is the rate of homosexual transmission, which was 61.5% (95% CI 59.1–63.8) in our study population and 58% (95% CI 56.7–59.4) in the whole cohort. High dropout rates have also been a problem in other cohort studies such as EuroSIDA and MACS, where 43% and 32% of HIV patients, respectively, had to be excluded, because of missing HBsAg test results. Intensified HBsAg testing, which is recommended by new Chilean guidelines,[49] will help to include more patients in future studies. Another limitation of our study is the lack of a complete set of serological markers of HBV and other important parameters such as HBV viral load, HBV genotype, liver enzymes, and hepatitis D co-infection. Due to limited financial resources in many countries including Chile, HBsAg is the only test widely available, therefore the case definition used in our study is common in prevalence studies of chronic HBV infection in resource-poor settings. Still, it creates a heterogeneous group, which includes cases of chronic active and inactive HBV. Studies analyzing different subgroups defined by serological markers within the population of HIV patients in Chile are currently underway.

In conclusion, our study revealed a prevalence of chronic HBV infection of 8.4% within the Chilean HIV population, which indicates a markedly elevated HBV risk compared to the general population. Treatment response and overall mortality after 12 months of ART were not influenced by HBV co-infection. Still, in patients with hepatitis B co-infection, the ART regimen was more frequently changed than in those without co-infection, which might be related to a higher risk of hepatotoxic drug effects. Our analysis reflects the problems in an upper middle-income South American country, where up to now epidemiological and clinical features of HBV/HIV co-infection have been poorly studied, and neither HBV serological testing nor vaccination is widely available for HIV patients. Further studies will help to overcome these obstacles and assist in the planning of targeted immunization programs in this setting.

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