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HIV/HBV COINFECTION: ASSOCIATED FACTORS WITH HBV FUNCTIONAL CURE

COINFECÇÃO HIV/HBV: FATORES ASSOCIADOS À CURA FUNCIONAL DA HBV

COINFECCIÓN VIH/VHB: FACTORES ASOCIADOS A LA CURA FUNCIONAL DEL VHB

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ABSTRACT
HIV research has remained frequent since its discovery. HIV/HBV co-infection is highly significant as it impacts on the natural history of chronic HBV infection, increasing morbidity and mortality. **Objective:** To identify the prevalence of functional cure in patients with HIV/HBV coinfection and the possible factors associated with this cure. **Method:** This is a retrospective cohort study conducted between July 2023 and August 2024 in two healthcare centers in Fortaleza. **Results:** Of the 175 coinfected patients included in the study, only 146 had access to control HBsAg. In the comparative analysis between the two groups, factors such as the absence of positive HBeAg and lack of detection of HBV-DNA were statistically significant for HBsAg clearance. **Conclusion:** These results suggest that proper control of HBV, particularly in patients with negative HBeAg, is associated with a higher prevalence of functional cure.
Keywords: *HIV; Hepatitis B Virus; Highly Active Antiretroviral Therapy; Hepatitis B Surface Antigens.*

RESUMO
As pesquisas sobre o HIV permanecem frequentes desde sua descoberta. A coinfecção HIV/HBV tem grande importância, pois tem impacto na história natural da infecção crônica pelo HBV, aumentando a morbi-mortalidade. **Objetivo:** Identificar a prevalência de cura funcional nos pacientes com a coinfecção HIV/HBV e os possíveis fatores associados a essa cura. **Método:** Trata-se de uma coorte retrospectiva, conduzida entre julho/2023 a agosto/2024 em dois centros de saúde de Fortaleza. **Resultados:** Dos 175 pacientes com a coinfecção incluídos no estudo, somente 146 tiveram acesso ao HBsAg de controle. Na análise comparativa entre os dois grupos, fatores como ausência de HBeAg positivo e indetecção do HBV-DNA foram estatisticamente significativos para negativação do HBsAG. **Conclusão:** Esses resultados sugerem que o bom controle do HBV, principalmente em pacientes com HBeAG negativo, estão associados a uma maior prevalência de cura funcional.
Descritores: *HIV; Vírus da Hepatite B; Terapia Antirretroviral de Alta Atividade; Antígenos de Superfície da Hepatite B.*

RESUMEN
Las investigaciones sobre el VIH siguen siendo frecuentes desde su descubrimiento. La coinfección VIH/VHB tiene gran importancia, ya que impacta la historia natural de la infección crónica por el VHB, aumentando la mortalidad. **Objetivo**: Identificar la prevalencia de la cura funcional en pacientes con coinfección VIH/VHB y los posibles factores asociados a esta cura. **Método:** Se trata de una cohorte retrospectiva realizada entre julio de 2023 y agosto de 2024 en dos centros de salud de Fortaleza. **Resultados:** De los 175 pacientes con coinfección incluidos, solo 146 tuvieron acceso al HBsAg de control. En el análisis comparativo entre los dos grupos, factores como la ausencia de HBeAg positivo y la indetección del ADN del VHB fueron estadísticamente significativos para la negativización del HBsAg. **Conclusión:** Estos resultados sugieren que un buen control del VHB, especialmente en pacientes con HBeAg negativo, está asociado con una mayor prevalencia de cura funcional.
Descriptores: *VIH; Virus de la Hepatitis B; Terapia Antirretroviral Altamente Activa; Antígenos de Superficie de la Hepatitis B.*

INTRODUCTION

Even forty years after its discovery, HIV continues to be widely studied, remaining with the status of a diverse and long-lasting pandemic, so that, in Brazil, in

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2023, 46,495 new cases of HIV infection were reported (1,2). However, with the advent of antiretroviral therapy (ART), the natural history of the disease has been modified (3).

Currently, about 250 million people are living with the hepatitis B virus (HBV) worldwide. In Brazil, in 2023, 10,091 new cases of HBV infection were reported (4). Because it has a mode of transmission similar to that of HIV, some patients acquire co-infection with these two agents. According to worldwide data, between 7-8% of people diagnosed with HIV are co-infected with HBV (5, 6). This prevalence may vary, depending on the population evaluated. In a study conducted in the state of Ceará, however, the prevalence of co-infection was lower (3.7%) (7).

The HIV/HBV association has a significant impact on the natural history of chronic HBV infection, so it can exacerbate liver disease, increase mortality, and may result in increased replication, HBV reactivation, and increased chronicity. There may also be an increased risk of hepatotoxicity from ART. HIV-induced immunodeficiency may also be aggravated in those with active HBV replication (5, 8).

With the introduction of effective ART, there was a decrease in the mortality of coinfected patients. However, when compared to patients monoinfected with HIV, significantly higher morbidity and mortality are also observed (9).

Loss of hepatitis B surface antigen (HBsAg) is the therapeutic goal of HBV infection, although it does not always mean viral eradication. The definition of functional cure is represented by the loss of HBsAg, with or without Anti-HBs seroconversion, and is associated with a reduction in the risk of hepatocellular carcinoma. This functional cure, although an infrequent event in monoinfected chronic HBV patients, has a slightly higher prevalence among coinfected patients (9, 10).

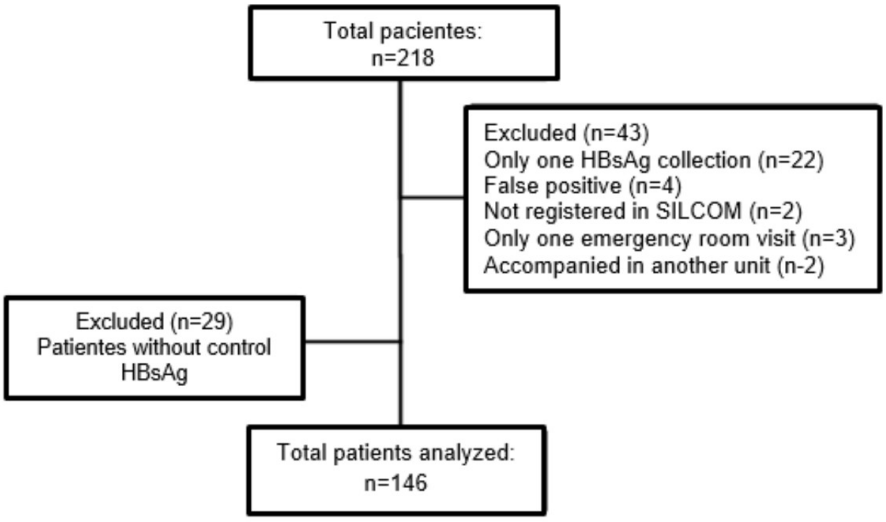
The aim of the present study is to identify the prevalence of functional cure in patients with HIV/HBV co-infection and the possible factors associated with this cure.

METHODS

This is a retrospective cohort conducted between July 2023 and August 2024 in two health centers in Fortaleza, Ceará: a public referral hospital specializing in infectious disease care (São José de Doenças Infecciosas Hospital) and a specialized HIV/AIDS care service (NAMI - Integrated Medical Care Center). All patient data were taken from physical and electronic medical records.

The cohort included all patients Co-infected with HBV-HIV from these centers, adults, aged ≥18 years, who were followed up between 2014-2024, with at least two consultations within six months. Patients were considered to have chronic HBV only if they had been HBsAG positive for more than 6 months. Sustained loss of HBsAg was considered functional cure. HBV-DNA suppression was defined as the non-detection of its serum levels. Cases of acute hepatitis B, patients with only one visit, and patients with no laboratory data available were excluded from the study (Figure 1).

Figure 1 – Flowchart for selecting the sample of patients with HIV/HBV co-infection followed at HSJ* and NAMI** (2014-2024).



*São José Hospital for Infectious Diseases, ** Integrated medical care center

The SPSS 16.0 program was used for data analysis. The patients were classified into two groups: with and without functional cure. Measures of frequency and central tendency were calculated. To compare the two groups, the chi-square test was performed for categorical variables, and the Student's t-test or the Mann-Whitney test for numerical variables, depending on the Kolmogorov-Smirnov test. A p-value of < 0.05 was considered significant. The study was reviewed and approved by the Ethics Committee of the institutions (nº 6.113.810).

RESULTS

A total of 218 patients were evaluated, and 43 were excluded: 22 because they had only one HBsAg collection alone and without follow-up, 4 were considered false positives, 2 were not registered in the drug logistics control system (SICLOM), 13 had only one emergency room visit, and 2 were followed up in another unit (Figure 1).

Of the remaining 175 patients, 146 had access to the control HBsAg, in which 23 patients (15.75%) were negative for the surface antigen. Of these, 17 seroconverted to Anti-HBs.

Among the participants, 91 were men (62%), 57 (39%) had at least completed 1st or 2nd degree, 79 were single (54%), 50 were homosexual (34%) and 130 were on treatment with tenofovir (89%). The univariate analysis of the epidemiological variables showed no statistically significant difference between the two groups studied (Table 1).

In the analysis of clinical-laboratory variables, both groups had a mean initial CD4 count above 300 cells/dL and HIV viral loads slightly higher than 3 log, suggesting no significant difference in the status of HIV infection at the beginning of follow-up. Throughout follow-up, both groups showed a similar improvement in immune recovery (increased CD4 levels) and HIV virologic control (reduced HIV viral load). The non-undetection of HBV viral load and HBeAg antigen positivity were more prevalent in the group without functional cure ($p = 0.01$ and $p = 0.001$, respectively).

More than 90% of the patients in both groups used tenofovir, and there was also no difference in the duration of HBV treatment. No statistically significant differences were observed in the analysis of the other clinical-epidemiological variables analyzed. (Table 1).

The most requested imaging test was abdominal ultrasound, performed in 111 patients (63.4%), with 17% already showing signs of chronic liver disease on examination. Only 19 patients (13%) underwent hepatic elastography. Absence of fibrosis (F0) was identified in 10 (52.6%) of the patients.

During the data collection period, 9 patients without treatment for HBV were detected. Of these patients, 2 were losing follow-up, 1 was transferred to another city, 4 received drug-free regimens with action against HBV. There was one death due to recurrence of visceral leishmaniasis. Finally, one patient did not start therapy against HBV because he had undetectable HBV-DNA.

Table 1 - Comparative analysis of epidemiological and clinical-laboratory variables of HIV/HBV co-infected patients with and without functional cure (July/2023-August/2024).

Variable		HBsAg negative	HBsAg positive	*p*
Epidemiological variables				
Gender	Male	17 (73,9%)	74 (60,2%)	0,21
	Female	6 (26,1%)	49 (39,8%)	
Mean age (in years)		49,3 (+/- 11,6)	51,3 (+/-10,3)	0,40
Education		2 (8,7%)	4 (3,2%)	
Illiterate				
10 Complete or Incomplete		4 (17,4%)	25 (20,3%)	0,58
20 complete or incomplete		8 (34,8%)	20 (12,3%)	
Complete or incomplete higher education		0	8 (6,5%)	
Marital status				
Married/common-law partnership		6 (26%)	27 (21,9%)	0,72
	Single	13 (56,5%)	66 (53,7%)	
	Widow(er)	2 (8,7%)	2 (1,6%)	
Sexual Orientation	Homosexual	7 (30,4%)	43 (34,9%)	
	Heterosexual	7 (30,4%)	31 (25,2%)	0,60
	Bisexual	2 (8,7%)	9 (7,3%)	
Illicit drug use		8 (34,8%)	37 (30%)	0,74
Alcohol use		4 (17,4%)	26 (21,1%)	0,78
Smoking		3 (13%)	16 (13%)	1,0
HCV carrier		1 (4,3%)	2 (1,6%)	0,40
Clinical-laboratory variables				
Mean time to diagnosis of HBV (in years)		9,8 (+/-2,9)	12 (+/-6)	0,20
Average HBV Treatment Time (in years)		7,3 (+/-2,6)	8,2 (+/-5,3)	0,77
Initial HIV viral load (in log)		3,5 (+/-1,9)	3,3 (+/-1,8)	0,54
Initial CD4 (in cells/dL)		389,9 (+/-344)	301,7 (+/-236)	0,47
HIV viral load prior to HBV diagnosis (in log)		2,88 (+/-2,1)	2,7 (+/-2)	0,58
CD4 before diagnosis of HBV (in cells/dL)		389,6 (+/-317)	341,3 (+/-267,5)	0,68
Last HIV viral load (in log)		0,6 (+/-0,3)	0,7 (+/-0,12)	0,23
Last CD4 (in cells/dL)		582,9 (+/-75)	525,5 (+/-27,8)	0,44
Initial HBV viral load (in log)		2,67 (+/-1,5)	3,1 (+/-2,8)	0,75
AST before treatment for HBV (in U/L)		60 (+/-10,3)	54 (+/-6,7)	0,56
TGP before treatment for HBV (in U/L)		98,3 (+/-20,2)	57 (+/-6)	0,30
Albumin before treatment for HBV (in g/dL)		3,9 (+/-0,66)	3,8 (+/-0,76)	0,90
INR before treatment for HBV		1,0 (+/-0,06)	1,1 (+/-0,42)	0,51
Platelets prior to treatment for HBV (U/mL)		205.000 (+/-72.466)	185.000 (+/-64.757)	0,32

Treatment for HBV		21 (91,3%)	116 (94,3%)	0,63
	TDF	20 (95,2%)	103 (88,9%)	0,69
	Entecavir	1 (4,8%)	6 (5,1%)	0,70
	TAF	0	7 (6,0%)	0,30
Presence of fibrosis on hepatic elastography		1 (4,3%)	7 (5,7%)	0,70
	Degree of fibrosis F1	0	2 (28,5%)	
	F2	0	1 (14,5%)	0,86
	F3	1 (100%)	2 (28,5%)	
	F4	0	2 (28,5%)	
FIB4	≤0.7	1 (4,3%)	4 (3,2%)	0,58
	>0,7	22 (95,7%)	119 (96,8%)	
Cirrhosis		1 (4,3%)	13 (10,5%)	1,0
	CHILD-PUGH 1	1 (100%)	10 (76,9%)	0,78
	CHILD-PUGH 2	0	3 (23,1%)	
HBV Viral Load Suppression		14 (60,9%)	57 (46,3%)	**0,01**
HBeAg positive		1 (4,3%)	52 (42,2%)	**0,001**
Total		23 (15,8%)	123 (84,2%)	

DISCUSSION

According to Brazilian data from 2024, about 5% of HBV infection cases are co-infected with HIV (4). Prolonged suppression of HBsAg, called functional cure, is one of the ideal outcomes for the treatment of HBV, as well as the indetection of HBV-DNA levels (11).

Of the 146 patients analyzed, 15.8% achieved functional cure, a high rate compared to other cohorts. Chihota *et al*., in a cohort study conducted in Zambia, showed a functional cure rate of 10.2% at two years after initiation of ART containing tenofovir (9). Two other cohort studies conducted in China have shown similar results, with an incidence of functional cure between 8.1% – 11.3% (12, 13). In another cohort study conducted in Germany, however, a higher rate of HBsAg serological clearance (18%) was observed. In this study, the mean follow-up time of patients treated with tenofovir was 11 years. The authors conclude that the prolonged duration of tenofovir therapy may be a factor associated with this high functional cure rate (14).

Several factors are possibly associated with the occurrence of functional cure of HBV in HIV/HBV co-infected patients cited in the literature: lower initial baseline HBV viral load levels, higher mean age, greater increase in CD4 lymphocyte levels after initiation of ART, very low pre-treatment baseline CD4 lymphocyte levels, presence of HBV genotype B, longer duration of use of ART containing tenofovir (10, 12, 13, 14).

In the present study, there was no difference in the comparative analysis between the two groups when several of these factors were evaluated, such as mean age, CD4 lymphocyte levels, and HIV viral load (both before the start of treatment and the last test performed). Similarly, no statistically significant difference was observed when comparing the percentages of patients who were adequately treated for hepatitis B (p = 0.63). In addition, a high percentage of tenofovir use and a similar mean duration of treatment for HBV were observed in both groups, possibly because tenofovir is the drug of choice for the treatment of HBV.

In the univariate analysis, sustained loss of HBsAg was associated with continued suppression of HBV viral load (p = 0.01). According to data in the literature,

virological control of HBV with suppression of viral load reduces the risk of complications, such as hepatocarcinoma, elevated liver transaminases, and cirrhosis (15, 16). Thus, keeping the HBV viral load undetectable is an important goal in the treatment of co-infected patients. In addition, non-suppression of the HBV viral load is related to a lower chance of achieving functional cure. The non-viral suppression of HBV would be related to the progression of liver disease, often associated with increased levels of ALT, and associated with a less likely negative HBsAg (17,18).

In this study, HBeAg-positive patients were less likely to be functionally cured (p = 0.001). Jain *et al,* in an American multicenter cohort, where 571 patients were followed for chronic HBV infection for 88 months, observed that those HIV/HBV coinfected who were HBsAg-negative more frequently had HBeAg-negative at baseline. In coinfected individuals who initially presented HBeAg positive, the incidence of functional cure was lower. In the population monoinfected with HBV and, therefore, HIV-negative, this factor was not statistically relevant. This result suggests that HBeAg negativity, i.e., good viral control, is associated with a higher chance of functional cure (19,20).

During the study, it was detected that nine patients were not undergoing adequate treatment against HBV. In three cases, there was loss to follow-up (two due to abandonment and one due to transfer), making it impossible to identify the start of treatment at a later time. Another patient ended up dying from visceral leishmaniasis. However, in the other cases, it was not possible to identify a condition that would justify the non-initiation of adequate treatment for HBV. This finding points to the need for more frequent training in the appropriate management of patients with HIV/HBV co-infection with professionals working in the care of these individuals.

It was noteworthy that a very small number of patients had access to the liver fibrosis assessment test (13%). Liver elastography is an excellent noninvasive modality for predicting liver fibrosis in patients with chronic hepatitis B (21). The indication for this test would be for patients over 30 years of age and with a FIB-4 value greater than 0.7 (11). In this cohort, of the 146 patients, 139 had FIB-4 greater than 0.7 and were over 30 years of age, indicating the need for the test to better assess the degree of disease progression.

CONCLUSION

This study had some limitations. As this was a retrospective study, with data collection from secondary sources, there was difficulty in obtaining some data. In addition, it was not possible to accurately assess the patients' adherence to treatment. In addition, part of the sample was excluded due to lack of laboratory data.

In conclusion, these findings suggest that adequate treatment of HBV and the absence of HBeAg positivity are possibly associated with a higher chance of functional cure of HBV in coinfected patients. It also points to the need for research with larger samples and warns about the need for continuous training of professionals in charge of the care of these patients, especially with regard to the use of ART, always ensuring the maintenance of an active agent against HBV in the scheme. It is worth emphasizing the

importance of carrying out measures to make the necessary tests for the proper follow-up of these patients more accessible, including hepatic elastography.

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