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By Giorgiana-Nicoleta Lungu

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HIV-HBV coinfection and liver fibrosis in long time monitored patients from the former Romanian pediatric HIV cohort – a small study single center experience

Giorgiana-Nicoleta Lungu[1], Florentina Dumitrescu[2,3], Anca Duduveche[2,3], Andreea Marcu[2,3], Lucian-Ion Giubelan[2,3]

[1]Doctoral School, University of Medicine and Pharmacy of Craiova
[2]"Victor Babes" Hospital of Infectious Diseases and Pulmonology from Craiova
[3]University of Medicine and Pharmacy from Craiova, Infectious Diseases department

Correspondence: Giorgiana-Nicoleta Lungu, lungugiorgiananicoleta@gmail.com

Abstract

The aim of this study was to determine de degree of liver fibrosis with the help of a non-invasive method - transient elastography - in a long term monitored HIV-HBV coinfected group of patients (from the former Romanian pediatric cohort) and to assess the implication of various factors as potential risk factors for the development of liver fibrosis. We have reviewed a total of 61 patients (Px) that were in the evidence of the HIV Department of the "Victor Babes" Hospital of Infectious Diseases of Craiova, from which we randomly selected a group of 37 patients that are attending monthly the HIV department. Mean age of the patients was 34.03±2 years old and they were monitored for a long period of time, mean duration of monitorization was 26.11±4.31 years. Patients have been splitted into group A (13 Px) with various degrees of liver fibrosis and group B (24 Px) without liver fibrosis; the mean value of liver stiffness was higher in group A vs group B 11.27±5.72 vs.4.93±0.98 kPa, p<0.0001. Mean value of nadir CD_4 was lower in group A. No significant differences were found between the 2 groups related to the number of associated risk factors, duration of treatment with AZT, ddI, ddC, d4T, NNRTIs or RTV. Longer duration with Lamivudine alone was associated with group A, while dual therapy (Tenofovir based) was characteristic with group B. In conclusion in a long-time monitored HIV-HBV coinfected patients (from the former Romanian pediatric HIV cohort) liver fibrosis is associated with longer use of 3TC and shorter use or Tenofovir.

Keywords: HIV-HBV coinfection, liver fibrosis, Romanian HIV pediatric cohort

Introduction: Liver fibrosis (LF) is the consequence of chronic liver inflammation produced by various factors that lead to the accumulation of certain proteins (mainly collagen) in the liver. Long term development of LF concludes with the occurrence of cirrhosis and liver failure which, with the exception of liver transplantation cases, can lead to the death of the patients. Latest estimations of the burden of chronic liver diseases (including liver cancers, responsible for 600000 up to 900000 deaths) show that the condition is responsible for one up to two millions of deaths annually or 2-4% of all deaths worldwide [1-3]. The most studied factors that impairs liver function are chronic viral hepatitis, alcoholism and non-alcoholic hepatic steatosis.

HIV infection is also a global threat; currently there are about 39 million people infected and another 40 million lost their lives due to the infection [4]. The current estimation of chronic HBV infection is 296 million people suffering (in 2019), with a 1.5 million newly infected annually [5].The exact number of HIV-HBV coinfections is not known, but a recent review of the worldwide data estimates a prevalence of HIV-HBV coinfections of 7.6% (IQR 5.6-12.1), or 2.7 million people coinfected, suggesting that 1 case in 100 persons with HBV infection also have HIV infection as well [6].

A large number of children from Romania were infected with HIV in the past, most of them being born during 1987-1989 (the so called Romanian pediatric HIV cohort). It is not known the exact route of infection, but is considered to be iatrogenic. Also, the time of infection it is considered to be their first year of life. A significant proportion of those children were also coinfected with HBV. Today, most of the HIV infected people from our country, under medical surveillance and monitoring are survivors from that cohort [7].

Objective. To evaluate liver fibrosis in long-time monitored HIV-HBV coinfected patients (from the former Romanian HIV pediatric cohort) using liver transient elastography-Fibro Scan.

Methods. This is a prospective study (January 2022-June 2023) performed at the "Victor Babes" Hospital of Infectious Diseases and Pulmonology from Craiova. We have reviewed a total of 636 patients parenterally infected with HIV during early childhood, from which 183 were alive at the beginning of 2022, 271 were deceased and 182 lost from follow up; from those alive, we have randomly selected a number of 37 HIV-HBV coinfected patients to perform liver transient elastography (Fibroscan). Level of fibrosis were quantified as follow: normal value (1.6-5.5 kPa), F1 grade (7-7.1 kPa), F2 grade (7.2-9.5 kPa), F3 grade (9.6-12.5 kPa) and F4 grade or cirrhosis (>12.5 kPa).Several factors (beside chronic HBV infection) were considered risk factors for liver fibrosis and / or inflammation (body mass index – BMI -, coinfections with hepatitis B, C and / or D virus, Cytomegalovirus infection, tuberculosis, antiretroviral treatments – drugs and duration -, antifungal and/or antineoplastic treatments, prophylaxis with Trimethoprim-Sulfamethoxazole, alcohol consumption, presence of dyslipidemia), introduced into a Microsoft Excel database and analyzed; every risk factor represents 1 point and a total score for risk factors were attributed to each participant; we have formed two main groups, A with patients with HIV-HBV coinfection and liver fibrosis and B those coinfected, but without liver stiffness. Statistical comparisons were made using Chi^2 with Yates' correction (two tailed) and unpaired t test the level of statistical significance being $p<0.05$.

Every participants signed up an informed consent for participation to the present study and publication of data.

Results. Group A consists of 13 patients with liver fibrosis and group B consists of 24 individuals without liver stiffness.

General characteristics

21 patients are males (57%), most of them (19, 51.4%) live in rural settings and majority of them(19, 51.4%) are from Dolj county. Mean age is 34.03 ± 2 years and the patients were monitored for an average of 26.11 ± 4.31 years. Average age when they were detected with HIV infection 7.91 ± 4.05 years, with no statistical difference between the two groups. Based on their clinical and immunological data they are classified (Classification of HIV infection, CDC, 1993) as: B1 = 1 (2.7%), B2 = 3 (8.11%), B3 = 16 (43.2%), C1 = 2 (5.41%), C2 = 2 (5.41%) and C3 = 13 (35.1%), also with no statistical differences between groups.

Data regarding liver transient elastography:

Mean value of liver stiffens is higher in group A vs group B (11.27 ± 5.72 vs 4.93 ± 0.98 kPa, p<0.0001). Data regarding liver fibrosis and grading are presented in Table I.

Insert Table I

Item	Group A (n=13)	Group B (n=24)
F1	1	No liver fibrosis
F2	6	
F3	4	
F4 (cirrhosis)	2	

Table I – Data regarding liver fibrosis and grading for the considered group.

Data regarding risk factors for liver fibrosis and / or inflammation

The average number of considered risk factors for liver fibrosis and / or inflammation is similar in both groups (8.84 ± 1.4 vs 8.33 ± 2.18, p is not statistically significant). Details of every considered item are presented in Table II.

Insert Table II

Risk factor	Group A (n=13) No.of Px.	Group B (n=24) No. of Px.	p value
Persisting presence of HBs Ag	13	24	**0.0001**
Presence of anti HDV antibodies	0	1	NS
Presence of anti HCV antibodies	0	0	-
CMV exposure	2	3	NS
Past or present tuberculosis	4	11	NS
Past or present antifungal treatment	11	21	NS
Past or present PCP prophylaxis	12	20	NS
Past or present antineoplastic therapy	1	2	NS
Past or present AZT use	13	21	NS

Past or present ddI use	6	10	NS
Past or present ddC use	8	12	NS
Past or present d4T use	9	14	**NS**
Past or present NNRTI (EFV, ETR) use	13	19	NS
Past or present RTV use	11	24	NS
Obesity	1	0	NS
Dyslipidemia	7	10	NS
Past or present heavy alcohol use	4	8	NS

Table II – Risk factors for liver fibrosis and / or inflammation for the two studied groups
Legend: HBs Ag – Hepatitis B virus surface antigen, HDV = hepatitis D virus, HCV = hepatitis C virus, PCP = Pneumocystis jiroveci pneumonia, AZT = Zidovudine, ddI = Didanosine, ddC = Zalcitabine, d4T = Stavudine, NNRTI = non-nucleoside reverse transciptase inhibitor, EFV = Efavirenz, ETR = Etravirine, RTV = Ritonavir, NS = not statistically significant, Px=patients

Immunological, virological and therapeutic data

The average CD4 count is slightly higher in group A vs group B (463.71 ± 227.31 vs 450.53 ± 201.75 cells/mm^3, p value is not statistical significant). Six patients from group A and 3 from group B have mean CD4 count less than 200 (p=0.06, proximal to statistical significance). Also mean value for nadir CD4 is lower in group A compared with group B (80.46 ± 98.39 vs 137.88 ± 187.8, p value is not statistical significant).

Average viral load for HIV is 19611.52 ± 36626.84 in group A and 42499.38 ± 139851.81 copies/mm^3, but without statistical significant difference.

Duration of antiretroviral treatment (ART) is similar for both groups (263.85 ± 40.7 vs 258.54 ± 56.89 months).

Certain antiretrovirals (Lamivudine – 3TC, Emtricitabine – FTC, Tenofovir – TNF) have also active against HBV. Data regarding anti HBV therapy are shown in Table III.

Parameter	Group A (n=13)	Group B (n=24)	p value
3TC therapy (months)	227.69 ± 32.3	168.29 ± 77.17	**0.01**
FTC therapy (months)	4.15 ± 6.65	16.08 ± 29.73	NS
TDF therapy (months)	12.92 ± 19.88	46.92 ± 46.91	**0.01**
Total anti HBV therapy (months)	236.46 ± 31.13	202.21 ± 63.79	NS

Table III – Duration of anti HBV therapy in considered groups and statistical significance

There are no statistical significant differences between group A and B as regarding the duration of treatment with AZT, ddI, ddC, d4T, NNRTI or RTV, but the average length of treatment is higher for group A.

Discussion

From the 636 HIV-infected patients identified with parenteral transmission during the early childhood, a number of 153 were chronically infected with HBV (only 439 were

tested), that is 24.06% from total, or 53,5% from those tested. Thus makes HBV infection a prime factor to be considered in relation with liver fibrosis.

There are many causes and additional risk factors for liver fibrosis in people living with HIV: demographic (older age, male gender), individual (heavy alcohol use, tobacco use, herbal medicine use, non-adherence to prescribed antiretroviral regimen), HIV-related factors (increased viral load, low CD4 cell count, use of AZT, ddI, ddC or d4T), coinfections (hepatitis B ± D, hepatitis C, schistosomiasis), metabolic (type 2 diabetes mellitus, obesity, dyslipidemia, metabolic syndrome), as well as certain genetic factors [8-12]. The number of risk factors is translated into the number of liver related events and it seems that the higher the number, the higher the probability of liver fibrosis development [12]. In patients without HIV infection, metabolic factors (if steatosis is present) are more important than viral factors; also, in spite of effective antiviral therapy, progression of HBV infection might remain present at a low level and leads to liver fibrosis [13, 14]. Effective highly antiretroviral therapy seems to lower the risk of liver stiffness development [15]. Our study have included some of those factors (hepatitis C or D, use of certain antiretrovirals, obesity, dyslipidemia or heavy alcohol use), but we have not found statistic differences. We have also considered other factors that might lead to liver fibrosis and/or inflammation (CMV exposure, antibacillary treatment, antifungal treatment, chemotherapy, prophylaxis with Trimethoprim-Sulphamethoxazole), but we failed to notice any statistical significant differences. The number of considered risk factors are similar for both group. While those risk factors were considered individually, it was impossible to study their overlapping and effects on liver function.

It was established that the use of Tenofovir/Emtricitabine, entry inhibitors or integrase strand transfer inhibitors are associated with better liver function; also, "older" antiretrovirals have a higher negative impact on liver function than the "newer" ones [16-19].

Our data show that for the group A (those with liver fibrosis) there are a statistical significant difference as compared with group B for the treatment with 3TC (longer in group A) and Tenofovir (longer in group B). We suspect that longer use of 3TC produced the specific YMDD mutation inside HBV genotype and it would have been interesting to detect that alteration, however we were not able to work this out for the present study.

Limitation of the study

The authors acknowledges that they have included only a small number of cases; also, the information about HBV viremic level and resistance to certain antivirals are not available.

Conclusion

In a long-time monitored HIV-HBV coinfected patients (from the former Romanian pediatric HIV cohort) liver fibrosis is associated longer use of 3TC and shorter use or Tenofovir.

Conflict of interest: none

Institutional Review Board Statement: This study was approved by the Committee of Ethics and Academic and Scientific Deontology of Craiova, Romania (approval no. 78/07.09.2020). Access to the database for this study was approved by the Ethics Committee of "Victor Babes" Clinical County of Infectious Diseases and Pulmonology.

Author's contribution: Conceptualization – Giorgiana-Nicoleta Milcu, Lucian-Ion Giubelan, Florentina Dumitrescu; Software: Lucian-Ion Giubelan; Methodology:

Giorgiana-Nicoleta Lungu, Anca Duduveche, Andreea Marcu; Resources: Florentina Dumitrescu Lucian-Ion Giubelan; Supervision:
Lucian-Ion Giubelan. All authors have read and agreed the published version of the manuscript.

Data availability statement: The data presented in this study are available upon request from the corresponding author. The data are not publicly available due to the patient's personal data protective policy of the university and hospital.

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Abbreviations: HIV-human immunodeficiency virus, HBV-hepatitis B virus, LF-liver fibrosis, BMI-body mass index, CMV- Cytomegalovirus, HBsAg-Hepatitis B virus antigen, HDV-hepatitis D virus, HCV-hepatitis C virus, PCP-Pneumocystis jiroveci pneumonia, AZT-Zidovudine,ddI-Didanosine,ddC-Zalcitabine,d4T-Stavudine,NNRTI-non-nucleoside reverse transcriptase inhibitor, EFV-Efavirenz, ETR-Etravirine, RTV-Ritonavir, NS-not statistically significant,Px-patients.

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