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HIV-HBV coinfection in HIV population horizontally infected in early childhood between 1987-1990

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GENERAL PART-THEORETICAL DATA

SPECIAL PART-PERSONAL RESEARCH

Key words: *HIV-HBV coinfected subjects (CoS), immune reconstitution, virological response, HBe seroconversion, HBs seroconversion, cirrhosis, liver-related mortality*

Abstract

Although the first cases of HIV infection were reported three decades ago (MMWR, June 5, 1981), HIV/AIDS still represents a major public health problem. Antiretroviral therapy (ART) in HAART regimen fundamentally modified the epidemiological, clinical and prognostic evolution in HIV infection: morbidity and mortality rate due to opportunistic infections and cancer decreased, survival and quality of life in HIV infected population increased, but, at the same time, non-AIDS-related morbidity and mortality due to HBV infection increased. Both HIV-1 and HBV may lead, by their own complex pathogenic mechanisms, to chronic infections, malignancies and death; none can be cured using currently available therapies, as resistance to therapy usually occurs in time, diminishing clinical benefit. The combination of these two infections would only exacerbate such evolutions and is not a rare condition.

The first part, **theoretical data,** is a review of the literature focusing epidemiology, etiopathology, general clinical features, diagnosis, therapeutic strategies of HIV, HBV infection and HIV-HBV coinfection.

The second part, **personal research**, followed the classical steps: importance of the problem and argumets for choosing this topic, the objectives, material and methods, discussions and conclusions of the study.

Importance of the problem and arguments for choosing this topic. At the end of December 2010, UNAIDS estimated 34 million worldwide HIV infections, 90% (approximately 30.6 million) were adults. Approximately 10% of global HIV infected population are estimated to associate with chronic HBV infection; the prevalence of chronic HBV infection is about 10 times higher in HIV infected than in general population. HIV-HBV coinfected population is globally estimated as 3-6 million.

In Romania, according to the National Commission for Fight against AIDS, at the end of 2010, there were 16 697 cumulative cases of HIV/AIDS, 9 837 (58.92%) were pediatric HIV infections (ages between 0-14 years at the time of HIV infection diagnosis).

Romania's case is unique given at least two epidemiological features: the number of pediatric HIV cases and the route of HIV infection (thousands of children born between 1987-1990 to HIV seronegative mothers, horizontally infected in early childhood, most of them were institutionalized and infection was nosocomial or iatrogenic, through medical and surgical instruments incorrectly sterilized, contaminated with blood and blood-derived products); as HIV and HBV have similar transmission paths, this pediatric population may also have been exposed to HBV infection.

Chronicity risk of HBV infection is influenced by the age at the time of exposure: neonates or below 1 year - about 90%, 1-5 years - 25-50%, more than 5 years - about 5%.

Concomitance of the two infections, and exposure age are two particular conditions in these patients, both capable to influence the evolution of the two infections.

In HIV-HBV coinfection, the relationship between the two viruses is complex and not fully understood.

Opinions seem to be unanimous regarding the influence of HIV infection on the natural history of HBV infection, as HIV seems to affect all phases of HBV infection: the chronicity rate of HBV infection increases, the HBe and HBs seroconversion decreases, the HBV viral load increases, the risk of developing cirrhosis, hepatocellular carcinoma and liver-

related mortality increases. If HIV infected subjects subsequently acquire HBV infection, the chronicity rate is higher compared to persons with no HIV infection and lower CD4 + lymphocytes cells count is associated with higher risk of chronicity. A person already exposed to HBV infection, having performed HBs seroconversion and then HIV infected, is at risk of HBV reactivation or reinfection due to anti HBs disappearance if the immunity decreased.

Regarding the influence of HBV infection on the evolution of HIV infection, studies document less significant influence: HBV infection increases the hepatotoxicity associated with ART in HAART regimen, but it does not influence the response of HIV infection to ART or the progression of HIV infection; however it increases liver-related mortality.

Studies were conducted on populations having acquired HIV and HBV simultaneously or consecutively in adolescence or adulthood. Studies on pediatric HIV-HBV coinfection (the cohort of HIV-HBV children horizontally coinfected in early childhood) are scarce, so that the relationship between the two viruses in children is less documented.

In my clinical experience, I have met HIV-HBV coinfections, noticed the particularities of their clinical evolution and their treatment difficulties. Most of the cases had in common an epidemiological feature: a simultaneous coinfection in early childhood. Thus, my interest was aroused for this epidemiological situation and for the consequences of the particular clinical evolution in each infection taken separately. Therefore, I have considered useful to carry out a further investigation of these patients.

The ***objectives*** of the study are to define the relationship between the two viruses (ie, HIV and HBV) in the HIV group horizontally infected in early childhood. Therefore I have been interested in:

1. HBV influence on the immunological, virological and clinical progression of HIV infection and mortality in HIV patients horizontally infected in early childhood;
2. HBV effects on the response to ART in antiretroviral-naive patients, HIV-HBV horizontally coinfected in early childhood;
3. impact of HIV infection on the clinical and biological evolution of HBV in HIV-HBV horizontally coinfected subjects during 1987-1990.

Material and methods. Study groups were selected among HIV-infected subjects, registered at the Regional Centre for Monitoring HIV/AIDS in Craiova (CRC), established in 1994 as a "regional center for the care of HIV-infected child and his family" and subjects with chronic HBV infection registered at the Infectious Diseases Clinic of the Infectious Diseases and Pneumology Hospital "Victor Babes" Craiova since 2000.

HIV infection was documented as follows: in adults and children aged more than 18 months, using two positive ELISA tests (HIV antibody present) and confirmatory Western Blot test; in children aged less than 18 months, PCR-RNA viral load of HIV was performed.

HBV documentation: minimum 2 Atg HBs positive determinations at least 6 months apart.

Vertical HIV infection was ruled out by testing for HIV mothers between 1990-1995 Only one third of the mothers were tested for HBV infection, but, as assessed (see p. 69), the chances of vertical transmission of HBV infection are minimal and have no influence on the study results.

Statistical analysis: primary health records (medical information from the patient record files) supplied the database. Data processing software packages used EPI2000, SPSS,

Data Analysis module of Microsoft Excel, XLSTAT for MS Excel. Descriptive statistics used Microsoft Excel, aiming indicators of central tendency and dispersion: mean, standard deviation (SD), median, quartiles, range between quartiles (IQR). Univariate analysis used tests: Chi ², Fisher, Student, Wilcoxon-Mann-Whithey (for checking gap distribution of two groups whose values have not a normal distribution, gaussian). For survival analysis Kaplan Meier survival curves were used. For comparison of survival curves, generalized Wilcoxon test and log-rank test were used.

Results. Personal research results sums up four subchapters: a description of the HIV-1 infected groups and three substudies.

The *description of HIV-1 infected groups* assessed the epidemiological features, place and importance of HIV-HBV coinfection in HIV infected patients registered at CRC from its establishment (1994) up to 31.12.2010.

This first analysis brought the following conclusions:

• Approximately two thirds of HIV patients, alive and in active records (e.g. a PIH presenting at least twice a year for a clinical examination at CRC), are young adults, survivors of the parenteral exposure to HIV in early childhood between 1987 to 1990, situation similar to that noticed at the national level.

• One of the most important coinfections in HIV infected subjects is HBV coinfection: about one quarter of HIV infected patients associate HBV coinfection and about 1/3 of HIV horizontally infected patients are HBV coinfected; the risk of HIV-HBV coinfection is 2.5 times higher among HIV horizontally infected subjects compared to HIV infected subjects by other routes of transmission.

• Approximately three quarters of HIV-HBV coinfected subjects and almost all HIV-HBV coinfected patients with a parenteral way of HIV transmission acquired both infections horizontally in early childhood.

•HIV-HBV coinfected subjects are at risk of developing end-stage liver disease; approximately 1/10 of HIV-HBV coinfected patients developed cirrhosis.

• The risk of liver-related death in HIV-HBV coinfected subjects is approx. 3 times higher than in the rest.

Substudy I - aimed to show the influence of HBV on immunological, virological and clinical progression of HIV infection and mortality in HIV horizontally infected subjects in early childhood between 1987 and 1990. It is a comparative observational study having a mixed character (retrospective since the establishment of the CRC to 31.12.2008 and prospective since 1.01.2009 to 31.12.2010). Substudy I included all subjects HIV-HBV horizontally coinfected in early childhood (CoS) and HIV horizontally infected subjects in early childhood with no HBV infection (non-CoS), selected among the 826 HIV infected group registered at CRC during the study period.

Results. General characteristics: CoS-149 subjects, non-CoS-411 subjects, gender ratio M: F was at CoS-1, 29 vs non-CoS-1, 08 (p Chi2 = 0.340, p Fisher = 0.389), area of origin R: U-1 CoS was1.19 vs non-CoS-1.11 (p Chi2 = 0.705, p Fisher = 0.774), mean age at 31/12/2010 was at CoS-21.94 ± 0.68 years vs non-CoS-21.79 ± 1.04 years (p Student = 0.177).

Baseline characteristics:

- HIV clinical category was in CoS-category A-2 cases (1.34%), category B-115 cases (77.18%), category C-32 cases (21.48%) vs non-CoS-category A-7 cases (1.70%), category B-288 cases (70.07%), category C-116 cases (28.22%) (p Chi2 = 0.254);

- The mean of CD4 + cells count (assessed for 143 subjects from CoS group and 366 subjects in group non-CoS) was in CoS-256.80 ± 259.37 cells/ml vs non-CoS-235.40 ± 227.71 cells/ml (p Student = 0.360);

- Clinical-immunological category of HIV infection was the CoS-A1-1 case (0.7%), A2-1 case (0.7%), B1-17 cases (11.89%), B2- 43 cases (30.07%), B3-49 cases (34.27%) and C3-32 cases (22.38%) vs non-CoS: A1-1 case (0.27%), A2-2 patients (0.55%), A3-2 patients (0.55%), B1-29 patients (7.92%), B2-97 cases (26.50%), B3-136 cases (37.16%), C1-4 patients (1.09%), C2-12 patients (3.28%), C3-83 cases (22.68%) (p Chi2 = 0.261);

- Mean HIV viral load (estimated for 117 subjects from CoS group and 291 subjects in group non-CoS) was in CoS-3.94 ± 1.22 lg copies/ml vs non-CoS-4.12 ± 1.3 lg copies/ml (p Student=0.117).

AIDS-associated clinical events during the study were noticed in CoS-49 subjects vs non-CoS-96 subjects (pChi2 = 0.073).

Characteristics at the last assessment:

- HIV clinical category was in CoS-category B-68 cases (45.64%), category C-81 cases (54.36%) vs non-CoS-category A-5 cases (1.22%), category B-194 cases (47.20%), category C-212 cases (51.58%) (pChi2=0.362);

- The mean CD4 + cells count (assessed for 145 subjects from CoS group and 381 subjects in non-CoS) was in CoS-361.71 ± 348.03 cells/ml vs non-CoS-358.85 ± 328.04 cells/ml (p Student=0.930);

- Clinical-immunological category (for CoS group assessed in 145 subjects and non-CoS group 381 subjects) was in CoS: B1-4 subjects (2.76%), B2-19 subjects (13.10%) , B3-45 subjects (31.03%), C1-1subiect (0.69%), C2-12 subjects (8.28%), C3-64 subjects (44.14%) vs non-CoS: category A2 -2 subjects (0.52%), A3-2 subjects (0.52%), B1-13 subjects (3.41%), B 2-59 subjects (15.49%), B3-114 subjects (29, 92%), C1-4 subjects (1.05%), C2-20 subjects (5.25%), C3-167 subjects (43.83%) (p Chi2 = 0.799);

- Mean HIV viral load was at CoS-2.98 ± 1.35 lg copies/ml vs non-CoS-3.18 ± 1.44 lg copies/ml (p Student = 0.124).

At 31.12.2010 subject status was: death in CoS-46 cases (30.87%) vs nonCoS-122 cases (29.68%), lost of evidence in CoS-7 (4.70%) vs non-COS -38 (9.25%), alive and in active evidence in CoS-96 subjects (64.43%) vs non-SC-251 subjects (61.07%) (p Chi2 = 0.216).

Liver-associated mortality was reported in CoS-16 cases (50%) vs non-CoS group-11 cases (18.33%) (p Chi2 = 0.001, RR = 2.73, CI95% [1.44 <RR <5.15]).

AIDS-related mortality was recorded in non-CoS-44 cases (73.33%) vs CoS-12 cases (37.50%) (p Chi2 = 0.0008, RR = 1.96, CI95% [1.22 <RR <3.14]).

The mean length of survival was in CoS-20.75 ± 0.37 years vs non-COS-21.41 ± 0.29 years (p> 0.05).

These results lead to the following conclusions:

• HBV coinfection does not influence the progression of HIV infection to a more advanced clinical category.

• The incidence of AIDS-related clinical events is not influenced by the presence of HBV coinfection.

• HIV-HBV coinfection does not cause progression to a more advanced clinical and immunological category.

• Immune status of subjects with HIV infection is not influenced by the presence of HBV coinfection.

• HBV coinfection does not influence the HIV viral load.

• The presence of HBV coinfection increases liver-related mortality.

Substudy II - aimed to establish the influence of HBV infection on response to ART in antiretroviral-naive patients HIV-HBV horizontally coinfected in early childhood. It is a comparative observational study having a mixed character (retrospective since the establishment of the CRC to 31.12.2008 and prospective since 1.01.2009 to 31.12.2010). Substudy II enrolled HIV-HBV horizontally coinfected subjects in early childhood during 1987-1990 (Cos) and HIV horizontally infected subjects in early childhood during 1987-1990 with no HBV infection (non-CoS), who started their first ART regimen, selected from 826 HIV infected persons registered at CRC. We comparatively analyzed the immunological and virological response at 6-12 months after initiation of ARV regimens between CoS and non-CoS.

Results. General Characteristics: CoS-66 subjects, nonCoS-132 subjects, gender ratio M: F was at CoS-1.13 vs non-CoS-1.16 (p Chi2 = 0.920), area of origin R:U was in CoS-1.36 vs non-CoS-0.86 (p Chi2= 0.132), mean age at enrollment was at CoS-11.46 ± 3.03 years vs non-CoS-12.62 ± 3.40 years (p Student = 0.019).

Baseline characteristics:

- HIV clinical category was in CoS: category C-12 cases (18.18%), B-53 cases (80.30%), category A-1 case (1.52%) vs non-CoS: category C-36 cases (27.27%), B-93 cases (70.45%), A-3 cases (2.27%) (Chi2 p = 0.332);

- The mean CD4 + cells count was at CoS-148.33 ± 148.10 cells/mL vs non-CoS-163.17 ± 155.39 cells ml (p Student= 0.521);

- The mean HIV viral load was at CoS-5.06 ± 0.80 lgcopies/ml vs non-CoS-5.04 ± 0.84 lgcopies/ml (p Student = 0.978).

AIDS-associated clinical events during the study were noticed in CoS-2 cases (3.03%) vs non-CoS-9 cases (6.82%) (p Chi2 = 0.282).

Characteristics at the last assessment:

- HIV clinical category was in CoS: category C-14 cases (21.21%), category B-52 cases (78.79%) vs nonCoS: category C-45 cases (34.09%), category B-84 cases (63.64%), category A-3 cases (2.27%) (p Chi2 = 0.066);

- The mean increase in CD4 + cells count was at CoS-177.07 ± 141.68 cells/mL vs non-CoS-176.02 ± 191.75 cells/ml (p Student = 0.969);

- HIV immunological category was in CoS: category 3-15 cases (22.73%), category 2-42 cases (63.64%), category 1-9 cases (13.64%) vs non-CoS: category 3-34 cases (25.76%), category 2-72 cases (54.55%), category 1-26 cases (19.70%) (p Chi2 = 0.425),

- Mean decrease HIV viral load was at CoS-5.04 ± 0.79 lg copies/ml vs non-CoS-4.69 ± 2.04 lg copies/ml (p Student = 0.375)

- HIV viral load was in CoS <400 copies/ml-21 cases (31.82%), 400-10^4 copies/ml-4 cases (6.06%), > 10^4 copies/ml-4 cases (6 , 06%), unspecified-37 cases (56.06%) vs non-CoS: <400 copies/ml-41 cases (31.06%), 400-10^4 copies/ml-6 cases (4.55%), > 10^4 copies/ml-14 cases (10.61%), unspecified-71 cases (53.79%) (p Chi2 = 0.741).

The results lead us to conclude that in HIV-HBV coinfected individuals, at the initiation of the first ARV regimens:

• The mean increase in CD4+ cells count is not dependent on the presence of HBV coinfection

• The immunological reconstruction achieved (ie final immunological category) is not influenced by the presence of HBV coinfection

• The mean decrease of HIV viral load is not dependent on the presence of HBV

• Virologic response (ie VL <400copii/ml) is not influenced by the presence of HBV coinfection

Substudy III - aimed to determine the influence of horizontally acquired HIV infection during 1987-1990 on clinical and biological evolution of HBV in HIV horizontally infected subjects in early childhood during 1987-1990. It is a comparative observational study having a mixed character (retrospective since the establishment of the CRC to 31.12.2008 and prospective since 1.01.2009 to 31.12.2010). Study groups were represented by HBV-HIV horizontally coinfected subjects in early childhood during 1987-1990 (CoS) and subjects with no HIV infection with chronic HBV infection, horizontally acquired during 1987-1990 (non-CoS), selected among 826 HIV infected patients registered at CRC, and among other 498 patients with chronic HBV infection registered at the Infectious Diseases Clinic of Infectious Diseases and Pneumology Hospital "Victor Babes" Craiova.

Results. General characteristics: lot CoS-149 subjects, non-CoS-74 group subjects, gender ratio M: F was at CoS-1.29 vs non-CoS-1.11 (p Chi2 = 0.604); area of origin R:U was in CoS -1.19 vs non-CoS-1.06 (p Chi2 = 0.671), mean age at 31.10.2010 was at CoS-21.94 ± 0.68 years vs non-CoS-30.43 ± 9.13 years (p Student<0.0001).

During the study period, chronic HBV infection led to cirrhosis in 15 cases (10.07%) in CoS vs 1 case (1.35%) in non-CoS (OR = 8.17, CI 95% 1.10 <RR <169.14; Chi2 = 5.640, p Chi2 = 0.018). HBeAg seroconversion was noticed in CoS-41 subjects (85.42%) vs non-CoS-72 subjects (97.30%) (OR = 6.15, CI 95% 1.09 <OR <45.13; Chi2 = 6.014, p Chi2 = 0.014). HBs seroconversion were noticed at CoS-8 subjects (5.35%) vs non-COS-11 subjects (14.86%) (OR = 3.08, CI 95%, 1.08 <RR <8.88; Chi2 = 5.720, p Chi2 = 0.017).

Mean HBV viral load was at CoS- 682173.06±1079320.09 UI/ml vs non-COS-256333.19±847373.31 UI/ml (p = 0.036 Student). HBV viral load > 2000 IU was recorded in CoS- 19 subjects (57.57%) vs non-COS-10 subjects (15.87%) (OR = 7.19, CI 95%, 2.48 <OR <21.39, Chi2 = 17.86, p Chi2 <0.0001)

Mean ALAT was at CoS-130. 25 ± 252.38 U/l vs non-CoS-240.04 ± 197.41 U/l (p Student = 0.006). ALAT values which do not exceed 2 times the maximum permissible value were recorded in CoS-32 subjects (50%) vs non-CoS-11 subjects (14.86%) (OR = 5.73, CI95%, 2.39 <OR <13.96; Chi2 = 19.75, p Chi2 <0.0001).

In CoS group 6 subjects were recorded with HBV chronic hepatitis HBeAg positive (22.22%), HBV chronic hepatitis HBeAg negative-8 subjects (29.63%), innactive carriers of HBsAg-13 subjects (48.15 %) vs non-CoS: HBV chronic hepatitis HBeAg positive-2 subjects

(3.23%), HBV chronic hepatitis HBeAg negative-7 subjects (11.29%), innactive carriers of HBsAg - 53 subjects (85.48%) (Chi2 = 14,840; p Chi2 <0.0001).

Death was recorded in CoS in 46 cases (30.87%) vs non-CoS 1 case (1.35%) (RR = 20.73, CI 95%, 2.92 <RR <147.05; Chi2 = 23.81, p Chi2 <0.0001).

The results allow us to conclude that HIV infection influences the HBV evolution in HIV-HBV coinfected subjects, as follows:

• HBeAg seroconversion is significantly decreased; chronic hepatitis Atg HBe positive is significantly more common among coinfected people

• HBs seroconversion is significantly less common; "cured" HBV chronic infections were significantly less frequent among coinfected

• The mean level of HBV viral load is significantly higher and significantly more frequent, HBV viral load is above the "alert" level (ie > 2000UI/ml).

• Intensity of hepatocytolisis syndrome is significantly lower; the mean of serum transaminases is significantly lower, rarely exceeding the "alert" level (ie 2xN).

• Evolution of liver disease to its final stages is accelerated; among CoS Atg HBs innactive carriers are significantly less frequent and cirrhosis is significantly more common.

• Deaths are significantly more common among CoS.

General conclusions. The results of the studies lead to the following conclusions:

• One of the most important coinfections encountered in HIV infected patients is HBV coinfection.

• Most HIV patients, alive and in active records, are young adult survivors of parenteral exposure to HIV in early childhood during 1987-1990.

• HBV coinfection is a frequent condition in the HIV population horizontally infected in early childhood during 1987-1990.

• Almost all HIV-HBV coinfected subjects having horizontally acquired HIV infection in early childhood associated both infections (ie, HIV and HBV) simultaneously.

• The influence of HBV infection on the evolution of HIV infection in HIV-HBV horizontally coinfected subjects in early childhood is less significant: the progression of HIV infection toward a more advanced clinical category is independent of HBV infection, the incidence of AIDS-related clinical events is not influenced by the HBV coinfection, natural progression of HIV infection to a more advanced clinical and immunological category does not depend on the HBV coinfection, immune status is not influenced by the HBV coinfection, immune reconstruction levels achieved (ie CD4+ cells level) do not depend on the HBV coinfection, virological status does not depend on the HBV coinfection, level control of HIV replication is independent of the HBV coinfection and liver-related mortality increases due to HBV coinfection.

• HBV infection does not influence the response to ART in HIV-HBV horizontally coinfected subjects in early childhood given the following findings: the mean increase in CD4+ cells count within the first 6-12 months consecutive to applying ART regimens was independent of the HBV coinfection, immunological reconstruction level at 6-12 months after applying the first ART regimens was not influenced by the HBV coinfection, the mean decrease in plasma HIV viral load was independent of the HBV coinfection and HIV replication control level was independent of HBV coinfection.

• HIV infection influences almost all the phases of the HBV infection: HBeAg seroconversion decreases, the frequency of HBeAg positive chronic hepatitis increases; HBs seroconversion decreases, the frequency of "cured" HBV infection decreases; the control of HBV replication is negatively influenced, HBV viremia is higher, often above the "alert" level (ie> 2000UI/ml); the intensity of hepatocytolisis syndrome diminishes, transaminases frequently evolving below the "alert" level (ie <2xN); the progression to end-stage liver disease accelerates, liver cirrhosis is significantly more frequent and Atg HBs innactive carrier is significantly less common; the overall mortality rate increases.