Original Paper

HBV influence on Response to Antiretroviral Therapy in Horizontally HIV-HBV Coinfected Patient during Early Childhood

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ABSTRACT: Background: There are few studies on pediatric HIV-HBV coinfection, so evidences about relationships between the two viruses are scarce. Objectives: influence of HBV infection on virological and immunological response to antiretroviral therapy (ART) in antiretroviral-naïve horizontally HIV-HBV coinfected subjects during early childhood. Material and methods: observational study on 826 HIV+ subjects in evidence of Craiova Regional Centre (CRC); we analyzed the immunological and virological response at 6-12 months after starting first antiretroviral regimens compared in 2 groups: horizontally HIV-HBV coinfected subjects during early childhood (CoS) versus horizontally HIV infected subjects during early childhood without HBV infection (non-CoS). Results: Number of subjects: CoS-66 subjects, non-CoS-132 subjects. Demographic data: CoS-gender ratio F:M=0.886, the majority lived in rural area (57.58%), mean age on diagnosis-9.288±4.607 years, non-CoS-gender ratio F:M=0.859, the majority lived in urban area (53.79%), mean age on diagnosis-10.742±5.107 years. At baseline, HIV category was: CoS-A-1.52%, B-80.30%, C-18.18%, non-CoS-A-2.27%, B-70.45%, C-27.27% (p Chi^2=0.332), the mean CD4+ cell count was: CoS-148.33±148.10 cells/ml, non-CoS-163.17±155.39 cells/ml (p Student=0.521) and the mean HIV viral load (HIV VL) was: CoS-5.06±0.80 lgcopies/ml (for 29 subjects), non-CoS-5.04±0.84 lgcopies/ml (for 61 subjects) (p Student=0.978). At the end of the studied period, the mean increase in CD4+ cell count was: CoS-177.068±141.676 cells/ml, non-CoS-176.015±191.751 cells/ml (p Student=0.969) and the mean decrease in HIV VL was: CoS-5.04±0.79 lgcopies/ml, non-COS-4.69±2.04 lgcopies/ml (p Student=0.911). Conclusions: The presence of HBV coinfection does not influence immunological or virological response to ART.

KEY WORDS: *CoS, non-CoS, virological response, immunological response, ART*

Introduction

Because of the shared routes of transmission, HIV infected subjects (HIS) are also at risk for HBV infection, so as expected, the prevalence of HBV infection is higher among HIS compared with HIV uninfected subjects. Up to 80-90% of HIS have at least one specific serological marker of HBV infection and aproximatelly 10% of HIS have chronic HBV infection [1-10]. The prevalence of chronic HBV infection is approximately 10 times higher in people living with HIV than the general population (higher in homosexual than iv drug users, or heterosexual) [2,6].

There are 3-6 million HIV-HBV coinfected persons worldwide [4,6,7,10-12]. The prevalence of HIV-HBVcoinfection, route of transmision, age, and the sequence of the two infection varies markedly among HIS, but one of the main determinant is, according to some authors, the geographical location [2,5,13-15]. Thus, in areas with high endemicity of HBV infection, the prevalence of HIV-HBV coinfection among HIS reaches up to 25%, in most cases infection with HBV beeing transmitted horizontally, in childhood (<5 years), HIV infection beeing acquired later as adolescence or young adult through sexually transmission. In areas of low endemicity, HIV-HBV coinfection prevalence among HIS does not exceed 5-7%, in most cases infection with HBV and HIV is acquired in adulthood, simultaneously or consecutively through sexual (homosexual or heterosexual), or percutaneous (intravenous drug users) route.

In Romania, a retrospective study conducted in 2004 at the Institute of Infectious Diseases "Prof. Dr. Matei Bals "on 938 HIV-infected patients (HIS) aged> 14 years, found a prevalence of at least one serological marker for HBV infection of 37.2%, 13.53% having chronic HBV infection [16]. Another case-control study conducted between 2002-2003 at Constanța on 161 HIV infected adolescents without evidence of liver injury, aged 13-18 years (cases) compared with 356 similar adolescents without evidence of liver disease (controls), communicates a prevalence of 78% of at least one specific serological marker of HBV among coinfected population versus 32% among the population without HIV infection, and a

prevalence of chronic hepatitis HBV of 44% among cases compared with 7.9% among controls [17]. The study population was represented by horizontally HIV-infected children durind early childhood between 1987-1990, which very probably in the same period and by the same route have been infected with HBV.

Both, HIV and HBV, by different pathogenic mechanisms, may lead to chronic infections, malignancies and death and none can be cured with currently available therapies; resistance to therapy usually occurs after a period of use and is associated with the decrease of the clinical benefit, the combination of the two infections, a situation not uncommon, exacerbates these issues. In HIV-HBV coinfection, the relations established between the two viruses are complex and not fully understood.

Objectives

Analyze the influence of HBV on response to antiretroviral therapy (ART) in antiretroviral-naive patients horizontally HIV-HBV coinfected during early childhood between 1987-1990.

Methods

Observational study on a population of 826 HIS in evidence of Craiova Regional Center for Monitoring and Evaluation of HIV/AIDS (CRC) during 1994-2010. Of the study population were selected two groups: horizontally HIV-HBV coinfected subjects during early childhood between 1987-1990 (CoS) and horizontally HIS during early childhood between 1987-1990 without HBV infection (non-CoS), to which was initiated the first ART regimen. We compared the immunological and virological response at 6-12 months after the initiation of antiretroviral regimen between the two groups. Criteria for inclusion in the 2 groups are listed below.

Inclusion criteria in CoS group:

1. Horizontally HIS with date of birth> 1984.
2. HIS with chronic HBV infection documented by at least two determinations of HBs Ag, at least 6 months apart, the first beeing conducted simultaneously or within 6 months after HIV diagnosis. We chose this as a inclusion criteria as we considered that the assessment of the route of HIV transmission is also valid for the HBV route of transmission (both viruses having similar transmission routes), in terms of the route of transmission (horizontally) and of the age at time of aquiring infection (early childhood).
3. HIS without previous ART
4. HIS who had at least a determination of the CD4+ cell count prior to initiating first ART regimen and at least another one determination in the first 6-12 months after the initiation of ART regimen.

Inclusion criteria in non-CoS group:

1. Horizontally HIS with date of birth>1984.
2. HIS without chronic HBV infection documented by the repeted absence of HBs Ag assessments during the monitoring program.
3. HIS without previous ART.
4. HIS who had at least a determination of the CD4+cell count prior to initiating first ART regimen and at least another one determination in the first 6-12 months after the initiation of ART regimen.

Exclusion criteria for study groups:

1. Horizontally HIS with date of birth≤1984; It was chose this exclusion criteria considering that although, they probably aquired HIV infection during 1987-1990, this happened after age 3 so not in early childhood.
2. HIS with unspecified HBV status (HIS deceased or lost from the records shortly after HIV diagnosis)
3. HIS with previous ART regimen.
4. HIS at which the rhythm of CD4+ cell count determination did not meet the inclusion criteria.

For subjects who met inclusion criteria, the following data were collected from primary documents:

1. Clinical data: demographics, personal history, route of HIV transmission, clinical examination data.
2. Data on ART: ART regimens used.
3. Laboratory data:

3.1. CD4+ cell count: flow cytometry, FACS-COUNT flowcytometry; results are expressed as number cells/ml.

3.2. HIV viral load determination using chain polymerization; results are expressed in copies/ml; the detection limit was different over time, depending on the method used (initially 400 copies/ml using the Amplicor HIV-1 Monitor than 176 copies/ml using NucliSens HIV RNA QT and now 50 copies/ml using the COBAS TaqMan HIV-1).

3.3. HBs Ag determination: ELISA-quality method.

4. Other data: serology for *Toxoplasma gondi*, HDV, CMV, HCV-using ELISA 3rd generation method.

Collected data were analyzed comparatively in CoS group vs non-CoS group.

Response to ART was assessed by analyzing the immune response (CD4+ cell count at 6-12 months after initiation of the first antiretroviral regimen) and viral response (HIV viral load at 6-12 months after initiation of the first ART regimens) comparatively in the two groups.

For statistical analysis we used Microsoft Excel, following indicators of central tendency and dispersion: mean, standard deviation (SD), median, quartiles, range between quartiles (IQR). Univariate analysis used tests: Chi square and Student. The results were summarized in tables and/or graphs and figures. Graphs were made using Microsoft Excel XP.

Results

I. Baseline Characteristics

Of 826 HIS in evidence of CRC during studied period, 66 met the inclusion criteria for CoS group, and 132 for nonCoS group.

I.1. Demographic characteristics of the patients

It was noticed a slight predominance of males in both groups. (Table no. I). No statistically significant differences were registered in the gender distribution of the subjects in the two groups (Chi^2 = 0.010, p Chi^2= 0.920) (Table I).

Distribution by area of origin: in the CoS group were predominantly rural subjects-38 subjects (57.58%) vs non-CoS group in which prevailed urban subjects-71 subjects (53.79%), but the difference was not statistically significant (Chi2 = 2.273, p Chi^2= 0.132) (Table I).

The mean age at the time of HIV infection diagnosis was lower in CoS group-9.29 ± 4.61 years compared with non-CoS group-10.74 ± 5.11 years, but the difference was not statistically significant (p Student = 0.053) (Table 1).

Table 1. Demographic data of CoS vs non-CoS and statistical significance

Variable	CoS (n=66)	non-CoS (n=132)	Statistical significance
Sex F M	 31 35	 61 71	Chi^2=0,010 p Chi^2=0,920 (NS)
Area of origin R U	 38 28	 61 71	Chi^2=2,273 p Chi^2=0,132 (NS)
Age at the time of HIV infection diagnosis Mean, SD Median, IQR	 9,288±4,607 ani 10 (0-18) ani	 10,742±5,107 ani 12 (1-20) ani	p Student=0,053 (NS)

I.2. CDC Category of HIV Infection

Clinical category at enrollment in non-CoS group were: category C-27.27% of subjects, B-70.45%, A-2.27% compared to CoS group: category C-18.18%, B-80.30%, A-1.52%. (Fig.1). There were no statistically significant differences in distribution according to clinical category of HIV infection at baseline between the two groups (p Chi^2 = 0.332) (Fig.1).

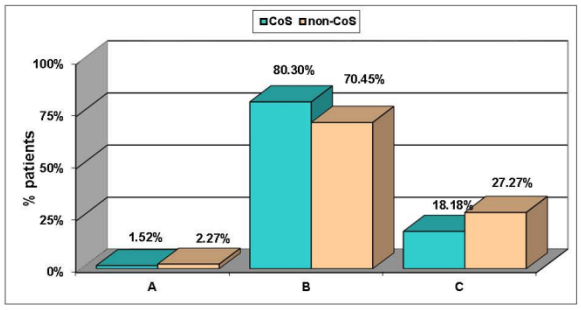

Fig.1. Baseline CDC clinical category of HIV infection in CoS vs non-CoS

At baseline, a higher proportion of non-CoS were in SIDA category (clinical and/or immunological) compared to CoS (72.74% of non-CoS vs 63.63% of CoS), but the difference was not statistically significant (Fig.2).

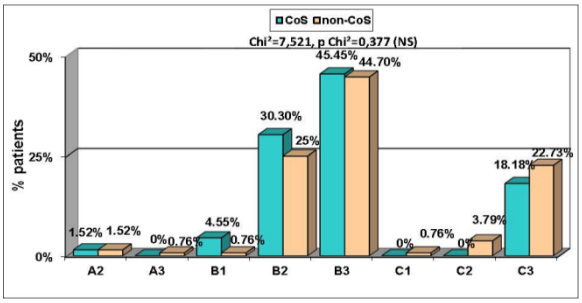

Fig.2. Baseline CDC clinical and immunological category of HIV infection in CoS vs non-CoS

I.3 Immunologic Status

In CoS group the mean CD4+ cell count was 148.33 ± 148.10 cells/ml, with a median of 112.5 (1-628) cells/mL compared with non-CoS group: the mean CD4+ cell count-163.17 ± 155.39 cells/ml, with a median of 127.5 (1-847) cells/ml, the difference being statistically insignificant (p = 0.521 Student) (Table no. II).

Although many subjects from non-CoS group were, at baseline, in AIDS immunological category compared with CoS (67.42% and 63.64% respectively), the distribution of subjects in the two groups depending on the degree of the immunosuppression showed no statistically significant differences (p Chi^2 = 0.645, p Fisher = 0.570) (Table 2).

Table 2. Baseline immunological and virological status in CoS vs non-CoS and statistical significance

Variable	CoS	Non-CoS	Statistical significance
Baseline CD4 (cells/ml)			
Mean, SD	148,33±148,10	163,17±155,39	p Student=0,521 (NS)
Mediana, IQR	112,5 (1-628)	127,5 (1-847)	
Baseline CD4 level (cells/ml)			
<200	42 (63,64%)	89 (67,42%)	Chi^2=0,878
200-500	21 (31,82%)	40 (30,30%)	p Chi^2=0,645 (NS)
>500	3 (4,55%)	3 (2,27%)	p Fisher=0,570 (NS)
Total	66 (100%)	132 (100%)	
Baseline HIV VL HIV (lgcopies/ml)			p Student=0,978 (NS)
Mean, SD	5,06±0,80	5,04±0,84	
Mediana, IQR	4,95 (3,81-6,33)	5,10 (2,60-6,44)	
Baseline HIV VL HIV level (copies/ml)			
<400	0 (0%)	1 (0,76%)	Chi^2=0,925
400-10.000	3 (4,55%)	4 (3,03%)	p Chi^2=0,819 (NS)
>10.000	26 (39,39%)	56 (42,42%)	
Neprecizat	37 (56,06%)	71 (53,79%)	
Total	66 (100%)	132 (100%)	

I.4 HIV Viral Load

HIV VL could be assessed for 29 subjects in CoS group and for 61 subjects in non-CoS group.

In CoS group the mean HIV VL was 5.06 ± 0.80 lgcopii / ml, with a median of 4.95 (3.81 to 6.33) lgcopies/ml, compared with non-CoS group: mean HIV VL-5, 04 ± 0.84 lgcopies/ml, with a median of 5.10 (2.60 to 6.44) lgcopies/ml, the difference being statistically insignificant (p = 0.978 Student) (Table 2).

One subject from group non-CoS had HIV VL at baseline below 400 copies/ml HIV, the number of subjects with HIV VL under 10000 copies/ml and over 10000 copies/ml was similar in the 2 groups (p Chi^2 = 0.818) (Table 2).

II. ART Regimens

ART regimens used in the two groups during the studied period are shown in Fig.3. No statistically significant differences were recorded in terms of ART regimens used in the two groups (p Chi^2 = 0.377) (Fig.3).

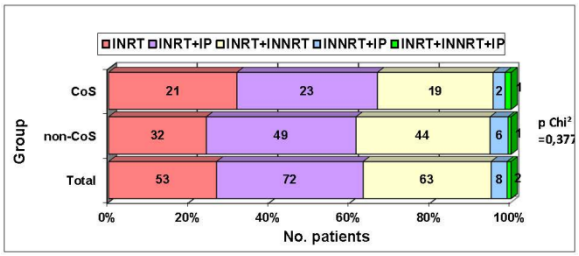

Fig.3. ART regimens used in CoS vs non-CoS and statistical significance

III. CDC Category of HIV Infection at the Study Endpoint

At the end of the studied period, although a higher proportion of non-CoS were in clinical category C compared to CoS (34.09% and 21.21% respectively), the difference was not statistically significant (Chi^2 = 5.420, p Chi^2 = 0.066) (Fig.4)

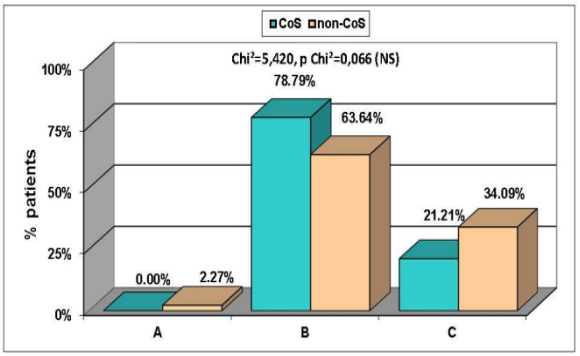

Fig.4. CDC clinical category of HIV infection at the endpoint of the study in CoS vs non-CoS and statistical significance

At the end of the studied period, 74.25% of non-CoS were in AIDS clinical and/or immunological category compared with 63.63% of CoS, the difference was not statistically significant (Chi^2 = 10.350, p Chi^2 = 0.170) (Fig.5).

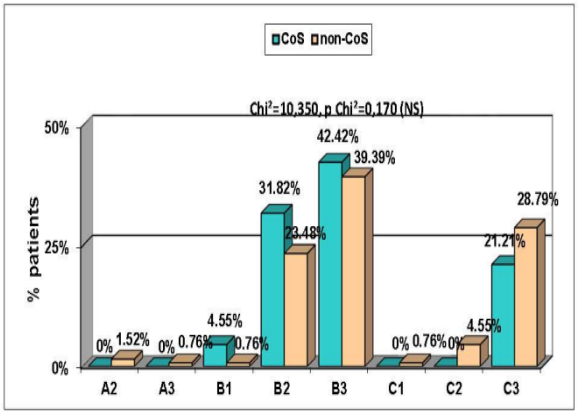

Fig.5. CDC clinical and immunological category of HIV infection at the endpoint of the study in CoS vs non-CoS and statistical significance

IV. Coinfections other than HBV coinfection

Coinfections in the 2 groups during the studied period is shown in Fig.6; there were no statistically significant differences in their repartition between the two study groups.

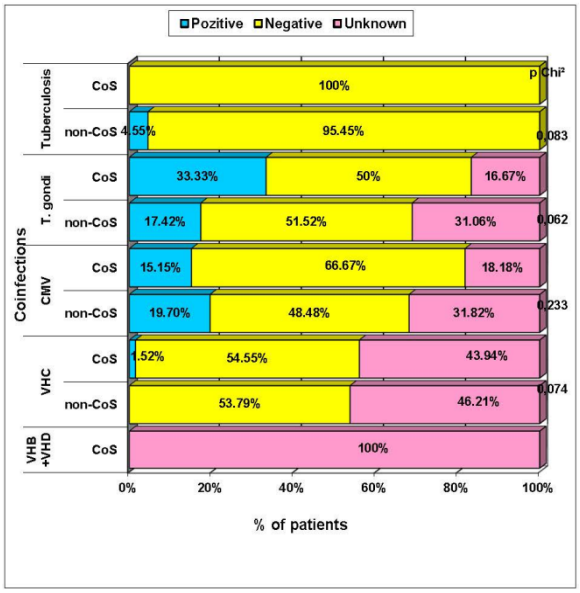

Fig.6. Coinfections other than HBV in CoS vs non-CoS and statistical significance

V. Immunological Response to ART

Following 6-12 months after ART initiation, in the CoS group, the mean CD4+ cell count was 325.40 ± 193.85 cells/ml, with a median of 320 (IQR: 10-1045) cells/mL compared with non-CoS group, where the mean CD4+ cell count was 339.18 ± 225.93 cells/ml, with a median of 273.5 (IQR: 9-1074) cells/ml, the difference being statistically insignificant (p Student = 0.672) (Table 3).

Table 3. Immunological and virological status at the endpoint of the study in CoS vs non-CoS and statistical significance

Variable	CoS	non-CoS	Statistical significance
Final CD4 (cells/ml)			
Mean, SD	325,40±193,85	339,18±225,93	p Student=0,672 (NS)
Mediana, IQR	320 (10; 1045)	273,5 (9; 1074)	
Final CD4 level (cells/ml)			
<200	15 (22,73%)	34 (25,76%)	Chi²=1,709
200-500	42 (63,64%)	72 (54,55)	p Chi²=0,425 (NS)
>500	9 (13,64)	26 (19,70)	
Total	66 (100%)	132 (100%)	
Increase CD4 (cells/ml)			
Mean, SD	177,068±141,676	176,015±191,751	p Student=0,969 (NS)
Mediana, IQR	172,5 (-67,5; 767)	137 (-166; 828	
Final HIV VL (lgcopies/ml)			
Mean, SD	2,86±0,98	2,95±1,16	p Student=0,705 (NS)
Mediana, IQR	2,60 (1,70-5,86)	2,60 (1,70-5,80)	
Final HIV VL level (copies/ml)			
<400	21 (31,82%)	41 (31,06%)	
400-10000	4 (6,06%)	6 (4,55%)	Chi²=1,250
>10000	4 (6,06%)	14 (10,61%)	p Chi²=0,741 (NS)
Nedeterminat	37 (56,06%)	71 (53,79%)	
Total	66 (100%)	132 (100%)	
Decrease HIV VL (lgcopies/ml)			
Mean, SD	5,04±0,79	4,69±2.04	p Student=0,375 (NS)
Mediana, IQR	4,95 (3,78-6,26)	5,07 (-5.66-6,44)	

Subjects distribution of the 2 groups according to the degree of immunosuppression at the end of the studied period was similar (Chi^2= 1.709, p Chi^2 = 0.425) (Table 3).

At 6-12 months after ART initiation in CoS group, the mean increase in CD4+ cells count was 177,068 ± 141,676 cells/ml, with a median of 172.5 (-67.5, 767) cells/ml compared with non-CoS group, where the mean increase in CD4+ cell count was 176,015 ± 191,751 cells/ml, with a median of 137 (-166, 828) cells/ml, the difference was not statistically significant (p Student = 0.969) (Table 3).

VI. Virological Response to ART

HIV viral load could be assessed for 29 HIS in CoS group and for 61 HIS in non-CoS group.

By 6-12 months following ART initiation, in the CoS group, the mean HIV VL was 2.86 ± 0.98 lgcopies/ml, with a median of 2.60 (IQR: 1.70 to 5.86) lgcopies/ml, compared with non-CoS group, where the mean HIV viral load was 2.95 ± 1.16 lgcopies/ml, with a median of 2.60 (1.70 to 5.80) lgcopies/ml; the difference was not statistically significant (p Student = 0.705) (Table 3).

Subjects distribution in the two groups according to their HIV VL at the end of the studied period was similar in the 2 groups: HIV VL <400 copies / ml was recorded at 31.82% in CoS, vs 31.06% of non –CoS, HIV VL medium (400 to 10,000 copies/ml) in 6.06% of CoS, vs 4.55% of non-CoS and HIV VL high (> 10,000 copies/ml) in 6.06% of CoS respectively 10.61% of non-CoS (Table 3).

By 6-12 months following the initiation of ART, the mean HIV VL decrease in CoS group mean was-5.04 ± 0.79 lgcopies/ml, with a median of 4.93 (IQR: 3.78 to 6.26) lgcopies/ml, compared to group non-CoS group, where the mean decrease was-4.69 ± 2.04 lgcopies/ml, with a median of 5.07 (IQR: -6.66 to 6.44) lgcopies/ml, the difference being statistically insignificant (p Student = 0.375) (Table 3).

Discussion

The two study groups were homogeneous as regards of distribution according to the main demographic parameters: gender, provenance, age at time of the HIV infection diagnosis.

At baseline, subjects of the two study groups had a uniform distribution in terms of the main parameters used in monitoring HIV infection: CDC category of HIV infection, the CD4+ cell count and HIV VL level.

Distribution of subjects in the two groups according to CDC category at the end of the studied period was similar.

By 6-12 months following initiation of ART, mean CD4+ cell count was similar in the 2 groups: CoS-325.40 cells/mL vs non-CoS-339.18 cells/mL. Distribution of subjects in the two groups according to the level of HIV-induced immunosuppression was similar. Mean increase of CD4+ cell count at the end of the study was comparable: 177.07 cells/mL in CoS group vs 176.01 cells/mL in non-CoS group. These data are consistent with data obtained by other studies[18-21].

A Danish study conducted on a population of 3180 HIV infected subjects, including 178 HIV-HBV coinfected (DHCS cohort), communicate similar increase of CD4+cell count at 12 months after initiation of ART in HIV-HBV coinfected as in HIV infected subjects [18].

Deborah Konopnicki et al. communicates the data of a study cohort (EuroSIDA cohort): the percentage of subjects with an increases of CD4+ cell count more than 25% from baseline and the parcentage of subjects with CD4+ cell count more than 500 cells/mL at 6-12 months after the initiation of ART were similar in HIV-VHB coinfected subjects as in HIV infected subjects [19].

In HIV-NAT cohort consisting of 692 HIS, ART-naïve, of which 60 HIV-HBV coinfected, WP Law et al. analyze the response at 4, 8, 12, 24, 36 and 48 weeks after initiation of ART. Although at 4 and 8 weeks after the establishment of ART, HIV-HBV coinfected subjects had a mean increase in CD4+cell count lower than subjects infected only with HIV, this issue was temporarily; by 48 weeks after establishment ART the mean increase of CD4+ cell count was similar in the two group[20].

In another cohort study (AHOD cohort) conducted on 2086 Australian subjects with HIV infection, of which 101 were HIV-HBV coinfected, the authors noticed that the mean increase of CD4+ cell count by 12 months after starting ART was similar regardless of their HBV status[21].

In our study, the mean HIV VL at 6-12 months following ART initiation was similar regardless of the status of HBV infection: 2.86 lgcopies/ml in CoS and 2.95 lgcopies/ml in non-CoS. Subjects distribution of the two groups according to their HIV VL level at the end of the study was similar. The mean decrease of HIV VL following 6-12 months after ART initiation was comparable in the two groups: 5.04 lgcopies/ml in CoS and 4.69 lgcopies/ml in non-CoS. Similar data has been reported in other studies [18-21].

The study conducted by Omland L.H. et al. on the DHCS cohort communicate a similar virological response at 12 months after starting ART, regardless of their HBV status [18].

Deborah Konopnicki et al., in a cohort study (EuroSIDA cohort), noticed that the proportion of subjects with undetectable HIV VL at 6-12 months after initiation of ART was similar in HIV-HBV coinfected compared with subjects infected only with HIV [19].

In HIV-NAT cohort is was noticed a decrease of about 1.5 times of the HIV VL at 48 weeks after initiation of ART, regardless of their HBV status [20].

The study of Lincoln D. et al. communicate a virological response (undetectable HIV plasma viremia), at 12 months after starting ART similar in HIV-HBV coinfected subjects as in subjects infected only with HIV [21].

Conclusions

In horizontally HIV-HBV coinfected patients during early childhood, ART-naïve, at 6-12 months after initiation of HAART:

1. The mean increase of CD4+ cell count is not dependent on the presence of coinfection with HBV.
2. Immunological reconstruction level reached (ie final immunological category) is not influenced by the presence of coinfection with HBV
3. The mean decrease of HIV VL does not depend on the presence of coinfection with HBV
4. Virological response (ie HIV VL <400copies/ml) is not influenced by the presence of coinfection with HBV.

Abbreviations

ART-Antiretroviral Therapy

CRC-Craiova Regional Center for Monitoring and Evaluation of HIV/AIDS

CoS-HIV-HBV coinfected subjects

ELISA-Enzyme-linked immunosorbent assay

HBs Ag-HBs antigen

HIS-Hiv infected subjects

IQR-Range between quartiles

non-CoS-HIV infected subjects without HBV infection

NS-No statistical significance

SD-Standard deviation

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