CHARACTERISTICS OF CO INFECTION WITH HEPATITIS B VIRUS AMONG ROMANIAN PATIENTS INFECTED WITH HUMAN IMMUNODEFICIENCY VIRUS

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CHARACTERISTICS OF CO INFECTION WITH HEPATITIS B VIRUS AMONG ROMANIAN PATIENTS INFECTED WITH HUMAN IMMUNODEFICIENCY VIRUS (Abstract). Aim: To determine the epidemiological and viroimmunological features and outcome of HIV/HBV-co infected patients cared in the Iasi HIV/AIDS Regional Center. Material and Methods: This retrospective study included 252 patients diagnosed with HIV infection and associated hepatitis B virus (HBV) infection assessed at the Hospital of Infectious Diseases in the interval 2000-2013 and treated with antiretroviral drugs active against both HIV and HBV. Results: The prevalence of HIV/HBV co infection was 19.9%. A slightly higher frequency of this co infection was found among males (53.2%); most patients belonged to age group 20-29 years (86.5%), mean age was 25.56 years. The predominant route of transmission was parenteral (58.5%), followed by heterosexual transmission (40.1%). The mean CD4 cell count was 246.20 cells/mm³, in over 41% of cases CD4 count ranging from 200 to 499 cells/mm³. The mean HIV plasma viral load was 142,906 copies/ml. ALT levels varied between 10-323 IU/l, average 49.90 IU/l, over 65% of subjects having pathological levels. In 21.8% of the cases, total cholesterol was very high, and in 16.8 % of the patients the serum triglyceride levels were below the reference range (160 mg %). Conclusions: Our results suggest that HIV-positive patients, chronic hepatitis B infection has a high incidence, especially in younger age groups and is correlated with significant degrees of immunosuppression. Keywords: HIV/HBV CO INFECTION, VIROLOGICAL RESPONSE, IMMUNE RESPONSE, ART.

Infection with human immunodeficiency virus (HIV) continues to be a major health problem, the average number of people infected worldwide by the end of 2011 being approximately 34 million. Although the introduction of effective antiretroviral therapy resulted in a significant decrease in the number of deaths related to acquired immunodeficiency syndrome (AIDS), with the extension of life expectancy liver disease has become the most common cause of death among HIV-infected patients, accounting for 14 to 18% of all deaths in this population (1, 2, 3).

Worldwide, hepatitis B is the leading cause of chronic liver disease, accounting for up to half of all cases of cirrhosis and hepatocellular carcinoma; it is estimated
that approximately 400 million people are infected with hepatitis B virus (HBV), most cases occurring in regions in Asia and Africa, where the virus is endemic (4).

Due to the common routes of transmission, HBV and HIV infections coexist in about 3-6 million people worldwide, the prevalence of chronic HBV infection being 10 times higher in HIV-infected people than in the general population (5). HBV/HIV co infection rate mostly depends on the affected community and HBV transmission route, which differs depending on the geographic area (6,7). The prevalence of HIV/HBV co infection in Europe is about 9% (8), while in Romania it reaches about 35-37%, much higher than the European average (9, 10).

HBV infection is considered an opportunistic infection in HIV-infected patients, the co infection with these two viruses causing complex interactions. HIV infection modifies the natural history of chronic hepatitis B by enhanced replication of HBV and higher serum HBV DNA levels, lower rates of HBsAg and HBeAg seroconversion, increased fibrosis, and faster progression to liver cirrhosis (11, 12). HBV may accelerate immunodeficiency and the course of HIV infection by a direct activation of HIV replication and induction of a state of persistent immune activation (13).

This study aimed to describe the epidemiological and viroimmunological features and the course of chronic HBV infection and to determine its prevalence in the HIV-infected patients receiving care and treatment in the Iasi Regional HIV/AIDS Centre.

MATERIAL AND METHODS
This retrospective study (2000-2013) included 252 patients (female 46.8%, male 53.2%, mean age 25.6 years) with HIV/HBV co infection receiving care and treatment in the Iasi Regional HIV/AIDS Centre.

The epidemiological, clinical, and treatment data were collected retrospectively from patients monitoring and clinical records.

The followed parameters were: epidemiological (mode of transmission, age, gender) viroimmunological (dynamics of CD4 and HIV plasma viral load), metabolic (transaminase, total cholesterol and triglyceride levels), and therapeutic. CD4 count was determined by flow cytometry according to CDC classification, and differentiated into < 200, 200-499, and ≥ 500 cells/ml. The evolution of HIV viremia was followed, the undetectable HIV viral load (viral suppression) being based on the analysis of the lower limit of quantification (HIV RNA 50 copies/ml).

Co infection with HBV was defined as the persistence of positive HBsAg in at least two determinations at a minimum interval of 6 months, including the cases of chronic infection and inactive HBV carrier status. The patients with HCV infection or HBV/HCV and HBV/HDV co infection were excluded to avoid possible interactions.

Highly Active Antiretroviral Therapy (HAART) was defined as a combination of at least three antiretroviral (ARV) drugs, including the association of two nucleoside reverse transcriptase inhibitors with either a protease inhibitor, or with a non-nucleoside reverse transcriptase inhibitor. Particular attention was paid to the therapeutic history of drugs active against HBV replication used to treat HIV infection: lamivudine (3TC), emtricitabine (FTC), tenofovir (TDF).

The evaluation and interpretation of the
results was based on the frequency and structure indicators processed with SPSS statistics using Student t-test, $\chi^2$ test, Pearson correlation coefficient and the linear trend. P values 0.05 were considered significant.

RESULTS

Over the 14-year study period, the 1358 HIV-infected patients cared and treated in the Iasi Regional HIV/AIDS Centre had periodic serologic testing for HBV; HBsAg was present in 252 of them; thus, the incidence of chronic hepatitis B was 19.19%.

In our series, HIV/HBV co-infection was slightly more common among males (53.2%); in terms of age group distribution, as expected, most patients were in the age group 20-29 years (86.5%), the proportion of patients under age 19 and over age 50 being lower. Mean age was 25.56 years, range 6-59 years, with a wide coefficient of variance (40.07%) (tab. I).

In most patients (58.5%) HIV infection was transmitted by parenteral routes, followed by heterosexual transmission (40.1%); 2.4% of HIV infections occurred through homosexual contact, and transmission through injecting drug use was not reported.

### TABLE I

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Number</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex, n (%)</td>
<td>135</td>
<td>53.2%</td>
</tr>
<tr>
<td>Age years ≤ 19</td>
<td>1</td>
<td>0.4</td>
</tr>
<tr>
<td>20-29</td>
<td>218</td>
<td>86.5</td>
</tr>
<tr>
<td>30-39</td>
<td>15</td>
<td>6.0</td>
</tr>
<tr>
<td>40-49</td>
<td>15</td>
<td>6.0</td>
</tr>
<tr>
<td>50-59</td>
<td>3</td>
<td>1.1</td>
</tr>
<tr>
<td>Median age (yrs.)</td>
<td>25.56</td>
<td></td>
</tr>
</tbody>
</table>

According to CDC classification, most of the study patients were in advanced stages of HIV infection: 46.82% stage C, 34.9% stage B, and 18.25% stage A.

![Fig 1. Baseline CDC clinical category of HIV infection](image)

A large number of patients had a significant degree of immunosuppression with a CD4 lymphocyte count < 200 cells/mm³ (48.4%) while > 500 cells/mm³ were found in only 10.3% of the study patients. The individual CD4 count ranged from 3 to 1069 cells/mm³, with an average CD4 count of 246.20 cell/mm³.

HIV viral load ranged from undetectable, in 18.3% of the subjects, to a maximum of 4,600,000 copies/ml. About 26.2% of the cases had plasma levels above 100,000 copies/ml, the average viral load being 142,906 copies/ml (tab. II, fig. 2).

Hepatic cytolysis syndrome was a parameter constantly followed throughout the study: 65% of subjects had alanine aminotransferase (ALT) levels above the reference limit (32 IU/l) and 36.1% exceeded the mean value of 49.9 IU/l in the study group.

The following metabolic abnormalities, common in HIV-infected patients, were found in the study patients. Thus, total cholesterol levels above the reference limit were found in 21.8% of subjects, while the
individual levels of serum triglycerides ranged from 11 to 256 mg%, average 130.72 mg%.

There were a small percentage of cases that had no indication for treatment, while over 98% of patients required antiretroviral therapy, a fact accounted for by the age of the study group, most of them being multiple treatment-experienced patients. It is worth mentioning that all HIV/HBV-coinfected patients received antiretroviral therapeutic agents with dual action against HIV and HBV, 92.3% receiving lamivudine alone or in co-formulations, in only 3.6% of the cases the therapeutic option being tenofovir (fig.3).

**TABLE II**

Characteristics of patients with HBV/HIV co-infection

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Number</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transmission, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterosexual</td>
<td>101</td>
<td>40.1%</td>
</tr>
<tr>
<td>Homosexual</td>
<td>6</td>
<td>2.4%</td>
</tr>
<tr>
<td>Nosocomial</td>
<td>145</td>
<td>57.5%</td>
</tr>
<tr>
<td>Baseline CDC classification</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Class A</td>
<td>46</td>
<td>18.25%</td>
</tr>
<tr>
<td>Class B</td>
<td>88</td>
<td>34.9%</td>
</tr>
<tr>
<td>Class C</td>
<td>118</td>
<td>46.82%</td>
</tr>
<tr>
<td>CD4(cells/ml)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;200</td>
<td>122</td>
<td>48.4%</td>
</tr>
<tr>
<td>200-499</td>
<td>104</td>
<td>41.3%</td>
</tr>
<tr>
<td>&gt;500</td>
<td>26</td>
<td>10.3%</td>
</tr>
<tr>
<td>CD4 mean (cells/ml)</td>
<td>246.2</td>
<td></td>
</tr>
<tr>
<td>Viral load copies/ml&gt;100 000</td>
<td>66</td>
<td>26.2%</td>
</tr>
<tr>
<td>10,000-100,000</td>
<td>81</td>
<td>32.1%</td>
</tr>
<tr>
<td>0-10,000</td>
<td>59</td>
<td>23.4%</td>
</tr>
<tr>
<td>undetectable</td>
<td>46</td>
<td>18.3%</td>
</tr>
<tr>
<td>Viral load, mean (copies/ml)</td>
<td>142,906</td>
<td></td>
</tr>
</tbody>
</table>

![Fig. 2 Baseline virological status](image-url)
Characteristics of co-infection with hepatitis B virus among Romanian patients infected with HIV

**DISCUSSION**

High rates of HBV infection have been described among HIV-infected population worldwide, and the risk of HBV-associated end-stage liver disease appears to be increased in HIV-co infection; thus, for a specific serological surveillance and proper initiation of treatment very important is to estimate its regional prevalence (14).

Our study provides the first information on hepatitis B co-infection among the population infected with the HIV in Northeastern Romania. Our data show a prevalence of 19.19%, lower than that reported by two previous studies conducted in our country (10, 15), possibly because they included a selected population of HIV-infected children and adolescents, respectively. Our study emphasizes that HIV-infected patients are at a 2.5-3 times higher risk for HBV infection compared to the general population of Romania.

The epidemiology of HBV/HIV co-infection is complex and incompletely elucidated, and co-infection rates depend on the prevalence of HBV infection in the general population and the dominant transmission routes of HIV infection (16, 17). The epidemiology of HIV infection in Romania is unique in Europe as almost all cases are attributed to horizontal transmission, nosocomial, of the virus during early childhood. In our study population study, co-infection was mainly associated with this mode of transmission, sexual transmission being prevalently recorded during the last 5-7 years of the study. Our study showed that intravenous drug use, a known risk factor for co-infection is virtually absent in the cohort of HIV-infected patients in Northeastern Romania (17). Surprisingly, this did not lead to a significantly lower rate of co-infection compared to other HIV populations in Europe with a much higher rate of
intravenous drug use (18).

A statistical association regarding the risk factors for HBV infection showed a higher prevalence in the age group 20-29 years, a known and observed fact in our country, due to the higher risk of exposure to the two viruses by parenteral route. The predominance of male gender was also observed, as described previously in many population groups, probably because of more frequent exposure to risk factors involved in transmission, especially sexual contact with a greater number of partners.

The significant percentage of patients in advanced stages of disease compared with other studies can be explained on one hand by the epidemiological characteristics of HIV infection in our country, most patients being part of the cohort of long-term survivors, on the other hand by the possible influence of HBV on the acceleration of HIV disease progression (19,20).

The lack of a significant immune response against HBV is reflected in the average levels of transaminases which showed pathological levels in more than half of HIV/HBV-co-infected patients in the study group.

A 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 and HBV genotype. Due to limited financial resources, in many countries HBsAg remains the only widely available test for the diagnosis of chronic hepatitis B in HIV-infected patients. Another limitation may be due to the retrospective design of the study that enrolled mostly compliant patients with good adherence to ARV therapy, coming for regular checkups.

CONCLUSIONS

In this study provides new insight into the current epidemiology and clinical features of HBV/HIV co-infection in North-eastern Romania. Current data reveal a prevalence of chronic HBV infection of 19.19% in the HIV-infected population, indicating a significantly increased risk compared with the general population.

Our findings highlight the importance of proper management of patients infected with human immunodeficiency virus which has to include prophylaxis, regular screening for HBV infection, and administration of potent anti-HBV therapy in co-infected patients according to current guidelines.

REFERENCES

Characteristics of co infection with hepatitis B virus among Romanian patients infected with HIV


