STUDY REGARDING THE INCIDENCE OF CO - INFECTION HIV-HCV HEPATITIS INFECTIONS

VICTORIA BÎRLUŢIU

Hospital of Infectious Diseases Sibiu

Abstract: *Hepatitis B virus (HBV) and hepatitis C virus (HCV) are responsible for approximately 550-600 million illnesses. Although they belong to different virus families (the Hepadnaviridae family, respectively Flaviviridae), they still have in common the capacity to invade and multiply into the lymphatic system; they are essentially noncytopatogen; they are able to determine chronic hepatic infections, alone or in association with other kinds of viruses that may also have chronic evolution. Therapy for chronic hepatitis arouse a very large interest, especially within the last few years, being associated with a variable virusological response rate, related to the resistance to treatment, a particular situation being considered as hepatitis viruses and HIV coinfection. The prevalence of the HBV is estimated to 10% of HIV infected patients. In endemic affected countries, the ratio is much higher (Southeast Asia, Subsaharian Africa). The hepatitis C (HCV) and HIV viruses association is related to the way the coinfection is transmitted, especially by intravenous drugs injection and by homosexual relations. The coinfection's recognition is made by using serological methods: the persistence of the VHB for more than 6 months confirms the chronic hepatitis, while the key-marker for C hepatitis is represented by the persistence of ARN-HCV in serum. The treatment for HIV infection decreases dramatically the risk of opportunist infections. On the other hand, in hepatitis viruses' coinfection it doesn't happen the same, due to an important ARV drug hepatotoxicity. This is the reason for which in these cases, the chronic hepatitis is the main cause of morbidity and mortality. The most hepatotoxic anti HIV agents are the non-nucleozidic inhibitors of reverse transcriptase (RT)- Nevirapin, in particular. On the other hand, the nucleozidic analogues (except didanosin ddI and d4T) have a low level of hepatotoxicity. The protease inhibitors boosted with ritonavir are not as toxic as complete ritonavir doses.*

Keywords: *HBV-HIV; HCV-HIV coinfection*

Rezumat: *Virusurile hepatitice HBV şi HCV, sunt responsabile de aproximativ 550-600 milioane de îmbolnăviri. Deşi încadrabile în familii diferite-Hepadnaviridae şi respectiv Flaviviridae, au în comun capacitatea de a invaţa şi a se multiplica la nivelul sistemului limfatic, sunt esenţial necitopatogene, pot determina infecţii cronice hepatice, singure sau asociate altor tipuri de virusuri cu potenţial cronic evolutiv. Terapia hepatitelor virale suscită un interes deosebit în ultimii ani, fiind asociată unei rate de răspuns virusologic variabilă, în raport cu instalarea rezistenţei la tratament, o situaţie particulară constituind-o coinfecţia cu virusuri hepatitice-HIV. Se estimează asocierea virusului hepatitic B (HBV) la 10% dintre pacienţii infectaţi HIV, în ţările cu endemicitate, proporţia fiind mult mai mare (Asia de Est, Africa Sub-Sahariană). Asocierea virusului hepatitic C (HCV) cu HIV, este legată de modul de transmitere a coinfecţiei, în principal prin administrarea de droguri intravenos şi prin relaţii homosexuale. Confirmarea coinfecţiei se realizează prin metode serologice: prezenţa VHB peste 6 luni, confirmă hepatita cronică, în timp ce pentru hepatita C, marker-ul cheie îl reprezintă ARN-HCV persistent în ser. Dacă terapia infecţiei HIV, aduce reale beneficii asupra riscului de infecţii oportuniste, nu acelaşi lucru se întâmplă în coinfecţiile cu virusurile hepatitice, datorită unei importante hepatotoxicităţi medicamentoase ARV, astfel că hepatitele cronice la aceşti pacienţi reprezintă o importantă cauză de morbiditate şi mortalitate. Inhibitorii nonnucleozidici de reverstranscriptază (RT) - în particular nevirapin - sunt cei mai hepatotoxici agenţi antiHIV, în timp ce analogii nucleozidici (cu excepţia didanosinei ddI şi d4T) sunt recunoscuţi cu cea mai redusă hepatotoxicitate. Inhibitorii de protează boostaţi cu ritonavir sunt mai puţin hepatotoxici, în comparaţie cu administrarea dozelor complete de ritonavir de altădată.*

Cuvinte cheie: *coinfecţii HBV-HIV; HCV-HIV*

The simultaneous anti-HCV-HIV therapy risks developing high-level side effects. For instance, association between ddI and ribavirin increases the risk of pancreatitis, lactic acidosis, cirrhosis, while zidovudine raises the risk of severe anemia.

The mechanisms of ARV hepatotoxicity in HBV or HCV patient are shown in table nr. 1.

Table nr. 1: The mechanisms of ARV hepatotoxicity

Mitohocondrial toxicity
NRTIs (especialyl ddI and d4T)
Use to appear after prolonged exposure
Hypersensibility
Nevirapine, abacavir
Precocious appearance, in first 12 weeks
Frequent induces rash
HLA-linked
Direct toxicity (intrinsec and idiosincrasyc)
PIs and NNRTIs
Variable depending on drug
Intrinsec toxicity depends on dose
Immune rehabilitation

NRTIs = nucleozidic inhibitors of reverse transcriptase RT, NNRTIs = non- nucleozidic inhibitors of reverse transcriptase RT, IPs = protease inhibitors

The mechanism of ARV toxicity depends on the moment of hepatotoxicity appearance (Table nr. 2)

Table nr. 2: The mechanisms of ARV toxicity

	Precocious appearance	**Belated appearance**
Interval	1-4 weeks	4-8 months
Mechanism	immune-mediated	Direct toxicity, cumulative
Dose-dependence	no	yes
Role of C hepatitis	no	yes
Role of CD4+ cells	yes	no
Example	abacavir, nevirapine	d4T, ddI, nevirapine, tipranavir

The main problem occurs when the **hepatitis B and C viruses** are able to provoke asymptomatic, occult or silent infections. This has been shown by recent studies based on nucleic acid testing of the two viruses.

Occult HCV infection is defined by the impossibility to detect HCV RNA by current serological methods, but it can be identified from peripherical mononucleous (PMBCs) or hepatic tissue, even without clinical or biochemical proof, using molecular tests, knowing that in HIV patients usually doesn't occur Anti-HCV (antibody to HCV). Therefore, the detection is possible by reverse transcription-PCR (RT-PCR) or transcription-mediated amplification (TMA), RT-PCR/NAH –nucleic acid hybridization.

HCV RNA detection is possible even in cases with persistent hepatic cytolysis, made from PBMCs or from hepatic tissue. The CD4 and CD8 T lymphocytes, B lymphocytes and monocytes are also support cells of the multiplication.

Occult HBV infection is defined as the case when the viral ADN is recognisable in serum, lymphoid cells and/or hepatic tissue, in absence of infection's serological markers (such as HBS Ag), clinical symptoms or biochemical characteristics. The evidence of Anti-HBc (antibody to HBc) in absence of HbsAg doesn't exclude the occult infection. The diagnosis in these situations could be made by identifying the replaceable intermediates of the genome, such as covalent closed circular DNA (cccDNA) and virus-specific mRNA.

The HCV or HBV detection is extremely important in supporting a sustained virusological response to combined IFN-alpha and Ribavirin therapy, respectively IFN-alpha therapy; this detection is even more evident by ex vivo PBMCs stimulation with different subsets of lymphocyte-activating mitogens.

Establishing standardized testing protocols for serum samples, plasma and PMBCs in coinfected HIV patients, would bring an important benefit in order to initiate the ARV therapy after deciding the therapy for hepatic infections.

Recognizing the real incidence of occult hepatitis will certainly have a significant impact for the future, in searching an efficient therapy for viral hepatitis, both at hepatic level and lymphatic system. It will also have an epidemiologic significance in restricting the widespread of hepatic viruses.

HIV – HBV coinfection is responsible for the increase from 10-15% to 3-6 times of the risk for the HBV infection to become chronic. It is accepted that 10-40% of the patients with negative Ag HBs and positive Ac HBc, verified through PCR for ADN-VHB, evolve to chronic, especially the ones with CD4 under 500/mm^3.

After the hepatic B virus enters hepatocytes, it determines the production of ARNm, reverse transcription through ADN polymerase with the production of viral ADN, which, together with core particle, will build new infectious virions, released from hepatocyte and affecting new hepatocytes, beginning another replicating cycle. In the first phase of HBV infection, the patient is asymptomatic, because the hepatocytes are not affected, although the viral reproduction is present. Ag HBc is expressed at the hepatocytes' surface, is recognized by CD8+ cytotoxic T cells, which will destroy the AgHBc expressing hepatocytes. This immunological response determines the deterioration of hepatic cytolysis samples, and the patient could remain asymptomatic.

Afterwards, HVB clearance follows, with Ac Hbe production, and Ac HBs appearance as a healing marker. Immunological decline in Hiv infected patient could bring the reactivation of HBV infection, in patients with already existing positive AcHBs.

If in HIV infected patient, Hbe, Ac HBs do not occur 6 months after the infection, we may consider a chronic evolution in these cases; these patients may remain asymptomatic, with transitory/persistent high values of transaminases, the hepatic biopsy rending evident necroinflamator activity, with hepatic necrosis, variable degrees of fibrosis and annual risk of cirrhosis in 12% cases.

In 5-20% of HBV chronic infection evolving to cirrhosis, it is possible to develop hepatocarcinoma, 20-30 years after the prime-infection, especially when other risk factors are involved, as smoking, alcohol, HDV and HIV coinfection, HCV coinfection - in this case the hepatitis C virus replication prevails, suppressing hepatitis B virus replication.

The therapy of chronic HBV infection in HIV seropositive patient, initially performed with high-dose interferon alpha-2b (10 million three times weekly dose, subcutaneous administration or 5 million daily dose for 4 months) in the last few years done with pegylat alfa-2a interferon, 180 μg once weekly, brings a sustained virological response only in 10% cases.

Lamivudine (3TC), inhibitor of HIV-reverse transcriptase and ADN HVB polymerase, is associated to the suppression of HBV replication, normalization of hepatocytolisis after one year in coinfected patients, histological improvement, under caution of resistance mutants YMDD appearance in 3 years after initiating the treatment, in 50%cases.

For these patients, we take into consideration the antiviral therapy with **tenofovir disoproxil fumarate** (TDF) 300 mg daily or **adefovir dipivoxil** 10 mg daily, **emtricitabina** (FTC).

In HIV infected patients with immunological and virusological status able to temporise the antiretroviral treatment, the association of **chronic B hepatitis** imposes to start treating the HBV infection first and only afterwards, to continue with HIV infection treatment.

Certain anti HVB agents were approved in patients co-infected with HIV: interferon pegylat alpha-2a, lamivudine, adefovir and entecavir. Elective is considered **entecavir** treatment (guanosine analog) with antiretroviral action but also with a certain risk of selecting the **M184V** lamivudine-associated resistance mutation.

Entecavir achieves superior virologic and biochemical response compared to lamivudine for patients with Hbe-Ag-positive or negative chronic hepatitis B infection.

The studies show that associating entecavir in those patients with ARV resistance mutations, like Q151M, responsible for crossing resistance to nucleozidic inhibitors of reverse transcriptase RT NRTi, paradoxical, grants hyper susceptibility to entecavir.

Clevudine, telbivudine, being tested in experimental studies, without having an antiHIV action, represents a promising therapy for HBV infection.

Telbivudine, being tested in GLOBE clinical trials, proves superiour clinic efficiency to lamivudine 2 years after treatment, 63% of Hbe-Ag-positive patients developing virological response, compared with 48% for lamivudine. The evaluation of pharmacokinetic interaction between telbivudine and tenofovir (an anti-HIV nucleotide with anti-HVB action), doesn't point out significant effects, tenofovir being a possible alternative when resistance to telbivudine develops.

In co-infected patients, we'll take into consideration associated therapy with 2 active agents to HBV, respective lamivudine and tenofovir.

HCV-HIV coinfection is present in one third of HIV infected patients, with negative consequences by the risk for a more rapid evolution to cirrhosis, hepatic carcinoma and also the hepatotixicity of antiretroviral therapy, forcing the C hepatithis prime intention therapy followed by ARV therapy. In HCV monoinfected patients, 25% have normal values of aminotransferases, while in coinfected patients only 7-9% may present normal values, because of ARV therapy exposure, alcohol abuse, a certain kind of VHC serotype (genotype 3 is seldom associated with normal ALAT, ASAT values, compared to genotype 4). Normal values of ASAT and ALAT are histological correlated with severe fibrosis in 25-40% cases, compared to 10-30% in HCV monoinfection, recent studies showing that 12-14% of severe fibroses in those coinfected patients, are in fact hepatic cirrhosis.

The therapy of C hepatitis for HIV seropozitive patients is similar to the one of monoinfected patients, respective interferon pegylat alfa-2a 180μg weekly and ribavirine (1000 mg daily in patients with weight under 75 kg, respective 1200 mg daily for weight over 75 kg), for 48 weeks, with chances to reduce treatment to 24 weeks in patients with genotype 2 and 3, who achieve a rapid virological response (in 4 weeks). On the other hand, in genotype 1 and 4, with precocious virologycal response (in 12 weeks) but not a rapid one (RVR), the extension of therapy to 60-72 weeks is taking into consideration.

HCV associated to HIV infection treatment is characterized by reduced virological response (25-34% for genotype 1, 55% for genotype 2 and 3) and a high incidence of side-effects, especially for genotype 1b, with multiple quasispecies and changes in non-structural 5A (NS5A) protein. In HCV-HIV coinfection, patients with good response to interferon have a large complexity of NS5A quasispecies compared with the non-responsive ones; on the other hand, a large number of mutations within V3 field of NS5A is predictive for a favourable response. The new compounds used in hepatitis C treatment have structural HCV enzymes as specific target, in conformity with they can be classified as: nucleoside and non-nucleoside analogues inhibiting the HCV

polymerase, protease inhibitors (Table nr. 3), combined with interferon pegylat and ribavirine in order to prevent rapid resistance due to monotherapy.

Table nr.3: Prime intention therapy of HCV infection

Interferons	Polymerase inhibitors		Protease inhibitors
	Nucleoside analogues	Non-nucleoside analogues	
• Albuferon • interferon	• NM283 • R126 • R1479 • MK-0608	• HCV-796 • BI-2071	• Telaprevir • SCH-3034 • GS-9132 • BI-1230

Valopicitabine (NM-283) is an cytidine analog, currently in phase 2 trials and has shown potent anti-HCV activity, by competitive inhibition of HCV NS 5B polymerase, extremely efficient taken along with pegylated interferon (association with ribavirine is not rcommended, it could only be additive). **Protease inhibitors** are the most powerful anti-HCV agents, actioning at NS3 protease level; recent studies has reported other antiretroviral agents, as: A156T, ACH-806, acethylthiouree inhibitors, with NS4A inhibiting action. In HCV/HIV coinfected patients with CD4 cell count over 350/mm^3 we begin with HCV therapy, but when CD4 cell count<200/ mm^{3}se we choose to start with HAART therapy. **Telapevir** is now considered as the most active proteaze inhibitor for HCV, in genotip 1 naive patients to interferon, with rapid virological response (after 4 weeks from interferon pegylat, ribavirine and telaprevir treatment) in 79% cases, compared with only 11% in standard therapy (pegylat and ribavirin).

Studies which associated anti-HCV and ARV therapy, contains reports of patients who developed important rate of hemolytic anemia and neutropenia, secondary to zidovudine treatment, after 4 weeks of therapy. Didanosyne association it is also prohibit. Ribavirine raise the risk of intracelular fosforilation of didanosine metabolit, raising the risk of acute pancreatitis, lactic acidosis, decompensated cirrhosis.

3% of HIV infected population in middle income countries associate 2-many hepatitic viruses infections. In coinfected HBV/HCV patients, usually prevail C virus replication, when HCV antibodies are negative, with a high-level of viral load due to PCR. They also have a high-risk of hepatocarcinoma.

Starting from this premise, we proposed for this study to render evident the association between hepatic infections and HIV.

In HIV infected patients, with negative serological markers for HBV and HCV, we suggest to supplement investigations with PCR for ARN HCV, respective PCR for ADN HBV.

The purpose of this project is to establish the actual size of the HIV-hepatic viruses co-infection, partially estimated through current serological methods, study that can be further extended to national level. The gathered information will give the patients infected with HIV the chance to the first intention therapy for B or C chronicle hepatitis, avoiding the unfavourable evolution under HAART therapy of these co-infections or the initiation of the HIV therapy with the smallest hepatic impact and active towards the B, C virus, where the therapy with pegylat interferon is not recommended. In absence of the HBV infection markers, or after their identification, the patients infected with HIV could benefit of protection through the vaccine against HBV.

We will take into study 100 HIV infected patients, coming from Sibiu and Regional Centre Tg. Mures. We will make usual hepatic determinations and serological tests (Ag HBs, AcHBc, AgBe, AcHBe in those patients with HBV positive) followed by AgHD and Ac HCV determinations. For those patients with HBV and HCV non-conclusive serological determinations, we will determine ADN VHB and ARN VHC due to PCR. We will also determine CD4 values in those patients with positive PCR and negative serological markers, in order to establish the CD4 level for which the viral charge for hepatitic viruses represents the only way to diagnose HIV-HBV/HCV coinfections. Those patients with biochemical and virological criteria for antiretroviral therapy for B or C hepatitis, will be completely evaluated by hepatic biopsy, abdominal echography, gastrofiberscopy, in order to present their medical documents for the National Committee. Depending on the real incidence of coinfections, we will sustain a special program for these patients for rapid initiation of antihepatitic antiviral therapy, followed by HAART therapy. This project is feasible due to the interdisciplinary participation between doctors of different specialities (infectious, internal, gastro-enterological and microbiological diseases).

This project is very important and with real impact in HIV infected patient attitude and treatment. Preliminary information will be made complete after extend national evaluation. Maybe we will revaluate the way of HAART therapy initiation, after treating the hepatitic viruses confections.

Starting with the fundamental research, we aimed at putting into practice the current knowledge regarding the occult hepatic infections, which can be associated through similar methods of transmitting the HIV infection, with the possibility of starting the HBV, HCV therapy previously to the antiviral therapy, and the amelioration of the life expectancy of the patients with HIV-hepatic viruses co-infection.

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