

Risk of mother-to-child transmission in HIV-hepatitis B virus coinfection

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ABSTRACT

Introduction. Human immunodeficiency virus (HIV) and hepatitis B virus (HBV) are two major causes of death worldwide. These two viruses share routes of transmission, and therefore, HIV–HBV coinfection is common and is associated with low plasma levels of CD4 T lymphocytes and accelerated liver disease progression. Maternal HIV and HBV infections have been individually associated with preterm birth and low birth weight.

Case presentation. We describe the case of a 28-year-old patient, 14 weeks pregnant, asymptomatic, who performed Elisa-HIV 1,2 test within prenatal screening, with a positive result, in 2018. From the medical history, we mention that the patient is known for about 5 years with HBV-hepatitis D virus coinfection, for which she underwent interferon treatment for a year. ART was initiated after one month with lamivudine / zidovudine + lopinavir / ritonavir. The patient was adherent to ART (adherence $\geq 95\%$) during pregnancy. Before birth, the immunovirological evaluation revealed the suppression of maternal HIV viral load, a moderate degree of immunosuppression and undetectable HBV-DNA. The patient gave birth by caesarean section to a female child, with a gestational age of 36 weeks, birth weight of 1730 g, length = 43 cm, head circumference = 30 cm, APGAR score = 8 points. The child received antiretroviral prophylaxis with retrovir+epivir, human hepatitis B immunoglobulin and was vaccinated against hepatitis B. The newborn was not vertically infected with HIV and HBV.

Conclusions. Good adherence to ART during pregnancy has been associated with HIV viral load and HBV-DNA suppression and it led to the birth of a child who has not been infected with HIV or HBV. Maternal HIV-HBV coinfection was a significant risk factor for preterm birth and low birth weight.

Keywords: HIV, hepatitis B virus, coinfection, maternal-fetal

INTRODUCTION

Human immunodeficiency virus (HIV) and hepatitis B virus (HBV) are two major causes of death worldwide. These two viruses share routes of transmission, and therefore, HIV–HBV coinfection is common and is associated with low plasma levels of CD4 T lymphocytes and accelerated liver disease progression [1].

HIV-HBV coinfection has become a major public health issue. According to the World Health Organization (WHO), there are 2.6 million HIV-HBV coinfecting people worldwide and chronic HBV infection affects an estimated of 5-20% of people living with HIV [2].

Among HIV-positive pregnant women, a European study reported an incidence of HBV coinfection of 4.9%. According to the European Center for Disease Prevention and Control, Romania has an estimated prevalence of HBV infection of 4.4% [3].

In the USA and Western Europe, sexual transmission accounts for the majority of HBV infections, most infections occurring in adolescents and young adults. In Asia and Sub-Saharan Africa perinatal transmission of HBV infection is more common, occurring in 90% of exposed infants [4].

Maternal HIV and HBV infections have been individually associated with preterm birth and low birth weight. Most studies on HBV coinfection in

HIV-infected pregnant women focused on mother-to-child transmission and on the impact of HBV infection on antiretroviral therapy (ART), while the potential impact of maternal HIV-HBV coinfection on pregnancy remains understudied. It has been reported an increase in rate of HIB transmission because of higher hepatitis viral load [5,6].

During pregnancy, it is possible to occur the syndrome of hepatic cytolysis induced by ART toxicity, hepatitis B flare following discontinuation of HBV treatment, immune reconstitution inflammatory syndrome or obstetric complications (HELLP syndrome, preeclampsia, hepatic steatosis). Therefore, the assessment of liver function of all HIV-HBV coinfecting pregnant women on ART is indicated every 3 months during pregnancy [7].

HBV is easily transmitted from mother to child during delivery. Without immunoprophylaxis, the risk of HBV infection among newborns from mothers who are both HbsAg-positive and HbeAg-positive (a marker of high virus titers) is approximately 85-100% and 90-95% of these infants become chronically infected with HBV [8,9].

ART can slow liver disease progression by restoring immune function and reducing immune activation and inflammation [10].

WHO recommends tenofovir disoproxil fumarate (TDF) / emtricitabine (FTC) as first-line ART among HIV-positive pregnant women. Nucleoside reverse-transcriptase inhibitors have other indications besides HIV infection. TDF or FTC are often used in the third trimester of pregnancy to reduce the risk of vertical HBV transmission [11,12].

In the presence of HIV coinfection, mother-to-child HBV transmission rates could be significant, because of the more frequent presence of HBe antigen and of the higher HBV-DNA levels, compared to mothers with only HBV infection [13].

Among women with high HBV-DNA levels viremia during pregnancy ($>10^9$ copies/ml), vertical HBV transmission rate is significant (32%), despite immunoprophylaxis. Women coinfecting with HIV-HBV are more immunosuppressed than HIV-monoinfected women, which is an independent risk factor for mother-to-child transmission [14].

WHO recommends HIV-positive people to be vaccinated with the HBV vaccine as soon as possible, regardless of CD4 lymphocyte count [2].

CASE PRESENTATION

We describe the case of a 28-year-old patient, from an urban area, 14 weeks pregnant, asymptomatic, who performed ELISA-HIV 1,2 test within prenatal screening, with a positive result, in 2018. From the medical history, we mention that the patient is known for about 5 years with HBV-hepatitis D virus coinfection, for which she underwent interferon treatment for a year. As a child, the patient underwent several parenteral therapies and many surgeries. Abnormal laboratory tests at the time of diagnosis of HIV infection are presented in table 1.

TABLE 1. Abnormal laboratory findings at the time of diagnosis

HIV Western Blot	Positive
HIV viral load (VL-HIV)	71,900 copies/ml
CD4	123 cells/mm ³
HBV-DNA	324 UI/ml
Hemoglobin (Hb)	11.7 g/dl
GPT	99.48 U/l
GOT	62.22 U/l
Cytomegalovirus antibodies IgG	Present

The abdominal ultrasound showed hepatomegaly – left hepatic lobe – anteroposterior diameter 5.2 cm, right hepatic lobe – craniocaudal diameter 16 cm, homogeneous and normoechoic; septate gallbladder; pancreas with normal appearance on ultrasound; enlarged uterus, echogenic amniotic fluid.

The patient received psychological counseling about the risk of mother-to-child transmission of HIV and HBV. ART was initiated after one month with lamivudine/zidovudine + lopinavir/ritonavir.

The patient was adherent to ART (adherence $\geq 95\%$) during pregnancy. The adherence was assessed by applying the adherence questionnaire which is filled in periodically by all HIV-infected patients, registered within Craiova Regional Center for Monitoring and Evaluation of HIV / AIDS: 20-22 points (adherence $\geq 95\%$), 18-19 points (80% < adherence < 95%) and <18 points (non-adherence – <80%) [15].

Before birth, the immunovirological evaluation revealed the suppression of maternal VL-HIV (<50 copies/ml) and a moderate degree of immunosuppression (Figure 1).

During pregnancy, the patient had urinary tract infections caused by *Escherichia coli* and *Klebsiella pneumoniae*, which were treated with cephalosporins, according to antibiograms (table 2).

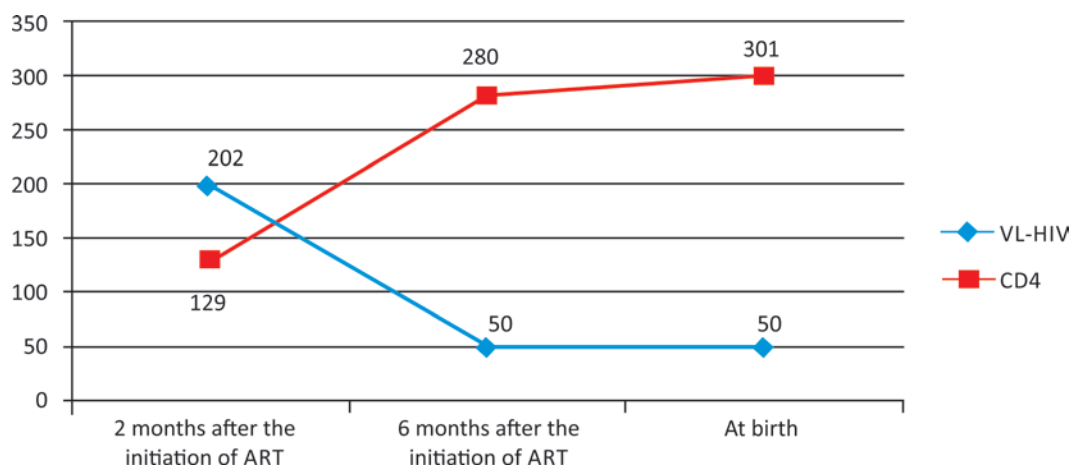


FIGURE 1. Immunovirological status during pregnancy

TABLE 2. Antibiograms

Antibiotic	<i>Klebisella pneumoniae</i>	<i>Escherichia coli</i>
Ampicillin	R	S
Ampicillin/Sulbactam	R	S
Piperacillin	R	S
Cefoxitin	S	S
Ceftazidime	S	S
Ceftriaxone	S	S
Cefepime	S	S
Ertapenem	S	S
Meropenem	R	S
Amikacin	S	S
Gentamicin	S	S
Ciprofloxacin	R	S
Levofloxacin	R	S
Nitrofurantoin	S	S
Sulfamethoxazole/ Trimethoprim	R	S

R – resistant; S – sensible

Biological investigations pointed out one month before birth, normocytic normochromic anaemia – medium form (Hb = 8.8 g/dl, MCH = 31 pg, MCV = 95 μm^3), hepatic cytolysis (GPT = 126 U/l, GOT = 105 U/l), alkaline phosphatase = 147 U/l, prothrombin index = 89%, undetectable HBV-DNA. The patient underwent treatment with hepatoprotectants and hygienic-dietary regime, with the improvement of serum transaminase levels.

The patient gave birth by caesarean section to a female child, with a gestational age of 36 weeks, birth weight of 1730 g, length = 43 cm, head circumference = 30 cm, APGAR score = 8 points. The newborn was evaluated at birth, at 6 weeks, 3 months, 6 months and 12 months by determining VL-HIV, which was undetectable. The child received antiretroviral prophylaxis with retrovir+epivir, human hep-

atitis B immunoglobulin and was vaccinated against hepatitis B. The newborn was not vertically infected with HIV and HBV.

DISCUSSIONS

The management of HIV-HBV coinfection remains a challenge and involves numerous measures for the prevention of vertical transmission. Detecting maternal HBV infection along with passive-active immunoprophylaxis in infants after delivery remain the most effective methods of preventing mother-to-child transmission of HBV infection [16].

A study that was performed between January 2000 and January 2012 in France included 21 HIV-HBV coinfecting pregnant women, who gave birth to 35 children. 26 of them (74%) had HBs antigen: 22 received immunoglobulin and 24 received a complete vaccine; their mothers had been administrated ART with lamivudine or tenofovir / emtricitabine during pregnancy. Eight children (23%) were negative for HBs antigen: 4 of them (11.5%) received immunoglobulin and a complete vaccine, in one child the vaccine was incomplete and in 3 children it was unknown whether they received immunoglobulin or vaccine; their mothers had been administrated ART with lamivudine or tenofovir / emtricitabine during pregnancy. One infant had HBs and HBc antigen: the vaccine was incomplete, it was unknown if he received immunoglobulin and the mother had been administrated lamivudine during the last trimester of pregnancy [17].

Prenatal screening for HIV and HBV can facilitate the implementation of prophylactic measures to reduce the vertical transmission of both viruses.

Among pregnant women with HBs antigen positive and HBV-DNA <200.000 copies/ml at the time of diagnosis and at 28 weeks of pregnancy, antiviral treatment is not indicated [18].

In our patient's case, the application of prenatal screening, the good adherence to ART and the appropriate immunoprophylaxis of the newborn led to the absence of mother-to-child transmission of HIV and HBV.

In Italy, a study was conducted between 2001 and 2016 to evaluate the impact of HBV coinfection on response to ART among HIV-positive pregnant women. The studied group included 1462 patients. The rate of HBV coinfection was 12%. Compared to the HBV-uninfected women, those coinfecting with HBV had a significantly lower median CD4 cell between the first and third trimester of pregnancy, VL-HIV being similar between the two groups (<50 copies/ml) in the third trimester. There were identified the following variables associated with a lower CD4 response in pregnancy: HBV coinfection, being on ART at conception, AIDS status [19].

A study that was performed at Craiova Regional Center for Monitoring and Evaluation of HIV / AIDS within „Victor Babes” Clinical Hospital of Infectious Diseases and Pneumoftiziologie of Craiova during January 1st, 2014 and December 31st, 2019, included 73 HIV-positive pregnant women. The rate of HBV

coinfection was 13.7%. For patients with complete prophylaxis measures, the rate of mother-to-child transmission of HIV was 3%, and the rate of transmission of HBV was 0%. The good adherence to ART was associated with the absence of mother-to-child transmission of HIV and HBV [20].

Another study that was conducted in southwest China between January 2013 and December 2016 included 13.198 pregnant women, with a mean age of 27.6 years. In the study group, the seroprevalence of HIV infection was 3.6%, 3.2% for HBV infection and 0.2% for HIV-HBV coinfection. Maternal HIV-HBV coinfection was a significant risk factor for low birth weight and perinatal mortality [1].

Preterm birth (gestational age <37 weeks) and low birth weight were found in the case that we presented and they were associated with maternal HIV-HBV coinfection.

CONCLUSIONS

Good adherence to ART during pregnancy has been associated with VL-HIV and HBV-DNA suppression and it led to the birth of a child who has not been infected with HIV or HBV.

Maternal HIV-HBV coinfection was a significant risk factor for preterm birth and low birth weight.

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REFERENCES

- Li C, Yang Y, Wang Y, Dong S, Yang Y, Shi Y, Li L, Jiang F, Chen Y, Jiang Q, Zhou Y. Impact of maternal HIV-HBV coinfection on pregnancy outcomes in an underdeveloped rural area of southwest China. *Sex Transm Infect.* 2020 Nov;96(7):509-515.
- Hepatitis B. Available at: <https://www.who.int/news-room/fact-sheets/detail/hepatitis-b> (accessed 21 May 2021).
- Landes M, Newell ML, Barlow P, Fiore S, Malyuta R, Martinelli P, Posokhova S, Savasi V, Semenenko I, Stelmah A, Tibaldi C, Thorne C. Hepatitis B or hepatitis C coinfection in HIV-infected pregnant women in Europe. *HIV Med.* 2008 Aug;9(7):526-34.
- Hoffmann CJ, Thio CL. Clinical implications of HIV and hepatitis B co-infection in Asia and Africa. *Lancet Infect Dis.* 2007 Jun;7(6):402-9.
- Benhammou V, Tubiana R, Matheron S, Sellier P, Mandelbrot L, Chenadec JL, Marel E, Khoshnood B, Warszawski J; ANRS CO11/CO11-EPF French Perinatal Cohort study group. HBV or HCV Coinfection in HIV-1-Infected Pregnant Women in France: Prevalence and Pregnancy Outcomes. *J Acquir Immune Defic Syndr.* 2018 Apr 15;77(5):439-450.
- Zou H, Chen Y, Duan Z, Zhang H, Pan C. Virologic factors associated with failure to passive-active immunoprophylaxis in infants born to HBsAg-positive mothers. *J Viral Hepat.* 2012 Feb;19(2):e18-25.
- What's New in the Guidelines. Available at: <https://clinicalinfo.hiv.gov/en/guidelines/perinatal/whats-new-guidelines> (accessed 16 May 2021).
- Jonas MM. Hepatitis B and pregnancy: an underestimated issue. *Liver Int.* 2009 Jan;29 Suppl 1:133-9.
- Mutagoma M, Balisanga H, Malamba SS, Sebuho D, Remera E, Riedel DJ, Kanters S, Nsanzimana S. Hepatitis B virus and HIV co-infection among pregnant women in Rwanda. *BMC Infect Dis.* 2017 Sep 11;17(1):618.
- Hepatitis C Virus/HIV Coinfection. Available at: <https://clinicalinfo.hiv.gov/en/guidelines/adult-and-adolescent-arv/hepatitis-c-virus-hiv-coinfection> (accessed 21 May 2021).
- Consolidated Guidelines on the Use of Antiretroviral Drugs for Treating and Preventing HIV Infection: Recommendations for a Public Health Approach. 2nd ed. Geneva: World Health Organization; 2016.
- Terrault NA, Bzowej NH, Chang KM, Hwang JP, Jonas MM, Murad MH; American Association for the Study of Liver Diseases. AASLD guidelines for treatment of chronic hepatitis B. *Hepatology.* 2016 Jan;63(1):261-83.
- Pirillo MF, Scarcella P, Andreotti M, Jere H, Buonomo E, Sagnò JB, Amici R, Mancini MG, Leone P, Ceffa S, Mancinelli S, Marazzi MC, Vella S, Palombi L, Giuliano M. Hepatitis B virus mother-to-child

- transmission among HIV-infected women receiving lamivudine-containing antiretroviral regimens during pregnancy and breastfeeding. *J Viral Hepat.* 2015 Mar;22(3):289-96.
14. King CC, Ellington SR, Kourtis AP. The role of co-infections in mother-to-child transmission of HIV. *Curr HIV Res.* 2013 Jan;11(1):10-23.
 15. Drăgănescu M, Iancu AV, Modrișan M, Arbune M. Aderența la tratamentul antiretroviral și trăsăturile de personalitate ale pacienților cu infecție HIV. Probleme de patologie infecțioasă la frontiere. Conferința Națională cu participare Internațională, Galați, 7-9 iunie 2018.
 16. Velicu O, Ciobanu R, Diaconu I, Brătilă E, Mitran M. Managementul gravidei cu hepatită virală B cronică-review de literatură și prezentarea experienței Spitalului Clinic de Obstetrică-Ginecologie „Prof. Dr. Panait Sîrbu”, București. *Ginecologia.ro* 2017.
 17. Sellier PO, Schnepf N, Amarsy R, Maylin S, Lopes A, Mazon MC, Flateau C, Morgand M, Ciraru-Vigneron N, Berthe A, Simoneau G, Evans J, Souak S, Matheron S, Benifla JL, Simon F, Bergmann JF. Short article: Hepatitis B virus status in children born to HIV/HBV coinfecting women in a French hospital: a cross-sectional study. *Eur J Gastroenterol Hepatol.* 2016 Mar;28(3):328-32.
 18. European Association for the Study of the Liver. Electronic address: easloffice@easloffice.eu; European Association for the Study of the Liver. EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection. *J Hepatol.* 2017 Aug;67(2):370-398.
 19. Floridia M, Masuelli G, Tamburrini E, Spinillo A, Simonazzi G, Guaraldi G, Degli Antoni AM, Martinelli P, Portelli V, Dalzero S, Ravizza M. HBV coinfection is associated with reduced CD4 response to antiretroviral treatment in pregnancy. *HIV Clin Trials.* 2017 Mar;18(2):54-59.
 20. Dumitrescu F, Marcu EA, Stănescu M, Giubelan L, Dragonu L, Stoian A, Berceanu C. Mother-to-child transmission of HIV infection in Craiova Regional Center. *Ro J Infect Dis.* 2020;23(2):114-19.