



## Occult hepatitis B virus infection: A major concern in HIV-infected patients

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### ABSTRACT

Human immunodeficiency virus (HIV)-infected patients are at risk of acquiring viral hepatitis, due to common routes of transmission. As the introduction of highly active antiretroviral therapy (HAART) reduced the frequency of opportunistic infections and improved survival, viral hepatitis emerged as an important cause of morbidity and mortality in HIV-infected cases. Occult hepatitis B virus (HBV) infection is characterized by presence of HBV infection without detectable hepatitis B surface antigen (HBsAg). There are conflicting reports on the impact of occult HBV infection on the natural history of HIV disease. In this review, we described the findings of studies on HIV and hepatitis B co-infection with focus on the prevalence of occult HBV infection. The results of this review demonstrated the importance of prevention, diagnosis and treatment of occult HBV infection in HIV-positive patients.

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#### ► Implication for Health policy/practice/research/medical education:

This article makes the importance of occult hepatitis B infection in patients with HIV as a prominent case. Infectious diseases specialists, hematologists and virologists should be aware about this important complication when they manage a patients with HIV infection. Physicians should check overt and occult HBV in all patients with Hepatitis B infection.

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## Background

Hepatitis B virus (HBV) infection is a serious global health problem, with two billion people infected worldwide and 360 million suffering from chronic HBV infection (1). HBV infection is the tenth leading cause of death worldwide, accounting for 520,000 to 1.2 million deaths each year (1-3). The prevalence of chronic HBV infection varies considerably in different geographical regions. China, sub-Saharan Africa and the Amazon Basin, have the highest prevalence with chronic carrier rates more than 7%. Japan, the Indian subcontinent and southern parts of Eastern and Central Europe have intermediate prevalence with 2% to 7% of the population are chronic carriers of HBV. The Middle-East, Bahrain, Iran and Kuwait have low prevalence of chronic HBV infection (<2%) (2, 4-7). The prevalence of hepatitis B surface antigen (HBsAg) in Iran was reported to be between 2.5% and 7.2% in 1979 (8). A more recent study showed that the prevalence of HBsAg is ranging from 1.7% to over 5% in different provinces (9). Occult HBV infection (OBI) is characterized by presence of HBV infection without detectable HBsAg. Most occult HBV carriers have very low viremia levels so the diagnosis of

OBI requires sensitive HBV-DNA PCR assay. A number of explanations for the persistence of HBV-DNA in HBsAg-negative samples have been proposed, including integration of HBV-DNA into host's chromosomes, mutations in the major hydrophilic loop of the S gene, the window period following acute HBV infection, underlying HCV co-infection, immunosuppression, poor ability of laboratory in detection of HBsAg and the presence of immune complexes in which HBsAg may be hidden (10-13). The clinical implications of OBI involve different clinical aspects. OBI harbors potential risk for HBV transmission through hemodialysis, blood transfusion and organ transplantation. It can cause cryptogenic liver disease, acute exacerbation of chronic hepatitis B, or even fulminant hepatitis and development of hepatocellular carcinoma (10). Human immunodeficiency virus (HIV) causes a chronic and latent infection in the body which induces extensive damage to the immune system. HIV-infected subjects show a quantitative depletion of CD4 cells and also an overall immune dysregulation (14). HBV is a frequent co-contaminant with HIV, because both share common modes of transmission (14) and it is an important cause of mortality and morbidity among HIV-infected persons (15). In co-infected patients, the mortality rate is 19 times higher than in HIV mono-infected individuals (16). The high rates of serological markers of HBV infection have been reported in HIV populations and can be as high as 68% (17-20). Isolated hepatitis B core antibodies (anti-HBc) are predominant serological pattern in these patients (17, 21) and can be associ-

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ated with OBI (19, 22). OBI in other high risk groups such as hemodialysis patients was reviewed and published in Iran (23). In this review, we described the findings of studies on HIV and HBV co-infection with focus on the prevalence of OBI.

## Hepatitis B Virus Infection in HIV-Infected Patients

HIV-infected patients are at risk of acquiring parenterally- or sexually-transmitted viruses including HBV. Approximately 20% of HIV-positive patients who acquire acute HBV infection develop chronic HBV infection compared to only 5% of HIV-negative persons (15). Chronic HBV infection affects 7%-10% of HIV-infected patients with large differences according to geographical region (7). After the introduction of highly active antiretroviral therapy (HAART) liver disease has emerged as a major cause of morbidity and mortality in HIV-infected subjects (24). In HIV-HBV co-infected patients, it has been suggested that HIV interferes with the natural history of HBV infection by enhancing HBV replication and higher HBV-DNA levels and decreased hepatitis B e-antigen (HBeAg) seroconversion, leading to more severe liver disease, more rapid progression of liver fibrosis and a higher rate of cirrhosis decompensation, end-stage liver disease and hepatocellular carcinoma (25, 26). There is controversial data on the activity of inflammatory liver disease in HBV-HIV co-infected patients. Some studies in Californian and French HIV-positive subjects showed increased necro-inflammatory activity (27, 28). In contrast, other studies from northern Europe and USA showed a significantly less severe necro-inflammatory activity in HIV-HBV co-infected men who have sex with men (MSM) (29, 30). Besides, one study from the Central African Republic identified a lower prevalence of chronic hepatitis B in HIV-infected vs HIV-uninfected individuals (31). On the other hand, studies from the Cote d'Ivoire, Malawi, Thailand and Tanzania have reported similar chronic hepatitis B prevalence between HIV-uninfected and HIV-infected subjects (32-35).

## OBI in HIV-Infected Patients

The prevalence of OBI in HIV-positive patients varies considerably from 0% to 89.5% in different geographical regions (17-20, 36). These discrepancies in the rate of OBI may reflect the diverse prevalence of HBV and HIV infections in different countries and the sensitivity of the assays used to detect the HBV-DNA. OBI is most frequently seen in patients with anti-HBc antibody as the only HBV serological marker. However, no anti-HBc or anti-HBs antibody could be detected in some individuals (37, 38). Nunez, et al, (18) did not detect HBV-DNA among 85 HIV-positive injection drug users and Bloquel, et al, (39) found OBI in 0.8% of French HIV-infected patients. In two studies from Brazil (40) and the Netherlands (41) the rate of OBI was reported to be 5% in HIV-infected patients. In two other studies in South Africa, almost 22% of HIV-infected people without HBsAg had detectable HBV-DNA (36, 42). In another study, in two cohorts of HIV-positive patients in UK, approximately 14% of patients had OBI (43). Hofer, et al, (17) identified HBV-DNA in 89.5% of patients who had isolated anti-HBc antibody. The other study by Firnhaber, et al, (44) showed that 88.4% of HIV-positive cases with isolated anti-HBc antibody had OBI. In another study in Iranian HIV-positive patients with isolated anti-HBc antibody, HBV-DNA was detected in 13.6% of the patients (25) compared to 24.5% of Indian and 28.7% of Lebanese HIV-infected patients with isolated anti-HBc (14, 45).

## OBI in HIV-HCV Co-Infected Patients

Thirty-five million people have HIV infection worldwide, and approximately 20% of them had chronic hepatitis C (HCV) infection (46). HCV infection affects 25% of HIV-positive subjects, with greater rates (approximately 75%) in persons acquired infection through contaminated blood or blood products and intravenous drug users. Some studies have demonstrated that HIV infection modifies the natural history of HCV infections, increasing the progression to chronic disease and cirrhosis (25). With the advent of HAART, there has been a significant decrease in opportunistic infections, so HCV has emerged as an important cause of morbidity and mortality in HIV-infected patients. A study in French HIV-infected patients showed that deaths due to HCV-related end-stage liver disease were more frequent in the HAART era than in the pre-HAART era (47). It was shown that HCV-HBV co-infection may result in a decrease in the replication of both viruses with greater effect on HBV. HCV core protein binds to HBV-DNA and suppresses HBV gene expression and replication (48). OBI may be encountered in HIV-HCV co-infected patients and may cause more severe liver disease and lower response to interferon therapy (49). Previous studies on the association between HCV infection and OBI persistence in HIV-infected cases have given conflicting results (17, 18, 21). The percentage of OBI in HIV-HCV-positive patients varies considerably in different studies from less than 1% (50), to 1.4%-5% (51-53), 10% (54), 33%-35% (20, 42) and more than 40% (55). In another study 21% of HIV-HCV co-infected patients had detectable HBV-DNA in their plasma and OBI was significantly higher in HCV co-infected subjects than HCV-negative cases (56). Laguno, et al, found that OBI presents in at least 6.3% of HCV-HIV patients and in more than 16% of cases with anti-HBc (57). Fabris, et al, showed that 13.4% of HCV-HIV co-infected patients had OBI (58). In another study in Iran HBV-DNA was detectable in 16.7% of HCV-HIV co-infected patients with isolated anti-HBc (59). Despite the reports regarding to strong association between HCV infection and OBI (58, 60-62), Jardim, et al, (40) reported no significant difference in the presence of HBV-DNA in HIV-positive patients with or without HCV infection. Daza, et al, (63) also found a very low rate of HBV-DNA in HIV-HCV co-infected patients. They reported that OBI is a rare finding in these patients.

## Conclusions

Hepatic abnormalities are common in HIV-infected subjects. Due to shared routes of transmission, chronic HBV and HCV infections frequently complicate HIV disease. To date, there are controversial evidences regarding the influence of HBV infection on HIV disease progression. While some early studies suggested that HBV-related liver disease may be less severe among HIV-infected patients, recent studies indicate an increased risk of liver-related morbidity and mortality among HIV-HBV co-infected patients. Current evidences demonstrated that OBI is relatively frequent in HIV-infected individuals. These data emphasize the importance of prevention, diagnosis and treatment of OBI in HIV-positive cases and all HIV-infected patients should be screened for evidence of resolved or active HBV infection. HCV infection is also common in HIV-infected individuals with parenteral exposure such as IDUs and recipients of blood products. Although the majority of HCV-HIV co-infected cases are asymptomatic, HCV infection may lead to the development of hepatic fibrosis, cirrhosis and hepatocellular carcinoma. There are conflicting reports on the impact of HCV infection on the natural history of HIV disease. With the advent of HAART, there has

been a significant decrease in opportunistic infections so HCV has emerged as an important cause of morbidity and mortality in HIV-infected patients. Taken together, these data provide evidences of the increasing importance of HCV among HIV-infected subjects. There is limited information on the clinical impact and management of HIV-infected patients with OBI. Further studies to provide sufficient data for management of the clinical consequences of these patients are suggested.

## References

- WHO. Hepatitis B. Dublin: World Health Organization; 2004 [updated 2004; cited 06-10-2010]; Available from: <http://who.int/inf-fs/en/fact204.html>.
- Kew MC. Epidemiology of chronic hepatitis B virus infection, hepatocellular carcinoma, and hepatitis B virus-induced hepatocellular carcinoma. *Pathol Biol (Paris)*. 2010;**58**(4):273-7.
- de Franchis R, Hadengue A, Lau G, Lavanchy D, Lok A, McIntyre N, et al. EASL International Consensus Conference on Hepatitis B. 13-14 September, 2002 Geneva, Switzerland. Consensus statement (long version). *J Hepatol*. 2003;**39**(Suppl 1):S3-25.
- Alavian SM, Fallahian F, Lankarani KB. The changing epidemiology of viral hepatitis B in Iran. *J Gastrointest Liver Dis*. 2007;**16**(4):403-6.
- Andre F. Hepatitis B epidemiology in Asia, the Middle East and Africa. *Vaccine*. 2000;**18**(Suppl 1):S20-2.
- Custer B, Sullivan SD, Hazlet TK, Illoeje U, Veenstra DL, Kowdley KV. Global epidemiology of hepatitis B virus. *J Clin Gastroenterol*. 2004;**38**(10 Suppl 3):S158-68.
- WHO. Hepatitis B vaccines. . Dublin: World Health Organization. ; 2003 [updated 2003; cited 06-10-2010]; Available from: <http://www.who.int/vaccines/en/hepatitisb.shtml>.
- Farzadegan H, Harbour C, Ala F. The prevalence of hepatitis B surface antigen and its antibody in blood donors and high risk groups in Iran. *Vox Sang*. 1979;**37**(3):182-6.
- Merat S, Malekzadeh R, Rezvan H, Khatibian M. Hepatitis B in Iran. *Arch Iran Med*. 2000;**3**(4):192-201.
- Hu KQ. Occult hepatitis B virus infection and its clinical implications. *J Viral Hepat*. 2002;**9**(4):243-57.
- Brechot C, Thiers V, Kremsdorf D, Nalpas B, Pol S, Paterlini-Brechot P. Persistent hepatitis B virus infection in subjects without hepatitis B surface antigen: clinically significant or purely "occult"? *Hepatology*. 2001;**34**(1):194-203.
- Zuckerman AJ. Effect of hepatitis B virus mutants on efficacy of vaccination. *Lancet*. 2000;**355**(9213):1382-4.
- Ackerman Z, Wands JR, Gazitt Y, Brechot C, Kew MC, Shouval D. Enhancement of HBsAg detection in serum of patients with chronic liver disease following removal of circulating immune complexes. *J Hepatol*. 1994;**20**(3):398-404.
- Gupta S, Singh S. Occult hepatitis B virus infection in ART-naive HIV-infected patients seen at a tertiary care centre in north India. *BMC Infect Dis*. 2010;**10**:53.
- Thio CL. Hepatitis B in the human immunodeficiency virus-infected patient: epidemiology, natural history, and treatment. *Semin Liver Dis*. 2003;**23**(2):125-36.
- Peters MG. Diagnosis and management of hepatitis B virus and HIV coinfection. *Top HIV Med*. 2007;**15**(5):163-6.
- Hofer M, Joller-Jemelka HI, Grob PJ, Luthy R, Opravil M. Frequent chronic hepatitis B virus infection in HIV-infected patients positive for antibody to hepatitis B core antigen only. Swiss HIV Cohort Study. *Eur J Clin Microbiol Infect Dis*. 1998;**17**(1):6-13.
- Nunez M, Rios P, Perez-Olmeda M, Soriano V. Lack of 'occult' hepatitis B virus infection in HIV-infected patients. *AIDS*. 2002;**16**(15):2099-101.
- Piroth L, Binquet C, Vergne M, Minello A, Livry C, Bour JB, et al. The evolution of hepatitis B virus serological patterns and the clinical relevance of isolated antibodies to hepatitis B core antigen in HIV infected patients. *J Hepatol*. 2002;**36**(5):681-6.
- Filippini P, Coppola N, Pisapia R, Scolastico C, Marrocco C, Zaccariello A, et al. Impact of occult hepatitis B virus infection in HIV patients naive for antiretroviral therapy. *AIDS*. 2006;**20**(9):1253-60.
- Santos EA, Yoshida CF, Rolla VC, Mendes JM, Vieira IF, Arabe J, et al. Frequent occult hepatitis B virus infection in patients infected with human immunodeficiency virus type 1. *Eur J Clin Microbiol Infect Dis*. 2003;**22**(2):92-8.
- Kao JH, Chen PJ, Lai MY, Chen DS. Occult hepatitis B virus infection and clinical outcomes of patients with chronic hepatitis C. *J Clin Microbiol*. 2002;**40**(11):4068-71.
- Hollinger FB, Habibollahi P, Daneshmand A, Alavian SM. Occult Hepatitis B Infection in Chronic Hemodialysis Patients: Current Concepts and Strategy. *Hepat Mon*. 2010;**10**(3):199-204.
- Kumar R, Singla V, Kacharya S. Impact and management of hepatitis B and hepatitis C virus co-infection in HIV patients. *Trop Gastroenterol*. 2008;**29**(3):136-47.
- Puoti M, Torti C, Bruno R, Filice G, Carosi G. Natural history of chronic hepatitis B in co-infected patients. *J Hepatol*. 2006;**44**(1 Suppl):S65-70.
- Azadmanesh K, Mohraz M, Aghakhani A, Edalat R, Jam S, Eslamifar A, et al. Occult hepatitis B virus infection in HIV-infected patients with isolated hepatitis B core antibody. *Intervirology*. 2008;**51**(4):270-4.
- Bonacini M, Govindarajan S, Redeker AG. Human immunodeficiency virus infection does not alter serum transaminases and hepatitis B virus (HBV) DNA in homosexual patients with chronic HBV infection. *Am J Gastroenterol*. 1991;**86**(5):570-3.
- Housset C, Pol S, Carnot F, Dubois F, Nalpas B, Housset B, et al. Interactions between human immunodeficiency virus-1, hepatitis delta virus and hepatitis B virus infections in 260 chronic carriers of hepatitis B virus. *Hepatol*. 1992;**15**(4):578-83.
- Perrillo RP, Regenstien FG, Roodman ST. Chronic hepatitis B in asymptomatic homosexual men with antibody to the human immunodeficiency virus. *Ann Intern Med*. 1986;**105**(3):382-3.
- Rector WG, Jr., Govindarajan S, Horsburgh CR, Jr., Penley KA, Cohn DL, Judson FN. Hepatic inflammation, hepatitis B replication, and cellular immune function in homosexual males with chronic hepatitis B and antibody to human immunodeficiency virus. *Am J Gastroenterol*. 1988;**83**(3):262-6.
- Kashala O, Mubikayi L, Kayembe K, Mukenba P, Essex M. Hepatitis B virus activation among central Africans infected with human immunodeficiency virus (HIV) type 1: pre-s2 antigen is predominantly expressed in HIV infection. *J Infect Dis*. 1994;**169**(3):628-32.
- Menendez C, Sanchez-Tapias JM, Kahigwa E, Mshinda H, Costa J, Vidal J, et al. Prevalence and mother-to-infant transmission of hepatitis viruses B, C, and E in Southern Tanzania. *J Med Virol*. 1999;**58**(3):215-20.
- Rouet F, Chaix ML, Inwoley A, Msellati P, Viho I, Combe P, et al. HBV and HCV prevalence and viraemia in HIV-positive and HIV-negative pregnant women in Abidjan, Cote d'Ivoire: the ANRS 1236 study. *J Med Virol*. 2004;**74**(1):34-40.
- Sutcliffe S, Taha TE, Kumwenda NI, Taylor E, Liomba GN. HIV-1 prevalence and herpes simplex virus 2, hepatitis C virus, and hepatitis B virus infections among male workers at a sugar estate in Malawi. *J Acquir Immune Defic Syndr*. 2002;**31**(1):90-7.
- Merican I, Guan R, Amarapuka D, Alexander MJ, Chutaputti A, Chien RN, et al. Chronic hepatitis B virus infection in Asian countries. *J Gastroenterol Hepatol*. 2000;**15**(12):1356-61.
- Lukhwireni A, Burnett RJ, Selabe SG, Mzileni MO, Mphahlele MJ. Increased detection of HBV DNA in HBsAg-positive and HBsAg-negative South African HIV/AIDS patients enrolling for highly active antiretroviral therapy at a Tertiary Hospital. *J Med Virol*. 2009;**81**(3):406-12.
- Aghakhani A, Banifazl M, Kalantar E, Eslamifar A, Ahmadi F, Razeghi E, et al. Occult hepatitis B virus infection in hemodialysis patients with isolated hepatitis B core antibody: a multicenter study. *Ther Apher Dial*. 2010;**14**(3):349-53.
- Torbenson M, Thomas DL. Occult hepatitis B. *Lancet Infect Dis*. 2002;**2**(8):479-86.
- Bloquel B, Jeulin H, Burty C, Letranchant L, Rabaud C, Venard V. Occult hepatitis B infection in patients infected with HIV: report of two cases of hepatitis B reactivation and prevalence in a hospital cohort. *J Med Virol*. 2010;**82**(2):206-12.
- Jardim RN, Goncalves NS, Pereira JS, Fais VC, Goncalves Junior FL. Occult hepatitis B virus infection in immunocompromised patients. *Braz J Infect Dis*. 2008;**12**(4):300-5.
- Cohen Stuart JW, Velema M, Schuurman R, Boucher CA, Hoepelman AI. Occult hepatitis B in persons infected with HIV is associated with low CD4 counts and resolves during antiretroviral therapy. *J Med Virol*. 2009;**81**(3):441-5.
- Mphahlele MJ, Lukhwireni A, Burnett RJ, Moropeng LM, Ngobeni JM. High risk of occult hepatitis B virus infection in HIV-positive patients from South Africa. *J Clin Virol*. 2006;**35**(1):14-20.
- Nebbia G, Garcia-Diaz A, Ayliffe U, Smith C, Dervisevic S, Johnson M, et al. Predictors and kinetics of occult hepatitis B virus infection in HIV-infected persons. *J Med Virol*. 2007;**79**(10):1464-71.
- Firnhaber C, Viana R, Reyneke A, Schultze D, Malope B, Maskew M, et al. Occult hepatitis B virus infection in patients with isolated core antibody and HIV co-infection in an urban clinic in Johannesburg, South Africa. *Int J Infect Dis*. 2009;**13**(4):488-92.
- Ramia S, Mokhat J, Ramlawi F, El-Zaatari M. Occult hepatitis B virus infection in HIV-infected Lebanese patients with isolated antibodies to hepatitis B core antigen. *Int J STD AIDS*. 2008;**19**(3):197-9.
- Soriano V, Vispo E, Labarga P, Medrano P, Barreiro P. Viral hepatitis and HIV co-infection. *Antiviral Res*. 2010;**85**(1):303-15.
- Rosenthal E, Poiree M, Pradier C, Perronne C, Salmon-Ceron D, Geffray L, et al. Mortality due to hepatitis C-related liver disease in HIV-infected patients in France (Mortavic 2001 study). *AIDS*. 2003;**17**(12):1803-9.
- Jardi R, Rodriguez F, Buti M, Costa X, Cotrina M, Galimany R, et al. Role of hepatitis B, C, and D viruses in dual and triple infection: influence of viral



- genotypes and hepatitis B precore and basal core promoter mutations on viral replicative interference. *Hepatology*. 2001;**34**(2):404-10.
49. Piroth L, Lafon ME, Binquet C, Bertillon P, Gervais A, Looftvoet E, et al. Occult hepatitis B in HIV-HCV coinfecting patients. *Scand J Infect Dis*. 2008;**40**(10):835-9.
  50. Rodriguez-Torres M, Gonzalez-Garcia J, Brau N, Sola R, Moreno S, Rockstroh J, et al. Occult hepatitis B virus infection in the setting of hepatitis C virus (HCV) and human immunodeficiency virus (HIV) co-infection: clinically relevant or a diagnostic problem? *J Med Virol*. 2007;**79**(6):694-700.
  51. Pogany K, Zaaijer HL, Prins JM, Wit FW, Lange JM, Beld MG. Occult hepatitis B virus infection before and 1 year after start of HAART in HIV type 1-positive patients. *AIDS Res Hum Retroviruses*. 2005;**21**(11):922-6.
  52. Quarleri J, Moretti F, Bouzas MB, Laufer N, Carrillo MG, Giuliano SF, et al. Hepatitis B virus genotype distribution and its lamivudine-resistant mutants in HIV-coinfecting patients with chronic and occult hepatitis B. *AIDS Res Hum Retroviruses*. 2007;**23**(4):525-31.
  53. Piroth L, Carrat F, Larrat S, Goderel I, Martha B, Payan C, et al. Prevalence and impact of GBV-C, SEN-V and HBV occult infections in HIV-HCV co-infected patients on HCV therapy. *J Hepatol*. 2008;**49**(6):892-8.
  54. Lo Re V, 3rd, Frank I, Gross R, Dockter J, Linnen JM, Giachetti C, et al. Prevalence, risk factors, and outcomes for occult hepatitis B virus infection among HIV-infected patients. *J Acquir Immune Defic Syndr*. 2007;**44**(3):315-20.
  55. Raffa G, Maimone S, Cargnel A, Santantonio T, Antonucci G, Massari M, et al. Analysis of occult hepatitis B virus infection in liver tissue of HIV patients with chronic hepatitis C. *AIDS*. 2007;**21**(16):2171-5.
  56. Morsica G, Ancarani F, Bagaglio S, Maracci M, Cicconi P, Cozzi Lepri A, et al. Occult hepatitis B virus infection in a cohort of HIV-positive patients: correlation with hepatitis C virus coinfection, virological and immunological features. *Infection*. 2009;**37**(5):445-9.
  57. Laguno M, Larrousse M, Blanco JL, Leon A, Milinkovic A, Martinez-Rebozler M, et al. Prevalence and clinical relevance of occult hepatitis B in the fibrosis progression and antiviral response to INF therapy in HIV-HCV-coinfecting patients. *AIDS Res Hum Retroviruses*. 2008;**24**(4):547-53.
  58. Fabris P, Biasin MR, Giordani MT, Berardo L, Menini V, Carlotto A, et al. Impact of occult HBV infection in HIV/HCV co-infected patients: HBV-DNA detection in liver specimens and in serum samples. *Curr HIV Res*. 2008;**6**(2):173-9.
  59. Ramezani A, Mohraz M, Aghakhani A, Banifazl M, Eslamifar A, Khadem-Sadegh A, et al. Frequency of isolated hepatitis B core antibody in HIV-hepatitis C virus co-infected individuals. *Int J STD AIDS*. 2009;**20**(5):336-8.
  60. Squadrito G, Pollicino T, Cacciola I, Caccamo G, Villari D, La Masa T, et al. Occult hepatitis B virus infection is associated with the development of hepatocellular carcinoma in chronic hepatitis C patients. *Cancer*. 2006;**106**(6):326-30.
  61. Ikeda K, Marusawa H, Osaki Y, Nakamura T, Kitajima N, Yamashita Y, et al. Antibody to hepatitis B core antigen and risk for hepatitis C-related hepatocellular carcinoma: a prospective study. *Ann Intern Med*. 2007;**146**(9):649-56.
  62. Marque-Juillet S, Benghalia K, Monnier S, Fernand-Laurent C, Mazon MC, Harzic M. [Should patients infected with HIV be screened for occult hepatitis B?]. *Pathol Biol (Paris)*. 2010;**58**(2):e39-42.
  63. Daza R, Parra J, Martinez N. Occult HBV infection in HIV-HCV co-infected patients negative for HBsAg. 2nd International AIDS Society Conference on HIV Pathogenesis and Treatment; 2003 July 2003; Paris, France. 2003. p. 986.