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Hepatitis B prophylaxis in HIV-infected patients

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summary

The risk of infection with hepatitis B virus is higher in HIV-infected patients due to shared risk factors. Unfortunately, the efficacy of immunisation against HBV in this group is much worse than in general population. Especially patients with low CD4 cell count and high HIV viral load present with lower rate of response. Therefore the use of double vaccine doses or prolongation of the vaccination schedule is recommended in those whose post-vaccination anti-HBs titers are less than 10 mIU/ml. It is uncertain how to manage the patients with "isolated" anti-HBc, where other serological markers of HBV infection are negative. Some recommend vaccination in these patients as well.
It is advisable to measure HBV DNA in patients with "isolated" anti-HBc, as a part of them may present with occult hepatitis B.

key words

hepatitis B prophylaxis, vaccination, HIV infection

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Individuals at risk of HIV infection are even more exposed to infection with hepatitis B, as the routes of transmission for both these viruses are the same. The prevalence of HIV/HBV coinfection ranges between 7–9% (1, 2). Chronic hepatitis B develops more frequently in HIV-infected people and these patients have also higher levels of HBV viraemia and are at a higher risk for liver-related mortality (3, 4).

For these reasons vaccination against hepatitis B is highly recommended for all HIV-infected patients lacking prior immunity. However, the response to the vaccine differs substantially in this population from the population of healthy people. More than 95% of healthy immunocompetent people achieve a protective immune response after a standard 3-dose vaccination series (5). The duration of protection of hepatitis B vaccine is still the question of debate. Results of meta-analysis of long-term protection provided by hepatitis B vaccine in healthy subjects revealed, that overall risk of HBV breakthrough infection in vaccinated people during the period of up to 20 years was only 0,007% (6). This means that the protection after 3 or 4 doses of hepatitis B vaccine persists for at least 20 years in the great majority of immunocompetent individuals.

In HIV-infected individuals the response rate to HBV vaccine is much lower at 18–62% (7, 8, 9). These patients less frequently acquire the concentration of anti-HBs antibodies above 10 mIU/ml. Mean level of anti-HBs in HIV-positive vaccinees is significantly lower than in healthy population (10). More interestingly, it has been demonstrated that HIV-positive people may be still susceptible to HBV infection even in case of "seroprotective" anti-HBs level of > 10 mIU/ml (11,12). The authors of the former of those studies concluded, that HBV vaccination was not substantially associated with reduced risk of HBV infection in their cohort of HIV-infected individuals. However, vaccinees with anti-HBs level of > 10 mIU/ml did not develop chronic HBV infection (only acute, self resolving infection) (11, 12).

It is supposed, that hepatitis B-specific memory B cells (HSMBC) are responsible for the efficacy of the vaccine. In HIV-infected individuals reduced memory B cell proliferation and altered B cell phenotypes were measured (13). It has been shown, that HSMBC frequencies are significantly lower in HIV-positive than in HIV-negative patients and that they directly correlate with HBsAb titers (13).

High HIV RNA load, low CD4 nadir, low current CD4 level, low CD19 cell percentage, age older than 40 years, male gender, alcohol abuse, African-American race were described as risk factors for lack of vaccine response (14–18). There are also associations of HLA-DRB1 alleles with antibody response to HBV vaccine (19).

It is recommended that common HBV vaccination schedule be modified in HIV-infected subjects – double doses or increased number of injections should be considered (18, 20–22). It is advisable especially when the post-vaccination anti-HBs titer is less than 10 mIU/ml.

Polish guidelines recommend normal vaccination schedule in all patients with negative HBV serology (e.i. HBsAg -, anti-HBs -, anti-HBc -), regardless of CD4 level. It is permissible to use double dose of the vaccine, especially if the first vaccination cycle was ineffective – anti-HBs titer below 10 mIU/ml. It is also possible to give one booster dose in such a case. Patients should be tested for the level of anti-HBs antibodies one month after vaccination and then yearly (23).

There are several studies on application of adjuvants, which increase immunogenicity of HBV vaccine in HIV-infected individuals: rhGM-CSF (recombinated human granulocyte-macrophage colony-stimulating factor) (24) and CpG oligodeoxynucleotides as toll-like receptor 9 agonists (25).

"Isolated" anti-HBc antibodies

Whereas a recommendation of vaccination against hepatitis B applies to every patient with a negative HBV serology, it is still uncertain how to manage HIV-infected individuals with "isolated" antibodies to hepatitis B core antigen (anti-HBc). This term means that no other serological marker of HBV infection, neither HBsAg nor anti-HBs are detected in these individuals.

Usually, those who underwent hepatitis B, present with antibodies to both hepatitis B surface (anti-HBs) and hepatitis B core (anti-HBc) antigens. The titer of anti-HBs is an indicator of immunisation against hepatitis B. However, there are multiple patients with "isolated" anti-HBc (or "anti-HBc-alone") in population of HIV-positive people – estimated 10,6–23,8% (26–29).

Clinical importance and significance of isolated anti-HBc is unclear. The reasons for this phenomenon might be: a false positive result, late immunity after resolved HBV infection or, finally, an occult HBV infection.

It has been shown that "isolated" anti-HBc are 2–4 times more frequent in patients with HCV infection (30–32). "Isolated" anti-HBc in presence of chronic hepatitis C may be connected with some dysfunctional antibody production attributable to HCV infection (32).

It has been described in literature that some individuals with isolated anti-HBc may still acquire HBsAg (32, 33). There is controversy in patients with anti-HBc only, but some recommend vaccination against HBV in these people, as they may be not immune (34). It is advisable to check anti-HBs titer after the first dose of the vaccine. In the case of increased anti-HBs titer, continuation of the vaccination might not be necessary (34).

Occult hepatitis B

Occult hepatitis B is defined as positive HBV-DNA in patients with negative HBsAg. It is relatively frequent in HIV-positive patients – the prevalence varies depending on the studied groups and geographical region from 2% to 28,5% (26–28, 35–42). It usually appears in patients with "isolated" anti-HBc (26, 28, 35–37, 41), though the presence of anti-HBs or absence of any HBV marker does not rule out occult hepatitis B (36, 43). Its presence is often correlated with HCV infection (36, 40, 41, 44). Although it may be sometimes connected with hepatic flares (35), most often transaminase levels are persistently normal in subjects with occult hepatitis (27, 37, 43–45). Some authors correlate low CD4 level (< 200 cells/μl) with higher frequency of occult hepatitis B (38, 42) – it may be viewed as opportunistic reactivation of HBV.

It is recommended to check HBV-DNA in patients with "isolated" anti-HBc and in those with entirely negative HBV serology, but revealing unexplained hepatopathy. Clinical importance of occult hepatitis is uncertain. It seems that it does not have any significance in general population, but probably might be important in patients subjected to immunosuppressive treatment or HIV-posi-