

REVIEW

Insights on common vaccinations in HIV-infection: efficacy and safety

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Summary

HIV-infected patients are at increased risk for both vaccine-preventable diseases and their complications, with mortality rates higher than in non-HIV-infected individuals. Consequently, international guidelines generally recommend inactivated vaccines in HIV-patients, even if HIV-related immunode-

ficiency may impair efficacy; live vaccines are usually not recommended in these patients because of safety concerns. The aim of this short article is to review current knowledge about both efficacy and safety of vaccines in HIV-infected individuals.

Introduction

Human Immunodeficiency Virus (HIV) infection is a leading cause of morbidity and mortality [1]. If untreated, HIV leads to a progressive impairment of the cellular immunity, thus increasing the risk of opportunistic infections and malignancies [2, 3].

Parameters most commonly used to monitor the advancement of the disease include the plasmatic HIV viral load (HIV-RNA) and the serum CD4-T cell count [4]. Indeed, a detectable plasmatic HIV-RNA reflects an active viral replication, while a reduced CD4-T cell count suggests an impoverishment of the immune response against infections and cancers. On the other hand, an undetectable plasmatic HIV-RNA and an increased serum CD4-T cell count are both markers of favorable response to antiretroviral therapy (ART), the latter being also associated with a dramatic reduction in the risk of opportunistic infections [5, 6]. However, despite immunovirological control with ART, HIV infection remains associated with residual perturbations of the immune cellular response, including both T- and B-cells [7]. If we accept the idea that even in immunovirological controlled HIV-infected patients the immune system does not work normally, it is conceivable that immune response to vaccines may remain sub-optimal, as well.

Attempting to deal with this important matter, in this paper we review current literature about efficacy of vaccinations in HIV-infected adults, as well as safety concerns regarding the administration of live vaccines.

Impact of vaccine-preventable diseases in HIV patients

HIV-infected patients are at increased risk for the development of both vaccine-preventable diseases and their

complications, with higher mortality rates than in non-HIV-infected individuals.

Streptococcus pneumoniae pneumonia is a leading cause of death worldwide, although its survival has dramatically improved in the last century due to improved nutrition and life conditions together with public health measures and the advent of the antibiotic era [8]. As regards the impact of HIV infection on the outcome of this disease, mortality of *S. pneumoniae* pneumonia and/or bacteremia has been reported to be higher in HIV-infected patients than in HIV non-infected subjects, even after the introduction of ART [9, 10].

An association between increased mortality and HIV infection has also been reported for influenza in patients with severe immunodeficiency, with high influenza-attributable risk of acute cardiopulmonary event [11]. For these reasons both anti-pneumococcal and anti-influenza vaccines are recommended for HIV-infected individuals, with preference, in the case of influenza, for inactivated vaccines [12-14]. An inactivated influenza vaccine should thus be administered annually to all HIV-infected individuals [12]. Of note, avoiding the development of influenza through vaccination is also an indirect way to prevent bacterial pneumonia which can occur as a complication of the viral disease [12].

The considerable impact of some other vaccine-preventable diseases in HIV-infected patients is not only related to their acute-phase mortality, but it also derives from the high prevalence of these diseases in the HIV population, with effects on long-term morbidity and mortality. For example, international guidelines recommend vaccination of HIV-infected patients against hepatitis A virus (HAV), hepatitis B virus (HBV) and human papillomavirus (HPV), even if complete and reliable data regarding efficacy of these vaccines in HIV-infected patients are not available [13].

It has been demonstrated that HIV-infected patients are at higher risk for HBV infection in comparison with non-HIV-infected subjects, since HBV shares the same routes of transmission of HIV. In addition, HBV infection significantly increases liver-related mortality in HIV-1-infected patient [15], especially for those with low CD4-T nadir count [15, 16]. Moreover, due to some shared risk factors (i.e., intravenous drug use and being a man who have sex with man), also vaccination against HAV should be considered in HIV-infected patients [17, 18].

Similarly to hepatotropic viruses, the prevalence of HPV-related diseases in HIV-infected patients is higher than in non-HIV-infected individuals. Therefore, HIV women are at higher risk for developing cervical intraepithelial neoplasm and cervical cancer in comparison with the general population [19-23]. Accordingly, HPV vaccine is strongly recommended for HIV-infected girls aged 9 through 26 years by Italian and ACIP guidelines, while only a moderate recommendation is provided by American guidelines, due to the lack of complete efficacy data in the HIV population [12-14].

Finally and obviously, HIV-infected individuals are at risk of preventable diseases such as tetanus, diphtheria and pertussis with no difference with respect to the general population, and should therefore receive specific vaccinations.

Detailed international schedules for different types of vaccinations in both HIV-infected and non-HIV-infected patients can be found at <http://www.cdc.gov/vaccines/hcp/acip-recs/index.html> [14].

Efficacy and immunogenicity of different vaccines in the HIV setting

The vaccine efficacy in preventing disease in HIV-infected patients has been demonstrated for *S. pneumoniae* and influenza viruses associated diseases.

As regards *S. pneumoniae*, Rodriguez-Barradas et al compared 692 non-HIV-infected and 934 HIV-infected subjects in a randomized clinical trial, the 59% of whom were vaccinated with the 23-valent pneumococcal polysaccharide vaccine [24]. The primary endpoint was time to the first pneumonia event, after controlling for HIV-specific variables. They found that the anti-pneumococcal vaccination significantly reduced the risk of pneumonia (HR 0.65, 95% CI 0.42-1.00, $p = 0.05$) in HIV-infected patients, while the impact of vaccination in non-HIV-infected was not significant [24].

A recent systematic review investigated the efficacy and the effectiveness of influenza vaccination in 1562 HIV-patients [25]. Data was retrieved from 3 randomized-controlled trials (RCT) and 3 observational studies. The authors observed a pooled efficacy of 85% in preventing laboratory-confirmed influenza (95% CI 22-97%) among adult patients, while this effect was not confirmed in young children [25]. In the 3 observational studies, a favorable effect of vaccination was reported only in one of them, with an effectiveness of 71% (95% CI 44-85%) in preventing laboratory-confirmed influ-

enza [15]. However, it should be noted that a high risk of bias was reported in all the 3 observational studies included [15].

For other vaccines, such as those against HBV, HAV, and HPV, immunogenicity has been used as a surrogate marker for clinical effectiveness in several observational studies, while no randomized trials have still validated their efficacy and effectiveness in preventing disease [26].

Two studies compared rates of serological response to HBV vaccination in HIV-infected vs. non-HIV-infected individuals. In the first, Irungu et al. found that the nonresponse to HBV vaccine was higher in 310 HIV-infected patients than in 293 non-HIV-infected subjects (35% vs 14%, $p < 0.001$) [27]. In the second study, Collier et al. compared 16 HIV-infected and 68 non-HIV-infected children and found that subjects who were HIV-infected frequently lacked protective levels of anti-HBs titers after three doses of 20 µg of recombinant HBsAg in comparison to HIV-uninfected individuals (44% vs 9%, $p = 0.002$) [28].

About HAV, Neilsen et al. investigated 90 HIV-infected and 44 non-HIV-infected subjects, both receiving a 2 dose vaccination course [29]. The authors observed that among patients tested for seroconversion after two vaccination doses the HAV seroconversion rate was significantly lower in HIV-positive patients in comparison with HIV-negative subjects (88.2% vs 100%, respectively, $p = 0.03$) [29]. In addition, in the subgroup of HIV-infected patients, baseline CD4-T cell count was considerably higher in those who showed serological response to HAV vaccination than in those who did not (mean baseline CD4-T cell count 540/µL vs 280/µL, respectively, $p = 0.033$) [29]. On the other hand, Wallace and coworkers studied HAV seroconversion rates after vaccination among 90 HIV-infected and 90 non-HIV-infected patients. In this experience, antibody responses were sustained among the non-HIV-infected subjects (100%, 95%CI 95-100) and HIV-infected subjects with CD4-T cell count higher than 300/µL (100%, 95%CI 87-100), but they decreased among patients who had had CD4-T cell counts lower than 300 cells/mm³ at enrollment (87%, 95%CI, 66-97) [30]. Finally, Tseng et al. reported an unfavorable association between HIV infection and response to HAV vaccination independently from receiving either two or three doses of HAV vaccine ($p = 0.01$) [31].

With regard to HPV vaccination in adults, a phase 2 open-label multicenter trial found the 3-dose quadrivalent HPV vaccine to be immunogenic in 99 young HIV-infected women aged 16-23 years. The observed seroconversion rates were as high as 100% for HPV-6, 11, 16, and 18 among women on ART [32]. Moreover, Wilkin et al. found that the same vaccine was immunogenic among 109 HIV-infected men ≥ 18 years, with seroconversion rates of 98% for HPV-6 (59/60), 99% for HPV-11 (67/68), 100% for HPV-16 (62/62), and 95% (74/78) for HPV-18 (74/78) [33].

Finally, optimal revaccination strategies for patients with no serological response to vaccination schedules are still under debate.

Impact of vaccination on HIV-infection

Interestingly, some authors have highlighted responses to vaccination from an HIV standpoint, aiming at elucidating any possible impact of different vaccines on the course of the HIV-related disease.

For influenza vaccination, Durando et al. did not report any increase in both HIV replication and CD4-T cell count following influenza vaccination with two different virus subunit vaccines at three time points, whereas Calmy et al. detected transient increases in HIV-RNA levels in 3 of 66 (4.5%) previously aviremic HIV patients who received two doses of an AS03-adjuvated flu pandemic vaccine [34]. Of note, these transient increases did not recur after boosting with a non-AS03-adjuvated influenza vaccine. Similarly, Onlamoon et al. observed detectable plasmatic HIV-RNA levels among 8/37 previously aviremic HIV-infected patients (22%) who received a monovalent non-adjuvated influenza A H1N1 2009 vaccine, even though a concomitant increase in lymphocytes activation was not observed [35].

Two clinical trials did not report any effect on plasmatic HIV-RNA and serum CD4-T cell count after HAV and HBV vaccination, respectively [27, 29, 36]. Similarly, Levin et al. did not observe significant changes in CD4-T cell counts in HIV-infected children receiving a live attenuated varicella vaccine, whereas an increase in CD4-T cell activation was observed by Stanley et al. following tetanus immunization, resulting in an enhanced CD4-T cells susceptibility to both HIV infection and replication [37, 38].

Finally, it is worth noting that no ART failure was observed in the study of Calmy et al., which, as detailed above, reported an increase in HIV RNA levels following vaccination [34]. However, this possibility remains of some concern, since HIV drug resistance mutations can be selected in presence of low-level viremia [39, 40]. Whether or not this risk is also present during transient increases of HIV-RNA in the post-vaccination period deserves further investigations.

Safety of vaccination in HIV patients

When administering vaccines, as well as any other medication, the development of adverse events may occur. To this regard, inactivated vaccines are generally reported to be well tolerated in HIV patients, with the most frequent side effects being mild and transient local reactions, including pain, redness, swelling, and mild systemic reaction, like headache, fever and general discomfort [24, 30, 36, 41-46]. Although Wallace et al. described a slightly higher rate of systemic adverse reactions in HIV-infected individuals receiving HAV vaccination in comparison with both HIV infected subjects receiving placebo and non-HIV-infected subjects receiving HAV vaccination (37% vs 23% vs 21%, respectively), no other differences in the incidence of vaccine-related adverse events between HIV-infected and non-HIV-infected subjects have been reported so far [30].

A particular safety concern regarding vaccines administration in HIV patients is the possibility for a live vaccine itself to cause disease. In fact, live-attenuated vaccines might be harmful in patients with severe immunodeficiency. For this reason, international guidelines do not recommend measles vaccination in severely immunosuppressed patients. Anecdotal reports confirm that measles vaccination is potentially dangerous in these patients. For example, an HIV-infected patient who received measles vaccination developed deadly giant-cell pneumonitis one year after. Genomic sequence analysis revealed that the measles virus in lung tissue was similar to vaccine viruses [47]. In addition, in the pre-HAART era several case reports described the development of severe disease after varicella and BCG vaccines in HIV-infected adults [48-50]. Whether or not live vaccines might be used in patients achieving good immunovirological response is a matter of concern. Several recent investigations reported that live vaccines against varicella, zoster and yellow fever were safe in HIV-infected children and adults [37, 46, 51]. However, it should be noted that these studies largely involved those HIV patients without a severe degree of immunodeficiency [37, 46, 51]. Nevertheless, live-attenuated vaccines remains contraindicated in HIV-infected patients with low CD4-T cell count (i.e. < 200/ μ L) [14].

Conclusions

Despite the lack of a complete and reliable efficacy data, avoiding the development of preventable diseases through vaccination might be critical in HIV-infected individuals, especially because the immunovirological competence in these patients might be questionable even after viral response and apparently complete immunological recovery. Indeed, these patients should follow tailored vaccination schedules, to prevent diseases that carry a high burden in terms of morbidity and mortality in the HIV population, such as *S. pneumoniae* pneumoniae, influenza, HBV and HPV infection. Vaccines should be administered without waiting for full CD4-T cell count recovery, although immunodeficiency is a possible risk factor for lack of response to vaccination. Finally, inactivated or subunits vaccines should be preferred, since further studies are needed to adequately investigate the safety of live vaccines in HIV-infected patients.

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