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VACCINES AGAINST HPV IN PEOPLE LIVING WITH HIV: A REVIEW

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Abstract – *Human Papilloma Virus (HPV) infection represents the most common sexually transmitted infection worldwide.*

The best weapon to control the HPV infection is the primary prevention that includes interventions related to lifestyle and sexual habits and HPV-vaccination.

HPV vaccination must be recommended not only for young girls, but also for boys, MSM and HIV-infected people. People Living with HIV (PLWHA) have high rates of persistent HPV infection if compared with HIV-uninfected people.

Several data from HIV negative population have confirmed vaccine safety and efficacy, but there is limited data available on the efficacy of the vaccine among HIV-infected people.

In this review, we considered the studies published about anti-HPV vaccination in PLWHA that we found performing a research on PUBMED (Bethesda, MD, USA) with the aim to point out the main aspects of vaccination in this particular population.

KEYWORDS: *Human immunodeficiency virus (HIV), Human papilloma virus (HPV), Vaccination, safety, Efficacy, Cancer, Adverse effects.*

INTRODUCTION

With the introduction of the antiretroviral therapy (ART), life expectancy of the patients living with HIV (PLWH) almost approached that of the general population, determining an increase in the total number worldwide[1-38].

HIV infection is now a long-term condition and the management of infection must consider the co-infections and comorbidities[2,5].

PLWH have a high prevalence of HPV infection and related disease that may complicate HIV infection[2-10].

Prolonged survival provides more time for the development of cervical, anal, and other HPV-related cancers, and demands effective HPV prevention and management strategy[1-4].

HPV infection represents the most common sexually transmitted infection worldwide, causing a substantial burden of disease in men and women[37].

The transmission of HPV is not exclusively sexual: it is also possible the indirect transmission through the use of infected underwear or towels, in domestic and public environments or swimming pools; furthermore, although rare, the maternal-fetal transmission is possible at the time of childbirth[39].

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The infection is accountable for 4.5% of all cancers (630,000 new cancer cases per year) in the world: 8.6% in women and 0.8% in men[2,3].

HPV is a small, non-enveloped virus included in the family of Papillomaviridae: its genome consists of a single molecule of double-stranded, circular DNA associated with histone-like proteins, protected by an icosahedral capsid[2].

HPV infects basal epithelial cells: most HPV infections are self-limiting and cleared by the host's immune system within 24 months. However, persistent infections with oncogenic subtypes can cause cervical cancer, vulvar cancer, oropharyngeal cancer, penile cancer and anal cancer[2-4].

More than 200 different HPV types have been described, divided into high-risk HPV (subtypes -16, 18, 31, 33, 35) and low-risk HPV (subtypes 6, 11, 40, 42, 43). HPV-16 and HPV-18 are most frequently associated with a persistent infection, so they are responsible for most of the neoplastic lesion[2,6].

The aim of this review is to point out the main aspects of anti-HPV vaccination in PLWHA, its importance, efficacy and safety.

MATERIALS AND METHODS

On June 26th, 2019, we performed a review of the literature to resume all the characteristics of HPV vaccines and their safety in PLWHA. We searched PubMed (Bethesda MD, USA) applying "Papillomavirus", "HIV infection", "Vaccination", "Efficacy" "Safety" "Adverse effects". We included only recent articles written in English, full-text available, identifying 82 records. We excluded 11 articles after reading title and abstract. At the end of the assessment we included in our review 71 articles.

The importance of primary prophylaxis

The best weapon to control the HPV infection is the primary prevention that includes interventions related to lifestyle and sexual habits and HPV-vaccination[38].

Condoms offer considerable protection against various sexually transmitted infections, including HIV; however, its efficacy in preventing HPV infections is less clear[30,32].

Lams et al[40] showed that consistent and correct condom use may offer good but limited protection against HPV infections because it does not cover the entire anogenital area.

However, the protection against HPV is limited by the persistence of the virus on surfaces, in swimming pools, in public toilets[39].

HPV vaccination can potentially prevent cancer[2-5,41]; HPV vaccines have been shown to reduce rates of cervical dysplasia (CIN), the precursor of invasive cervical cancer[42].

The quadrivalent vaccine has been effective in preventing not only anal HPV infections, but also anal intraepithelial neoplasia (AIN) in young men. HPV vaccines also decrease the risk of recurrence of AIN in MSM. However, the nine-valent HPV vaccine (9vHPV) should protect against 87% of vulvar cancers if protection is complete[42].

This is the reason why HPV vaccination must be recommended not only for young girls, but also for boys, MSM and HIV-infected people through age 26 that have not been previously vaccinated or have not completed the vaccine schedule[43-45].

Recommendations for vaccination in people living with HIV/AIDS (PLWHA) do not differ from those for the general population: according to guidelines, the vaccines should be administered before sexual debut because they cannot confer protection against the development of neoplasms after the infection[46,37].

In Italy, the vaccination against high-risk HPV (hrHPV) subtypes is recommended routinely for children of both sexes starting at age 11 or 12 years[2,46].

Three anti-HPV vaccines are available: the bi-valent Cervarix™ (GlaxoSmithKline), the quadrivalent Gardasil® (Merck & Co., Inc., Kenilworth, NJ, USA) and the 9vHPV Gardasil-9®(Merck & Co., Inc., Kenilworth, NJ, USA)[2,38,39].

The bivalent HPV vaccine targets subtypes 16 and 18, which cause 70% of cancers; the quadrivalent vaccine (4vHPV) extends this coverage by additionally targeting subtypes 6 and 11, which cause most of genital warts; the 9vHPV vaccine is against HPV-serotypes 6, 11, 16, 18, 31, 33, 45, 52 and 58[2,46].

The vaccine consists of virus-like particles (VLPs) generated by the expression of the major capsid protein L1 from HPV serotypes with an aluminum adjuvant[46]. Since the VLPs contain no viral DNA, they cannot infect cells, reproduce or cause disease[1-6].

In terms of immunogenicity, the bivalent anti-HPV vaccine induces higher immune response when compared with the quadrivalent vaccine, reflecting the different adjuvant system used in each vaccine type[35-37]. All three vaccines require a 3 shot series over a 6-month for complete protection. However, difficulties in completing all three vaccines have been observed in the general population. Low income, minority race, and low level of education are all risk factors for failure to receive all three injections[45,47].

The Role of HIV in HPV Infection

People Living with HIV (PLWHA) have high rates of persistent HPV infection if compared with HIV-uninfected people and they are more likely to have HPV-related anogenital disease despite widespread use of antiretroviral treatment and the immunologic reconstitution associated with[1-29].

Earlier studies reported anal HPV prevalence rates of 76% in HIV-infected women and 46% in HIV-uninfected women and cervical prevalence rates of 48% to 73% compared to 28% in HIV-uninfected women[2,48].

Despite the immunologic reconstitution associated with the use of combination antiretroviral therapy (cART), the prevalence of anogenital HPV infections and diseases remains high. In a recent cohort of HIV-infected women receiving effective antiretroviral therapy (SUN study), anal and cervical HPV infections were highly prevalent, with anal HPV prevalence rates of 90% and cervical rates of 83%[48].

The increased risk of HPV-related cancer is influenced by the high susceptibility, lower ability to clear infection and reactivation of infection due to HIV induced- immunosuppression[1-4,48].

Moreover, HIV infection is often associated with greater drugs use, alcohol use and smoking which may play a role in the persistence of HPV infection[3-10,47].

Vaccination against HPV in PLWHA

Several data from HIV negative population have confirmed vaccine safety and efficacy[40-42].

Among HIV-negative women without prior exposure to HPV-16 or -18, the quadrivalent HPV vaccine demonstrated 98% efficacy in preventing CIN and 100% of genital warts, and similar results were also reported with 9-valent HPV vaccine[40].

PATRICIA trial[49] showed a 93% vaccine efficacy for Cervarix®; Gardasil® was similarly evaluated in two very large multi-center trials (FUTURE I and FUTURE II), which showed a 98% vaccine efficacy rate for HPV-related cervical lesions and a 100% rate for other anogenital lesions which included HPV-related vulvar and vaginal disease[50].

In a trial led by Giuliano et al[51], 4065 healthy boys and men aged 16 to 26 were tested and the efficacy of the vaccine in preventing external genital lesions was 90.4%.

Palefsky et al[52] evaluated the efficacy of vaccination against AIN (Anal Intraepithelial Neoplasia) among 602 MSM (Men Who Have Sex With Men) and it was 77.5%.

The use of the vaccine among 700 black women prevented 100% of cervical and vulvar disease[45].

There is limited data available on the efficacy of the vaccine among HIV-infected people[48].

Kojic et al[52] examined safety and serostatus of HPV types 6, 11, 16, and 18 in HIV-infected women showing that the quadrivalent HPV vaccine is safe and immunogenic among seronegative women aged 13-45 years, with a percentage of seroconversion >75% for all HPV types included in the vaccine. In HPV-seropositive women, vaccination induced a significant increase in antibody levels.

It is important ensuring an appropriate antibody response to HPV vaccine to establish long term immunity[2,53].

Poor responses to standard vaccination series have been documented in HIV-infected patients: both HIV viremia and CD4+ cell counts probably can influence the response, in fact seroconversion proportions were higher among women with baseline CD4 cell counts >200 cells/μL[2,54-60].

Adverse effects

Local symptoms, which include pain, redness and swelling at the injection site, are the most frequent AEs reported in literature[61,62].

Among vaccine-related systemic effects, headache and fatigue are the most common. Other general symptoms included headache, syncope, fatigue, gastrointestinal symptoms, arthralgia, rash, myalgia, urticarial and fever[61].

A trial conducted by Levin et al[63] described the type and the frequency of AEs reported after the first dose of quadrivalent anti-HPV vaccine in HIV-infected children; AEs were infrequent and their occurrence was similar in vaccine and placebo groups, except for injection site reactions, more frequently occurring in the vaccine group. Injection-site reactions were mainly slight effects[60].

Other studies[65-70] report that vaccines are generally safe and well-tolerated for PLWHA.

Further studies and trials to examine the long-term efficacy of HPV vaccination in HIV-infected individuals are needed.

CONCLUSIONS

HPV infection is one of the most common infections worldwide and its clinical importance is associated with the well-known link with cancer. The natural history of HIV infection has been profoundly modified by the introduction of HAART, but HIV-infected people still have higher risk of developing HPV-related diseases. In comparison to their HIV-negative counterparts, PLWH have a higher prevalence of HPV infection with increased HPV persistence, higher risk of HPV-related tumors, and faster disease progression. This is the reason why vaccination and screening programs are essential weapons, especially among PLWHA. Vaccination against HPV is safe and effective: promoting it is the best tool to decrease the disease burden of HPV.

Conflict of interest:
The Authors declare that they have no conflict of interests.

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