CSIRO PUBLISHING
Sexual Health, 2014, **11**, 511–523
http://dx.doi.org/10.1071/SH14015

Review

Vaccination against oncogenic human papillomavirus infection in HIV-infected populations: review of current status and future perspectives

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Abstract. ***Background*:** Men and women with HIV infection are at increased risk of developing cancers associated with human papillomavirus (HPV). The two licensed prophylactic HPV vaccines protect against *de novo* infection with HPV-16 and HPV-18, which cause the majority of HPV-associated cancers. Currently, no vaccine efficacy data are available for persons with HIV infection. Nevertheless, some countries have implemented specific HPV vaccination recommendations for HIV-positive populations. To specifically recommend prophylactic HPV vaccination in people with HIV, the vaccines must be safe and immunogenic in immunosuppressed people at a high risk of HPV infection. This review aims to summarise the current knowledge from published HPV vaccine trials in HIV-infected populations, to compile scheduled and ongoing HPV vaccine trials with HIV-positive study populations and to extrapolate the relevant knowledge about HPV vaccine efficacy in HIV-negative populations to an HIV context. ***Methods*:** The databases PubMed, Scopus and ClinicalTrials.gov were searched for peer-reviewed articles and scheduled or ongoing clinical HPV vaccine trials enrolling HIV-positive persons. ***Results*:** Current data indicate that prophylactic HPV vaccines are safe and immunogenic in different HIV-positive populations (children, female adolescents, adults). Increased immunogenicity has been reported in persons on antiretroviral therapy compared with antiretroviral-naïve persons, whereas no clear association has been found between $CD4^+$ cell count at immunisation and vaccine response. Several scheduled and ongoing HPV vaccine trials aim to determine vaccine efficacy against disease endpoints in HIV-infected study populations. ***Conclusion*:** Prophylactic HPV vaccination appears safe, immunogenic and, by extrapolation, likely to reduce HPV-associated cancer development among persons with HIV infection.

Additional keywords: anal cancer, cervical cancer, genital warts, immunisation.

Received 14 January 2014, accepted 5 August 2014, published online 9 September 2014

Introduction

Prior to the widespread introduction of population-based vaccination programs, infection with human papillomavirus (HPV) was the most common sexually transmissible infection worldwide and persistent HPV infection caused more than 600 000 cancers worldwide per year, including cervical cancer, anal cancer, penile cancer, vulval and vaginal cancer and oropharyngeal cancers.[1] HIV-infected individuals are at high risk of HPV infection and all types of HPV-associated cancers occur at higher rates in HIV-positive people compared with the general population.[2] HIV-infected women are at high risk of persistent HPV infections that may transform into malignant lesions and, ultimately, invasive cervical cancer. The cancer risk is closely related to women's immune status and, since 1993, invasive cervical cancer has been classified as an AIDS-defining disease.[3] Studies linking HIV/AIDS and cancer registries have reported a 2- to 22-fold increased risk of cervical cancer among HIV-positive women compared with the general female population in the same geographical area.[4] Among people with HIV infection, the highest rates of anal cancer are found among men who have sex with men (MSM). An 80-fold increased risk of anal cancer development has been reported among HIV-infected MSM compared with the background male population.[5]

HPV genotypes 16 (HPV-16) and 18 (HPV-18) cause most HPV-associated cancers.[6–11] Currently, there are two licensed prophylactic HPV vaccines, a bivalent vaccine[12] (Cervarix; GlaxoSmithKline, Middlesex, UK) and a quadrivalent vaccine[13] (Gardasil; Merck, Whitehouse Station, NJ, USA). Both vaccines offer protection against infection with HPV-16 and -18 and Gardasil additionally protects against the two most common causative agents of genital warts, HPV-6 and -11. HPV vaccine efficacy has been demonstrated for both vaccines against cervical disease in large trials conducted in female adolescents and young adults.[14–18] Furthermore, the bivalent vaccine has demonstrated efficacy against persistent oncogenic anal HPV infection in young women.[19] In addition, protection against anal and anogenital disease has been established in a males for the quadrivalent vaccine.[20,21] HPV vaccine efficacy has not been evaluated in HIV-positive study populations.

However, Australian and US guidelines recommend that HPV vaccination be considered for HIV-positive individuals.[22,23]

Compared with healthy individuals, HIV-infected individuals often have reduced immune responses to various immunisations (e.g. influenza vaccination,[24,25] hepatitis B virus vaccination[26] and pneumococcal vaccination[27]). Nevertheless, vaccination remains a common clinical tool to reduce the risk of secondary infections in people with HIV. Vaccine recommendations for people with HIV-infection have generally been based on data from safety and immunogenicity trials, combined with clinical assessment of need (e.g. high rates of hepatitis B infection or high morbidity associated with influenza in people with HIV). Accordingly, clinical recommendations about HPV vaccination in people with HIV might be established without direct efficacy data. For prophylactic HPV vaccination to be recommended in people with HIV, the vaccines have to be safe and immunogenic despite chronic immunosuppression. A high degree of previous and prevalent HPV-16 and -18-infections in this particular population might decrease the expected vaccine efficacy.[28,29]

We conducted a systematic search of the present literature to review the available data from published trials of the safety and immunogenicity of HPV vaccines in HIV-positive study populations. In addition, we aimed to describe the ongoing and scheduled HPV vaccine trials in HIV-positive study populations, with enhanced attention given to trials evaluating the study vaccine against disease endpoints. Finally, we discuss the implications of these findings in the context of the current knowledge on HPV vaccine efficacy from HIV-uninfected study populations.

Methods

The review was conducted in concordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[30] Studies were included if they reported data from trials that investigated either one or both of the licensed HPV vaccines in HIV-positive persons. Scheduled and ongoing trials were included if they were designed to test safety, immunogenicity or HPV (bivalent or quadrivalent) vaccine efficacy in HIV-positive persons.

Search strategy

A search of two electronic databases was conducted in November 2013 using standard research procedures. The databases were PubMed and Scopus. Search terms were entered with combined sets of terms relating to HPV vaccine or Gardasil or Cervarix, and HIV. In PubMed, article types were restricted to 'clinical trials'; in Scopus, document types were restricted to articles. The search results from the two databases were collated and duplicate publications were removed (Fig. 1).

Inclusion and exclusion criteria

Two authors reviewed titles and abstracts for the following inclusion criteria:

- a clinical trial on safety and immunogenicity of either one or both of the HPV vaccines (bivalent or quadrivalent);
- an HIV-positive study population; and
- published in English.

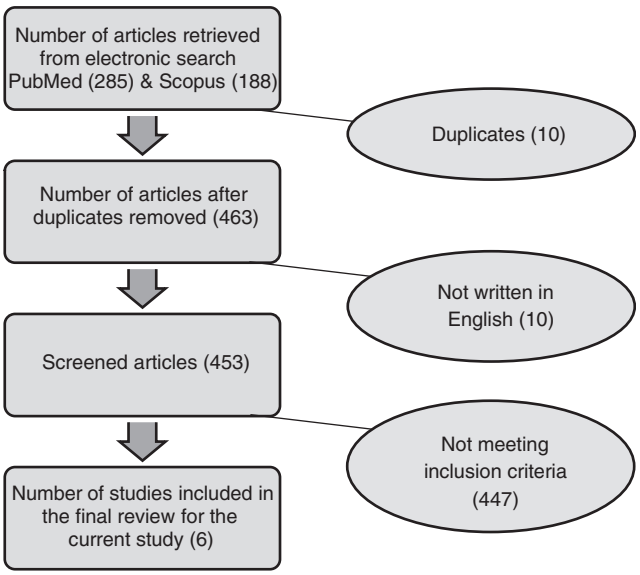

Fig. 1. Process of searching for and selecting papers for this review.

Reference lists were not searched. We did not have any exclusion criteria.

Furthermore, published and unpublished studies were investigated through ClinicalTrials.gov (accessed 13 August 2014), which was searched for HPV vaccine immunogenicity or efficacy trials enrolling HIV-positive study subjects up until 18 November 2013. The combination of search terms used was: (1) Gardasil or Cervarix, and (2) HIV. In trials listed as 'completed', the ClinicalTrials.gov identifier was entered into the electronic databases PubMed and Scopus to retrieve all published trials.

Results

Published HPV vaccination trials enrolling HIV-infected persons

In total, 473 records were identified by searching databases for clinical trials on completed HPV vaccination trials enrolling HIV-infected persons. After removing duplicate publications, 463 remained. Of these, 453 records were written in English. Through screening of abstracts, six independent articles were identified that reported results from relevant clinical trials in HIV-positive study populations and used either one or both of the HPV vaccines as study intervention. Table 1 summarises the study characteristics, immunologic outcome measures and main results from the six identified studies.

Studies in HIV-infected children

Levin *et al.*[31] conducted a double-blinded placebo-controlled safety and immunogenicity trial that enrolled and randomised 126 HIV-infected boys and girls aged 7–12 years to quadrivalent HPV vaccination or placebo injections. Vaccines were administered at 0, 8 and 24 weeks, and the vaccine schedule was well tolerated. Vaccination had no adverse effects on $CD4^+$

Table 1. Summary of published immunogenicity results from completed human papillomavirus (HPV) vaccine trials in HIV-infected populations

ART, Antiretroviral therapy; CLIA, competitive Luminex-based immunoassay; LIA, Luminex-based immunoassay; CTLs, cytotoxic T lymphocytes; PBNA; pseudovirion-based neutralisation assay HGAIN, high-grade anal intraepithelial neoplasia

Study	Study population	Study vaccine	Study design	Vaccination schedule	Follow-up	Serological assays	Serological endpoints	Main results
Toft *et al.*[36]	HIV-infected women ($n=30$) and men ($n=61$) aged 22–72 years	Bivalent and quadrivalent	Double-blinded, randomised head-to-head trial	0, 6 and 24 weeks	Up to 12 months	PBNA	Neutralising antibody geometric mean antHPV-16 and -18 titres	Anti-HPV-16 antibody titres were comparable between vaccine groups Anti-HPV-18 titres were 7.6-fold higher in the Cervarix versus Gardasil group[A] Anti-HPV-16 and -18 titres were higher among women than in men
Denny *et al.*[34]	HIV-infected ($n=120$) and HIV-negative ($n=30$) women aged 18–25 years	Bivalent	Double-blinded, placebo-controlled trial	0, 4 and 24 weeks	Up to 12 months	ELISA	Geometric mean anti-HPV-16 and -18 antibody titres	7- and 12-month antibody titres ~50% and 70% lower in HIV-infected women compared with HIV-uninfected women, respectively. Vaccination induced sustained anti-HPV-16 and -18 $CD4^+$ T cell responses
Kahn *et al.*[33]	ART-treated[B] HIV-infected ($n=69$) and nor treated with ART[C] ($n=30$) HIV-infected women aged 16–23 years	Quadrivalent	Open-label trial	0, 8 and 24 weeks	28 weeks	CLIA	Geometric mean anti-HPV-6, -11, -16 and -18 antibody titres	Nonsignificant trends towards lower antibody titres in the no-ART group than in the ART group were reported. All participants on ART seroconverted to HPV-6, -11, -16 and -18, and antibody titres were comparable to an HIV-negative comparison group[D] Seroconversion ranged from 92.3% for HPV-18 to 100% for HPV-6 among no-ART participants, and anti-HPV-18 antibody titres were significantly lower than in the HIV-negative comparison group for no-ART participants
Weinberg *et al.*[32]	HIV-infected boys and girls aged 7–12 years receiving three ($n=31$) or four ($n=99$) vaccine doses	Quadrivalent	Nonblinded, randomised trial	Four-dose group: 0, 8, 24 and 96 weeks	Four-dose group: 100 weeks	CLIA, LIA, ELISA	HPV-6, -11, -16 and -18 seroconversion rates and antibody titres	All participants in the four-dose group seroconverted to HPV-6, -11, -16 and -18, and seroconversion ranged from 97% for HPV-18 to 100% for the other vaccine types in the three-dose group[E]

(*continued next page*)

Table 1. (*continued*)

Study	Study population	Study vaccine	Study design	Vaccination schedule	Follow-up	Serological assays	Serological endpoints	Main results
				Deferred three-dose group: placebo at 0, 8 and 24 weeks; vaccines at 96, 104 and 120 weeks	Deferred three-dose group: 124 weeks			Antibody titres were significantly higher in the four-dose group compared for the three-dose group Cross-reactive antibodies against HPV-31 were induced in the four-dose group but not the three-dose group 69% and 39% of children in the four-dose group developed mucosal specific HPV-16- and -18 IgG antibodies, respectively 60% and 52% of children developed CTLs for HPV-16 and -31, respectively, four weeks after the third vaccine dose. A fourth vaccine dose did not significantly increase these numbers
Levin *et al.*[31]	HIV-infected boys and girls aged 7–12 years ($n = 126$)	Quadrivalent	Double-blinded, placebo-controlled trial	0, 8 and 24 weeks	28 weeks	CLIA	HPV-6, -11, -16 and -18 seroconversion rates and antibody titres	Seroconversion rates ranged from 97% for HPV-18 to 100% for the other vaccine-types Antibody titres for HPV-6 and -18 were 30–50% lower compared with an HIV-negative age-matched historical comparator group
Wilkin *et al.*[35]	HIV-infected men aged 22–61 years without HGAIN ($n = 109$)	Quadrivalent	Single-arm, open-label trial	0, 8 and 24 weeks	Up to 18 months[F]	CLIA	HPV-6 -11, -16 and -18 seroconversion rates and antibody titres	Seroconversion rates ranged from 95% for HPV-18 to 100% for HPV-16 Antibody titres were lower compared with an historical comparator group[G]

[A]Among participants who were HPV DNA-negative and seronegative for HPV-18 at study entry.
[B]Participants had received ART for at least 6 months at the time of study entry, with two HIV RNA plasma loads <400 copies mL^{-1}.
[C]Participants were either naïve to ART or had not received ART for at least 6 months before study entry.
[D]Historical comparison group of 267 HIV-negative women.
[F]Both groups had serological follow-up visits 4 weeks after administration of the last vaccine dose.
[F]A 28-week follow up period was reported in the research paper.
[G]The authors specifically indicated that anti-HPV-16 titres were 50–60% lower compared with historical comparator groups consisting of healthy men and women. The comparator groups were younger than the study participants and, interestingly, the reported antibody concentrations were comparable to those obtained in HIV-uninfected men who have sex with men aged 18–26 years.

cell counts or HIV RNA levels. The vaccine was immunogenic, with seroconversion rates ranging from 97% to 100% for the HPV types included in the vaccine. Antibody geometric mean titres for HPV-6 and -18 were 30–50% lower compared with an HIV-negative age-matched historical comparator group.

Weinberg *et al*.[32] later published additional immunogenicity data from the trial described above, comparing the immunogenicity of a four-vaccine schedule to the standard three vaccines regimen. Vaccines were administered at 0, 8, 24 and 96 weeks in a four-vaccine group whereas study participants in a deferred three-dose arm received a placebo at 0, 8 and 24 weeks, and vaccinations at 96, 100 and 124 weeks. The immune responses were compared at 4 weeks after administration of the final vaccine. All participants (100%) in the four-dose group seroconverted to all four HPV vaccine types, and seroconversion ranged from 97% to 100% in the three-dose group. In the four-vaccine group, anti-HPV-18 antibody concentrations were comparable to those achieved after a standard three-dose regimen in healthy age-matched historical controls. In the four-vaccine group, mucosal anti-HPV-16 and -18 antibodies were detected in 69% and 39%, respectively (no results from the three-vaccine group were presented). Cross-reactive antibodies to HPV-31 were increased from baseline values in the four-vaccine group but not in the standard three-vaccine group.

In conclusion, two studies from the same cohort have documented acceptable safety and solid immunogenicity for the quadrivalent HPV vaccine in HIV-infected children. High seroconversion rates were found using the standard three-vaccine regimen but antibody titres were increased by giving a fourth vaccine dose after 96 weeks. No immunogenicity and safety data were available for the bivalent HPV vaccine in HIV-infected children.

Studies in young HIV-infected women

Kahn *et al*.[33] recently published immunogenicity and safety results from an open-label trial that enrolled and immunised 99 HIV-infected women aged 16–23 years using the quadrivalent vaccine in a standard three-dose regimen. Sixty-nine women had received antiretroviral therapy (ART) for at least 6 months at the time of study entry and 30 were either naïve to ART or had not received ART during the 6 months that preceded study entry. Results were assessed according to ART status and an historical HPV vaccination group of 267 HIV-negative women was used for comparison. Only one Grade 3 adverse event (fatigue) was reported and the vaccine was generally well tolerated. Antibody responses were measured 4 weeks after the final vaccine dose. Seroconversion rates for vaccine HPV types ranged from 92% to 100% among participants not treated with ART, whereas all ART-treated participants seroconverted for all four vaccine serotypes. Neither seroconversion rates nor geometric mean titres differed significantly between the non-ART and the ART groups. Anti-HPV-18 antibody titres were significantly lower for non-ART participants compared with the HIV-negative control group, whereas antibody titres did not differ between ART-treated participants and the HIV-negative control group.

Denny *et al*.[34] recently published data from a partially blinded, placebo-controlled trial investigating the safety and immunogenicity of the bivalent HPV vaccine in young women. HIV-positive women ($n = 120$) aged 18–25 years were assigned to receive the bivalent vaccine or a placebo in a standard regimen with vaccinations at 0, 1 and 6 months. Thirty HIV-negative women were enrolled as an open-label control group and received bivalent vaccinations at 0, 1 and 6 months. CD4+ cell counts and HIV RNA levels were unaffected by vaccination. Serologic responses were evaluated for up to 12 months. Baseline seropositivity proportions for HPV-16 and -18 were high among HIV-positive women assigned to the bivalent vaccination, 85.4% and 64.3% respectively, compared with 63.5% and 50% among HIV-negative controls. HPV DNA status was not assessed in the trial. All study participants assigned to the bivalent vaccination arm remained seropositive for both serotypes at 12 months. Antibody titres at 7 and12 months for both serotypes were ~50% and 70% lower in HIV-infected compared with HIV-uninfected women, respectively. Baseline CD4+ T-cell count and HIV viral load were not associated with vaccine-induced antibody titres.

In conclusion, both the quadrivalent and the bivalent HPV vaccine appear to be safe and very immunogenic in young HIV-infected women. ART-treated, HIV-infected young women and age-matched HIV-negative women had comparable antibody responses to the quadrivalent HPV vaccine. In contrast, serologic antibody responses to the bivalent HPV vaccine were lower in young HIV-infected women compared with uninfected women. Currently, studies comparing the safety and immunogenicity of the two HPV vaccines in young HIV-infected women have not been conducted.

Studies in HIV-infected adults

Wilkin *et al*.[35] published data from a single-arm open-label trial evaluating the safety and immunogenicity of the quadrivalent vaccine in HIV-infected men ($n = 109$) aged 22–61 years. Vaccination did not alter CD4+ cell counts or HIV RNA levels. No serious adverse events attributable to vaccination were observed. Seroconversion rates ranged from 95% to 100% for vaccine HPV types. Antibody concentrations were comparable to those previously reported in HIV-uninfected MSM aged 18–26 years but were lower compared with historical comparator groups consisting of young healthy women and heterosexual men. A multivariate linear regression analysis showed that current ART treatment at baseline was the only baseline characteristic associated with increased serologic responses to vaccination.

One article reported the results from a double-blind, randomised head-to-head trial that compared the safety and immunogenicity of the bivalent and quadrivalent vaccines among HIV-infected women and men ($n = 91$) aged 22–72 years.[36] None of the vaccines negatively affected $CD4^+$ cell counts or HIV RNA levels. Injection site reactions were more common in the bivalent compared with the quadrivalent vaccine group, but both vaccines were generally well tolerated. Neutralising anti-HPV-16 and -18 antibody titres were evaluated up to 12 months using a highly sensitive pseudovirion-based neutralisation assay. Anti-HPV-16 antibody

titres were comparable between vaccine groups and anti-HPV-18 titres were higher in the Cervarix group compared with the Gardasil group at 7 and 12 months. Anti-HPV-16 and -18 titres were higher among women compared with men. Antibody titres were not compared with HIV-negative controls.

In conclusion, acceptable safety data and convincing immunogenicity data are available for both HPV vaccines in adult HIV-positive study populations. Very high seroconversion rates were reported in HIV-positive men vaccinated with the quadrivalent HPV vaccine. Higher ant-HPV-18 antibody titres were found in HIV-positive men and women following vaccination with the bivalent vaccine compared with the quadrivalent HPV vaccine.

Ongoing, scheduled or complete, unpublished HPV vaccination trials in HIV-positive study populations

Twelve relevant ongoing or scheduled trials were identified from ClinicalTrials.gov. The 12 trial protocols are summarised in Table 2. Four trial protocols were designed to evaluate the efficacy of the quadrivalent vaccine against disease endpoints and will be reviewed below.

NCT00941889 is a scheduled trial sponsored by Washington University School of Medicine. Thirty HIV-infected subjects with anal warts that require surgical treatment will be randomised 1 : 1 to receive either a three-vaccine quadrivalent vaccination series or a placebo. The study is designed to evaluate if quadrivalent HPV vaccination has an effect on the persistence and recurrence of surgically treated anal condylomata during an 18-month follow-up period. The study was last updated on ClinicalTrials.gov on 14 August 2009 and had an estimated study completion date in 2011. We have not been able to find any evidence that the study was actually completed.

NCT01928225 is a scheduled placebo-controlled, randomised, double-blinded trial sponsored by the University of Witwatersrand, South Africa. The trial is not yet recruiting study participants, but 180 HIV-infected women with high-grade squamous intraepithelial cervical lesions on biopsy are planned to be enrolled in a trial designed to evaluate if pretreatment with the quadrivalent HPV vaccine will result in a reduced occurrence of cervical cancer precursors during a 52-week follow-up period after surgical treatment of high-grade squamous intraepithelial lesions. The estimated study completion date is August 2016.

NCT01461096 is an ongoing placebo-controlled, randomised, double-blinded trial sponsored by the National Institute of Allergy and Infectious Diseases. Five hundred and sixty-four HIV-infected men and women over 27 years of age are planned to be enrolled in this trial designed to evaluate if the quadrivalent HPV vaccine can prevent anal HPV infection in HIV-infected men and women. A follow-up period of 3–4 years is scheduled. The main outcome measures are time to first incident; persistent anal HPV-6, -11, -16 and -18 infection; and biopsy-proven high-grade anal intraepithelial neoplasia occurrences or reoccurrences after 52 weeks. The estimated study completion date is August 2016.

NCT01209325 is an ongoing open-label single-arm trial sponsored by the AIDS Malignancy Clinical Trials Consortium. One hundred and fifty HIV-infected MSM aged 13–26 years are planned to be enrolled in this trial designed to evaluate the efficacy of the quadrivalent HPV vaccine against incident anal disease caused by vaccine HPV types. A follow-up period of 2 years is scheduled and the main outcome measures are incident anal intraepithelial neoplasia, anal or perianal condyloma, high-grade anal intraepithelial neoplasia associated with vaccine HPV types and persistent anogenital infection with vaccine HPV types. The estimated study completion date is December 2014.

In summary, four scheduled or ongoing trials aim to investigate vaccine efficacy of the quadrivalent HPV vaccine in different HIV-positive study populations. Two trials focus on anal disease in young HIV-infected MSM, and adult men and women, respectively; two trials investigate the effects of combining HPV vaccination and surgical interventions in HIV-infected persons with established HPV-associated lesions. We found no scheduled or ongoing trials investigating the efficacy of the bivalent HPV vaccine in HIV-positive populations.

Discussion

In the present article, we aimed to review and summarise the current knowledge of HPV vaccination in HIV-positive patients. Six original immunogenicity and safety papers were identified and two of these used the same study cohort. No restrictions of trial outcomes or study population characteristics were applied. Based upon the few available studies, both licensed HPV vaccines appear safe and immunogenic in different HIV-positive populations (children, female adolescents, adults), with very high seroconversion rates but lower antibody responses than HIV-negative populations. ART may increase immune responses to vaccination, but data are quite sparse. Some studies reported lower antibody titres in HIV-positive patients compared with HIV-uninfected study populations. This holds in particular for HPV-18. The clinical significance of this observation remains elusive, as no studies have been able to establish a correlation between serologic antibody titre levels and clinical protection against disease. No long-term follow-up data have been published from HIV-positive study cohorts and thus the duration of potentially protective vaccine-elicited immune responses are currently unknown. Results obtained from efficacy trials in healthy study populations with more than 4 years of follow-up[14,37] have not revealed any time-dependent decrease in vaccine-induced protection. As demonstrated by the studies identified in this review, HPV vaccination in people with HIV will result in a robust immunological response, meaning that the vaccinated person is likely to be better protected against future infections.

Clinical implications

The scheduled studies of HPV vaccine efficacy in HIV-positive study populations reviewed in this article may provide useful evidence. However, these trials might be too small to provide definitive answers about vaccine efficacy. Currently, HPV vaccination recommendations in persons with HIV must be based on the best available data as outlined in this review. The expected vaccine efficacy in most HIV-infected populations will be affected by previous HPV-16 and -18 exposure. Table 3 summarizes selected HPV vaccine efficacy trials

Table 2. Scheduled, undergoing and completed unpublished human papillomavirus (HPV) vaccine trials in HIV-infected individuals

Details of the studies were sourced from (ClinicalTrials.gov on 18 November 2013). NIAID, National Institute of Allergy and Infectious Diseases; HSIL, high-grade squamous intraepithelial lesion; LEEP, loop electrosurgical excision procedure; HGAIN, high-grade anal intraepithelial neoplasia; MSM, men who have sex with men; AIN, anal intraepithelial neoplasia; IMPAACT, International Maternal Pediatric Adolescent AIDS Clinical Trials Group

Study population	Clinicaltrials.gov identifier	Sponsor	Location	Study vaccine	Status	Estimated study completion or completion date	Study	Main immunological and clinical outcome measures
Female and male HIV-infected ($n = 50$) and uninfected ($n = 50$) subjects aged 13–27 years	NCT01512784	University of Milan	Italy	Quadrivalent	Recruiting	July 2013	Open-label controlled trial designed to evaluate and compare the safety and immunogenicity of the quadrivalent HPV vaccine in HIV-infected vs healthy young adults	Serologic responses
150 male HIV-infected subjects aged >18 years	NCT00666107	Southern California Institute for Research and Education	USA	Quadrivalent	Unknown[A]	June 2012	Open-label single-arm trial designed to evaluate the immunogenicity and safety of the quadrivalent HPV vaccine in HIV-infected men	Serologic responses, incident anal HPV infections
180 HIV-infected boys and girls aged 9–14 years	NCT01446718	Nelly R. Mugo	Kenya	Quadrivalent	Not yet recruiting	December 2014	Open-label single-arm trial designed to evaluate the immunogenicity and safety of the quadrivalent HPV vaccine in HIV-infected men	Serologic responses
30 HIV-infected subjects aged >18 years with anal warts that require surgical excision or ablation	NCT00941889	Washington University School of Medicine	USA	Quadrivalent	Enrolling participants by invitation only	July 2011[B]	Randomised, placebo-controlled trial designed to evaluate if the quadrivalent HPV vaccination has an effect on the persistence and recurrence of surgically treated anal condylomata during an 18-month follow up period	Persistence and recurrence of anal warts
600 HIV-infected and uninfected females aged 15–25 years	NCT01031069	GlaxoSmithKline	Brazil, India, Thailand	Bivalent, quadrivalent	Recruiting	December 2016	Phase IV observer-blind head-to-head trial designed to directly compare the safety and immunogenicity of the bivalent and the quadrivalent vaccine among HIV-infected and healthy young women	Serologic responses, B- and T-cell responses
150 HIV-infected women aged >18 years	NCT00667563	AIDS Malignancy Clinical Trials Consortium	India	Quadrivalent	Completed	November 2012	Open-label single-arm trial designed to evaluate the immunogenicity and safety of the quadrivalent HPV vaccine in HIV-infected women	Serologic responses
105 HIV-infected and HIV-negative adolescents and young adults aged 12–26 years	NCT00798265	National Cancer Institute	USA	Quadrivalent	Completed	February 2013	Open label single-arm trial designed to evaluate and compare the safety and immunogenicity of the quadrivalent HPV vaccine in HIV-infected adolescents vs HIV-negative persons of the same age	Serologic responses

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Table 2. (*continued*)

Study population	Clinicaltrials.gov identifier	Sponsor	Location	Study vaccine	Status	Estimated study completion or completion date	Study	Main immunological and clinical outcome measures
319 HIV-infected women aged 13–45 years	NCT00604175	NIAID	USA, Brazil, Puerto Rico, South Africa	Quadrivalent	Completed	November 2012	Open-label trial designed to evaluate the immunogenicity and safety of the quadrivalent HPV vaccine in HIV-infected young and adult women; study participants were divided into three arms according to their CD4+ cell count	Serologic responses
180 HIV-infected women aged >18 years with cervical HSIL on biopsy.	NCT01928225	University of Witwatersrand, South Africa	South Africa	Quadrivalent	Not yet recruiting	August 2016	Placebo-controlled, randomised, double-blinded trial designed to evaluate if pretreatment with the quadrivalent HPV vaccine will result in a reduced occurrence of cervical cancer precursors during a 52-week follow-up period after LEEP of cervical HSIL	HSIL on cervical cytology or HSIL on cervical biopsy
564 HIV-infected men and women >27 years of age	NCT01461096	NIAID	USA, Brazil, Puerto Rico	Quadrivalent	Ongoing, not recruiting	August 2016	Placebo-controlled, randomised, double-blinded trial designed to evaluate if the quadrivalent HPV vaccine can prevent anal HPV infection in HIV-infected men and women; a follow-up period of 3–4 years from enrolment of the last participant in the study is scheduled	Time to first incident, persistent anal infection of HPV-6, -11, -16 or -18; biopsy-proven HGAIN occurrences or reoccurrences after 52 weeks
110 HIV-infected children aged 7–12 years	NCT01206556	International Maternal Paediatric Adolescent AIDS Clinical Trials Group	USA, Puerto Rico	Quadrivalent	Ongoing, not recruiting	July 2014	Cohort study to determine the duration of vaccine-specific antibody responses in HIV-1 infected children previously enrolled in IMPAACT P1047[C]	Serologic responses up to 5 years after completion of study
150 HIV-infected MSM 13–26 years of age	NCT01209325	AIDS Malignancy Clinical Trials Consortium	USA	Quadrivalent	Recruiting	December 2014	Open-label single-arm trial designed to evaluate the efficacy of the quadrivalent HPV vaccine against incident anal disease caused by vaccine HPV types	Incident AIN, anal or perianal condyloma, or HGAIN associated with vaccine HPV types; persistent anogenital infection with vaccine HPV types

[A]Recruitment status was last updated on November 2010. At that time, recruitment status was 'Active, not recruiting'.
[B]Last updated 14 August 2009.
[C]References by Levin *et al.*[31] and Weinberg *et al.*[32]

Table 3. Summary of selected human papillomavirus (HPV) vaccine efficacy trials conducted among HIV-negative, non-HPV-naïve populations

CIN1$^+$, cervical intraepithelial neoplasia Grade 1; CIN2+, cervical intraepithelial neoplasia Grade 2; CIN3$^+$, cervical intraepithelial neoplasia Grade 3; CI, confidence interval; AIS, adenocarcinoma *in situ*; EGL, external genital lesions; MSM, men who have sex with men; HGAIN, high-grade anal intraepithelial neoplasia; AIN, anal intraepithelial neoplasia

Reference	Design	Study vaccine	Study population	Study group characteristics	Endpoints[A]	Follow-up period	Vaccine efficacy	Main findings
The FUTURE II Study Group[40]	Subanalyses from randomised, placebo-controlled, double-blinded trial	Quadrivalent vaccine	Women aged 15–26	(A) HPV-16 or -18 seronegative, DNA-positive subjects (vaccine group: $n=423$, control group: $n=402$); (B) HPV-16 or -18 seropositive and DNA-positive subjects (vaccine group: $n=498$, control group: $n=524$)	Incident related CIN2$^+$, CIN3$^+$ or AIS related to HPV-16 and -18	Median: 36 months	(A) 10.6% reduction (95% CI: <0–46); (B) 1.2% reduction (95% CI: <0–35)	The quadrivalent vaccine does not reduce progression to cervical precancers in women with ongoing HPV-16 or -18 infections at the time of vaccination
Hildesheim *et al.*[38]	Subanalysis from randomised, controlled, double-blinded trial	Bivalent vaccine	Women aged 18–25	HPV-16 or -18 DNA-positive subjects (vaccine group: $n=1088$, control group: $n=1101$)	Clearance rates for cervical HPV-16 and -18 infections	12 months	−2.0% reduction (95% CI: −24.3 to 16.3)	The bivalent vaccine has no therapeutic effect on prevalent HPV-16 or -18 infections
Olsson *et al.*[51]	Subanalysis from three randomised, placebo-controlled, double-blinded trials	Quadrivalent vaccine	Women aged 16–26	HPV-6, -11, -16 or -18 seropositive and DNA-negative subjects (vaccine group: $n=1243$, control group: $n=1283$)	Incident CIN1+, -2+ or 3+, or AIS-associated with vaccine type for which women were DNA-negative at enrolment	Median: 40 months	100% reduction (95% CI: 28.7–100)	The quadrivalent vaccine has proven effect against development of cervical disease by HPV vaccine-types in young women with serological signs of previous infection
Szarewski *et al.*[39]	Subanalysis from randomised, placebo-controlled, double-blinded trial	Bivalent vaccine	Women aged 15–25	HPV-16 or -18 seropositive and DNA-negative subjects (vaccine group: $n=1719$, control group: $n=1770$)	Incident CIN1+ associated with vaccine type for which women were DNA-negative at enrolment	Median: 39.4 months	67.2% reduction (95% CI: 10.9–89.9)	The bivalent vaccine has proven effective against development of cervical disease by HPV vaccine-types in young women with serological signs of previous infection

(*continued next page*)

Table 3. (*continued*)

Reference	Design	Study vaccine	Study population	Study group characteristics	Endpoints[A]	Follow-up period	Vaccine efficacy	Main findings
Castellsague *et al.*[44]	Randomised, placebo-controlled, double-blinded trial	Quadrivalent vaccine	Women aged 24–45	Women with no history of cervical disease or genital warts in the 5 years before inclusion in study (vaccine group: $n=1908$, control group: $n=1911$)	Combined endpoint: ≥6 of months persistent infection, CIN1+–3+ or EGL caused by vaccine HPV types	48 months (median)	47.2% reduction (95% CI: 33.5–58.2)	The quadrivalent vaccine has proven effective against development of anogenital disease caused by vaccine HPV types in adult women
Joura *et al.*[43]	Retrospective analysis of data from FUTURE I and II Studies	Quadrivalent vaccine	Women aged 15–26 years	Women enrolled in FUTURE I or FUTURE II studies who received surgery for precancerous cervical lesions (vaccine group: $n=587$, control group: $n=763$)	Incidence of subsequent CIN1+ or worse irrespective of causal HPV type[B]	1.3 years (median)	48.3% (95% CI: 19.1–67.6)	The quadrivalent vaccine has proven effect on subsequent cervical disease among women who receive surgery for precancerous cervical lesions
Palefsky *et al.*[21]	Subanalysis from randomised, placebo-controlled, double-blinded trial	Quadrivalent vaccine	MSM aged 16–26 years	MSM included in the study had five or fewer lifetime sexual partners and no history of anogenital warts or anal intraepithelial neoplasia (vaccine group: $n=299$, control group: $n=299$)	AIN related to HPV-16 or -18; persistent anal infection with HPV-16 or -18[C]	2.9 years (median)	55.2%[D] (95% CI: 8.5–79.3) for AIN related to HPV-16 and -18, 57.5% (95% CI: 33.2–73.6) for persistent anal infection with HPV-16 or -18	The quadrivalent vaccine has proven efficacy in MSM on persistent anogenital infection with vaccine HPV types

[A]The most relevant endpoints for the overall purpose of the present review have been selected from each trial or analysis.
[B]The incidence rates for subsequent disease were calculated with case counting starting 60 days after cervical surgery or diagnosis of vulvar or vaginal disease.
[C]Persistent infection was defined as detection of the same HPV type in an anogenital swab or biopsy specimen collected at two or more consecutive visits 4 months or more apart.
[D]Results are presented for the intention-to-treat population, which consisted of participants who were or were not seropositive or DNA-positive for the vaccine HPV types at enrolment, and who received at least one dose of vaccine or a placebo, and returned for follow-up. Vaccine efficacy was higher in a defined per-protocol analysis that consisted of study participants who were seronegative and had HPV DNA-negative swab and biopsy specimens on Day 1 for relevant vaccine types, were negative for vaccine type DNA to Month 7 and did not have any protocol violations.

conducted among HIV-negative, non-HPV-naïve populations. In healthy young women, HPV-vaccination had no therapeutic effects on HPV-16 and -18 infections or associated lesions that were already established at the time of vaccination.[15,38] However, prevalent infection by one HPV type included in the vaccines did not reduce the vaccine-induced protection against other HPV vaccine types.[39,40]

In many countries, HPV vaccination programs primarily target preadolescents around 12 years of age (i.e. before most individuals' sexual debut). In HIV-infected preadolescent girls, prior exposure to HPV will not be a major issue, and the available safety and immunogenicity data unambiguously favours vaccination. Some countries, including Australia, already offer HPV vaccination to preadolescent boys in national vaccination programs, although substantial protection for boys against HPV-associated disease is expected through herd immunity induced by vaccinating girls. HIV-infected preadolescent boys have increased risk of developing disease if they do get a HPV infection and hence recommending HPV vaccination in this population seems justified. So far, safety and immunogenicity data are only available for the quadrivalent HPV vaccine in HIV-infected preadolescent children.[31,32] Including a fourth vaccine dose at 96 weeks increased the immune responses significantly and could be considered for HIV-positive preadolescents, particularly among those who are not on ART at the time of primary immunisation or have low $CD4^+$ cell counts.[32,33,41] However, a fourth dose may not be necessary in most cases. Recent data from immunocompetent young women suggest that two doses, or even one dose, of the bivalent HPV vaccine, could be as efficacious as three doses in protecting against persistent HPV-16 and -18 infections.[42]

Convincing immunogenicity data are available for young HIV-infected women aged 18–25 years for the bivalent vaccine[34] and HIV-infected women aged 16–23 years for the quadrivalent vaccine.[33] High seroconversion rates were observed for both vaccines. Many countries currently offer catch-up HPV vaccination programs to young women until the mid-20s despite the fact that prior exposure to HPV vaccines types or prevalent infection may become an important issue for women of that age. In healthy young women, prior exposure to the HPV types included in the vaccines did not abolish the beneficial effects of HPV vaccination.[37,38] This is an important finding that strongly favours HPV vaccination of young HIV-positive women. Interestingly, even in young HIV-infected women with prevalent HPV infection or cervical dysplasia, HPV vaccination may also be beneficial. In the FUTURE (Females United to Unilaterally Reduce Endo/Ectocervical Disease) studies, some of the young women ended up receiving surgery for precancerous cervical lesions. Among those women, follow-up revealed that persons in the vaccine arm had significantly lower risk of developing subsequent new HPV-related disease than persons in the control arm.[43] A scheduled trial (NCT01928225) will evaluate if pretreatment with the quadrivalent HPV vaccine could result in similar reductions of subsequent cervical disease after surgery in HIV-infected women aged >18 years. In the light of the available immunogenicity and efficacy data, HPV vaccination appears highly likely to be at least partly efficacious in young HIV-infected women.

Only one of the immunogenicity trials in HIV-infected study populations enrolled adult women and they were enrolled alongside adult men. Sex-specific seroconversion rates were not evaluated in the study but women immunised by either of the HPV vaccines had high antibody titres against HPV-16 and -18.[36] The efficacy of the quadrivalent HPV vaccine was previously investigated in healthy adult women in a randomised, placebo-controlled, double-blinded trial,[44] where 3819 women aged 24–45 years with no history of cervical disease or genital warts in the past 5 years before inclusion were enrolled in a study with a mean follow-up period of 4 years. Vaccine efficacy was 47.2% (95% confidence interval (CI): 33.5–58.2) against a combined endpoint: incidence of persistent infection ($\geq$6 months' duration), cervical intraepithelial neoplasia or external genital lesions related to HPV-6, -11, - 16 and -18. The potential efficacy of HPV vaccination in adult women scheduled to receive surgery for precancerous cervical lesions has not been investigated in women aged 24–45 years. Immunogenicity data from HIV-positive adult women are convincing, albeit very few. Vaccine efficacy in healthy adult women is lower than in healthy young women. There are still many unknowns surrounding the potential effects of vaccinating adult HIV-positive women against HPV.

Only the quadrivalent HPV vaccine is licensed for use in males and the indication differs by geographical region. In the US, the vaccine is licensed against anogenital warts, anal cancer and associated precancerous lesions,[45] whereas in Europe[46] and Australia,[47] the only approved indication for men is prevention of anogenital warts. Solid antibody responses following HPV vaccination were observed in the two trials that included male HIV-positive adults.[35,36] Vaccine efficacy has been established against persistent anal HPV-16 and -18 infection among 602 HIV-negative MSM aged 16–26 years.[21] During a follow-up with a median of 2.9 years, vaccine efficacy was 57.5% (95% CI: 33.2–73.6) against persistent anal infection with HPV-16 and -18 and 55.2% (95% CI: 8.5–79.3) against anal intraepithelial neoplasia related to HPV-16 and -18. However, only men with a maximum of five lifetime sexual partners were included in the trial and these efficacy results may not be generalisable to MSM populations. In a recent cohort study among 258 HIV-negative MSM aged 26–39 years, the median number of lifetime sexual partners was 50.[48] Thus, in the general MSM population, prevalent HPV infections are likely to be more frequent than in this efficacy trial, which may reduce the vaccine's efficacy in a real-life setting. In addition, HIV-positive MSM are more likely to have prevalent HPV-16 or -18 infections at the time of vaccination than HIV-negative MSM.[29] Nevertheless, even with lower vaccine efficacy in this high-risk population, it may still be appropriate to recommend HPV vaccination, since anal cancer rates are worryingly high among HIV-infected MSM.[5,49,50] The potential efficacy of vaccinating HIV-positive young and adult MSM will be evaluated against anal intraepithelial neoplasia in two separate trials (NCT01461096 and NCT01209325). The results from these trials will be pivotal in deciding if HPV vaccination also reduces the risk of precancerous anal lesions in this particular high-risk population.

Conclusions

Based on the current available knowledge reviewed in this paper, both HPV vaccines appear to be safe and highly immunogenic in people infected with HIV. In the light of their high risk of HPV-associated cancers, recommending HPV vaccination in HIV-positive individuals of both sexes up to the age of 26 years seems to be very reasonable. Furthermore, it may also be justified to recommend HPV vaccination in HIV-infected women aged 26–45 but the expected vaccine efficacy would be less than among younger women. Finally, HPV vaccination of HIV-infected women before surgical treatment of precancerous cervical lesions may be justified. The current data strongly suggest that HPV vaccination induces protective immunity against vaccine-specific HPV infection in persons with HIV.

Competing interests

MT has received a lecturer fee for an HIV Symposium organised by GlaxoSmithKline. LØ has received a lecturer fee from both GlaxoSmithKline and Sanofi-Pasteur Merck Sharp & Dohme (MSD).

Acknowledgements

The authors thank the Institute of Clinical Medicine at Aarhus University for funding the study.

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