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REVIEW

A systematic review of immunogenicity, clinical efficacy and safety of human papillomavirus vaccines in people living with the human immunodeficiency virus

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ABSTRACT

The human papillomavirus (HPV) is the most prevalent sexually transmitted infection worldwide. People living with the human immunodeficiency virus (HIV) are at high risk of HPV infection. This systematic review evaluates the immunogenicity, clinical efficacy, and safety of prophylactic HPV vaccines in people living with HIV. We registered the protocol for this review in the International Prospective Register of Systematic Reviews (CRD42018109898) and prepared the review following the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA). Five randomized trials with 1042 participants are included in this review. One trial with 120 participants compared the bivalent HPV vaccine to placebo, three trials with 830 participants compared the quadrivalent vaccine to placebo, and another trial with 92 participants compared the quadrivalent to the bivalent vaccine. There was low to moderate certainty evidence suggesting that seroconversion was higher among participants in the vaccine arms compared to the placebo arms for both vaccines. In one study with very low certainty evidence, participants who received the bivalent vaccine had higher anti-HPV-18 geometric mean titers (GMTs) compared to those who received the quadrivalent vaccine, despite little difference in anti-HPV-16 GMTs between the two vaccines. There were no differences in the incident and persistent HPV infections in both groups. None of the studies reported data on the incidence of precancerous lesions, or cancer. There were no reports of serious adverse events following vaccination in any of the trials. None of the included studies assessed the effects of HPV vaccines in adolescents living with HIV. Very limited evidence suggests lower immunogenicity of HPV vaccines in HIV positive compared to HIV-negative people. Finally, the long-term effect of the HPV vaccine in the incidence of cervical precancerous lesions and cervical cancer needs to be monitored. There is an urgent need for more high-quality randomized controlled trials that can address these gaps.

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human papillomavirus; human immunodeficiency virus; quadrivalent HPV vaccine; bivalent HPV vaccine

Introduction

Human papillomavirus (HPV) infection is the most common sexually transmitted infection worldwide.[1] It is estimated that 75% of sexually active people are infected with HPV during their lifetime. Although most HPV infections are transient and asymptomatic,[2] persistent infection with high-risk HPV types may result in diseases.[3] Persistent HPV infection causes more than 600 000 cancers worldwide every year, including cervical, anal, vulvar and vaginal, penile, and certain oropharyngeal cancers.[4] It is also associated with other skin and mucosal lesions such as warts and benign papillomas.[5] Most of HPV associated morbidity and mortality is due to cervical cancer,[6] the fourth most common cancer in women worldwide, with an estimated 569,847 cases and 311,365 deaths in 2018.[7] To date, more than 200 HPV types have been identified and classified into two groups: high-risk and low-risk types.[8] High-risk HPV types, including HPV-16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58 and −59 are associated with cancers in humans,[9] while low-risk HPV types, including HPV-6, 11, 40, 42, 43, 44, 54, 61 and −72 cause benign diseases such as genital warts.[10] Among these HPV types, majority of HPV-related clinical diseases are associated with HPV-16, 18, 6 and −11. HPV types 16 and 18 cause approximately 70% of cervical cancer, HPV-6 and HPV-11 are responsible for approximately 90% of genital warts in both men and women.[11]

People infected with human immunodeficiency virus (HIV) are at high risk of HPV infection and developing HPV-associated cancers.[12] HPV infections are also more persistent in people living with HIV, which increases their risk of developing HPV-related cancers.[13] This is because the state of immunosuppression induced by HIV infection impairs the immune systems' ability to clear HPV infection.[14] HPV-associated cancers occur at higher rates in HIV-positive people compared with the general population.[15]

Vaccination is one of the most effective public health interventions for combating infectious diseases.[16] It is estimated that vaccines save approximately 2–3 million lives worldwide each year.[17] Currently, there are three prophylactic HPV vaccines used across the world: Cervarix, a bivalent HPV vaccine that targets HPV-16 and −18; Gardasil, a quadrivalent HPV vaccine that targets HPV-6, 11, 16, and −18; and

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Table 1. PubMed search strategy.

Search	Query
#1	Search (papillomaviridae[mh] OR papilloma virus*[tiab] OR papillomavirus[tiab] OR HPV*[tiab] OR papillomavirus infections[mh] OR papilloma virus infect*[tiab])
#2	Search (HIV Infections[MeSH] OR HIV[MeSH] OR hiv[tiab] OR hiv-1*[tiab] OR hiv-2*[tiab] OR hiv1[tiab] OR hiv2[tiab] OR hiv infect*[tiab] OR human immunodeficiency virus[tiab] OR human immunedeficiency virus[tiab] OR human immuno-deficiency virus[tiab] OR human immune-deficiency virus[tiab] OR (human immun*[tiab] AND deficiency virus[tiab]) OR acquired immunodeficiency syndrome[tiab] OR acquired immunedeficiency syndrome[tiab] OR acquired immuno-deficiency syndrome[tiab] OR acquired immune-deficiency syndrome[tiab] OR (acquired immun*[tiab] AND deficiency syndrome[tiab]))
#3	Search (papillomavirus vaccines[mh] OR gardasil[tiab] OR cervarix[tiab] OR vaccine*[tiab] OR vaccinat*[tiab] OR immuniz*[tiab] OR immunis*[tiab])
#4	Search (randomized controlled trial [pt] OR controlled clinical trial [pt] OR randomized [tiab] OR placebo [tiab] OR drug therapy [sh] OR randomly [tiab] OR trial [tiab] OR groups [tiab]) NOT (animals [mh] NOT humans [mh])
#5	Search (#1 AND #2 AND #3 AND #4)

Gardasil 9, a nonavalent HPV vaccine that targets HPV-6, 11, 16, 18, 31, 33, 45, 52, and −58.[18] All three vaccines are composed of non-infectious L1 protein subunits assembled into virus-like particles. They prevent HPV infections caused by targeted types by eliciting the production of neutralizing antibodies that bind to the viral particles and block their entrance into host cells.[19-21] These vaccines have shown a high degree of safety, immunogenicity, and efficacy in HIV-negative individuals.[22,23] However, little is known about their effects on people living with HIV. In this review, we evaluate the immunogenicity, clinical efficacy, and safety of prophylactic HPV vaccines in people living with HIV.

Methods

We registered the protocol for this review in the International Prospective Register of Systematic Reviews (PROSPERO),[24] and prepared the review following the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA).[25]

Criteria for considering studies for this review

We included randomized controlled trials conducted among HIV-positive people irrespective of their setting, age, sex, HIV stage, and antiretroviral therapy status. Eligible trials compared prophylactic HPV vaccines to placebo or any other vaccine, irrespective of the number of doses administered, vaccination schedule used, and the site of vaccine administration. Finally, eligible studies should have reported a least one of our outcomes of interest. Our primary outcomes included immunogenicity (measured using percentage of participants who seroconverted or mean antibody levels) and adverse events observed after HPV vaccine administration. Our secondary outcomes included incident and persistent infection with both vaccine and non-vaccine HPV types, cervical intraepithelial neoplasia, and invasive cervical cancer.

Search and selection of studies

We developed a comprehensive search strategy for searching electronic databases and other resources. On 10 October 2018, we searched the Cochrane Central Register of Controlled Trials (CENTRAL), PubMed, EMBASE, WHO International Clinical Trials Registry Platform, clinicaltrials.gov, and abstract databases of the International AIDS Society and the Conference on Retroviruses and opportunistic infections, for articles indexed from 2000 to the date of the search; with no language restrictions. We have provided the search strategy for one database, PubMed, in Table 1. We also conducted hand searches of the reference lists of included studies and related reviews. We exported all studies retrieved from the electronic searches into EndNote for deduplication and screening. Two review authors (EM and AW) independently screened the titles and abstracts to identify potentially eligible studies. Disagreements between the two authors were resolved by discussion and consensus. We obtained the full-texts of all potentially eligible studies. Two authors (EM and AW) independently screened the full texts and identified included studies, resolving discrepancies through discussion and consensus. Excluded studies are described in the table of excluded studies alongside their reasons for exclusion.

Data extraction and management

Two review authors (EM and AW) independently extracted data from each selected study using a structured and standardized data extraction form. Extracted data included study details (geographical locations, number of participants), intervention details (number of participants, type of vaccine, number of doses), comparator details (number of participants, type of comparator used), outcome details and funding sources. Differences between the two review authors were resolved by discussion and consensus.

Assessment of risk of bias in included studies

Two review authors (EM and AW) independently assessed the risk of bias in each included study using the Cochrane risk of bias tool for randomized controlled trials[26] The domains assessed include: random sequence generation, allocation concealment, blinding of participants, blinding of outcome assessors, completeness of outcome data, completeness of outcome reporting, and other sources of bias. Disagreements between the two authors were resolved by discussion and consensus. We had planned to asses for publication bias using a funnel plot, but this was not done due to the few number of included studies.

Data analysis

Data were entered into Review Manager 5.3 (RevMan 5.3) software and checked for accuracy. We calculated risk ratios with the 95% confidence intervals for dichotomous data such as seroconversion, and the mean difference for continuous data such as antibody levels. When the authors reported means and 95%

confidence intervals, we estimated the standard deviations using the sample size, and the upper and lower limits of the confidence intervals. Due to important difference in the study populations, interventions and outcome measures, we did not conduct a meta-analysis of the included studies but rather narratively synthesized the evidence. Finally, we assessed the quality of the evidence using the GRADE approach.[27]

Results

Results of the search

The search yielded 504 records. After removing 89 duplicates, 415 titles and abstracts were screened and 389 of them were not relevant. The full texts of 26 potential eligible publications were reviewed. Seventeen publications reporting data on five randomized trials were included.[4,28-43] The search and selection of studies for this review are described in Figure 1.

Description of studies

Study design

All the included studies were randomized trails. The characteristics of the five included studies[4,28,31,34,39] are summarized in Table 2.

Population

The studies were conducted among people living with HIV including: women aged 18–25 years,[28] adult men and women aged ≥18 years,[4] men who have sex with men (MSM) aged ≥18 years,[31] MSM and women aged ≥27 years,[39] and male and female children aged 7–12 years.[34] The study size ranged between 92 and 575 participants. Two trials were conducted in the United States of America (USA)[34,39] and the other three were carried out in South Africa,[28] Denmark[4], and Spain[31] between 2010 and 2018.

Intervention and comparator

Three trials compared bivalent HPV vaccine to placebo.[31,34,39] One compared quadrivalent HPV vaccine to bivalent vaccine,[4] and the other one compared bivalent vaccine to placebo.[28] In the study that compared the bivalent vaccine to placebo in asymptomatic HIV-positive women, the efficacy and safety of the vaccine were also assessed in a third arm comprising of HIV-negative women. In all five studies, three doses of the vaccines and placebos were administered in the respective intervention and comparator arms. In three trials, intervention vaccines were given at day 0, month 2 and month 6.[31,34,39] In the other two trials, intervention vaccines were given at day 0, month 1 and month 2[28] and at day 0, month 1.5 and month 6.[4]

Outcome measures

Primary outcomes

All five studies reported on immunogenicity and adverse events. The immunogenicity outcomes of these five included studies are summarized in Table 3. HPV specific antibodies were measured using enzyme-linked immunosorbent assay

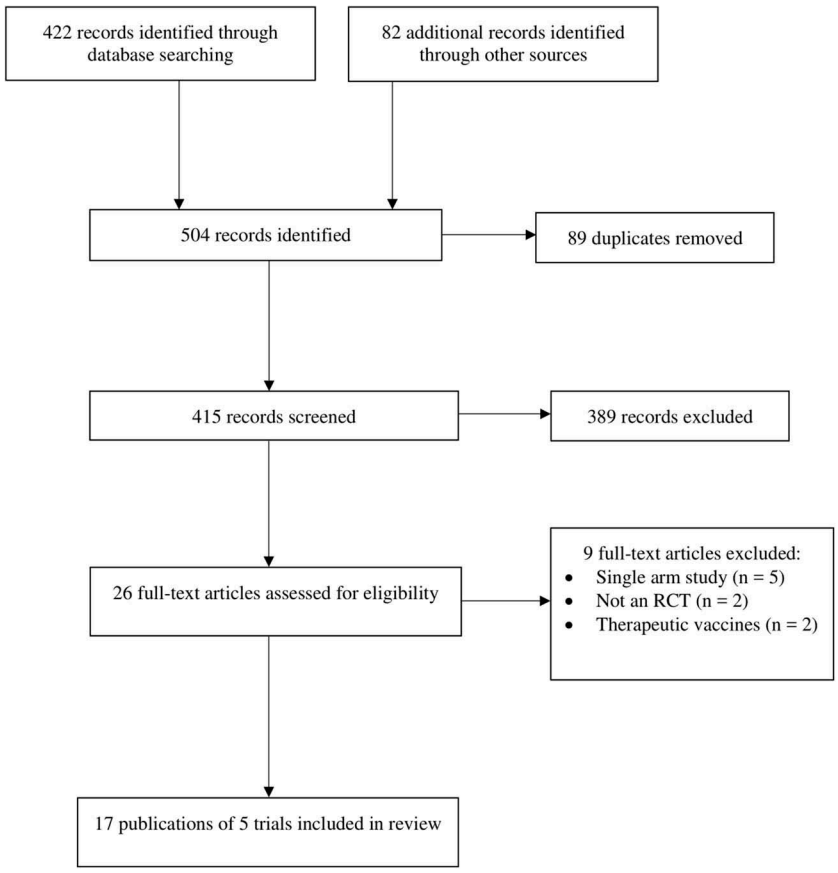

Figure 1. PRISMA flow diagram showing the study search and selection process.

Table 2. Characteristics of included studies.

Study	Country	Sample size	Participants	Intervention	Comparator	Outcomes assessed
Denny 2013[28]	South Africa	120	HIV-positive women aged 18 – 25 years from single center in Khayelitsha, Cape Town	60 vaccinated with bivalent HPV vaccine at 0, 1, and 6 months.	60 vaccinated with placebo at 0, 1, 6 months	Anti-HPV-16 and 18 antibodies were measured by ELISA. Adverse events were graded on a scale of 0 (absent) to 3 (preventing normal activities)
Hidalgo-Tenorio 2017[31]	Spain	129	HIV-positive Men having sex with men (MSM) from Spain	66 vaccinated with quadrivalent HPV vaccine (0.5ml). delivered at day 1, 2 and 6 months	63 vaccinated with placebo (0.5ml). delivered at day 1, 2 and 6 months	Anti-HPV-6, 11, 16, 18 antibodies were measured using ELISA. Adverse events were graded on a scale of 1–4
Levin 2010[34]	USA	126	HIV positive children aged 7–12 years, with a CD4% ≥15	96 vaccinated with quadrivalent HPV vaccine (0.5ml) at 0, 8, 24 weeks.	30 vaccinated with placebo (0.5ml) at 0, 8, and 24 weeks	Anti-HPV 6,11,16,18 antibodies were measured using a competitive Luminex immunoassay. Adverse events were graded (≥1 for injection reactions; ≥2 for all others). That occurred within 14 days of each vaccination were grouped into 5 defined toxicity categories.
Toft 2014[4]	Denmark	92	HIV-positive adults who attended outpatient clinic of Aarhus University Hospital,	46 vaccinated with quadrivalent HPV vaccine at 0, 1.5, and 6 months	46 vaccinated with bivalent HPV vaccine at 0, 1.5, and 6 months	Anti-HPV-16 and 18 antibodies were measured using pseudovirion-based neutralization assay. Adverse events were graded according to the common toxicity criteria version 2.0
Wilkin 2018[39]	USA & Brazil	575	HIV-infected adults aged ≥27 years from 24 sites in the U.S. and Brazil	288 vaccinated with quadrivalent HPV vaccine at 1, 8, and 24 weeks	287 vaccinated with placebo at 1, 8, and 24 weeks.	Anti-HPV-6, 11, 16, and 18 antibodies were measured using competitive Luminex-based immunoassay Adverse events were graded using Division of AIDS Table for Grading the Severity of Adult Adverse Events Version 1.0 Adverse events were solicited during clinical assessments and graded using Division of AIDS Table for Grading the Severity of Adult Adverse Events Version 1.0

(ELISA),[28,31] Luminex immunoassay,[34,39] and pseudovirion-based neutralization assay (PBNA).[4]

Secondary outcomes

One study reported on incidence and persistence of HPV infection.[4] None of the included studies reported on cervical intraepithelial neoplasia, and invasive cervical cancer as the duration of the trials too short for the development of cervical intraepithelial neoplasia and invasive cervical cancer.

Excluded studies

Nine studies[8,13,22,44-49] were excluded for reasons described in the characteristics of excluded studies (Table 4).

Risk of bias in included studies

The risk of bias in the included studies is summarized in Table 5. We assessed for selection bias in the included studies. All five studies described the methods used to generate the randomization sequence adequately and were judged as having low risk of bias. Three trials were at low risk of bias related to allocation concealment.[4,28,31] The other two trials were judged to have unclear risk of bias because the authors did not provide sufficient information regarding the methods used to conceal allocation in the intervention and comparison groups.[34,39] Three trials were at low risk of performance bias because participants and personnel were blinded.[31,34,39] The other two trials did not describe the blinding of participants and personnel clearly, thus we assessed them as having unclear risk of performance bias.[4,28] One trial was considered to be at low risk of detection bias because the outcome assessors were blinded.[31] The other four trials did not describe the blinding of outcome assessors and we considered them to be having unclear risk of detection bias.[4,28,34,39] We judged all the included trials to be at low risk of bias in relation to the completeness of outcome data. One trial was judged to be at low risk of reporting bias,[28] while the other four trials were judged to have an unclear risk of bias.[4,31,34,39]

Effects of HPV vaccines

Comparison of bivalent HPV vaccine to placebo

Seroconversion. One trial that compared bivalent HPV vaccine to placebo reported on seroconversion.[28] The study was conducted in Cape Town, South Africa among HIV-positive and HIV-negative women aged 18–25 years. At baseline, 85.4% and 73.0% were seropositive for HPV 16 while 64.3% and 56.8% were seropositive HPV-18 in the vaccine and placebo groups that included HIV-positive women, respectively. A third arm, consisting of HIV-negative women who also received the vaccine had baseline seroconversion rates of 63.6% and 50.0% for HPV 16 and 18, respectively. All HIV positive and negative participants who received the vaccine seroconverted for HPV-16 and HPV-18 1 month after the second dose and remained seropositive for both antigens 6 months after the third dose. Anti-HPV 16 and 18 antibody GMTs did not increase in the placebo group. However, anti-HPV-16 and 18 antibody GMTs increased in the vaccine groups. There were significant differences in anti-HPV

Table 3. The immunogenicity outcome of included studies.

Study	Vaccine studied	Time taken to determine immunogenicity end point	Measure of immunogenicity	Definition of seropositivity	Findings
Denny 2013[28]	Bivalent v/s placebo	One and six months after the third dose	Seroconversion rate and GMTs	Anti-HPV titers greater than or equal to 8 EU/ml for HPV- 16 and 7 EU/ml for HPV – 18	Three months after the third dose, all vaccinated participants seroconverted for HPV-16 and HPV-18 one month after the second dose and remained seropositive for both antigens 6 months after the third dose. No increase observed in the anti-HPV 16 and 18 antibody GMTs in the placebo group. There were differences in the anti-HPV-16 antibody GMTs between the HIV positive and HIV negative participants at one month (MD −4610.60 (95% CI: −6791.06; 2430.14)) and at 6 months (MD-2045.50 (95% CI: −2868.51; −1222.49)) after the third dose, with higher GMTs in HIV negative women. There were equally differences in the anti-HPV-18 antibody GMTs between the HIV positive and HIV negative participants at one month (MD −1757.20 (95% CI: −3268.07; −246.33)) and at 6 months (MD −678.20 (95% CI: −1182.29;-174.11)) after the third dose
Hidalgo-Tenorio 2017[31]	Quadrivalent v/s placebo	One month after third dose	Seroconversion rate	Not stated	One month after the third dose, more people seroconverted in the vaccine group compared to the placebo group (RR 2.51 (95% CI: 1.68; 3.75))
Levin 2010[34]	Quadrivalent v/s placebo	One month after third dose	Seroconversion rate and GMTs	Anti-HPV titer ≥20, 16, 20, and 24 mMU/mL, for HPV types 6, 11, 16, and 18, respectively	One month after the third dose, all vaccinated participants seroconverted to HPV-6, HPV-11, and HPV-16 antigens, except for HPV-18, where only 96% seroconverted. In the placebo group, there was no participant who seroconverted to HPV-6, HPV-11, and HPV 18, except for HPV-16 where only 4% seroconverted. The antibody GMTs in the intervention group, were significantly higher in the intervention group compared to the placebo group for HPV-6 (MD 548.00 (95% CI: 398.14; 697.86), HPV-11 (MD 1367.00 (95% CI: 1088.83; 1645.17), HPV-16 (MD 5225.00 (95% CI: 3966.35; 6483.65) and HPV 18, respectively
Wilkin 2018[39]	Quadrivalent v/s placebo	Four weeks after third dose	Seroconversion rate	Not defined	One month after the third dose, seroconversion rates in the vaccine group were higher than in the placebo group; 98.9%, 100%, 99.6% and 97.4% for HPV-6, HPV-11, HPV-16 and HPV-18, respectively, compared to corresponding 64, 45, 47 and 31% at baseline. At baseline, seroconversion in the placebo group was 61, 38, 47 and 33% for HPV-6, HPV-11, HPV-16 and HPV-18, respectively, and it did not change appreciably one month after the third dose.
Toft 2014[4]	Quadrivalent v/s bivalent	Four weeks after third dose	GMTs	Not defined	One month and 6 months after the third dose, the bivalent vaccine group had higher anti-HPV-18 GMTs compared to quadrivalent vaccine group. The absolute values of the antibody GMTs are not reported. However, the ratio of the anti-HPV 18 antibodies in the bivalent group compared to the quadrivalent group was 4.31 and 4.15 one month and six months after the third dose respectively. During the same period, there was no significant differences in anti-HPV-16 GMTs found between these two vaccines.

Table 4. Characteristics of excluded studies.

Study	Reason
Anderson 2009[44]	Randomized study assessing the safety, tolerability, and immunogenicity of novel HPV 16 vaccine (E6E7 ISCOMATRIX) for treatment of HPV-related anal epithelial neoplasia in HIV infected men who have sex with men. Not a prophylactic HPV vaccine.
Fontes 2016[8]	Non-randomized study evaluating the efficacy of a bivalent HPV vaccine in HIV-infected men. Not a randomized controlled trial
Giacomet 2014[13]	A non-randomized study evaluating the safety and immunogenicity of a quadrivalent HPV vaccine in HIV-infected and HIV-negative adolescents and young adults. Not a randomized controlled trial
Khan 2013[45]	Single arm study evaluating the immunogenicity and safety of a quadrivalent HPV vaccine in HIV-infected young women. No control arm
Kojic 2014[46]	Single-arm study evaluating the immunogenicity and safety of a quadrivalent HPV vaccine in HIV-1-infected women. No control arm.
McClymont 2019[22]	Single arm study assessing the efficacy of the quadrivalent HPV vaccine in HIV-infected girls and women. No control arm.
Money 2016[47]	Cohort study evaluating the immunogenicity and safety of the quadrivalent HPV vaccine in HIV-infected women. No control arm.
Palefsky 2006[48]	Non-randomized study testing the safety of a therapeutic HPV vaccine (SGN-00101) for treating high-grade anal intraepithelial neaoplasia in HIV -infected individuals. Not a prophylactic HPV vaccine.
Wilkin 2010[49]	Single-arm study assessing the safety and immunogenicity of the quadrivalent HPV vaccine in HIV-infected men. No control arm.

Table 5. Risk of bias summary.

	Denny 2013[28]	Toft 2014[4]	Hidalgo-Tenorio 2017[31]	Levin 2010[34]	Wilkin 2018[39]
Random sequence generation (selection bias)	+	+	+	+	+
Allocation concealment (selection bias)	+	+	+	?	?
Blinding of participants and personnel (performance bias)	?	?	+	+	+
Blinding of outcome assessment (detection bias)	?	?	+	?	?
Incomplete outcome data (attrition bias)	+	+	+	+	+
Selective reporting bias (reporting bias)	+	?	?	?	?
Other bias	?	+	+	+	?

+ low risk; - high risk; ? unclear risk

-16 GMTs between HIV positive and HIV-negative participants at 1 month (MD −4610.60 (95% CI: −6791.06; −2430.14)) and at 6 months (MD-2045.50 (95% CI: −2868.51; −1222.49)) after the third dose, with higher GMTs in HIV-negative women. There were equally differences in the anti-HPV-18 antibody GMTs between the HIV positive and HIV-negative participants at 1 month (MD −1757.20 (95% CI: −3268.07; −246.33)) and at 6 months (MD −678.20 (95% CI: −1182.29;-174.11)) after the third dose.

Adverse events. HIV positive and negative women who received the bivalent vaccine had a higher incidence of solicited local and general adverse events than HIV-positive women who received placebo, with most of them being mild and moderate, resolving spontaneously.[28] There was severe pain and swelling in 1.9% and 0.6% of the doses given to HIV-positive women who got the HPV vaccine and in 1.2% and 5.9% of the doses given to HIV-negative women who got the vaccine. No severe local adverse events were reported in the placebo group. Unsolicited adverse events were reported by 86.9% of HIV-positive women in the vaccine group and 86.7% of HIV-negative women in the vaccine group and 78.0% of HIV-positive women in the placebo group. The most commonly reported unsolicited adverse events were headache (19.7% and 23.7%, vaccine and placebo group in HIV-positive women and 13.3% in HIV-negative women in the vaccine arm, respectively) and upper respiratory tract infection (16.4%, and 16.9% in vaccine and placebo group, and 23.3% in HIV-negative women in the vaccine arm respectively, respectively). Medically significant adverse events were recorded by 11.1% and 9.6% of HIV-positive women in the vaccine group and placebo group, and 16.7% in HIV-negative women in the vaccine arm, respectively. There were six women with serious adverse events, none of them vaccine-related.

Comparison of quadrivalent HPV vaccine to placebo

Seroconversion. Although all three trials that compared quadrivalent HPV vaccine to placebo reported on this outcome, there was heterogeneity between these trials in the reporting of the outcome measures, hence the reported studies could not be meta-analyzed.[31,34,39] Hidalgo 2017[31] assessed seroconversion in 129 HIV-positive Spanish men who have sex with men. Although baseline anti-HPV antibodies are unknown, there were significantly more people who seroconverted in the vaccine group compared to the placebo group 1 month after the third dose (RR 2.51) (95% CI: 1.68; 3.75). Levin 2010[34] evaluated seroconversion in HIV-positive children aged 7 to 12 years. All vaccinated participants seroconverted to HPV-6, HPV-11, and HPV-16 antigens, except for HPV-18, where only 96% seroconverted 4 weeks after the third dose. In the placebo group, there was no participant who seroconverted to HPV-6, HPV-11, and HPV 18, except for HPV-16 where only 4% seroconverted. The antibody GMTs were significantly higher in the intervention group compared to the placebo group for HPV-6 (MD 548.00) (95% CI: 398.14; 697.86), HPV-11 (MD 1367.00) (95% CI: 1088.83; 1645.17), and HPV-16 (MD 5225.00) (95% CI: 3966.35; 6483.65) respectively. Wilkin 2018[39] assessed seroconversion in HIV-positive adults aged 27 years or older. One month after the third dose, seroconversion in the vaccine group was higher than in the placebo group; 98.9%, 100%, 99.6%, and 97.4% for HPV-6, HPV-11, HPV-16, and HPV-18, respectively, compared to corresponding 64%, 45%, 47%, and 31% at baseline. At baseline, seroconversion in the placebo group was 61%, 38%, 47%, and 33% for HPV-6, HPV-11, HPV-16, and HPV-18, respectively, and it did not change appreciably 1 month after the third dose although the authors do not report the exact values.

Adverse events. All three trials that compared quadrivalent vaccine to placebo reported adverse events.[31,34,39] However,

there was heterogeneity in the reporting of the adverse events between these trials. Due to this heterogeneity, the reported data findings could not be meta-analyzed. Hidalgo 2017[31] reported few adverse events, with these adverse events higher in the placebo group compared to vaccine group after the first (RR 0.62) (95% CI: 0.49;0.79), second (RR 0.91) (95% CI: 0.83;0.99), and third doses (RR 0.74) (95% CI: 0.61; 0.89), with injection-site pain being the most common adverse event. However, there were no grade 3 and grade 4 vaccine-related adverse events reported. There were also no serious adverse events related to the vaccine administration observed. Levin 2010[34] also found that adverse events were generally few in both the placebo group and vaccine group. There was no significant differences in grade 1 (RR 2.60) (95% CI: 0.85, 8.02), grade 2 (RR 0.91) (95% CI: 0.50, 1.64), grade 3 (RR 0.78) (95% CI: 0.16, 3.82), and grade 4 (RR 1.60) (95% CI: 0.08, 32.40) adverse events between the vaccine and placebo groups. Injection-site reaction was the most common reported adverse event. Wilkin 2018[39] reported that there were no grade 3, grade 4 serious adverse events related to the vaccination.

Comparison of quadrivalent HPV vaccine to bivalent HPV vaccine

Seroconversion. One trial involving 92 participants, comparing quadrivalent HPV vaccine to bivalent HPV vaccine reported on this outcome.[4] The trial was conducted in Denmark among HIV-positive adults. One month and 6 months after the third dose, the bivalent vaccine group had higher anti-HPV-18 GMTs compared to quadrivalent vaccine group. The absolute values of the antibody GMTs are not reported. However, the ratio of the anti-HPV-18 antibodies in the bivalent group compared to the quadrivalent group was 4.31 and 4.15 1 month and 6 months after the third dose, respectively. During the same period, there were no significant differences in anti-HPV-16 GMTs found between these two vaccines.

Adverse events. No serious adverse events were reported in this trial; both vaccines were well tolerated. However, injection-related adverse events were observed. Injection-site pain was more common in the bivalent vaccine group than in the quadrivalent vaccine group after the first (RR 0.39) (95%CI: 0.25; 0.60) and second doses (RR 0.40) (95% CI: 0.21, 0.77). Injection-site swelling was also more common in the bivalent vaccine group than in the quadrivalent vaccine group after the second dose (RR 0.22) (95% CI: 0.05; 0.95).

Discussion

Summary of main results

When the effects of HPV vaccines were compared to placebo in HIV-positive people, seroconversion rates in the vaccinated groups were higher compared to the placebo group. GMTs reported in two trials were also higher in the vaccinated group compared to the placebo group. In one trial that compared bivalent to quadrivalent vaccine, anti-HPV-18 GMTs were higher in the bivalent group compared with the quadrivalent group. However, there were no significant differences in anti-HPV-GMTs between these two vaccine groups. With regards to the safety of HPV vaccines in HIV-positive people, there were no serious vaccine-related adverse events reported in these five trials. The vaccines were generally safe and well tolerated. Injection-site reaction was the most common adverse event of HPV vaccines reported. In four trials where HPV vaccines were compared to placebo, seroconversion rates in the vaccinated groups were higher compared to the placebo group. Of these four trials, GMTs were reported only in two trials and they were higher in the vaccinated group compared to the placebo group. In one trial that compared bivalent to quadrivalent vaccine, anti-HPV-18 GMTs were in the bivalent group compared with the quadrivalent group. However, there were no significant differences in anti-HPV-GMTs between these two vaccine groups.

Overall completeness and applicability of evidence

Despite our comprehensive search, we found only five trials which met our inclusion criteria. Four out of five trials were conducted in high-income countries with a low burden of HIV/AIDS. Only one trial was conducted in South Africa, an upper middle-income country with a high burden of HIV/AIDS. Although all participants were HIV positive, they were generally healthy patients. Although all included studies administered three doses of the HPV vaccines, they differed in vaccination schedules, time taken to determine immunogenicity endpoint, and methods used to measure and interpret immunogenicity outcome. None of the included trials assessed the effect of the nonavalent HPV vaccine, one of the three recommended HPV vaccines, highlighting a gap in the evidence in this area. In addition, none of the included studies was conducted against HIV-positive adolescents, most affected group by HIV and HPV infection. We had intended to assess other outcomes such as histologically confirmed high-grade cervical intraepithelial neoplasia (CIN2, CIN3, and adenocarcinoma in situ (AIS)), and invasive cervical cancer. However, none of the included studies reported on these.

Quality of the evidence

We used the GRADE approach to assess the certainty of the evidence on the effects of HPV vaccines. The evidence on the effects of the bivalent HPV vaccine compared to placebo in people living with HIV was based on one study conducted amongst women 18–25 years old, including 120 participants. We graded the certainty of the evidence around the immunogenicity as moderate due to imprecision. The certainty of the evidence on the effects of the bivalent HPV vaccine in HIV-positive women compared to HIV-negative women was graded as low because we downgraded by two for important imprecision arising from the small study sample and the study design. The evidence around the effect of the quadrivalent HPV vaccine compared to placebo in people living with HIV was based on three studies with a highly diverse population, including MSM, Children 7–12 years and adults >27 years. We rated the certainty of evidence on the immunogenicity as

moderate in adults >27 due to risk of bias, moderate in MSM due to imprecision and low in children due to imprecision and risk of bias. The evidence around the effect of the quadrivalent HPV vaccine compared to the bivalent HPV vaccine in people living with HIV was based on one study in HIV-positive adults with only 92 participants. We rated the certainty of evidence on the immunogenicity as very low due to important imprecision.

Potential biases in the review process

We minimized potential biases in the review process by adhering to the Cochrane guidelines.[26] We conducted comprehensive searches of both peer-reviewed and gray literature, without limiting the searches to a specific language. Two review authors independently assessed study eligibility, extracted data, and assessed the risk of bias in each included study. We are not aware of any biases in the review process.

Agreements and disagreements with other studies or reviews

We found that people living with HIV who were vaccinated with HPV vaccines had high rates of seroconversion compared to the ones who received placebo. These findings are consistent with the findings of an unpublished report of HPV vaccines in HIV infected males and females produced by Cochrane Response.[50] However, the latter included only four studies published up to 2016.[4,13,28,34] We excluded one of the four studies from our review because it is not a randomized controlled trial.[13] Our review includes an additional two studies published in 2017 and 2018.[31,39] Our findings are also in agreement with the findings previously reported in non-randomized control and excluded studies.[8,13,45-47,49] The similar findings of high seroconversion rates were also reported in HIV-positive adolescents boys and girls vaccinated with quadrivalent HPV vaccine.[51] Our review also found that HIV-positive people vaccinated with the bivalent HPV vaccine had higher anti-HPV-18 GMTs compared to those who were vaccinated with the quadrivalent HPV vaccine. With regards to anti-HPV-16, the GMTs were similar in both groups. These findings are also in consistency with the findings of an unpublished report of HPV vaccines in HIV infected males and females produced by Cochrane Response.[50]

Authors' conclusions

Implication for research

None of the included studies assessed the immunogenicity and safety of HPV vaccines in adolescents. There were also no included studies that assessed the effects of the nonavalent HPV vaccine in people living with HIV. There is, therefore an urgent need for more high-quality randomized controlled trials that can address these gaps. There is also limited evidence suggesting that although the HPV vaccine is immunogenic in HIV-positive people, anti-HPV GMTs are lower in HIV positive compared to HIV-negative people. This could have implications on the number of doses to be administered in this population in order to optimize the benefits of the vaccines and warrants further research.

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

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Author's contributions

EJM and CSW conceived the study. EJM drafted the study protocol. EJM and ABW screened the titles, abstracts and full texts, and extracted data. ABW, PWM, and CSW provided content and methodological expertise. All the authors read, amended, and approved the final version of the study protocol for submission. CSW is the guarantor for this review.

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