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HPV infection and increased risk of HIV acquisition. A systematic review and meta-analysis

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Keywords

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Introduction

After 30 years of the HIV epidemic there are still an estimated two new infections for every individual starting treatment and no effective vaccine[1-2]. New interventions which address biological co-factors for HIV infection are urgently needed. There are established associations between sexually transmitted infections (STI), particularly Herpes simplex virus type 2 (HSV2), and HIV acquisition[3]. Recently, a number of descriptive studies have documented an association between human papillomavirus (HPV) infection and HIV acquisition.

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HPV, the primary cause of cervical cancer, is acquired rapidly after sexual debut and infection with multiple genotypes is common, making HPV a highly prevalent STI world-wide[4-7]. Approximately 40 HPV genotypes infect the human genital tract and are classified into two groups depending on their oncogenic potential: high-risk oncogenic and low-risk non-oncogenic genotypes. Symptomatic infection is rare and usually manifests as ano-genital condylomata and cervical, vulvar, anal or penile precancers or cancers[8]. There are two extremely effective vaccines offering protection against HPV infection or precancerous lesions caused by vaccine HPV genotypes. The bivalent vaccine protects against HPV 16 and 18 and the quadrivalent vaccine against HPV 16, 18 and HPV 6 and 11[9-11]. Both vaccines also show evidence of cross-protection against non-vaccine types (particularly HPV 31, 33 and 45)[12-13]. A vaccine targeting 9 HPV genotypes has entered phase III clinical trials (NCT00943722).

Collection, appraisal and synthesis of available evidence for the association of HPV with HIV acquisition would provide an important resource to assess the potential role of HPV in the HIV pandemic. The objectives of the current study were to collate and appraise the observational evidence for any longitudinal association between prevalent HPV infection and HIV acquisition; and to estimate the proportion of HIV infections attributable to HPV infection.

Methods

Search

Pubmed and Embase were searched using search terms for HPV, genital warts and HIV (see supplementary material for full list). Only nested case-control and cohort studies were included, cross-sectional studies were excluded because of the risk of reverse causality: HPV prevalence increases rapidly after HIV seroconversion[14]. All abstracts available on-line from the International AIDS Society, the International Society for Sexually Transmitted Diseases Research, the British HIV Association conferences, the Conference on Retroviruses and Opportunistic Infections and the International Papillomavirus Conference were searched. Reference lists of review articles and all articles identified in the systematic search were checked. The search was carried out up to 29th July 2011. All abstracts were reviewed independently by two authors (CH and NL). Inconsistencies were discussed and consensus reached on potential relevance. Full text copies of potentially relevant papers were then obtained.

Included studies

Only human studies were included, with no language or date restrictions. Only studies which identified HPV DNA using hybrid capture II or PCR were included: other methods lack sensitivity and specificity[15-16]. HPV samples could be clinician or self-collected since these have high concordance[17]. Studies were restricted to those where HPV status was determined prior to HIV infection. In papers that presented analysis from the same population, the study that gave the most detailed description of the cohort and study design was selected.

Bias

Assessment of bias was made using a component approach, similar to the Cochrane Collaboration's[18] and supported by PRISMA guidelines[19]. Studies were assessed on selection bias, timing of HPV test in relation to HIV, cohort retention, follow-up duration, adjustment for confounding and outcome reporting.

Data extraction

Data were independently extracted by two authors (CH and NL) using a piloted, standardised form. Either a hazard ratio (HR) or an odds ratio (OR) was extracted, since these approximate closely when the outcome is rare, as in this case. Extracted data included the association with HIV acquisition for: any HPV, high-risk and low-risk HPV genotypes, HPV 16/18, HPV 6/11/16/18 and HPV 6/11/16/18/31/33/45/52/58 and persistent and non-persistent HPV. Authors were contacted if the desired effect estimate was not published.

Meta-analysis

Studies conducted in (i) heterosexual male populations, (ii) men who have sex with men (MSM) and (iii) studies in women were considered separately. Meta-analyses were not performed if the effect estimates were not comparable (as in estimates for persistent and non-persistent HPV). Analyses were performed using STATA version 12.0 (StataCorp LP, Texas, USA). Random effects meta-analysis was used to produce summary effect estimates (presented as HR), which allow for between-study heterogeneity[20]. Meta-regression was not performed due to the large potential for false positive findings with a limited number of studies[21]. A sensitivity analysis was performed excluding unadjusted studies since lack of adjustment for confounders was not an exclusion criterion. Publication bias was assessed by funnel plot, which displays the log of the effect estimate against its standard error, and formally tested using Begg's test[22]. Population attributable fractions (PAF) of HIV due to prior HPV infection were calculated using $\mathrm{PAF}=\mathrm{p}'\left(\widehat{\theta}-1\right)/\widehat{\theta}$, where $\widehat{\theta}$ is the adjusted effect estimate for HIV acquisition in those with HPV, and p' is the prevalence of HPV prior to HIV acquisition in those who acquired HIV. PAFs were only calculated for infections with *any* HPV, since other effect estimates were either under-powered or unadjusted for the presence of other HPV genotypes.

Results

After duplicate removal, a total of 1139 titles and abstracts were identified (Figure 1). 1053 were excluded after abstract review, due to non-relevance or clear exclusion criteria, leaving 86 papers for full text review. Eight relevant studies were identified and data were extracted. Characteristics of included studies are summarised in Table 1. The 8 studies provided data from a combined total of 12,750 individuals. Studies included one nested case-control study and seven cohort studies. Six studies were in women, one in heterosexual men, and one in MSM. Meta-analysis was therefore only possible for studies in women. One study was conducted in the USA[23] and seven in sub-Saharan Africa. Of eight authors contacted for further analysis, five responded. No study had the primary aim of measuring the association between prevalent HPV and HIV acquisition.

Results of the meta-analysis showing HR and 95% CI for the individual studies and pooled measures of effect are shown in Figure 2(i-v).

HPV infection and HIV acquisition in women

Averbach[24], Low[25] and Smith-McCune[26] *et al* increased risk of HIV acquisition associated with infection with any HPV genotype compared to no HPV infection in women. The point estimate from all three were consistent with a harmful effect of HPV infection (aHR=1.71, aHR=2.40 and aHR=2.26 respectively) although the association was only statistically significant for two[24, 26]: the third had low power[25] Figure 2(i). There was strong evidence of an increased risk of HIV acquisition with any prevalent HPV genotype from the meta-analysis (summary HR=2.06 (95%CI=1.44-2.94), I^2=0%, *P* heterogeneity=0.66).

All but one[25] of six studies in women presented a separate effect measure for HIV acquisition associated with high-risk HPV. In these studies (Figure 2 (ii)), Averbach[24], Myer[27], Smith-McCune[26] and Veldhuijzen[28] *et al*, presented the effect estimate for infection with high-risk HPV compared to no HPV and Auvert *et al*[29] presented the effect estimate for infection with 2 or more high-risk HPV genotypes compared to infection with one or zero high-risk genotypes. These five effect estimates combine to show a doubling of HIV risk with prevalent high-risk HPV infection (summary HR=1.99 (95%CI=1.54-2.56), I^2=8.4%, *P* heterogeneity=0.36). Excluding the unadjusted study by Veldhuijzen *et al*[28], a strong association persisted (summary HR=1.90 (95%CI=1.50-2.40), I^2=0%, *P* heterogeneity=0.48, Forest Plot not presented).

Averbach[24], Smith-McCune[26] and Auvert[29] *et al* examined the risk associated with low-risk HPV infection in women. The latter study was excluded from the meta-analysis because the authors presented the linear trend involving the number of low-risk genotypes. In the two included studies, Averbach[24] compared infection with only low-risk genotypes (no high-risk) to no HPV, and Smith-McCune[26] compared infection with low-risk HPV irrespective of the presence of high-risk genotypes. A doubling of risk was seen with little evidence of heterogeneity between studies (Figure 2(iii) summary HR=2.01 (95%CI=1.27-3.20), I^2=0%, *P* heterogeneity=0.29). The excluded study did not find an association between the number of low-risk HPV genotypes and HIV acquisition (adjusted hazard ratio(aHR) = 0.95 (95%CI=0.68-1.30 *P* linear trend=0.76)).

Smith-McCune[26] and Averbach[24] reported the risk of HIV acquisition associated with persistent and non-persistent genotype specific HPV in women (Figure 2(iv) and (v)). Both tested for HPV three monthly and defined persistent infection as two consecutive visits where genotype-specific HPV was detected. In multiple genotype infection, Averbach[24] defined persistence as all genotypes present at the following visit, and defined non-persistence as loss of any one of these. Smith-McCune[26] defined persistence as the repeat detection of any one specific genotype, and allowed non-detection between positive visits. Non-persistence was defined as HPV infection in individuals with more than one follow-up visit, which did not meet persistence criteria. Averbach[24] assessed HIV risk for any persistent or nonpersistent HPV, whereas Smith-McCune[26] disaggregated by high-risk and low-risk genotypes. All estimates of HIV risk from a persistent genotype-specific HPV infection showed no association, aHR=0.82 (95%CI=0.45-1.50) from high-risk[26], aHR=1.24 (95%CI=0.59-2.60) from low-risk[26] and aHR=0.97 (95%CI=0.51-1.85) from any HPV[24]. However in all studies there was a significantly increased risk when type-specific HPV was non-persistent aHR=1.67 (95%CI=1.03-2.74) from high-risk, aHR=2.09 (95%CI=1.27-3.44) from low-risk[26] and aHR=5.4 (95%CI=2.9-9.9) from any HPV[24]. Only one study in women assessed the risk of HIV acquisition associated with cervical cytological abnormalities. Smith-McCune[26] found no evidence that atypical squamous cells of uncertain significance (ASCUS), or any more severe cytological abnormality, diagnosed before HIV acquisition, was associated with increased risk (unadjusted HR=1.38 (95%CI=0.80-2.34)).

We found no publication reporting the association between HPV vaccine-specific genotypes and HIV acquisition in women. Authors from two of the six studies provided this on request (Table 1), although only one provided the effect estimate for the association between nonovalent vaccine genotypes HPV 6/11/16/18/31/33/45/52/58 and HIV acquisition. Averbach[24] found no association between infection with bivalent (16 or 18) or quadrivalent vaccine genotypes (6 or 11 or 16 or 18) when compared to no infection with these genotypes adjusted for the presence of other genotypes, and HIV acquisition. Smith-McCune[26], found that although infection with bivalent vaccine genotypes was not associated with HIV acquisition, infection with quadrivalent vaccine genotypes was

associated with a doubling of HIV risk (aHR=2.00 (95%CI=1.00-3.99)). Further, they found that infection with nonovalent vaccine genotypes was associated with a more than 2.5 times increased risk (aHR=2.57 (95%CI=1.48-4.46)) when compared to no infection with those genotypes, even after adjustment for recent infection with other HPV genotypes and other prospectively collected confounders.

HPV infection and HIV acquisition in men

The systematic search revealed only one study in MSM and one in heterosexual men. Chin-Hong *et al*[23] found, in multivariable analysis, that infection with one HPV type compared with no HPV infection was not significantly associated with HIV acquisition in MSM (aHR=2.0 (95%CI=0.61-6.5)). However, the presence of infection with 2 or more HPV types compared with being HPV un-infected was associated with HIV acquisition (aHR=3.5 (95%CI=1.2-10.6)). In heterosexual men, Smith *et al*[30] found the presence of any HPV in the glans/coronal sulcus of the penis was associated with increased risk (aHR=1.8 (95%CI=1.1-2.9)). These authors repeated their original analysis, and compared HIV risk from infection with HPV 16/18, HPV 6/11/16/18 and HPV 6/11/16/18/31/33/45/52/58 to no infection with these genotypes adjusted for other HPV genotypes and confounding factors. Although these appeared to be associated with HIV, the associations were not statistically significant (Table 1).

One study in men assessed the risk of HIV acquisition associated with anal cytological abnormalities. Chin-Hong[23] found that in multivariable analysis, atypical squamous cells and low grade squamous intraepithelial lesions were not significantly associated with HIV acquisition (aHR=1.8 (95%CI=0.62-5.5) and aHR=1.2 (95%CI=0.44-3.23) respectively), consistent with results for cervical cytological abnormalities in women.

Bias within and across studies

Assessment of bias within studies is summarised in Table 2. Studies by Averbach[24] and Smith McCune[26] displayed a low risk of bias in all categories. Residual confounding, however, remains a concern in all studies.

Low[25], Veldhuijzen[28] and Smith[30] *et al* did not adjust for sexual behaviour, which is associated with both HIV and HPV acquisition[31-33]. Chin-Hong[23], Smith-McCune[26] and Averbach[24] *et al* were the only authors who repeated the collection of sexual behaviour data prospectively. Even with the best sexual behaviour measure, prospectively collected, it is reasonable to assume that residual confounding will persist. Most studies included the parameters of condom use[23-24, 26-27, 29], multiple recent partners [23-24, 26-27, 29] and high-risk sex partners[23-24, 26], but only some studies recorded other important confounders such as transactional sex[24, 26, 29].

The panel of STIs tested, and whether they were measured prospectively, varied by study (Table 1). In some studies, HSV2[27-29] and bacterial vaginosis (BV)[26-27, 29-30] were not tested for, although both are associated with HPV and HIV acquisition[3, 34-36]. One study did not test for low-risk HPV[27], and others did not adjust for the presence of low-risk or other HPV types, although high and low-risk HPV were identified as independent risk factors for HIV[24, 26]. Reassuringly, contacted authors presented the HIV risk associated with vaccine genotypes adjusted for the presence of other (potentially confounding) HPV genotypes, and still identified a positive association.

Weak evidence of publication bias was seen using Begg's test (P=0.06) (see supplementary Figure 1s for funnel plot).

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Population attributable fractions

Three studies provided sufficient data to allow calculation of the proportion of HIV infections attributable to prevalent HPV infection (Table 3). 21 and 37% of HIV infections in women in studies in Zimbabwe[24] and South Africa[29] were attributable to infection with prevalent HPV of any genotype at the visit prior to HIV acquisition. 28% of HIV infections in Kenyan heterosexual men[30] were attributable to infection with HPV at baseline.

Discussion

This systematic review of the literature provides the first summary of published evidence of the association between prevalent HPV infection and HIV acquisition. Seven of eight studies showed evidence of an association between these infections and, where it was possible to calculate a PAF, a high proportion of HIV infections are attributable to infection with any HPV genotype. Combining the studies in women revealed a near doubling of risk when an HPV genotype was identified prior to HIV acquisition, with similar associations seen in the two studies in men. Although these results appear similar to associations between other STIs, such as HSV2, and HIV acquisition[3], significant concerns are raised in the assessment of quality: only two of the eight studies had a low risk of bias in all domains. Further, studies were performed in populations with a high prevalence of STIs and high-risk sexual behaviour (three of the studies in women were in commercial sex workers for example), and results may not be generalisable to women outside these groups.

Study quality was assessed by a components approach. In this assessment, two studies were identified as having a high risk of bias in more than one category. Prospective testing for HSV2 and sexual behaviour, two potentially strong confounders of the association between HPV infection and HIV acquisition, was only performed in two studies leaving the remaining six with a high risk of residual confounding. It is particularly difficult to collect sufficiently detailed, rigorous, sexual behaviour data and for that reason, residual confounding may affect all studies. These concerns serve to illustrate the limitation of observational research in determining causation. Additionally, all studies included in this analysis were secondary analyses of data, and only one stated an *a-priori* analysis plan; in-spite of this however, only weak evidence of publication bias was seen.

It was not possible to perform meta-analyses of the association between HPV and HIV in MSM or heterosexual men because the systematic search only revealed one of each of these studies. Combining these two studies, or all eight, was considered inappropriate because of the implicit heterogeneity in HIV acquisition between MSM, heterosexual men and women. The findings in men were of a positive association, with similar effect estimates seen for the risk of HIV acquisition from prevalent HPV infection, adding plausibility to the findings in women. A specific limitation of the study in MSM was the lack of testing for penile HPV[23]. Although HIV is frequently acquired through receptive anal intercourse in MSM, penile acquisition by the insertive male partner is possible.

HPV may display viral latency, with persistence in tissue below the limit of detection[37]. If this theory is correct, detection of HPV at the cervix may not necessarily indicate infection and likewise, lack of detection may not indicate absence of infection. HIV infection leads to a 5-fold increase in multiple new HPV infections within 6 weeks of HIV seroconversion[14]. The association between prevalent HPV infection and HIV acquisition may therefore be due to reverse causality if a recent, undiagnosed HIV infection had led to a rapid increased HPV prior to HIV confirmation in these studies. However, this would occur in a minority of cases. To minimise the risk of associations due to reverse causality, we excluded one study which described a strong association between HPV infection and HIV

acquisition but included some HPV samples taken after HIV seroconversion[38]. Genital tract exposure to HIV prior to establishment of infection induces TLR-7. Since TLR-7 agonists (imiquimod) are used to treat genital warts, the observation seen in two studies that HPV clearance is association with HIV acquisition could in fact be attributed to HPV clearance being a marker of HIV exposure prior to infection rather than a risk-factor[24].

It is biologically plausible that prevalent HPV may increase the risk of HIV acquisition. It has been demonstrated that the E7 protein of HPV type-16 down-regulates an epithelial adhesion molecule called E-Cadherin[39], potentially increasing permeability of the genital lining to HIV. The lining of the genital tract contains Langerhans' cells (LC), which can internalise HIV, preventing onward infection[40]. In HPV-infected tissue, a reduced density and altered morphology of LCs has been demonstrated[41-43]. The host immune response to HPV is mediated by T-lymphocytes[44], and this response may increase HIV risk since T-lymphocytes are primary target cells for HIV. An increased presence of these cells has been seen in HPV-infected cervical tissue[45]. Further, HPV non-persistence, which is likely to be associated with a T-lymphocyte influx, was associated with HIV acquisition in 2 studies in this review[24, 26], when persistent infection was not. Elevated levels of cytokine IL-Iβ, which activates a promoter region in the HIV genome[46], have also been demonstrated in women with HPV-associated abnormal cervical cytology[47] and defensins and thrombospondins, anti-HIV proteins, are also lower in precancerous cervical lesions[48] (although in this review cytological abnormalities were not associated with HIV acquisition[23, 26]).

In one Zimbabwean study[24], 37% of HIV infections in women have been attributed to infection with any HPV genotype. This is due to the high prevalence of HPV in women who later became infected with HIV (63%) and a large effect measure (aHR=2.4). Lower proportions (21% and 28%) were identified in studies with smaller effect measures and HPV prevalence. Since the PAF assumes a fully causal relationship these results must be interpreted with caution. Although vaccines protecting against infection with increasing number of HPV genotypes are being developed, and cross-protection has been demonstrated with current vaccines[12-13], a pan-valent vaccine is not currently available and prevention of infection from all HPV genotypes is not currently possible. Despite their limitations, the PAF estimates are presented to give some indication of the overall effect of HPV on HIV acquisition in endemic settings, and suggest that effective HPV control measures might have a significant impact on the HIV epidemic.

The proportion of HIV infections attributable to infection with high-risk, low-risk, and vaccine-specific HPV genotypes are not presented. There were insufficient data from existing studies to provide accurate estimates for PAFs for vaccine-specific HPV genotypes since studies were not powered to detect this specific association. Assuming a causal effect from a small number of genotypes and attributing HIV to those genotypes could be misleading. Further robust observational studies are needed to address this issue.

In conclusion, meta-analysis of studies in women showed a strong association between prevalent HPV infection and HIV acquisition, although studies were at risk of residual confounding. In heterosexual men and MSM the findings were consistent with those in women, although there were insufficient studies to perform meta-analysis. Of the three studies which evaluated the association between detection of HPV genotypes available in vaccines and HIV acquisition, one found a strong independent association.

The HPV vaccine is highly effective in the primary prevention of HPV-associated cervical cancers and genital warts. Clarification of the findings presented in this study through well-conducted research is needed in high HPV/HIV settings, in order to assess whether HPV

vaccination might have an effect on HIV incidence. Surveillance of HIV incidence rates over time in counties implementing HVP vaccination of girls, and nested case control studies examining HPV vaccination status in HIV positive cases versus HIV negative controls, are necessary.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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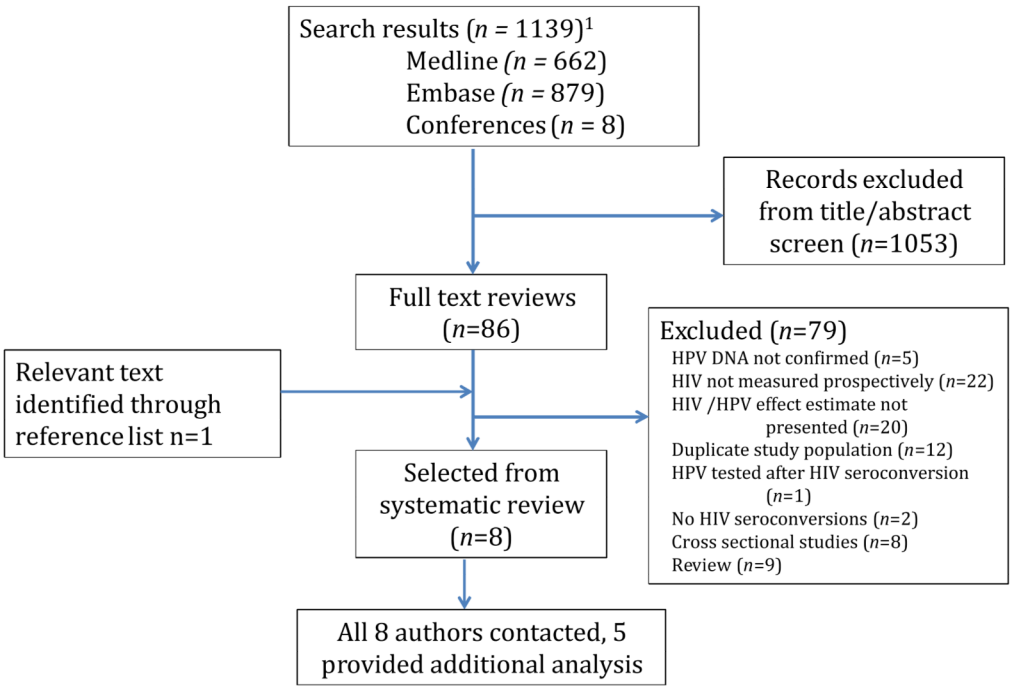

Figure 1. Results from the systematic search
[1]After removal of duplicates

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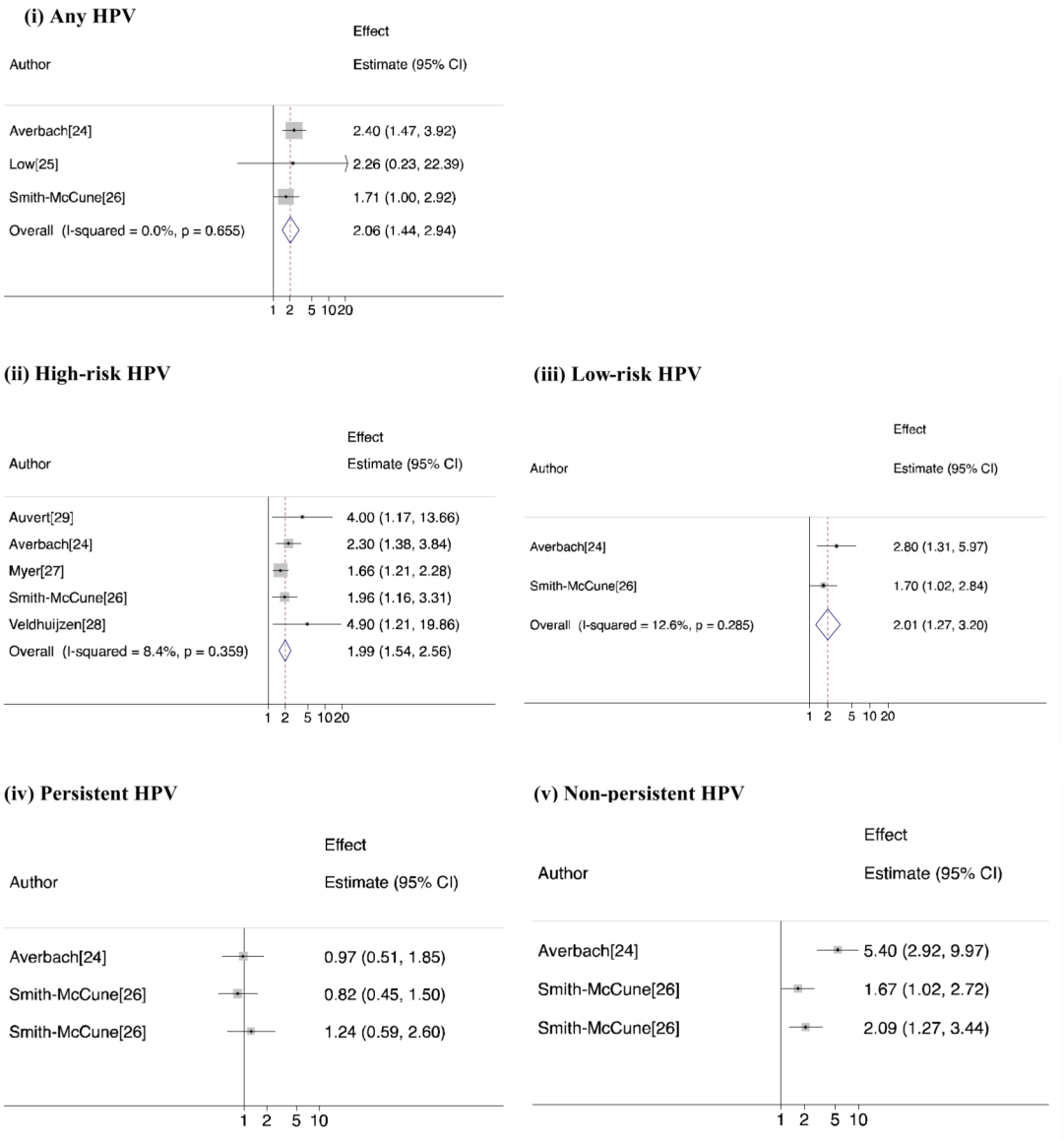

Figure 2. Meta-analysis of HIV risk in women associated with (i) Any HPV (ii) High-risk HPV (iii) Low-risk HPV (iv) Persistent HPV and (v) Non-persistent HPV

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Table 1

Summary of studies of the association of HPV and HIV acquisition

First Author, year	Study type (median follow-up per participant)	Participants, location	HPV prevalence	Number of HIV sero-conversions (cohort size or controls)	HPV genotypes	Comparison group	Confounding factors adjusted for[1]	Unadjusted HR (95 % CI)	Adjusted HR (95% CI)
Studies in Women									
Auvert, 2011[29]	Cohort (2.5yrs)	Microbicides trial in sex workers, South Africa	70.5% at baseline[5,18]	25 (88)	≥2 high-risk[15]	≤1 high-risk HPV	TV, NG, CT, TP and sexual behavior	-	4.0 (1.2-14.0)
Averbach, 2010[24]	Nested case control study (21.9 months, 3 months between HPV and HIV)	Hormonal contraception observational study, Zimbabwe	48.7% at visit before sero-conversion[19]	145 (446)	Any[16] High-risk[16] Low-risk[16] Non-persistent[16] Persistent[16] 16/18[16] 6/11/16/18[16]	No HPV No HPV No HPV No HPV No HPV No HPV 16/18 No HPV 6/11/16/18	BV, TV, NG, CT, HSV2, TP and sexual behavior	2.7 (1.7 – 4.1) 2.7 (1.7 – 4.3) 2.5 (1.3 – 4.6) 5.3 (3.2–9.0) 1.12 (0.6–2.0) 1.65 (0.96-2.72)[10] 1.63 (0.98-2.72)[10]	2.4 (1.5-4.0) 2.3 (1.4-3.9) 2.8 (1.3-5.9) 5.4 (2.9–9.9) 0.97 (0.51-1.85) 0.94 (0.46-1.92)[10] 0.94 (0.47 - 1.84)[10]
Low, 2011[25]	Cohort (1.7 years)	Sex workers observational HIV study, Burkina Faso	1.6% at baseline[6,19]	4 (183)	Any[17]	No HPV	HSV2	2.45 (0.26-24.85)[10]	2.26 (0.23-22.60)[10]
Myer, 2007[27]	Cohort (14.3 months)	Cervical cancer screening Study, South Africa	17.5% at baseline[19]	111 (4200)	High-risk[17]	No HPV	NG, CT and sexual behavior	1.72 (1.25-2.35)[10]	1.66 (1.21-2.28)[10]
Smith-McCune, 2010[26]	Cohort (21 months)	HIV prevention trial of diaphragm and gel, Zimbabwe	24.5% baseline[18]	88 (2040)	Any[16] High-risk[16] Low-risk[16] Non-persistent high-risk16 Non-persistent low-risk[16] Persistent high-risk[16] Persistent low-risk[16] 16/18[16] 6/11/16/18 6/11/16/18/31/ 33/45/52/58[8,16]	No HPV No HPV No HPV No HPV No HPV No HPV No HPV No HPV 16/18 No HPV 6/11/16/18 No HPV 6/11 /16/18/31/ 33/45/52/58[8]	TV, NG, CT, HSV2, TP, MC[9] and sexual behavior	1.50 (0.92–2.43) 1.95 (1.19–3.21) 2.02 (1.47-3.98) 2.42 (1.26-2.35) 1.01 (0.72-3.15) 1.50 (0.56-1.84) - - -	1.71 (1.00-2.92)[11] 1.96 (1.16-3.3) 1.7 (1.02-2.85) 1.67 (1.03-2.74) 2.09 (1.27-3.44) 0.82 (0.45-1.50) 1.24 (0.59-2.60) 0.84 (0.32-2.18)[10] 2.00 (1.00-3.99)[10] 2.57 (1.48-4.46)[10]

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First Author, year	Study type (median follow-up per participant)	Participants, location	HPV prevalence	Number of HIV sero-conversions (cohort size or controls)	HPV genotypes	Comparison group	Confounding factors adjusted for[1]	Unadjusted HR (95 % CI)	Adjusted HR (95% CI)
Veldhuijzen, 2010[28]	Cohort (16.6 months[2])	Sex workers observational HIV study, Rwanda	70% at baseline[7,19]	10 (366)	High-risk[17]	No HPV	None	4.9 (1.2-19.7)	-
Studies in men who have sex with men									
Chin-Hong, 2009[23]	Cohort (36 months[3])	Behavioural intervention study, Multicentre, USA	56.8% at baseline[12]	51(1409)	1type[12,17] 2 or more types[12,17]	No HPV No HPV	Self-reported STIs and sexual behavior	2.8 (1.04-7.4) 3.6 (1.5-8.4)	2.0 (0.61-6.5) 3.5 (1.2-10.6)
Studies in heterosexual men									
Smith, 2010[30]	Cohort[4]	Male circumcision trial, Kenya	50% at baseline[14]	63(2168)	Any type[13,17] High-risk[14,17] Low-risk[14,17] 16/18[14,17] 6/11/16/18[14,17] 6/11/16/18/31/ 33/45/52/58[8,14,17]	No HPV No HPV No HPV No HPV 16/18 No HPV 6/11/16/18 No HPV 6/11 /16/18/31/ 33/45/52/58[8]	HSV2 and MC	- - - - - -	1.8 (1.1-2.9) 1.5 (0.9-2.6) 1.8 (0.9-3.6) 1.8 (0.9-3.4)[10] 1.3 (0.7-2.5)[10] 1.4(0.8-2.7)[10]

[1] TV is *Trichomonas vaginalis*, NG is *Neisseria gonorrhoeae*, HSV2 is Herpes simplex virus type 2, TP is *Treponema pallidum*, CT is *Chlamydia trachomatis*, BV is *Bacterial vaginosis* and MC is male circumcision.

[2] Median time from HPV visit (at month 6 of the study) to HIV test follow-up

[3] Calculated from person years follow-up and number of participants

[4] In the original trial follow up was for 24 months. 1550 (71%) entered prolonged follow-up for 42 months. No median follow-up time was provided

[5] Prevalence of oncogenic at baseline, prevalence of non-oncogenic HPV was 60.2%

[6] In those who later became HIV positive

[7] Prevalence of oncogenic HPV In those who later became HIV positive, the prevalence of oncogenic HPV in those who remained HIV negative was 32%

[8] These HPV types are those covered by the nonovalent vaccine

[9] In this study, MC relates to circumcision status of regular partner at baseline or of new partner during return visits

[10] These unpublished data were provided by the authors and are additionally adjusted for the presence of other HPV genotypes

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[11] Unpublished data provided by the authors

[12] Anal sample

[13] Penile sample from glans/coronal sulcus

[14] Penile sample, any site

[15] HPV measured at two time points, and most recent used

[16] At visit prior to seroconversion

[17] At baseline

[18] Cervico-vaginal

[19] Cervical

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Table 2

Risk of bias within studies

First Author	Selection of participants[1]	Time of exposure ascertainment[2]	Loss to follow-up[3]	Outcome ascertainment[4]	Confounding[5,6]	Selective outcome reporting[7]
Auvert[29]	All trial participants who provided at least one HPV result (47% of trial population). Those excluded (53%) had similar baseline characteristics **Low risk**	First available HPV status was used (median follow-up 2.4y/2.2y in HPV uninfected/infected). Consistent results were seen using recent HPV results. **Low risk**	12% loss to follow-up at 48 weeks. **Unclear risk**	Median follow-up 2.5 years. **Low risk**	Adjusted for sexual behavior at baseline, no adjustment for HSV2 **High risk**	No a-priori plan. No response to request for additional analyses **High risk**
Averbach [24]	93% of cases included, exclusions due to missing information. Controls selected from within same cohort study **Low risk**	Repeated HPV testing, median 80 days between exposure and outcome **Low risk**	12% loss to follow-up at completion. **Low risk**	Median follow-up 21.9 months **Low risk**	Adjusted for prospective measurement of sexual behavior and HSV2 **Low risk**	Any HPV infection was the primary exposure of interest. Responded to request for additional analyses **Low risk**
Chin-Hong [23]	No description of how subset (30% of EXPLORE study) were selected from participants in main study **Unclear risk**	HPV assessed at baseline only, median time to outcome between 6 and 36 months[8] **Unclear risk**	Retention rate not documented. **Unclear risk**	Median follow-up 3 years **Low risk**	Adjusted for prospective sexual behavior, no adjustment for HSV2 **High risk**	Primary analysis assessed the association of HPV infection with HIV acquisition No additional analysis provided **Unclear risk**
Low[25]	No description of how subset (40%)of participants were selected from participants in main study **Unclear risk**	HPV assessed at baseline only, median time to outcome between 4 and 24 months **Unclear risk**	Retention rate not documented. **Unclear risk**	Median follow-up 1.7 years **Low risk**	Adjusted for HSV2, no adjustment for sexual behavior **High risk**	HPV analysis was not the primary aim of the publication. Additional analysis provided **Low risk**
Myer[27]	Cohort comprised of all HPV positives in main study and HPV negatives recruited over 1 year **Unclear risk**	HPV assessed at baseline only, median time to outcome between 6 and 24 months **Unclear risk**	25% loss to follow-up at 12months and 68% at 24 months. **High risk**	Median follow-up 14.3 months **Low risk**	Adjusted for baseline sexual behavior, no adjustment for HSV2 **High risk**	HPV analysis was not the primary aim of the publication. Additional analysis provided **Unclear risk**
Smith[30]	Cohort comprised of trial participants consenting to HPV testing (80%) **Low risk**	HPV assessed at baseline only, median time to outcome between 3 and 42 months **Unclear risk**	Retention rate not documented. **Unclear risk**	Median follow-up 42 months for 71% **Low risk**	Adjusted for HSV2, no adjustment for sexual behaviour **High risk**	No a-priori analysis plan. Additional analysis provided **Low risk**
Smith-McCune[26]	Cohort comprised of trial participants consenting to HPV	HPV assessed every 3 months. Recent infection was within 6 months	6% loss to follow-up. **Low risk**	Median follow-up 21 months	Adjusted for prospective sexual behavior and HSV2	A-priori analysis plan. Additional analysis provided

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First Author	Selection of participants[1]	Time of exposure ascertainment[2]	Loss to follow-up[3]	Outcome ascertainment[4]	Confounding[5,6]	Selective outcome reporting[7]
	sub-study (98%) **Low risk**	excluding concurrent visit **Low risk**		**Low risk**	**Low risk**	**Low risk**
Veldhuijzen [28]	Cohort comprised of those with HPV results from main study (92%) **Low risk**	HPV assessed at baseline only, median time to outcome between 3 and 18 months **Unclear risk**	12% loss to follow-up. **Low risk**	Median follow-up 16.6 months **Low risk**	No adjustment for confounders **High risk**	No a-priori plan. No additional analysis provided **Unclear risk**

[1] In case control studies here was a high risk of bias if >90% of cases were not included (and/or exclusion was related to exposure or outcome) or controls were not selected from within the cohort study. Unclear risk when this information was not available. In cohort studies, there was low risk of bias if the cohort were representative of the average individual in the population of interest, and both the exposed and unexposed were drawn from the same population. Unclear risk if this was not the case or not documented.

[2] Low risk if HPV was tested prospectively and/or the time between exposure and outcome was <1year. High risk if this time was ≥ 1 year and unclear risk if insufficient information was available.

[3] Low risk if retention was ≥80% at the end of the study. Unclear risk if information not available.

[4] High risk of bias if follow-up was not long enough for HIV to be acquired (less than 1 year). Low risk if median follow-up was at least 1 year and unclear risk if information not available.

[5] See table 1 for full list of confounders adjusted for.

[6] Low risk of bias if adjustment for prospective measurements of sexual behavior AND HSV2. Unclear risk if adjustment for sexual behavior OR HSV2 serology at baseline only. High risk if HSV2 OR sexual behavior not adjusted for.

[7] If (i)authors stated there was an a priori plan or stated which outcomes were of primary interest or (ii) authors responded to a request for further information and analysis then there was a low risk of bias. Of one of these was met this was unclear risk, if none were met this was high risk

[8] Where median time was not available in studies which tested baseline HPV only it is assumed to be between minimum follow-up HIV test frequency and total study follow-up.

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Table 3
Study-specific population attributable fractions

First Author	Study population	HPV genotype	Prevalence of HPV genotypes in HIV cases[1] (%)	Adjusted effect estimate (95% CI)	Population attributable fraction (%) (95% CI[2])
Averbach[24]	Women, Zimbabwe	Any HPV	63.4	2.4 (1.5-4.0)	37.0 (21.1-47.6)
Smith-McCune[26]	Women, Zimbabwe	Any HPV	50.0	1.7 (1.0-2.9)	20.8 (0-32.9)
Smith[30]	Heterosexual men, Kenya	Any HPV[3]	61.9	1.8 (1.1-2.9)	27.5 (5.6-40.6)

[1] Before HIV acquisition

[2] the C-I applies only to the proportion of HIV infections attributable to HPV in the individuals in these studies, and not in the wider population.

[3] HPV in glans/coronal sulcus of penis