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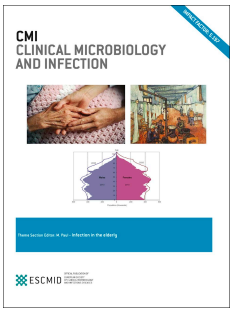

Pros and cons of circumcision – an evidence-based overview

Boris Friedman, MD, Johad Khoury, MD, Neta Petersiel, MD, Tal Yahalomi, Mical Paul, MD, Dr. Ami Neuberger, MD

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Pros and cons of circumcision – an evidence-based overview

(Invited Review)

Friedman Boris, MD, Khoury Johad, MD, Petersiel Neta, MD, Yahalomi Tal, Paul Mical, MD, Neuberger Ami, MD

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Postal Address: Rambam Medical Center, Unit of Infectious Diseases, 8 Haalya Hashnya St., Haifa, 3109601, Israel

Corresponding author: Dr. Ami Neuberger

Email address: a_neuberger@rambam.health.gov.il

Phone: 972-50-2062718

Fax 972-4-7771620

Abstract

Based on three large randomized controlled trials (RCTs) conducted in Africa, it can clearly be stated that circumcision lowers the risk of infection with the human immunodeficiency virus (HIV) and some sexually transmitted infections (STIs) among males in settings of high HIV and STI endemicity. Similar effects on STI risk may exist for females, although this may be partially due to an indirect effect of decreasing risk of infection among male partners. It is unknown whether circumcision prevents HIV acquisition in men who have sex with men (MSM), although there might be a protective effect for men who engage mainly in insertive anal intercourse. When the effects of adult circumcision on sexual function and satisfaction of men are examined, high-quality evidence strongly supports lack of harm. Whether circumcision alters sexual satisfaction of female partners is not known as fewer and smaller studies reported conflicting results. Circumcision rarely causes serious complications if practiced by trained practitioners, in a sterile setting, and with a proper follow-up. These conclusions are limited by the lack of high-quality data from areas outside of Africa. RCTs that assessed the effect of circumcising infants or MSM have not been conducted. Circumcision has well proven benefits for people residing in areas with high prevalence of STIs, including HIV, and is not unethical for those who choose to be circumcised or have their children circumcised on religious, social, or cultural grounds. For many others, a definite pro or con recommendation, based on a risk-benefit ratio, cannot be made.

Introduction

Few procedures generate as much controversy as male circumcision. While religious and social factors strongly influence the decision of many adults and parents about circumcision, others seek to understand in what ways, medically speaking, this procedure can bring benefits or cause harm. While reviewing the literature for this review we have made two observations: first, the abundance of very low-quality research, some of which are clearly biased unreservedly for or against circumcision; second, the fact that the bulk of trials and systematic reviews concentrate on one aspect of possible benefits or harms, but do not provide a general overview [1]. Thus, we have tried to filter out bad science, and provide a balanced discussion of the pros and cons of circumcision for the ones who have to make a very personal decision.

Methods

We searched PubMed and the Cochrane Library for the term "circumcision", filtering in PubMed for clinical trials and systematic reviews. We addressed primarily systematic reviews of randomized controlled trials (RCTs). Where unavailable, we searched for RCTs, and when RCTs were unavailable or insufficient we included observational studies in the literature review. We rated the quality of the evidence as very low, low, moderate ,or high. We based the rating primarily on the study design (high quality for RCTs and low quality for observational studies) and then downgraded or upgraded according to the studies' internal validity, following the GRADE recommendations [2]. We accepted the quality rating from systematic reviews using the GRADE system and risk of bias assessment from other systematic reviews. We used the terminology "affected" for high-quality evidence, "probably affected" for moderate quality evidence, "may be affected" for low quality evidence, and "effect not known" for very low quality or no evidence [3].

Circumcision and the risk of HIV acquisition

Heterosexual men

The inner surface of the foreskin contains Langerhans cells with human immunodeficiency virus (HIV) receptors, which explains the biological rationale for using male circumcision to decrease rates of HIV acquisition among men [4]. Early non-randomized studies that tried to assess the effects of circumcision on HIV could not control for religion and tradition as confounding factors. Three major RCTs comparing immediate vs. delayed (21-24 months) circumcision and assessing HIV acquisition in the interval were conducted in South-Africa, Kenya, and Uganda in the 2000s. All were stopped early when male circumcision was shown to decrease the rates of HIV acquisition in planned interim-analysis [5-7], (Table 1). A Cochrane review of these RCTs, which included a total of 11,500 men, showed that circumcision reduced HIV acquisition with an incidence risk ratio (IRR) of 0.46 (95% confidence interval (CI): 0.34 to 0.62) at end of follow-up. The number needed to treat (NNT) at 21 to 24 months was 56 (95% CI: 41 to 90). Circumcision prevented 17 HIV infections (95% CI: 11 to 24) over two years per 1,000 men, with a control event rate of 2.5% translating to a population yearly incidence of HIV acquisition of 1.25% [8]. The quality of the evidence was moderate to high, downgraded for unreliable randomization methods in two of the trials and early discontinuation in all three trials (although discontinuation rules were defined in all three).

The public health implications of male circumcision have not been studied adequately, as all RCTs assessed the intervention's effect on individuals rather than on populations. A few mathematical models, aimed to estimate the potential impact of increased circumcision coverage on the incidence of HIV in Africa, have been proposed. . A dynamical simulation model, for example, suggested that full coverage of circumcision could avert 0.3 (0.1-0.5) million deaths in the first 10 years and a further 2.7 (1.5-5.3) million in the next 10 years, in sub-Saharan Africa [9]. However, by definition, models can never account for all additional factors that can influence the impact of a specific intervention on disease incidence [10]. Increasing rates of antiretroviral coverage make long-term assessment of the procedure itself impossible, and the effect of circumcision on sexual risk taking is unknown. In the three RCTs described above, circumcised males practiced riskier sex behaviors,

leading to concerns about disinhibition and higher transmission rates of HIV. Other observational studies from Africa showed mixed results regarding the possibility of disinhibition following circumcision. Recently, a cohort study from Uganda found that, while the circumcision program attracts more sexually active males, it does not alter their sexual behavior [11-13].

Evidence outside of Africa comes mostly from observational studies. Such studies were conducted in the USA and Israel, where circumcision rates are high and HIV burden is relatively low, and similarly showed an inverse association between circumcision and HIV acquisition[14-15]. A systematic review of studies conducted in India included 13 observational studies, showing that circumcision may reduce HIV acquisition by approximately 40% (OR: 0.66; 95%CI:0.53–0.83) [16]. Since circumcision in India is almost exclusively practiced by Muslims, bias is likely (low quality evidence).

Following the publication of the RCTs from Africa, the Center for Disease Control and Prevention (CDC) announced in 2007 that there is "sufficient evidence to inform heterosexually active males about the significant, albeit partial, efficacy of medical circumcision in reducing the risk of HIV infection" [17]. Similarly, the WHO/UNAIDS recommends male circumcision as an efficacious intervention for HIV prevention in countries with high HIV incidence and low male circumcision prevalence[18].

Women

Since male circumcision reduces the incidence of HIV among men, it may indirectly reduce women's risk of exposure. Whether circumcision can directly prevent the acquisition of HIV by female partners of HIV-infected men is uncertain. Only one RCT, conducted in Uganda in 2009, addressed this issue and was discontinued early due to futility [19] . In this trial 922 discordant couples were enrolled and randomized either to circumcision or control (delayed circumcision for 24 months). Surprisingly, there was a small increase in the risk of HIV acquisition among women in the

intervention group, mainly due to early resumption of sexual activity before wound healing, and an increase in the viral load shortly after circumcision (high-level evidence). A systematic review summarizing this RCT and a few longitudinal observational studies showed that male circumcision probably does not reduce the risk for HIV among women (relative risk 0.80, 95% CI 0.53-1.36) [20].

Men who have sex with men (MSM)

To the best of our knowledge, no RCT assessed the impact of circumcision on the risk of HIV acquisition among MSM. A Cochrane systematic review published in 2011 included 20 observational studies in high- and middle-income countries with a total of 65,784 participants. The meta-analysis showed that circumcision may reduce HIV acquisition among MSM reporting an insertive anal role (seven studies), but might not have an effect among MSM practicing a receptive role (three studies), low-quality evidence [21]. Similar results were reported in another systematic review, highlighting the fact that a protective effect was demonstrated only in studies conducted before the highly active antiretroviral therapy era [22]. Recently, an observational study of the risk of HIV acquisition conducted among MSM in China, involving 1,155 men, showed that circumcised MSM were less likely to acquire HIV (aOR, 0.46; 95% CI, 0.24-0.89). Again, this protective effect was most pronounced among MSM who predominantly practiced insertive anal intercourse [23].

Adult circumcision and sexually transmitted infections

To provide an overview of the evidence on the effect of circumcision on the risk of acquisition of various sexually transmitted infections (STIs), we will separate infections into those whose incidence is decreased, those whose incidence is possibly decreased, and those whose incidence is unaffected by circumcision.

Heterosexual men

STIs whose incidence is decreased or likely to be decreased following circumcision include:

- Human papilloma virus (HPV), high-quality evidence: Large RCTs of immediate versus deferred circumcision, all of which were performed in Africa, included a total of 3,921 and 3,815 men in the intervention and control arms, respectively. These trials clearly demonstrate that circumcision decreases HPV infection rates among HIV-negative heterosexual men. Overall infection rates were 14.8-18% in the intervention group and 23.3-27.8% in the control group [24-27]. Among HIV-positive men included in an RCT performed in Uganda, circumcision decreased the risk of high-risk multiple HPV genotype infections (RR 0.40, 95% CI, 0.19-0.84), control event rate 24.7% [28]
- Mycoplasma (moderate quality evidence): In one RCT from Kenya, which included 2,784 men, the prevalence of *Mycoplasma genitalium* was 13.4% among uncircumcised men versus 8.2% among circumcised men. After adjustment for other risk factors for infection, being circumcised nearly halved the odds of *Mycoplasma genitalium* infection (aOR 0.54; 95% CI 0.29-0.99) [29].
- Genital ulcer disease (GUD): The clinical syndrome of GUD is caused mainly by STIs, and its incidence is assessed as a general estimate of STI incidence when specific microbiologic diagnoses are not available. Two large RCTs, which included 8,315 participants, showed that GUD incidence was halved among circumcised men, with a risk ratio of 0.51-0.52 [30] .Similarly, a prospective observational study of 746 men showed that an uncircumcised status was an independent risk factor for GUD (hazard rate ratio = 2.5) [31].

STIs whose incidence is possibly decreased by circumcision:

- Syphilis: One large RCT from Uganda, which included 5,534 men, showed no significant difference between circumcised and uncircumcised men in new acquisition of syphilis; adjusted hazard ratio, 1.10; 95% CI, 0.75 - 1.65; P = 0.44) [24]. On the other hand, another RCT, performed on 4761 males in Kenya and Uganda, showed that circumcision was associated with a 42% reduction in the incidence of syphilis (adjusted hazard ratio 0·58, 95% CI 0.37-0.91). In a subgroup analysis among HIV-infected men, a 62% reduction in the incidence of syphilis

was noted (0·38, 0·18-0·81), whereas a nonsignificant reduction in the incidence of syphilis was observed among men without HIV (0·64, 0·36-1·11) [31].

- Herpes Simplex Virus (HSV): RCTs from Uganda [24] and South Africa [32] showed a significant reduction in HSV infection rates after circumcision. Two other trials conducted in Kenya failed to show such a reduction [30-33]. The discrepancy between these trials was attributed to lack of specificity of the assay used in some trials, different prevalence of HSV at baseline, different age groups, and different numbers of sexual partners.

Finally, STIs whose incidence is probably not affected by circumcision include:

- Gonorrhea: One RCT [34] and one observational study [35], both performed in Africa, did not show a risk reduction of gonorrheal infection after circumcision.
- *Chlamydia*: one RCT did not show a relationship between circumcision status and *Chlamydia* infection [34].

The evidence summarized above derives mostly from an analysis of secondary outcomes in the circumcision RCTs conducted in Africa, performed to assess its effect on HIV acquisition. The effects of circumcision on STIs in non-African countries have not been studied rigorously. Based on observational studies conducted in the United States, it is likely that circumcision both prevents HPV and increases the likelihood for clearing existing HPV infections [36-37]. Data on HSV is conflicting as a cohort study conducted in Austria showed a protective effect of circumcision, while trials in America and India failed to demonstrate such an effect [38-40]. Studies conducted in the United States, India, and Austria demonstrated conflicting results with regard to the effect of circumcision on the incidence of HSV and syphilis [38-41].

<u>Female partners</u>

STIs whose incidence is decreased or likely to be decreased:

- HPV: Based on three RCTs conducted in Uganda, there is strong evidence that male circumcision decreases HPV infection rates in female partners of circumcised HIV-negative males [42-43], but does not affect HPV transmission

among couples when the men are HIV positive [44]. Outside of Africa, a meta-analysis on 1,913 couples included in case-control studies, showed that circumcision is associated with a lower risk of cervical cancer among monogamous female partners of men with multiple sexual partners; aOR, 0.42; 95% confidence interval, 0.23 - 0.79 [45].

STIs whose incidence is possibly decreased by circumcision:

- GUD and bacterial vaginosis: Based on a single RCT, the risk for GUD, bacterial vaginosis and trichomonas infection may be reduced in female partners of circumcised males [46]. Circumcision was not associated with a lower risk for bacterial vaginosis in one retrospective study conducted in the United States [47].
- *Chlamydia trachomatis*: In a multinational retrospective study, circumcision was associated with a lower risk for Chlamydia trachomatis infection in female sexual partners of circumcised males [48] .

STIs whose incidence is probably not affected by circumcision:

- HSV and genital mycoplasma: The risk of HSV and genital mycoplasma infections is probably not reduced in females whose sexual partners have been circumcised [49-50].

Men who have sex with men

To the best of our knowledge, no RCT assessed the effect of circumcision on the risk of STIs among MSM. In several observational trials no association between male circumcision and STIs was found [51-54]. The STIs assessed included HSV-2, syphilis, urethral gonorrhea, and urethral *Chlamydia* infection. One study reported a significant, protective effect of circumcision on the risk of syphilis acquisition, and no association for other STIs [55], while another reported no association for most STIs,

but a significantly greater risk of acquiring non-chlamydial non-gonococcal urethritis [56].

The effects of circumcision on sexual function and satisfaction

Men

Two of the RCTs conducted in Africa primarily assessed the effects of circumcision on HIV, also analyzed outcomes related to sexual function and satisfaction. In the trial conducted in Uganda, decreased sexual satisfaction or sexual dysfunction were reported equally by <2% of participants in both study arms [57] . In the trial from Kenya, circumcision similarly did not affect sexual dysfunction. Men in the intervention group reported increased penile sensitivity and enhanced ease of reaching orgasm, with 99.5% of circumcised participants reporting that they were "very satisfied" with the outcome [11, 58-59]. Participants in several large nonrandomized trials conducted in Africa similarly reported that they had either equal or improved sexual satisfaction following circumcision [60-61].
Evidence in middle- or high-income countries is mostly derived from low-quality observational trials, the majority of which did not account sufficiently for confounders. Such studies were conducted in China [62], Taiwan [63], Korea [64] several European countries[65-66], Australia [67], and the United States. Most studies reported either no harm or increased sexual satisfaction, while fewer studies reported some degree of sexual dysfunction. In one relatively large observational trial conducted among MSM in Australia, sexual dysfunction or decreased sexual satisfactions were similar among circumcised and non-circumcised participants[67].

Women

Few studies examined women's preferences regarding the status of partner circumcision. In the trial conducted in Uganda, nearly all women (97.1%) reported either no change or improved sexual satisfaction after their partners were circumcised [68]. The vast majority of women partners of male participants in the

trial from Kenya reported that they were very satisfied (92%) or somewhat satisfied (5%) with the outcome of circumcision [59]. Other large observational trials conducted in Africa reported similar results: In Malawi, women were more likely to report greater sexual pleasure with a circumcised partner[61], and similar results were observed in Zambia [60] . The only relatively large study conducted in a high-income country reported that circumcision might decrease sexual satisfaction among female partners. This analysis is limited by a cross-sectional design, and a low number of circumcised participants (125 out of 2,345 participants) [69] .

Complications of the circumcision procedure

Surgical circumcision

Conventional circumcision by surgical removal of the foreskin is the standard procedure used in most circumcision programs. Circumcision may result in early (intraoperative) or late (postoperative) complications [70-72]. Early complications tend to be minor and treatable: pain, bleeding, swelling or inadequate skin removal [70, 73]. Serious complications, such as amputation of the glans penis, occur only rarely [71-72]. Late complications may include pain, wound infection, edema, urinary retention and urinary tract infections (UTIs), meatal ulcer, meatal stenosis, foreskin adhesions, fistulas and loss of penile sensitivity [74]. Rates of reported complications vary greatly between studies, since these rates are affected by the setting of the surgical procedure and data collection methods [75-76].

Complication rates correlate with age, occurring least frequently in neonates and infants. In a systematic review the median frequency of any and serious adverse event following neonatal or infantile circumcision performed by medically trained providers was 1.5% (range 0-16%) and 0% (range 0-2%), respectively. In children aged one year old or older, the median frequency of any or serious adverse event was 6% (range 2-14%), and 0% (range 0-3%), respectively [77]. The simpler nature of the procedure among neonates - no need for suturing, and better healing - was hypothesized to underlie the lower rate of complications in this age group. In high-

and middle-income countries, but not in Africa, adverse events were observed most commonly among boys circumcised for medical, rather than religious or cultural reasons [78-80]. In a study that included boys circumcised mainly for phimosis in the United Kingdom, the frequency of any adverse events was 6.4%, and 2.8% required re-admission to hospital [78]; similar frequencies of readmissions were reported in a Danish study [79].

In middle- to high-income countries (Iran and Israel), some case-control studies found that UTIs were more likely to occur following circumcision by a traditional, rather than a medical provider [81-84]. Data from African countries clearly shows that the rate of complications is higher when conducted in a traditional setting [11, 76, 85-87]. A systematic review of complications after traditional male circumcision in South African found rates of 35% to 48%, and mortality rate of 0.2%. Poor postoperative care by traditional circumcisers is likely to contribute to increased complication rates [86-87] .

Non-surgical circumcision

In recent years, there has been an increase among adults in the use of circumcision devices that do not require suturing and hemostasis. A systematic review summarizing eight RCTs, including 3,314 patients, compared the safety and efficacy of conventional versus device-assisted circumcision[88]. A lower complication rate was observed in the device group in comparison with the conventional technique group (RR, 0.54; 95% CI, 0.39-0.74;). This difference was largely driven by lower bleeding and higher healing rates. Nevertheless, the expertise of the provider may be much more influential on the incidence of complications than the technique used[77, 87] .

Conclusions

The effects of circumcision are still largely debated, and conflicting conclusions were previously drawn from existing data.

It can be clearly stated that adult circumcision decreases the rate of HIV acquisition among men in settings with a high incidence of HIV and therefore indirectly reduces women's risk of exposure (Table 2). We do not know whether there is a direct effect of male circumcision on women's risk for HIV. There may be a transient increase in HIV acquisition risk if sexual intercourse occurs immediately after the procedure, before wound healing. It is also uncertain whether circumcision prevents HIV acquisition in MSM, although there might be a protective effect for men who mainly engage in insertive anal intercourse. The RCTs conducted in Africa provide ample evidence of the effect of circumcision for the prevention of several, albeit not all, STIs among men. Evidence among female sexual partners is of lower quality, but also seems to show a beneficial effect for some STIs. Evidence among MSM comes from observational trials, which may be inadvertently biased, so that no definite conclusions can be drawn. Severe adverse events after adult and infant circumcision are rare.

All these beneficial effects of circumcision are relevant for high HIV- and STI-endemicity settings. Whether circumcision carries benefit outside of Africa is unknown. We do not know the effects of circumcision following infant or child circumcision performed as part of religious or social ceremonies. In this setting the relevant outcomes might be UTIs in infants and life-long STI acquisition. In addition, the scope of this review does not allow for a full discussion of the epidemiological impact of a circumcision policy in Africa

Deciding whether to perform the procedure is easier for people residing in areas with high prevalence of STIs, including HIV, and for those who choose to be circumcised or have their children circumcised on religious, social, or cultural grounds. For many others, a definite pro or con recommendation, based on a risk-benefit ratio, cannot be made.

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Table 1: Randomized controlled trials of immediate vs. delayed surgical circumcision in Africa

	Auvert 2005[5]	**Bailey 2007**[6]	**Gray 2007**[7]
Location	Orange Farm, South Africa	Kisumu, Kenya	Rakai, Uganda
Study years	2002-2005	2002-2005	2002-2006
Age range (yrs.)	18-24	18-24	15-49
N patients	3,274	2,784	4,996
Duration of follow-up	21 months	24 months	24 months
Risk of bias [1]			
Selection bias [2]	High risk	Unclear	High risk
Other	None	None	None

[1] All trials stopped early based on pre-defined stopping rules. As the primary outcome (HIV acquisition) was objective, blinding was deemed less relevant and is not addressed.

[2] Based on the highest risk of random sequence generation and allocation concealment

Table 2: Effect of circumcision on the risk of acquiring human immunodeficiency virus (HIV) and other sexually transmitted infections (STIs) in randomized controlled trials (RCTs)

Pathogen or syndrome	**Countries**	**Effect of circumcision**	**Comments**
HIV			
• HIV among heterosexual men	South Africa [5] Kenya [6] Uganda [7]	RR[1] = 0.4 (0.24-0.68) RR = 0.47 (0.28-0.78) RR = 0.43 (0.24-0.75)	Relative risk similar in all three large RCTs
• HIV among females	Uganda [19]	HR[2] = 1.49 (0.62-3.57)	Circumcision of HIV-infected males did not reduce HIV-transmission to female partners
• HIV among MSM[3]	South Africa [21] - Insertive role - Receptive role	 OR[4] = 0.27 (0.17-0.44) OR = 1.2 (0.63-2.29)	Circumcision prevented HIV only in MSM practicing mainly insertive anal sex

STIs among heterosexual men			
• HPV[5]	Uganda [24] Uganda [25] Uganda [28]	aRR[6] = 0.65 (0.46-0.90) RR = 0.67 (0.51-0.89) RR = 0.4 (0.19-0.84)	Circumcision reduced HPV infection in both HIV- positive [22] and HIV - negative men
	South Africa [26]	PRR[7]- 0.66 (0.51-0.86)	
	Kenya [27]	RR- 0.34 (0.13-0.86)	
• Mycoplasma	Kenya [29]	OR = 0.54 (0.29-0.99)	
• Genital Ulcer Disease (GUD)	Kenya [24] Uganda [31] - HSV negative - HSV-positive	RR = 0.52 (0.37-0.73) PRR = 0.51 (0.43-0.74) PRR = 0.66 (0.51-0.69)	
• Syphilis	Uganda [24]	aHR = 1.1 (0.75 - 1.65)	In a sub-group analysis of the Ugandan trial circumcision was protective against syphilis among HIV-positive, but not among HIV-negative men

	Uganda [31]	RR = 0.58 (0.37-0.91)	
• HSV [8]	Uganda [24] South Africa [32] Kenya [30] Kenya [33]	aHR = 0.72 (0.56- 0.92) IRR = 0.45 (0.24 – 0.82) RR = 0.94 (0.70-1.25) HR = 0.88 (0.77-1.10)	In some, but not all trials there was a reduction in HSV incidence. Trials differed in prevalence of HSV at baseline, age groups, number of sexual partners, and assays used
• Gonorrhea	Kenya [28] South Africa [29]	IRR = 0.95 (0.68 – 1.34) OR = 0.97 (0.71-1.32)	No effect
• Chlamydia	Kenya [34] South Africa [35]	IRR[9] = 0.87 (0.65 – 1.16) OR = 0.58 (0.33 - 1.03)	No effect
STIs among females			
• HPV	Uganda [42] Uganda [43] Uganda [44]	RR = 0.72 (0.60-0.85) RR=0.66 (0.50-0.87) RR = 1.07 (0.86-1.32)	Circumcision reduced HPV infection rates of female partners of HIV negative men [36, 37], but not of HIV positive men [38]

• Genital Ulcer Disease	Uganda [46]	RR = 0.78 (0.63-0.97)	
• Mycoplasma	Uganda [50]	PRR = 1.0 (0.48- 2.12)	

[1] RR=relative risk [2] HR=hazards ratio [3] MSM=men who have sex with men [4] OR=odds ratio [5] HPV=human papilloma virus [6] aRR=adjusted risk reduction [7] PRR = prevalence risk ratio [8] HSV=herpes simplex virus [9] IRR = incidence rate ratio

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