# The Role of Circumcision in Preventing STIs

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**Core Messages**

- Male circumcision affords substantial protection against genital ulcer disease (GUD), human immunodeficiency virus (HIV), high-risk types of human papillomavirus (HPV), herpes simplex virus type 2 (HSV-2), *Treponema pallidum* (syphilis), *Haemophilus ducreyi* (chancroid), *Trichomonas vaginalis*, and *Candida albicans* (thrush).
- It offers little or no protection against *Neisseria gonorrhea*, *Chlamydia trachomatis*, and nonspecific urethritis.
- In the female sexual partner, circumcision of the male partner is associated with greatly reduced HPV, chlamydia, HSV-2, Trichomonas, and bacterial vaginosis.
- At the population level, increased rate of male circumcision should reduce heterosexually acquired HIV/AIDS, as well as genital HPV, penile and cervical cancer, prostate cancer, genital herpes, infertility in each sex, pelvic inflammatory disease, and ectopic pregnancy.
- Male circumcision is an important component of strategies to reduce the global burden of many STIs.

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## 54.1 Introduction

This chapter describes the effect of male circumcision on incidence of various sexually transmitted infections (STIs). Protection against STIs is just one of the many benefits that circumcision confers [1, 2].

## 54.2 Ulcerative and Nonulcerative STIs Other Than HPV and HIV

The first medical link between circumcision and protection against STIs concerned syphilis in 1855 [3]. This was confirmed in 1891, when protection against genital herpes (HSV-2) and urethritis was also noted [4]. Subsequent reports showed protection against syphilis and chancroid, but for nonulcerative STIs and HSV-2, both protection (1.3- to 3-fold) or no protection have been reported [5–18].

The reports of protection against nonulcerative STIs tend to be in earlier studies and those in developing nations, whereas more recent studies have tended to show little or no difference. However, it is important to note that some of these data are based on studies of men attending STI clinics. Such data should be viewed with caution, since any protective effect afforded by circumcision against a particular STI will mean lower presentation of circumcised men to a STI clinic. For this reason, reports in the literature that involve STI clinic attendees are likely to be biased away from detection of association with lack of circumcision. Studies involving general populations are therefore more likely to yield reliable data.

A review in 1998 of 11 studies [19] noted only 2 of 6 studies that showed an association of HSV-2 with

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lack of circumcision [15, 17]. For gonorrhea, it was 5 of 7 [16, 20] and with chlamydial, nongonococcal, or other types of urethritis, 2 of 8 [6, 9, 16].

A meta-analysis of ulcerative STIs examined 26 research articles (from the United States, United Kingdom, Australia, Africa, India, and Peru) and found circumcision protected against chancroid and syphilis, but for HSV-2, it was only 12% lower [21] (Table 54.1).

Consistent with this, a study by the US Centers for Disease Control and Prevention found 12% lower HSV-2 seroprevalence (13.7% vs. 11.6%) in circumcised men [22]. HSV-2 infection per sex act was 0.013 in uncircumcised men, compared with 0.0074 in circumcised men (RR 0.56; $P = 0.005$) [23]. Two small longitudinal studies of STIs common in New Zealand produced conflicting results. One found a 3.2-fold higher rate of STIs, including 2.5 times more chlamydia, to age 25 in the uncircumcised men [24]. The other saw no difference [25]. This included similar HSV-2 seroprevalence [7].

In two randomized controlled trials (RCTs), lower HSV-2 seroprevalence was seen in the men who had been circumcised. HSV-2 was 45% lower in the trial in Orange Farm, South Africa [26], and was 30% lower in the trial in Rakai, Uganda [27]. Interestingly, although HSV-2 seroincidence has been found not to differ between circumcised and uncircumcised men [7, 28], the incidence of genital ulcer disease (GUD), including herpetic lesions, has been reported to be twice as high in uncircumcised men [29]. This might suggest that circumcision reduces the recurrence of genital lesions arising from HSV-2 infection. Such a possibility is supported by a small Indian study that found recurrence to be 20 times lower in men who underwent circumcision compared to men who remained uncircumcised, and interval between bouts was longer in the circumcised men [30]. A study of Black heterosexual 18–25-year-old men attending an STI clinic in the United States found that, although HSV-2 did not differ, the seroprevalence of HSV-1 was 2.8 times higher in those who were not circumcised [28].

The data emanating from Rakai, Uganda, was from two RCTs in that locality. One of these (RCT-2) involved men with a higher sexual-risk profile. An initial report, focused primarily on HIV prevention, found that circumcision afforded 48% protection against GUD [31]. In a subsequent report, GUD was 39% lower in circumcised men in RCT-2 but did not differ in RCT-1 [32]. Later, GUD was found to be present in 1.9% of uncircumcised men and 0.8% of those who had undergone circumcision, and period prevalence of GUD was reported as being 46% lower in the circumcised [33]. Circumcision was associated with a reduction in GUD of 49% in those who were HSV-2 seronegative. No difference in syphilis seroprevalence was found [32], but only 2% of men were infected with this STI. Although it was suggested at the time that the RCT might have been insufficiently powered to reach a valid conclusion [34], positive syphilis serology was, however, found in 7% of men in each group in a later report, which also tested for *T. pallidum* DNA and found positive results for this organism in 7/56 swabs from genital ulcers in uncircumcised men, but none of the ulcers in 25 circumcised men [33]. In this report, HSV-2 seroprevalence was 27% and 28% in each respective group, and in men with genital ulcers, HSV-2 DNA was found in 48% and 39% of swabs ($P = 0.62$) [33]. None of the ulcers in either group contained DNA for *Haemophilus ducreyi* or HSV-1. A large proportion of those whose test was STI negative had a non-STI as a cause of the ulceration. It was suggested that most of the ulcers were a result of infection by non-STI pathogens of tears in the foreskin and its attached frenulum, pointing out that tearing occurs commonly in uncircumcised men during intercourse [33].

Incident syphilis was 2.9 times lower in a study in Sydney, Australia, of circumcised, as opposed to uncircumcised, men who had sex with men (MSM), and was ten times lower in those who only engaged in insertive anal intercourse [35]. Similarly, a study of MSM in Seattle, USA, found syphilis to be twofold lower in those who were circumcised and was completely absent from the 11% who said they were insertive-only [36]. In the US study, seroprevalence of HSV-2 was 34% lower, although in this and the Australian study, the differences in HSV-2 and HSV-1

**Table 54.1** Meta-analysis, showing protection by circumcision against ulcerative STIs

| STI | Studies | Relative Risk (Confidence Interval) |
|---|---|---|
| Syphilis | 14 of 14 studies | 0.61 (0.54–0.83)<br>0.53 (0.34–0.83)[a] |
| Chancroid | 6 of 7 studies | 0.12–1.11[b] |
| HSV-2 | 6 of 10 studies | 0.88 (0.77–1.01) |

[a]When circumcision was done prior to first sexual intercourse

[b]Individual study RR, since meta-analysis was not possible

seroprevalence as a function of circumcision status were not statistically significant.

A meta-analysis by Van Howe that reported higher sexually acquired urethritis in circumcised men [37] has been shown to be erroneous, since, astonishingly, much of the data he used bore little resemblance to that in the source publications cited, leading to a published critique [38] and an erratum by the journal that effectively invalidates his conclusions [39].

For nonspecific urethritis (NSU), a meta-analysis of the 10 studies sourced in Van Howe's report shows that NSU was in fact slightly but not significantly lower (not higher) in circumcised men: summary OR = 0.92 (95% CI 0.64–1.3) [38].

Similar findings were obtained in the RCT in South Africa, the prevalence of gonorrhea being lower in circumcised men but not significantly so: adjusted odds ratio (AOR) = 0.91 [40]. In this trial, *Chlamydia trachomatis* was 42% lower, and *T. vaginalis* was 46% lower, the latter showing a statistically significant 51% reduction in an as-treated analysis, with AOR being 0.47 [41]. An RCT in Kenya, however, observed similar prevalence of *N. gonorrhea*, *C. trachomatis*, and *T. vaginalis* in circumcised and uncircumcised men [42].

In an Australian survey, circumcised men had less penile candidiasis (OR 0.40) [43], where yeast infection can follow female sexual contact.

Why does the prepuce increase risk? The warm moist environment under the prepuce favors bacterial replication. It traps microorganisms in a pool of smegma, so facilitating transmission. The inner preputial lining, being mucosal, is delicate, so it and the frenulum can tear during intercourse (Fig. 54.1). The prepuce presents a larger area for infection. As such, it is more prone to Chancroid, although syphilis and HSV-2 infect the genitalia more widely.

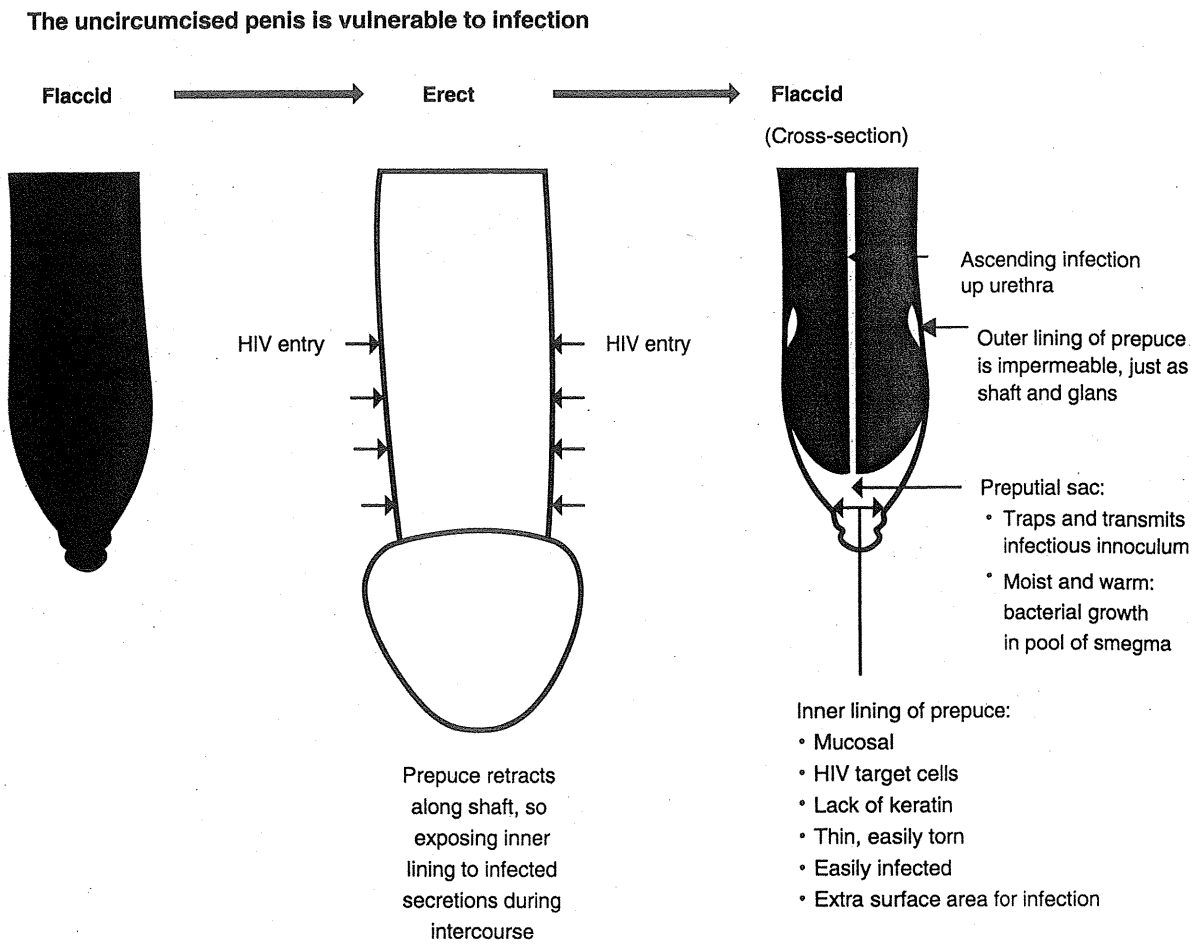


**Fig. 54.1** Aspects of the uncircumcised penis that increase its risk for infection during and after intercourse

## 54.3 HPV and Penile Cancer

### 54.3.1 Incidence

Lifetime penile cancer risk in an uncircumcised man is 1 in 600–900 (US and Danish data) [44], whereas in circumcised men, it is only 1 in 50,000–12,000,000 [45, 46]. Of the 50,000 penile cancer cases in the United States from 1930 to 1990 (10,000 being fatal), only 10 were in circumcised men [47], and these had been circumcised later in life. Thus, neonatal circumcision virtually abolishes the risk [48]. In five major series in the United States, starting in 1932 [49], not one man with invasive penile cancer had been circumcised neonatally [50]. Two other US studies found it was 22 times higher [51–53].

The overall annual incidence of malignant penile cancer (mostly squamous cell carcinoma) in the United States from 1973 to 2002 was 0.69/100,000 [54]. For 1993–2002, it was 0.58/100,000 overall, but was 1.01/100,000 in Hispanics (lower circumcision) compared with 0.51/100,000 in other Whites (higher circumcision) [54]. In the United States, the difference in rate according to race has been attributed to differences in circumcision prevalence [55]. The total lifetime cost of new HPV16 and -18 related cases of penile cancer in the United States in 2003 (25% of total cases) has been estimated as US$ 4.4 million [56].

When circumcision is performed later in life, protection is not as great [57], particularly if "vigorous" ritual circumcision is involved [58]. For carcinoma in situ (rarely fatal), the protective effect is lower [50, 52, 53].

Penile cancer is seen as an "emerging problem" in which "public health measures, such as prophylactic use of circumcision, have proven successful" [59], and "circumcision should be performed in childhood [as a] prophylactic [to penile cancer]" [60]. The rising incidence of penile cancer has, moreover, been linked to decreases in neonatal circumcision in certain countries [61, 62].

In underdeveloped countries, penile cancer incidence is much higher: three to ten cases per 100,000 per year [44]. Where circumcision is uncommon, it can represent 10–22% of all male cancers [63–65]. In Uganda, it is the most common malignancy in males, leading to calls for greater circumcision [66]. The low rate in Nigeria where men are circumcised contrasts with high rates in Uganda [67] and other noncircumcising locations such as Puerto Rico and Brazil [68, 69].

In Israel, where almost all males are circumcised, the rate of penile cancer is only 0.1/100,000 [67].

### 54.3.2 Cause

High-risk HPVs have been implicated in cancer of the penis. High-risk (oncogenic) HPVs are less common in circumcised men [70–77]. A large, multination study in 2002 involving Spain, Thailand, the Philippines, Columbia, and Brazil found HPV in 19.6% of 847 uncircumcised men, but only 5.5% of 292 circumcised men (AOR = 0.37) [71]. A meta-analysis in 2009 of data from 14 studies (5 United States, 2 Mexican, 2 Australian, and one each from England, Denmark, South Korea, Kenya, and a multinational study referred to above, and involving 5,880 circumcised and 4,257 uncircumcised men) found that the protective effect had an OR of 0.52 (95% CI = 0.33–0.82) [78] (Fig. 54.2). Low-risk HPV types that manifest as visible warts tend to occur more commonly on the shaft of the penis, a site of infection unlikely to be affected by circumcision, and the meta-analysis found that circumcision afforded only a slight reduction in these (OR 0.89; 95% CI 0.59–1.33) [78]. An earlier meta-analysis by Van Howe [79] has been criticized severely [80] and should be disregarded.

The protection afforded by circumcision against HPV is supported by two RCTs (reviewed in: [81]). In Uganda, among men aged 15–49 years, one can see a decrease in prevalence of high-risk HPV on swabs from the coronal sulcus from a prevalence of 38% at enrolment down to 18% at 24 months after having been circumcised, compared with a decrease from 37% to 28% in the men who remained uncircumcised, indicating a 35% efficacy of the circumcision [32]. Circumcised men were, moreover, 65% less likely to be infected by multiple high-risk HPV types. In the other RCT, in South Africa involving men aged 18–24 years, high-risk HPV in urethral swabs was 16% in urethral swabs 21 months after circumcision, compared with 25% in the men who were not randomized to the circumcision arm of the trial, pointing to a 35% efficacy [40]. It was further found that circumcision reduced the incidence of new high-risk HPV infection by 42% [81]. Protection against nonhigh-risk types was 34% [32].

The distribution of HPV types on the penis appears to be important, with much higher prevalence of

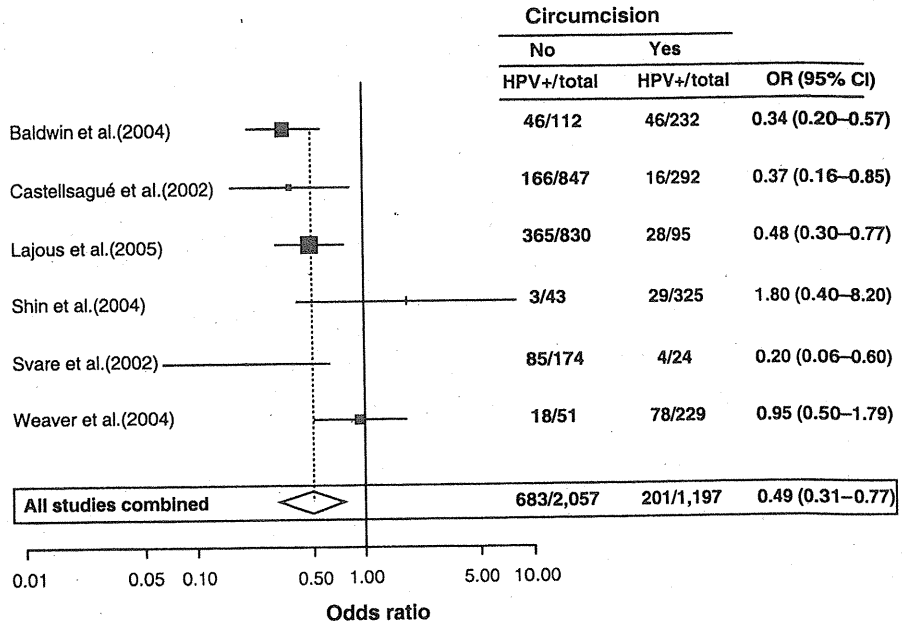


**Fig. 54.2** Meta-analysis of studies exploring the association between being circumcised and penile HPV (Adapted from data in [78, 80])

high- risk types with proximity to the tip of the penis. In one study, the distribution was 28% prepuce, 24% shaft, 17% scrotum, 16% glans, and 6% urine [82]. In another, involving uncircumcised men, high-risk HPV was 31% on the glans/coronal sulcus and 12% on the shaft [83]. The HIM study, involving men in the United States, Mexico, and Brazil, found both high-risk (OR 0.70) and low-risk (OR 0.63) HPV types to be lower in circumcised men [84], HPV prevalence ranging from 41% on the shaft to 4.7% in semen [85]. In this study, the strength of the association between circumcision and reduced HPV decreased with distance from the prepuce/urethra, AOR being 0.17 for the urethra, 0.44 for the glans/corona, 0.53 for the shaft, and no difference for scrotum, perianal area, anal canal, and semen [85]. A study in Hawaii found HPV infection of the glans/coronal sulcus was much higher in uncircumcised men (46% vs. 29%) [72].

Despite similar HPV seroprevalence [86], circumcised men clear penile oncogenic HPV infections six times faster than uncircumcised men [87]. This would further explain their lower risk of penile cancer, and of cervical cancer in their female partner(s). Indeed, in a study of healthy Mexican military men, OR for persistent HPV infection was ten times higher in those who were not circumcised [74].

High-risk HPVs are not easily seen and most infections are subclinical. Prevalence is higher in uncircumcised men with balanoposthitis [73]. Easily seen genital warts, however, are caused by low-risk HPV types [88]. The low-risk HPVs that cause these more commonly infect the shaft, as well as the penis generally, so, not surprisingly, circumcision has been reported to have less of a protective effect against low-risk types (OR 0.89; 95% CI = 0.59–1.33) [78]. RCT data showed protection against nonhigh-risk HPV of 34% (RR 0.65; 95% CI 0.49–0.91; $P = 0.01$).

Most (93%) men whose female partner had squamous intraepithelial lesions (SIL) had penile intraepithelial neoplasia (PIN) [89], consistent with the sexually transmission of HPV. Oncogenic HPV was found in 75% of patients with PIN grade I, 93% with PIN grade II, and 100% of PIN grade III (one step short of penile cancer), and PIN was more common in the uncircumcised [89]. Condom use may lower HPV infection [70].

Phimosis is associated strongly with invasive penile carcinoma (adjusted OR 16) [57] and 11 [90]), and phimosis is seen in 45–85% of patients [57, 91]. A notable feature is dysplastic changes in skin of the preputial sac [92]. The length of the prepuce is probably not a factor, however [93].

Smegma under the prepuce may be carcinogenic [94–97]. It causes chronic inflammation and recurrent infections leading to preputial adhesions and phimosis [57, 92]. Male horses produce large amounts of smegma and have a high penile cancer incidence (23% of cancers) [98]. Geldings do not get erections that would normally

help eliminate smegma and have ten times more penile cancer than stallions [98]. A study in Sweden found that despite affected men reporting a history of smegma, smegma was not, however, associated with invasive squamous cell carcinoma or carcinoma in situ [99].

Chronic-relapsing balanitis of bacterial, mycotic, or viral origin may increase risk of invasive penile cancer [100, 101]. It occurred in 45% of penile cancer patients, but only 8% of controls [52, 91]. Penile lichen sclerosis (balanitis xerotica obliterans [BXO]), an inflammatory disorder that can lead to meatal stenosis or phimosis, is associated with penile carcinoma (reviewed in [59]). Incidence in such patients is 28% [102]. Of these, 77% had squamous cell carcinoma and 23% carcinoma in situ. The rate of HPV infection is 2.6 times higher in BXO [103]. Although oncogenic HPVs were seen in 17% of BXO cases cf. 9% of controls, lichen sclerosis was considered a preneoplastic condition unrelated to HPV infection (reviewed in [59]). Recurrent HSV-2 balanitis may be cocarcinogenic [104, 105].

Of all factors, lack of circumcision is the primary prerequisite for penile cancer [50, 90, 106]. There is, moreover, no evidence that improved penile hygiene reduces penile cancer risk in an uncircumcised man [19, 57]. Circumcision in early childhood, by eliminating phimosis, helps prevent penile cancer [90]. Furthermore, the cause can be sexual transmission of oncogenic HPV in young men or, in older men, a mode unrelated to HPV (reviewed in [59]).

In view of the low 5-year survival [107, 108], and adverse physical, emotional, and psychosexual consequences [109], it is surprising that "despite overwhelming evidence from urological surgeons that neoplasm of the penis is a lethal disease that can be prevented by removal of the prepuce, some physicians continue to argue against routine newborn circumcision in a highly emotional and aggressive fashion" [61].

## 54.4 Prostate Cancer

Risk of prostate cancer correlates with a history of STIs [110–119]. If there is a role for a STI, the nature of this is unclear. There is no consistent evidence for HPV being involved, however. Human polyoma virus BKV [120] or xenotropic murine leukemia virus-related virus (XMVR) [121] could play a role. The common STI *T. vaginalis* has been implicated, especially for risk of extraprostatic prostate cancer (OR 2.2) and clinically relevant, potentially lethal prostate cancer (OR 2.7) [122]. Prostate cancer incidence is 1.6- to 2-fold higher in uncircumcised men [118, 123–125] and is low among Jews [126]. However, more research is needed to confirm the link with lack of circumcision, but if true, would account for 24–40% (45–67,000) extra prostate cancer cases in the United States (where 40% of 70-year-olds are not circumcised), and US$0.8–1.6B in extra costs for treatment and terminal care each year [127].

## 54.5 HPV and Cervical Cancer

There is now overwhelming evidence for a link between lack of male circumcision and increased risk of cervical cancer (see reviews [1, 2]). UNAIDS and IARC data from 117 developing countries noted a cervical cancer incidence of 35/100,000 women/year in 51 countries with a low (<20%) circumcision prevalence, but 20/100,000 women/year in 52 countries with a high (>80%), circumcision prevalence ($P < 0.001$) [128]. Of all factors, the strongest association was with lack of male circumcision.

In 2002, a large, well-designed study of 1,913 couples in five global locations in Europe, Asia, and South America found monogamous women whose male partner was "high-risk" (i.e., had had six or more sexual partners as well as early sexual debut) were 5.6 times more likely to have cervical cancer if the partner was uncircumcised (adjusted OR 0.42) [71]. Circumcision was also protective in women whose partner had an intermediate sexual behavior risk index (OR 0.50). Genital HPV types are highly infectious, meaning any skin-to-skin contact, such as during foreplay, could lead to infection. This study found no significant difference in HPV infection between condom users (OR 0.83) and nonusers (OR 0.67). The higher HPV infection in uncircumcised men could be because the more delicate, easily infected, mucosal lining of the prepuce, when retracted during intercourse, becomes wholly exposed to vaginal secretions of an infected woman (Fig. 54.1). Women with cervical cancer are, not surprisingly,

more likely to have partners with PIN [129], this being 93% in one study [89].

HPV can be transmitted to the mouth during oral sex and is an independent risk factor for some oral cancers [130]. In the past decade, breast tumors have also been found to contain high-risk HPVs [131, 132]. These were the same type(s) as present in the cervix of each patient [133, 134], so supporting a STI contribution to at least some breast cancers [135]. Consistent with this, women with HPV-positive breast cancer were significantly younger than those with HPV-negative breast cancer [136]. HPV-associated koilocytes have, moreover, been found in breast skin and lobules from normal and ductal carcinoma in situ and invasive ductal carcinoma [137, 138]. HPV can, moreover, be found in the bloodstream of cervical cancer patients [139] as well as male blood donors, attached to blood cells [140]. A viral etiology might include mouse mammary tumor virus (MMTV) and Epstein-Barr virus (EBV) [131]. A role for uncircumcised male partner(s) in sexual transmission of an STI responsible for mouth or breast cancer will require further research.

A vaccine against the two types of HPV seen in approx. 70% of cervical cancers is starting to be used in countries that can afford it. It offers only limited protection against the numerous other high-risk HPV types [141], is best given before commencement of sexual activity, was approved for girls only, and uptake has not been universal. A randomized, placebo-controlled, double-blind trial involving 5,455 women aged 16–24 found, however, that vaccination (with Gardasil) reduced the rate of cervical lesions by only 20% over the 3 years of the study [142]. In one analysis, HPV vaccination was found to not be cost effective, even under favorable assumptions for vaccination programs [143]. A review of cost-effectiveness studies by others, however, suggested that vaccination of girls against HPV might be cost effective [144]. For uptake of 80% in 12-year-old girls, the HPV vaccine could reduce cervical cancer by 38–82% after 60 years of an ongoing vaccination program should vaccine protection last 20 years [145]. Vaccination of boys, however, was not cost effective [144, 145]. Male circumcision thus offers a valuable adjunct to the vaccine. Male circumcision also offers protection against acquisition of several other common STIs by women.

## 54.6 Other STIs in Female Partners

### 54.6.1 HSV-2 in Women

History of sexual intercourse (ever) with an uncircumcised man increased risk of HSV-2 infection (OR 2.2; 95% CI 1.4–3.6, after multivariate logistic regression analysis) in 1,207 Pittsburgh women aged 18–30 years (HSV-2 seroprevalence 25%) [146]. A RCT saw two-fold higher HSV-2 infection over 12 months in 800 wives of uncircumcised men [147]. These women also had higher symptomatic GUD (increased 30%). However, a study in Africa showed no difference, although most represented reactivation of existing HSV-2 in this high prevalence setting [148]. Overall, it would seem that circumcision could help counter the worldwide epidemic of HSV-2.

### 54.6.2 Chlamydia in Women

A 5.6-fold higher seropositivity for *Chlamydia trachomatis* has been noted in women with an uncircumcised partner [149]. This study involved 305 couples in five countries. The finding also applied to women who had only ever had one sexual partner. *C. pneumoniae*, which is not transmitted sexually, did not differ. In uncircumcised men, infected cervicovaginal secretions may be trapped under the prepuce for longer, so increasing risk of penile urethral infection and transmission to the vagina during sex [149]. An African study was, however, negative [150].

### 54.6.3 Bacterial Vaginosis and Trichomonas in Women

Bacterial vaginosis (BV) is associated with a range of adverse health outcomes, including premature labor, postpartum endometriosis, pelvic inflammatory disease, and increased risk of STIs. A study in Pittsburgh, where incidence was 36 cases/100 woman-years, found that women who had had an uncircumcised male partner(s) in the preceding 4 months were 1.9 times more likely to have BV [151]. In a large RCT,

satisfies six of Hill's nine criteria of causality (strength of association, consistency, temporality, biological plausibility, coherence, and experiment) [179]. After considering all factors, lack of circumcision has emerged as the major driving force behind the AIDS epidemic [180].

In a meta-regression analysis of 27 studies, lack of circumcision in susceptible men was associated with an infectivity difference versus circumcised men of 8.1 transmissions per 1,000 exposures (range 0.4–16) [181]. Infectivity was, moreover, only weakly associated with geographical region (Africa versus United States/Europe) [181]. In high-risk contexts, such as when the male is uncircumcised, heterosexual infectivity can exceed 0.1, i.e., one transmission per ten contacts, which exceeds by two orders of magnitude the value of 0.001 that is cited commonly [181]. This was later extended to a meta-analysis of 43 publications based on 25 different study populations [182]. It showed female-to-male infectivity, during the asymptomatic phase, of 0.04% per sex act for high income countries and 0.38% for low income countries.

#### 54.7.2.1 United States

DNA sequencing of archival specimens suggested that HIV moved out of Africa to Haiti around 1966 and from there migrated to the United States around 1969, circulating cryptically in the latter for approx. 12 years before AIDS was first recognized in 1981 [183].

A report in 1993 of heterosexual men attending a STI clinic in New York City found HIV to be 2.1% in 405 who were uncircumcised, but only 0.6% in 308 who were circumcised (risk ratio = 4.1) [184].

Heterosexual contact accounted for 15% of HIV infections men in the United States in 2005, this route having grown by 42% over the years [185]. High-risk heterosexual contact accounted for 31–33% of HIV/AIDS cases diagnosed in 2006 [186, 187]. Men comprised 36% and women 64% of heterosexually acquired infections in 2007 [186]. In 2009, it was reported that, among African American men in Baltimore with known heterosexual exposure to infected partner(s), HIV was 51% lower in those who were circumcised [188]. The various findings have led to calls for greater circumcision in the United States [189].

#### 54.7.2.2 United Kingdom, Europe, Russia, and Central Asia

The low circumcision rate in these regions has been accompanied by a rise in heterosexual transmission, provoking calls in the United Kingdom for a change in circumcision guidelines [190]. The proportion of infections due to female to male transmission in Europe is much higher than in the United States, consistent with the influence of the much lower rate of circumcision in Europe [191–193].

#### 54.7.2.3 Asia

Adult HIV incidence in countries with high circumcision rates (Philippines, Bangladesh, and Indonesia) is 0.03–0.06%, compared with 1.8–2.4% for those with low circumcision rates (Thailand, India, and Cambodia) [192], being 3–6% in Thai military conscripts [194]. A prospective study in India of 2,298 men initially not infected saw a 6.7-fold higher HIV infection in the uncircumcised (adjusted RR 0.14) [195]. Another study found HIV incidence in Muslim men (circumcised) was 1% compared with 4.4% in Hindu men (uncircumcised) (OR 0.42), despite Muslim men having more sex partners and visits to commercial sex workers [196]. This finding was not influenced by concurrent infection with other STIs. A later study of 4,800 men noted 2.5 times higher HIV infection in those who were uncircumcised, with circumcision stated as being the factor having the highest impact on reducing HIV rate [197]. In another Indian study, of 1,925 men, HIV prevalence was 1.1% in the 90% who were uncircumcised but zero in the circumcised [198]. The clear benefits of circumcision have led to calls in India for physicians to inform patients in the interests of ethical responsibility [199]. Similarly, in China, there has been a call to establish surgical standards and training protocols for the promotion of circumcision for STI reduction [200].

#### 54.7.2.4 South America

In Rio de Janeiro 13% of 799 men aged <30 years were circumcised, and HIV prevalence in these was 70% lower than in those who were not circumcised [201].

circumcision of the male partner reduced the risk of any BV in their wives by 40% and severe BV by 61% [152]. *T. vaginalis* (TV) was reduced by 48% [152]. This contrasts with a prospective study that found no difference in trichomonal, chlamydial, or gonococcal infection in women in two African countries and Thailand [150].

## 54.7 Sexually Transmitted HIV

### 54.7.1 How the Prepuce Increases Infection Risk

Vaginal intercourse accounts for more than 80% [153] of the 30 million HIV infections in men worldwide [73]. A link with lack of circumcision was first proposed in 1986 [154] and now at least 50 epidemiological studies have confirmed higher HIV in heterosexual men who are uncircumcised [155–158].

During an erection, the prepuce is pulled half-way up the shaft of the penis (Fig. 54.1), so causing its thin keratin lining to become even thinner [159] and exposing its inner surface to vaginal secretions during intercourse [160]. These become trapped physically in the preputial sac, which provides a hospitable environment for pathogenic organisms in a pool of smegma [161]. The prepuce's high surface area, risk of tearing during intercourse, and inflammation (balanitis) were also invoked. Unlike the inner prepuce, the glans of each type of penis has a similar amount of protective keratin [160, 162]. Infected cells in vaginal fluids or semen can adhere to mucosal surfaces and migrate through lesions [163]. Preputial wetness, an indicator of poor hygiene, conveys a 40% increase in infection risk, possibly because virions attach for longer, healing after trauma is lower, and microulcerations caused by balanitis are more common [164]. Penile wetness is more common in men with a long prepuce [165]. Lesions, created by GUD (more common in the uncircumcised) also facilitate HIV entry [166].

HIV, applied to fresh preputial tissue in vitro, was taken up rapidly by the inner lining but not by the outer epithelium [167]. Simian immunodeficiency virus does the same to infect monkeys [168]. Surprisingly, however, in one study, glans, prepuce, meatus, and urethra in explant culture were reported to be equally susceptible to HIV infection [169].

The mucosal inner prepuce is rich in immune-system cells [167]. The urethra, although mucosal, lacks these, and it is not considered a site of HIV infection. Interestingly, circumcised men with high sexual activity have lower HIV, leading to a suggestion that repeated contact of the urethral meatus (that contains a small number of HIV receptors) [159] with subinfectious inoculums might induce an immune response [170]. The small area exposed would lessen the likelihood of the immune system being overwhelmed, as compared with the prepuce [170]. Mucosal alloimmunization may indeed protect against HIV [171].

Immune system cells in the inner lining of the prepuce act as a "Trojan horse" in uptake of HIV, which binds to receptors CD1a, CD4, CCR5, CXCR4, HLA-DR, and DC-SIGN, particularly on Langerhans cells, which are closer to the surface [172] and send dendritic projections up between keratinocytes [159].

Langerhans cells contain Langerin, which helps internalize and transport HIV to regional lymph nodes [173]. Direct HIV infection of T cells is at least as important, however [174, 175]. Success in establishing a systemic infection might, nevertheless, depend on early interaction of HIV with Langerhans cells [174]. At low viral loads Langerin is able to clear HIV, shunting it to intracellular granules for degradation, but this mechanism becomes overwhelmed at higher viral loads [176, 177].

Finally, larger foreskin surface area is associated with higher HIV prevalence [178].

### 54.7.2 Epidemiological Research – Heterosexual

In developing countries other than in Sub-Saharan Africa, adult HIV prevalence in 2004 was 0.76% for 11 with low (<20%) and 0.09% for 17 with high (>80%) rates of circumcision [128] – i.e., was eightfold higher where circumcision was less common. In Sub-Saharan African countries, these figures were 16% for 8 countries with low and 3% for 22 with high circumcision rates [128], independent of Muslim and Christian religion. The current data implicating male circumcision in the prevention of HIV infection

satisfies six of Hill's nine criteria of causality (strength of association, consistency, temporality, biological plausibility, coherence, and experiment) [179]. After considering all factors, lack of circumcision has emerged as the major driving force behind the AIDS epidemic [180].

In a meta-regression analysis of 27 studies, lack of circumcision in susceptible men was associated with an infectivity difference versus circumcised men of 8.1 transmissions per 1,000 exposures (range 0.4–16) [181]. Infectivity was, moreover, only weakly associated with geographical region (Africa versus United States/Europe) [181]. In high-risk contexts, such as when the male is uncircumcised, heterosexual infectivity can exceed 0.1, i.e., one transmission per ten contacts, which exceeds by two orders of magnitude the value of 0.001 that is cited commonly [181]. This was later extended to a meta-analysis of 43 publications based on 25 different study populations [182]. It showed female-to-male infectivity, during the asymptomatic phase, of 0.04% per sex act for high income countries and 0.38% for low income countries.

#### 54.7.2.1 United States

DNA sequencing of archival specimens suggested that HIV moved out of Africa to Haiti around 1966 and from there migrated to the United States around 1969, circulating cryptically in the latter for approx. 12 years before AIDS was first recognized in 1981 [183].

A report in 1993 of heterosexual men attending a STI clinic in New York City found HIV to be 2.1% in 405 who were uncircumcised, but only 0.6% in 308 who were circumcised (risk ratio = 4.1) [184].

Heterosexual contact accounted for 15% of HIV infections men in the United States in 2005, this route having grown by 42% over the years [185]. High-risk heterosexual contact accounted for 31–33% of HIV/AIDS cases diagnosed in 2006 [186, 187]. Men comprised 36% and women 64% of heterosexually acquired infections in 2007 [186]. In 2009, it was reported that, among African American men in Baltimore with known heterosexual exposure to infected partner(s), HIV was 51% lower in those who were circumcised [188]. The various findings have led to calls for greater circumcision in the United States [189].

#### 54.7.2.2 United Kingdom, Europe, Russia, and Central Asia

The low circumcision rate in these regions has been accompanied by a rise in heterosexual transmission, provoking calls in the United Kingdom for a change in circumcision guidelines [190]. The proportion of infections due to female to male transmission in Europe is much higher than in the United States, consistent with the influence of the much lower rate of circumcision in Europe [191–193].

#### 54.7.2.3 Asia

Adult HIV incidence in countries with high circumcision rates (Philippines, Bangladesh, and Indonesia) is 0.03–0.06%, compared with 1.8–2.4% for those with low circumcision rates (Thailand, India, and Cambodia) [192], being 3–6% in Thai military conscripts [194]. A prospective study in India of 2,298 men initially not infected saw a 6.7-fold higher HIV infection in the uncircumcised (adjusted RR 0.14) [195]. Another study found HIV incidence in Muslim men (circumcised) was 1% compared with 4.4% in Hindu men (uncircumcised) (OR 0.42), despite Muslim men having more sex partners and visits to commercial sex workers [196]. This finding was not influenced by concurrent infection with other STIs. A later study of 4,800 men noted 2.5 times higher HIV infection in those who were uncircumcised, with circumcision stated as being the factor having the highest impact on reducing HIV rate [197]. In another Indian study, of 1,925 men, HIV prevalence was 1.1% in the 90% who were uncircumcised but zero in the circumcised [198]. The clear benefits of circumcision have led to calls in India for physicians to inform patients in the interests of ethical responsibility [199]. Similarly, in China, there has been a call to establish surgical standards and training protocols for the promotion of circumcision for STI reduction [200].

#### 54.7.2.4 South America

In Rio de Janeiro 13% of 799 men aged <30 years were circumcised, and HIV prevalence in these was 70% lower than in those who were not circumcised [201].

#### 54.7.2.5 Middle East

Muslim men are circumcised and Middle Eastern countries have a very low prevalence of HIV [202]. HIV and syphilis were not seen at all in STI patients in Kuwait [203].

#### 54.7.2.6 Sub-Saharan Africa

##### Observational Studies

Striking differences in HIV incidences in Sub-Saharan Africa correlate with circumcision practice [204]. Rates in Botswana, Swaziland, and South Africa are 40%, 33%, and 25%, respectively, with most infections from heterosexual intercourse [205]. Risk from a single act of unprotected vaginal sex in a study of Kenyan truck drivers was 1 in 78 in an uncircumcised man and 1 in 200 in a circumcised man [206]. When 422 HIV-negative men in Nairobi were followed for a year a tenfold higher infection occurred in the uncircumcised (RR 8.2 by logistic regression analysis) [161]. Risk during a single exposure was one in six in this study.

Couples in Uganda, in whom one partner was HIV-positive, were followed prospectively for 30 months, and 17 seroconversions/100 person-years were observed in the uncircumcised men, but none in the circumcised, despite them having regular unprotected sex [207, 208]. Behaviors in Muslim men have been excluded [207]. Viral load is a factor, with no HIV transmission being seen for <1,500 copies of HIV-1 RNA/ml serum, but above this a dose-response increase in infection was noted [208]. For men with a viral load of less than 50,000 copies/mL, there was no transmission of HIV to the female partner if the man was circumcised, but if the man was not circumcised, transmission was 9.6/100 person-years [207]. Postcoital washing did not reduce HIV acquisition [209].

Fastidious matching of circumcised and uncircumcised Luo groups, each from nine Christian churches in Kenya, again noted higher HIV in the uncircumcised [210]. Frequency of sexual intercourse and higher rate of other risk factors did not contribute in a Ugandan study [211]. Muslims had a lower risk profile for all factors, except condom use (OR 0.3). Biological factors – circumcision and STIs – were more important than behavior; those who considered themselves at low risk being more likely to get a HIV infection [212]. Age at circumcision may [207, 213], or may not [210], be important.

A large systematic meta-analysis in 2000 of 27 studies, 21 of which had found lower HIV in circumcised men, showed, after adjusting 15 for potential confounding factors, 2.4-fold higher HIV in those not circumcised [157]. In men at high risk, HIV incidence was 3.7 times higher in the uncircumcised. Only one of these studies had verified circumcision status by physical examination [214]. Since self-report of circumcision status is often inaccurate (67–81% in African studies [215, 216] and 69–84% in studies in the United States [217, 218]), and some men have only a partial circumcision, the protective effect of circumcision could be even greater.

##### Randomized Controlled Trials

Three RCTs were begun in the early 2000s. The first involved 3,274 uncircumcised men aged 18–24 in a semiurban region of South Africa [219]. It was to run for 21 months, but so striking was the benefit of circumcision (60%) that at 18 months it was stopped so the control group could be offered circumcision. Protection was 61% after controlling for behavioral factors such as higher sexual activity in the intervention group. A per-protocol analysis to correct for the dilutional effect of cross-overs, so treating men who were actually circumcised as circumcised and vice-versa showed the protective effect was 76%. It concluded that "circumcision provides a degree of protection against acquiring HIV infection equivalent to what a vaccine of high efficacy would have achieved" and that circumcision "could be incorporated rapidly into the national plans of countries where most males are not circumcised," just as in South Korea, where circumcision has risen from virtually zero 50 years ago to 85% today [220]. Furthermore, circumcision "is an inexpensive means of prevention, performed only once, and ... over a wide age range, from childhood to adulthood" and "the number of HIV infections that could be avoided ... is high."

RCTs in Kenya [221] and Uganda [31] were similarly stopped early by the monitoring committees due to the marked preventative effect. These studies involved, respectively, 2,784 and 4,996 uncircumcised men aged 18–24 and 15–40 [31, 221]. In each, the as-treated protective effect of circumcision was 60%. Extensive analyses of the data dismissed a contribution from other, potentially confounding factors. After

excluding four invalid subjects in the Kenyan trial, 2-year HIV incidence was 1.6% in the circumcised group and 4.2% in the control group, i.e., the true protective effect was 68% [221]. The reduction in HIV infection after circumcision occurred irrespective of number of partners. Moreover, unlike the South African trial, the Kenyan and Ugandan RCTs saw no risk compensation. Only 1.5% [221] and 3.6% [31] of subjects had adverse events from the circumcision itself, and these resolved quickly. None reported moderate or severe pain, and almost all were "very," and none "not," satisfied with their circumcision [221]. At the time, just 10–20% of the HIV infections prevented by circumcision were considered to be due to reduction in STIs (primarily GUD) [222].

A random-effects meta-analysis of the RCT data and of 15 observational studies that adjusted for potential confounders found a RR of 0.42 for each [158] (Fig. 54.3). A meta-analysis by others of the RCT data obtained similar findings [223]. Meta-analysis of data for "as-treated" subjects yielded a summary RR of 0.35 (95% CI 0.24–0.54) [158]. Thus, circumcision reduced HIV infection by 65%. An extensive Cochrane review in 2009, incorporating the RCT results, concluded that "inclusion of male circumcision into current HIV prevention measures guidelines [sic] is warranted" [224]. Follow-up data from men in the Rakai trial in Kenyan showed that by 3.5 years, not only was the protective effect sustained, but it was increased [225], consistent with an earlier suggestion that "early stopping may have underestimated the effect [of circumcision]" [158].

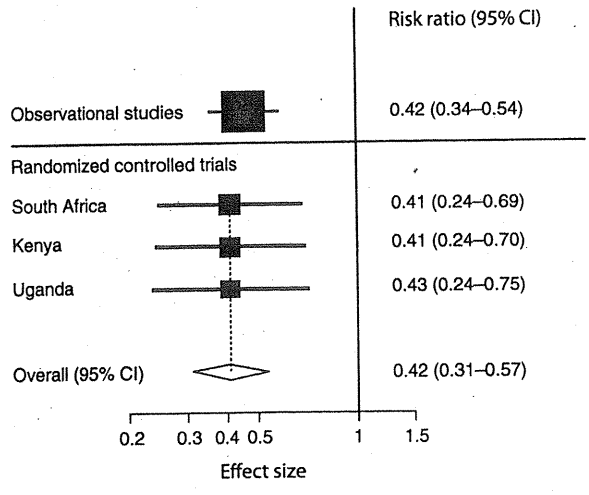


**Fig. 54.3** Effect of circumcision on HIV prevention. Shown is risk ratio for 15 observational studies that adjusted for potential confounding factors, and below this, a random effects meta-analysis of the RCTs intention-to-treat findings (Modified from [158], with correction)

### 54.7.3 Synergy with GUD?

Although the prepuce seems to be the weak point for HIV infection of uncircumcised men, a man with GUD or lesions anywhere on the penis will be at increased risk irrespective of circumcision status [226]. Indeed, men with HSV-2 appeared to have a two [227] or three to five times [228] higher risk of acquiring HIV, and men with both viruses seemed more likely to transmit HIV [227]. It has been suggested that HIV and HSV-2 may be in a vicious cycle of infection, each exacerbating infection by the other [29]. Such a synergy between each was seen in the South African RCT described earlier [23, 41].

In the Ugandan RCT, HSV-2 was not significantly higher, however, in HIV positive men, and it was suggested that HIV and syphilis are most likely markers of increased sexual activity [27]. An analysis of RCT data found that protection against STIs contributed little to the overall protective effect that circumcision has against HIV infection [229]. In the South African RCT, the protective effect of circumcision against HIV infection appeared, moreover, to be independent of HSV-2 serostatus [26, 41, 165]. Similarly, in the Kenyan RCT, only 8.6% of the reduction in HIV associated with circumcision was mediated by reduction in HSV-2, and for GUD was only 11% [33]. The Rakai data suggested that most of the reduction in HIV was from nonherpetic ulceration [33]. It was suggested that the ulcers responsible for HIV infection were likely caused by traumatic lesions of the foreskin, and attached frenulum in particular [33]. Such tearing occurs commonly when uncircumcised men have sexual intercourse [160]. Inflammation of the foreskin is more common in men who have HIV, HSV-2, or smegma [230]. HSV-2 suppressive therapy has, however, failed to decrease HIV acquisition in men, as seen in two RCTs [226]. A RCT in women similarly found HSV-2 suppressive therapy had no effect on them becoming infected with HIV [231]. HIV positive inflammatory cells are enriched in lesions caused by HSV-2 and persist for months after healing, so this might explain why anti-HSV-2 therapy has failed to reduce acquisition of HIV [232].

In men infected with high-risk (but not low-risk) HPV, prevalence of HIV is 3.8-fold higher [233].

Whether HPV facilitates HIV acquisition remains to be determined.

### 54.7.4 Implications, Lives Saved, and Costs

Other prevention measures "have often been unsuccessful in restricting the spread of HIV" [221]. In the case of antiretroviral therapy, the pace of new HIV infections is outstripping supply. And as far as a vaccine is concerned, "there is little promise that an effective vaccine will be available within the next 15 years" [221]. Prevention is preferable, and circumcision is cheaper than antivirals.

Condom use in the RCTs was low, despite free supply. Circumcision is once only, does not have to be "applied," is not inconvenient, apart for abstinence from sex for a few weeks, and reduces numerous other problems [1, 2]. Moreover, "neonatal circumcision or circumcision of younger boys will provide a simpler, safer, and cheaper option" [31].

Analysis of the dynamics of the epidemic suggests that heterosexual transmission of HIV probably peaked during the 1990s [234]. For a circumcision efficacy of 50%, when HIV incidence is 1.3/100 person-years (as in Uganda), 35 surgeries would prevent one HIV infection over 10 years if all underwent circumcision [31]. For South Africa (HIV 3.8/100 person-years), fewer circumcisions would achieve this. Targeting any age group in this country was shown to be cost effective, leading to a suggestion that the UNAIDS target age group range (12–30) should be widened to include older men [235]. The cumulative net cost for rolling out medical adult male circumcision in South Africa has been estimated as US$ 919 million for the first 5 years and would be US$672M over the first 10 years; over 20 years the net savings would be US$ 2.3 billion [236]. In Zambia, increasing circumcision to 100% (from 10%) would reduce adult HIV prevalence from 27% down to 7% [237]. WHO/ANAIDS estimates show circumcision could avert 2 million new infections and 0.3 million deaths over the next 10 years in Sub-Saharan Africa, and a further 4 million new infections and 3 million deaths in the 10 years after that, a quarter being in South Africa [238]. They equated circumcision with condom use or a vaccine. In South Africa, each 1,000 circumcisions would prevent 308 HIV infections over 10 years, at a cost of US$ 181 per HIV infection averted, a net saving of US$ 2.4 million [239]. For an 80% uptake of circumcision, HIV prevalence would be reduced by 45–67% in both men and women within a decade in countries with high HIV [240]. If uptake was 50%, HIV would be reduced 25–41% [240]. Other modeling predicted that, for a 60% efficacy, 19 surgeries would prevent one HIV infection in both sexes at a cost per infection averted of US$ 1,269 [241]. In Botswana scale-up of adult and neonatal circumcision to 80% by 2012 would avert 70,000 new HIV infections through 2025 at a cost per HIV infection averted of US$ 689 [242]. The reduction achieved could be sufficient to "abort the epidemic" [241]. By 2020, complete male circumcision in an average country could reduce HIV prevalence from 12% to 6% [243]. In Zimbabwe, the 25% HIV rate predicted for no circumcision would be just 13%. Circumcision cost (in Kenya) is US$ 20 for supplies, obtained locally, and US$ 13 for the procedure itself in a government hospital and US$ 77 in a private hospital [244]. To 1999, circumcision had likely prevented 10 million HIV infections in Africa and Asia [155]. For 14 Sub-Saharan countries in which circumcision is <20% and HIV >5%, and assuming >85% of men get circumcised, initial 5-year cost will be US$922M (private)/US$397M (public) [245]. This would require 1,912 circumcisers (0.23/10,000 adults). In years 6–10 the number needed would reduce to 504 and cost to US$ 208 million/US$ 84 million. This analysis found five to eight circumcisions would be needed to prevent one HIV infection. Although expensive, the roll-out of circumcision would be cost effective, sustainable, and have important other benefits to public health.

"Circumcision must now be deemed to be a proven intervention for reducing the risk of heterosexually acquired HIV infection in adult men" [31]. In March 2007, in endorsing circumcision, the WHO and UNAIDS stated "the efficacy of male circumcision in reducing female to male HIV transmission has now been proven beyond reasonable doubt. This is an important landmark in the history of HIV prevention" [246]. It went on to recommend circumcision for men and boys, as well as infants, since in infants circumcision is "less complicated and risky." The RCTs were an "extraordinary development" and circumcision a "potent intervention in HIV prevention." "Global expansion of male circumcision programs [is a] vital tool for control of HIV infection" [247].

### 54.7.5 Epidemiological Research – Men Who Have Sex with Men (MSM)

In New York City, the epicenter of the HIV epidemic, HIV prevalence in MSM is 8.4% [248], which is higher than in Uganda (7%) and Kenya (7.4%) [249]. However, unlike heterosexual transmission, the data for the effectiveness of circumcision in HIV prevention among MSM is not as consistent as it is for the former [248]. This can be attributed to the mixture of sexual practices – receptive anal intercourse is unlikely to relate to circumcision status, whereas insertive might.

Among the 15% who were uncircumcised in a Seattle study of MSM, HIV was 2.2 times higher [250]. A later study in Seattle of 4,749 men attending a STI clinic found no difference, however [36]. Findings in STIs clinics should, however, be viewed with caution because any protective effect that circumcision may have against STIs means a selective bias against attendance of circumcised men at STI clinics, meaning the population studied is not representative of the general population of men. In six US cities, a study of 3,257 mostly white MSM from 1995–1997 showed lack of circumcision doubled the risk of acquiring HIV [251]. A meta-analysis that excluded studies that did not meet rigid inclusion criteria found incidence of HIV was 51% lower in circumcised MSM [252]. Another study in the United States of 1,154 Black and 1,091 Latino MSM was negative, however [253]. A meta-analysis performed in the United States found HIV was 53% lower in circumcised men for studies conducted before the introduction of antiretroviral therapy [254]. These authors found that a protective effect of circumcision was more likely to be seen in higher quality studies. For MSM who were primarily insertive, those who were circumcised had 29% lower HIV infection [254].

In Lima, Peru, 4% of circumcised and 21% of uncircumcised MSM had HIV [255].

Logically, circumcision should be protective during insertive, but not receptive, anal intercourse. Indeed, in a study of MSM in Sydney, Australia, MSM who engaged only in insertive anal intercourse had an 89% lower HIV prevalence if they were circumcised [256]. Similarly, in Africa, men who were insertive-only were 80% less likely to have HIV [257]. In an STI clinic population in Seattle, men who were insertive-only had a 45% lower risk [36]. Nevertheless, a RCT should be helpful. Owing to the high rate of circumcision in the US population of MSM (70–80%), such a trial could be considered in countries such as in Peru and Ecuador (circumcision rate 10%) where there is strong support for doing so [258]. Modeling in a resource-rich setting (Sydney, Australia) showed that circumcision of MSM, especially those who were insertive only, would be cost effective for HIV prevention, with one infection prevented for every 118 circumcisions for men in the insertive-only category [259].

It has been suggested that anal intercourse may present a higher viral load than vaginal intercourse, higher load being known to increase infection risk [208].

A lesser-known high-risk activity of MSM – "docking" [260] – involves insertion of the penis under the prepuce of the partner. The ejaculate then makes direct contact with the inner preputial lining.

### 54.7.6 Epidemiological Research – The Female Partners

One would think that if a man is HIV-positive, whether he is circumcised or not should make little difference to whether a woman he has sex with will become infected [261]. Based on data from Africa, an exception might exist in the case of women from high-risk settings (hazards ratio = 0.16) [261]. A meta-analysis of all relevant studies found that male circumcision reduced the risk to women by 20%, which was not significant [262]. A later report noted a reduction in risk of 38% for seven sites in eastern Africa [263]. Of course, a reduction in HIV prevalence in men will lower the HIV prevalence and thus lower the risk to women indirectly [264].

### 54.7.7 Risk Compensation

The protection circumcision affords could lead men to increase risky sexual behavior ("risk compensation") [265]. But this did not happen in two of the three RCTs [31, 221, 266]. In the South African trial, all five sexual behavior factors increased, but HIV

infections were lower [219]. In the Kenyan trial, men in the circumcised arm were less likely to use condoms in the first 6 months after circumcision, but thereafter all risk behaviors did not differ [31], as seen by others [267]. Most men delayed sex after their circumcision, but early sex was not associated with HIV risk [268].

### 54.7.8 Acceptability and Satisfaction

Most population groups are willing to accept circumcision to reduce HIV. This includes those in Tanzania [216], Kenya [269], Botswana [270], and South Africa [271, 272]. Among cultures that normally did not circumcise, circumcision rate has increased to 23% overall, and to 57% among those with ≥8 years of education [216]. Mean age of getting it done was 17 years. Health was the main reason given.

A review of 13 studies from nine countries found 65% of men (range 29–87%) were willing to get circumcised, and 69% of women (range 47–79%) preferred circumcision for their partner [273]. Furthermore, 79% (50–90%) of men and 81% (70–90%) of women wanted to get their sons circumcised.

A follow-up survey in Kenya 30 days after circumcision showed 99% of the men were very satisfied, as were 92% of their partners, and 96% had resumed general activities within the first week [244, 274]. None of the men and only 0.3% of partners were very dissatisfied with the outcome. By 3 days, 83% of those with regular employment had resumed working, rising to 93% by 1 week and 99% by 1 month [274]. Resumption of sex occurred in 10% by 1 month and by 65% by 3 months [274]. Much the same was seen in Zimbabwe [275]. At 3 months 98.5% of men were "very satisfied" in the South African RCT [219], as were 99.5% in the Kenyan RCT [221].

### 54.7.9 Ethical and Other Challenges

Obstacles that could impede the full roll-out of circumcision include cost, supply of sufficient competent circumcisers, circumcision training, adequacy of clinics and resources, best age, risk compensation, conflict between individuals within families, societal objections, prioritization of individuals in the face of limited resources, education to ensure circumcision is not seen as a panacea, and ethical issues such as obstacles to changing the culture, and the need make circumcision safer in cultures that do circumcise [276]. Increased uptake might lead to stigmatization of uncircumcised men as being less "safe" [277]. Ensuring safe circumcisions will require all stakeholders to work together [278].

The challenges seem minor, however, when compared with the perceived benefit. Many concerns have little validity. Most cultures are neutral on circumcision [279]. Those generally opposed include Indians of Hindu or Sikh faiths. But even here, a study in India of mostly Hindu mothers with male children found that after being informed about the risks and benefits of circumcision 81% said they would definitely have their sons circumcised if it was provided in a safe hospital setting free of charge, and 7% said they would probably have it done [280].

As stated by Stemple "At this nexus of health and rights, it is important not to pit one set of rights against another artificially. ...." To move unnecessarily incrementally [sic!] as a result of violations concerns risks reinforcing too simplistic a conceptualise of right – thwarting efforts to realize the highest attainable standard of health for populations in urgent need of HIV preventions strategies. A violations-only approach to human rights is unduly limiting; indeed it overlooks the duty of states affirmatively to create conditions necessary for the fulfilment of rights. Symbolically, a non-violative, rights-respecting rollout [of circumcision] is indispensable to encouraging men to elect 'the procedure [281]' and, to quote from Clark and coworkers from the Institute of Catholic Bioethics, "Mandating neonatal male circumcision is an effective therapy that has minimal risks, is cost efficient and will save human lives. To deny individuals access to this effective therapy is to deny them the dignity and respect all persons deserve. Neonatal male circumcision is medically necessary and ethically imperative" [282].

The speed of the roll-out of circumcision will be increased by enlisting and training paramedical as well as traditional and religious figures [283]. A voucher system has been suggested [283]. More funding and doctors are needed. Had a "parachute approach" to evidence-based medicine been applied

in the early 1990s millions of lives would have been saved [284].

### 54.7.10 Condoms

Condoms, when always used, reduce HIV infection by 80–90% [285]. Condom use remains low, however [286], with 45% of the sexually active population of western countries not using them [287]. In Zimbabwe, 78% had never used condoms [288]. In US studies, 38% of US adults [289] and 16% of men and 24% of women [290] never used condoms during heterosexual sex with a nonprimary partner. Of female STI clinic attendees in Baltimore, 25% stated consistent use and 48% had not used them in the previous 2 weeks [291]. Male DNA was, however, detected in the vagina in all, albeit at higher levels in nonusers [291]. Among American college students, 40% had not used condoms in the previous 6 months and <50% intended to use them in the next month [292]. Only 25% of younger Australians always used condoms, 25% never having done so [293]. In Mexico 51% of young men and 23% of young women reported using condoms, consistent use being 30% [294]. Of 13,293 Mexican public school students, among the 37% with high HIV/AIDS knowledge, condom use was higher in males (OR 1.4), but lower in females (OR 0.7) [295].

Condoms can, moreover, be applied incorrectly, may break, and certain cultures may object to their use. Even when the female partner was known to be infected and condoms were made available continuously, 89% did not use them [208].

Interestingly, it has been found that condom use did not influence rate of HIV transmission, only circumcision status did [160]. A review of ten studies from Africa found no association between condom use and reduction in HIV infection, one finding it increased infection [296]. Similarly, in a large Indian study, odds of having HIV were significantly higher for those who said they had used condoms always or often in the past 6 months [197]. Condom use ever was associated with a 2.7-fold higher HIV prevalence in another study from India, and it was suggested that this may be because those with high-risk behavior start using condoms after they learn that they have become infected [198]. Alternatively, the apparent ineffectiveness of condoms may be because men assess their risk and use condoms accordingly. For example, in the Kenyan RCT, men used condoms 70% of the time with sex workers, 40% of the time with casual partners, and 18% of the time with their usual partner. Moreover, unless a condom is used during all sex play then the risk remains of contact between the inner lining of the prepuce and HIV-laden secretions, sperm (in the case of homosexual sex), and cells or tissues of an infected sex partner. Diaphragms have been found to provide no protection against HIV [297].

Circumcision should be promoted as part of a package that includes safe-sex (condoms) and fidelity. There are now two "ABC's: 'abstinence, behavior and condoms', and 'antivirals, barriers and circumcision'. Consistent condom use has not reached a sufficiently high level, even after many years of widespread and often aggressive promotion, to produce a measurable slowing of new infections" [298]. Unlike most other approaches, circumcision is a practical, once-off preventative strategy whose effectiveness has been proven. Funding and resources have, however, been allocated disproportionately to each measure, and increased focus is needed for male circumcision programs [298].

### 54.7.11 Misinformation from Opponents of Circumcision

There has been a concerted attempt by individuals and organizations opposed to male circumcision to distort and otherwise misrepresent the findings that have emanated from good research studies that have attested to the benefits of circumcision. In the case of HIV, a meta-analysis by Van Howe [299] has been criticized by some leading figures in the field for its incorrect use of statistical methods and other transgressions [300, 301]. More recently, an opinion piece by others countering the evidence that circumcision can prevent HIV infection has led to a detailed rebuttal by 48 authors that included academic experts worldwide, as well as representatives of WHO, UNAIDS, and the World Bank [193]. The latter publication documents the reasons for scale-up of circumcision in the fight against HIV/AIDS.

## 54.8 Conclusion

Male circumcision is a very effective component of STI-prevention messages, especially as condoms are not a panacea, even when used consistently [302]. Indeed, when coupled with the enormous evidence for other extensive benefits of this low risk procedure over the lifetime of males, the current evidence leads to a conclusion that circumcision should be regarded as "a biomedical imperative for the twenty-first century" [1]. So strong is the evidence that male circumcision is now regarded as a "surgical vaccine" for STI prevention. Moreover, to quote a UNAIDS document, "access to accurate information about male circumcision is a human right" [303]. Globally, 30% of males aged 15 years or more are circumcised [279], a high number for an intervention such as this. Although males can be circumcised at any age, the neonatal period appears best, since at this age the procedure is cheaper, simpler, more convenient, safer, does not involve stitches, need involve only a local anesthetic, means no anxiety by the male or others later about whether to have it done, can be pain-free, and is most likely to result in an optimum outcome. Efforts aimed at further increasing the rate of circumcision internationally should help in lowering the burden of STIs around the world.

**Take-Home Pearls**

- Circumcision prevents several types of common STIs.
- Risk to men of HIV infection acquired heterosexually is reduced at least threefold.
- Risk of syphilis is halved.
- Risk of HPV infection is reduced two- to fourfold.
- Risk of invasive penile cancer is reduced more than 20-fold.
- Risk of HSV-2, thrush, and trichomonas in men is reduced by up to half.
- Risk of cervical cancer (caused by high-risk HPV) in the female partner is reduced by two- to sixfold.
- Risk of Chlamydia in the female partner may be reduced by up to sixfold.
- Risk of HSV-2 in the female partner is halved.
- Risk of bacterial vaginosis and trichomonas in the female partner is reduced by half.
- There are many other benefits of circumcision besides STI prevention, including a marked reduction in urinary tract infections over the lifetime, elimination of phimosis and paraphimosis, lowering of balanitis and other inflammatory skin conditions, and improved genital hygiene.
- Good research, including data from two RCTs, has shown there is no adverse effect of male circumcision on sexual function, satisfaction, or sensitivity of the penis.
- While circumcision can be performed at any age, the neonatal period is the best time.

## References


1. Morris, B.J.: Why circumcision is a biomedical imperative for the 21st century. BioEssays **29**, 1147–1158 (2007)
2. Morris, B.J.: Circumcision: an evidence-based appraisal - medical, health and sexual (Review). http://www.circinfo.net (>1,000 refs) (2010)
3. Hutchinson, J.: On the influence of circumcision in preventing syphilis. Medical Times and Gazette II:542-543. www.historyofcircumcision.net (1855)
4. Remondino, P.C.: 1891 History of circumcision: from the earliest times to the present: moral and physical reasons for its performance, with a history of eunuchism, hermaphrodism, etc. and of the different operations practiced upon the prepuce. Physicians' and students' ready reference series; No. 11 (Republished 1990). FA Davis, Philadelphia
5. Asin, J.: Chancroid; a report of 1, 402 cases. Am. J. Syph. Gonorrhea Vener. Dis. **36**, 483–487 (1952)
6. Cook, L.S., Koutsky, L.A., Holmes, K.K.: Circumcision and sexually transmitted diseases. Am. J. Public Health **84**, 197–201 (1994)
7. Dickson, N., van Roode, T., Paul, C.: Herpes simplex virus type 2 status at age 26 is not related to early circumcision in a birth cohort. Sex. Transm. Dis. **32**, 517–519 (2005)
8. Diseker, R.A., Peterman, T.A., Kamb, M.L., et al.: Circumcision and STD in the United States: cross sectional and cohort analysis. Sex. Transm. Infect. **76**, 474–479 (2000)
9. Donovan, B., Basset, I., Bodsworth, N.J.: Male circumcision and common sexually transmissible diseases in a developed nation setting. Genitourin. Med. **70**, 317–320 (1994)
10. Hammond, G.W., Slutchuk, M., Scatliff, J., et al.: Epidemiologic, clinical, laboratory, and therapeutic features of an urban outbreak of chancroid in North America. Rev. Infect. Dis. **2**, 867–879 (1980)
11. Hand, E.A.: Circumcision and venereal disease. Arch. Dermatol. Syphilol. **60**, 341–346 (1949)
12. Hart, G.: Factors associated with genital chlamydial and gonoccocal infection in males. Genitourin. Med. **69**, 393–396 (1993)

13. Latif, A.S., Katzenstein, D.A., Bassett, M.T., et al.: Genital ulcers and transmission of HIV among couples in Zimbabwe. AIDS **3**, 519–523 (1989)
14. Parker, J.D., Banatvala, J.E.: Herpes genitalis; clinical and virological studies. Br. J. Vener. Dis. **43**, 212–216 (1967)
15. Parker, S.W., Stewart, A.J., Wren, M.N., et al.: Circumcision and sexually transmissible diseases. Med. J. Aust. **2**, 288–290 (1983)
16. Smith, G., Greenup, R., Takafuji, E.: Circumcision as a risk factor for urethritis in racial groups. Am. J. Publ. Health **77**, 452–454 (1987)
17. Taylor, P.K., Rodin, P.: Herpes genitalis and circumcision. Br. J. Ven. Dis. **51**, 274–277 (1975)
18. Wilson, R.A.: Circumcision and venereal disease. Can. Med. Assoc. J. **56**, 54–56 (1947)
19. Moses, S., Bailey, R.C., Ronald, A.R.: Male circumcision: assessment of health benefits and risks. Sex Transm. Inf. **74**, 368–373 (1998)
20. Laumann, E.O., Maal, C.M., Zuckerman, E.W.: Circumcision in the United States. Prevalence, prophyactic effects, and sexual practice. J. Am. Med. Assoc. **277**, 1052–1057 (1997)
21. Weiss, H.A., Thomas, S.L., Munabi, S.K., et al.: Male circumcision and risk of syphilis, chancroid, and genital herpes: a systematic review and meta-analysis. Sex. Transm. Infect. **82**, 101–109 (2006)
22. Xu, F., Markowitz, L.E., Sternberg, M.R., et al.: Prevalence of circumcision and herpes simplex virus type 2 infection in men in the United States: the National Health and Nutrition Examination Survey (NHANES), 1999-2004. Sex. Transm. Dis. **34**, 479–484 (2007)
23. Mahiane, S.G., Legeai, C., Taljaard, D., et al.: Transmission probabilities of HIV and herpes simplex virus type 2, effect of male circumcision and interaction: a longitudinal study in a township of South Africa. AIDS **23**, 377–383 (2009)
24. Fergusson, D.M., Boden, J.M., Horwood, L.J.: Circumcision status and risk of sexually transmitted infection in young adult males: an analysis of a longitudinal birth cohort. Pediatrics **118**, 1971–1977 (2006)
25. Dickson, N.P., van Roode, T., Herbison, P., et al.: Circumcision and risk of sexually transmitted infections in a birth cohort. J. Pediatr. **152**, 383–387 (2008)
26. Sobngwi-Tambekou, J., Taljaard, D., Lissouba, P., et al.: Effect of HSV-2 serostatus on acquisition of HIV by young men: results of a longitudinal study in Orange Farm, South Africa. J. Infect. Dis. **199**, 958–964 (2009)
27. Tobian, A.A.R., Charvat, B., Ssempijja, V., et al.: Factors associated with the prevalence and incidence of herpes simplex virus type 2 infection among men in Rakai, Uganda. J. Infect. Dis. **199**, 945–949 (2009)
28. Van Wagoner, N.J., Geisler, W.M., Sizemore, J.M., Jr., et al.: Herpes simplex virus in African American heterosexual males: the roles of age and male circumcision. Sex Transm. Dis. **37**, 217–222 (2010)
29. Bailey, R.C., Mehta, S.D.: Circumcision's place in the vicious cycle involving herpes simplex virus type 2 and HIV. J. Infect. Dis. **199**, 923–925 (2009)
30. Jerath, V.P., Mahajan, V.K.: Does circumcision influence recurrences in herpes genitalis? Indian J. Dermatol. Venereol. Leprol. **75**, 575–578 (2009)
31. Gray, R.H., Kigozi, G., Serwadda, D., et al.: Male circumcision for HIV prevention in men in Rakai, Uganda: a randomised trial. Lancet **369**, 657–666 (2007)
32. Tobian, A.A.R., Serwadda, D., Quinn, T.C., et al.: Male circumcision for the prevention of HSV-2 and HPV infections and syphilis. N. Engl. J. Med. **360**, 1298–1309 (2009)
33. Gray, R.H., Serwadda, D., Tobian, A.A.R., et al.: Effects of genital ulcer disease and herpes simplex virus type 2 on the efficacy of male circumcision for HIV prevention: analyses from the Rakai trials. PLoS Med **6**, e1000187 (8 pp.) (2009)
34. Golden, M.R., Wasserheit, J.N.: Prevention of viral sexually transmitted infections–foreskin at the forefront. N. Engl. J. Med. **360**, 1349–1351 (2009)
35. Templeton, D.J., Jin, F., Prestage, G.P., et al.: Circumcision and risk of sexually transmissible infections in a community-based cohort of HIV-negative homosexual men in Sydney, Australia. J. Infect. Dis. **200**, 1813–1819 (2009)
36. Jameson, D.R., Celum, C.L., Manhart, L., et al.: The association between lack of circumcision and HIV, HSV-2, and other sexually transmitted infections among men who have sex with men. Sex Transm. Dis. **37**, 147–152 (2010)
37. Van Howe, R.S.: Genital ulcerative disease and sexually transmitted urethritis and circumcision: a meta-analysis. Int. J. STD AIDS **18**, 799–809 (2007)
38. Waskett, J.H., Morris, B.J., Weiss, H.A.: Errors in meta-analysis by Van Howe. Int. J. STD AIDS **20**, 216–218 (2009)
39. Anonymous: Erratum for Van Howe, Int. J. STD AIDS **18**(12), 799–809. Int. J. STD AIDS **20**, 592 (2009)
40. Auvert, B., Sobngwi-Tambekou, J., Cutler, E., et al.: Effect of male circumcision on the prevalence of high-risk human papillomavirus in young men: results of a randomized controlled trial conducted in orange farm, South Africa. J. Infect. Dis. **199**, 14–19 (2009)
41. Sobngwi-Tambekou, J., Taljaard, D., Nieuwoudt, M., et al.: Male circumcision and *Neisseria gonorrhoeae*, *Chlamydia trachomatis*, and *Trichomonas vaginalis*: observations in the aftermath of a randomised controlled trial for HIV prevention. Sex. Transm. Infect. **85**, 116–120 (2009)
42. Mehta, S.D., Moses, S., Agot, K., et al.: Adult male circumcision does not reduce the risk of incident *Neisseria gonorrhoeae*, *Chlamydia trachomatis*, or *Trichomonas vaginalis* infection: results from a randomized, controlled trial in Kenya. J. Infect. Dis. **200**, 370–378 (2009)
43. Richters, J., Smith, A.M., de Visser, R.O., et al.: Circumcision in Australia: prevalence and effects on sexual health. Int. J. STD AIDS **17**, 547–554 (2006)
44. Kochen, M., McCurdy, S.: Circumcision and risk of cancer of the penis. A life-table analysis. Am. J. Dis. Child. **134**, 484–486 (1980)
45. Wiswell, T.E.: Neonatal circumcision: a current appraisal. Focus Opin. Pediat. **1**, 93–99 (1995)
46. Wiswell, T.E.: Circumcision circumspection. N. Engl. J. Med. **36**, 1244–1245 (1997)
47. Schoen, E.J.: The relationship between circumcision and cancer of the penis. CA Cancer J. Clin. **41**, 306–309 (1991)
48. Schoen, E.J.: Neonatal circumcision and penile cancer. Evidence that circumcision is protective is overwhelming. Br. Med. J. **46**, 313 (1996)
49. Wolbarst, A.L.: Circumcision and penile cancer. Lancet **i**, 150–153 (1932)

50. Maden, C., Sherman, K.J., Beckmann, A.M., et al.: History of circumcision, medical conditions, and sexual activity and risk of penile cancer. J. Nat. Cancer Inst. **85**, 19–24 (1993)
51. Carver, B.S., Venable, D.D., et al.: Squamous cell carcinoma of the penis: a retrospective review of forty-five patients in northwest Louisiana. South Med. J. **95**, 822–825 (2002)
52. Schoen, E.J., Oehrli, M., Colby, C.J., et al.: The highly protective effect of newborn circumcision against invasive penile cancer. Pediatrics **105**, e36 (4 pp.) (2000)
53. Schoen, E.J., Wiswell, T.E., Moses, S.: New policy on circumcision – cause for concern. Pediatrics **105**, 620–623 (2000)
54. Barnholtz-Sloan, J.S., Maldonado, J.L., Pow-sang, J., et al.: Incidence trends in primary malignant penile cancer. Urol. Oncol. **25**, 361–367 (2007)
55. Goodman, M.T., Hernandez, B.Y., Shvetsov, Y.: Demographic and pathologic differences in the incidence of invasive penile cancer in the United States, 1995–2003. Cancer Epidemiol. Biomarkers Prev. **16**, 1833–1839 (2007)
56. Hu, D., Goldie, S.: The economic burden of noncervical human papillomavirus disease in the United States. Am. J. Obstet. Gynecol. **198**, 500.e1–500.e7 (2008)
57. Tsen, H.F., Morgenstern, H., Mack, T., et al.: Risk factors for penile cancer: results of a population-based case-control study in Los Angeles County (United States). Cancer Causes Control **12**, 267–277 (2001)
58. Seyam, R.M., Bissada, N.K., Mokhtar, A.A., et al.: Outcome of penile cancer in circumcised men. J. Urol. **175**, 557–561 (2006)
59. Micali, G., Nasca, M.R., Innocenzi, D., et al.: Penile cancer. J. Am. Acad. Dermatol. **54**, 369–391 (2006)
60. Sanchez Merino, J.M., Parra Muntaner, L., Jiminez Rodriguez, M., et al.: Epidoid carcinoma of the penis. Arch. Esp. Urol. **53**, 799–808 (2000)
61. Dagher, R., Selzer, M.L., Lapides, J.: Carcinoma of the penis and the anti-circumcision crusade. J. Urol. **110**, 79–80 (1973)
62. Sandeman, T.F.: Carcinoma of the penis. Australasian Radiol. **34**, 12–16 (1990)
63. American Cancer Society: Cancer statistics. http://www.cancer.org/docroot/CRI/content/CRI_2_4_1X_What_are_the_key_statistics_for_penile_cancer_35.asp?rnav=cri (2005)
64. Gross, G., Pfister, H.: Role of human papillomavirus in penile cancer, penile intraepithelial squamous cell neoplasias and in genital warts. Med. Microbiol. Immunol. **193**, 35–44 (2004)
65. Narayana, A.S., Olney, L.E., Loening, S.A.: Carcinoma of the penis: analysis of 219 cases. Cancer **49**, 2185–2191 (1982)
66. Dodge, O.G., Linsell, C.A.: Carcinoma of the penis in Uganda and Kenya Africans. Cancer **18**, 1255–1263 (1963)
67. World Health Organization: International Agency for Research on Cancer 1966–1997: Cancer Incidence in Five Countries, vol. 1–7 (1997)
68. Favorito, L.A., Nardi, A.C., Ronalsa, M., et al.: Epidemiologic study on penile cancer in Brazil. Int. Braz. J. Urol. **34**, 587–591 (2008)
69. Villa, L.L., Lopez, A.: Human papillomavirus sequence in penile carcinomas in Brazil. Int. J. Cancer **37**, 853–855 (1986)
70. Baldwin, S.B., Wallace, D.R., Papenfuss, M.R., et al.: Condom use and other factors affecting penile human papillomavirus detection in men attending a sexually transmitted disease clinic. Sex. Transm. Dis. **31**, 601–607 (2004)
71. Castellsague, X., Bosch, F.X., Munoz, N., et al.: Male circumcision, penile human papillomavirus infection, and cervical cancer in female partners. N. Engl. J. Med. **346**, 1105–1112 (2002)
72. Hernandez, B.Y., Wilkens, L.R., Zhu, X., et al.: Circumcision and human papillomavirus infection in men: a site-specific comparison. J. Infect. Dis. **197**, 787–794 (2008)
73. Kohn, F.-M., Pflieger-Bruss, S., Schill, W.-B.: Penile skin diseases. Andrologia **31**(suppl 1), 3–11 (1999)
74. Lajous, M., Mueller, N., Cruz-Valdez, A., et al.: Determinants of prevalence, acquisition, and persistence of human papillomavirus in healthy Mexican military men. Cancer Epidemiol. Biomarkers Prev. **14**, 1710–1716 (2005)
75. Niku, S.D., Stock, J.A., Kaplan, G.W.: Neonatal circumcision (Review). Urol. Clin. N. Am. **22**, 57–65 (1995)
76. Shin, H.R., Franceschi, S., Vaccarella, S., et al.: Prevalence and determinants of genital infection with papillomavirus, in female and male university students in Busan, South Korea. J. Infect. Dis. **190**, 468–478 (2004)
77. Svare, E.I., Kjaer, S.K., Worm, A.M., et al.: Risk factors for genital HPV DNA in men resemble those found in women: a study of male attendees at a Danish STD clinic. Sex. Transm. Infect. **78**, 215–218 (2002)
78. Bosch, F.X., Albero, G., Castellsagué, X.: Male circumcision, human papillomavirus and cervical cancer: from evidence to intervention. J. Fam. Plann. Reprod. Health Care **35**, 5–7 (2009)
79. Van Howe, R.S.: Human papillomavirus and circumcision: a meta-analysis. J. Infect. **54**, 490–496 (2007)
80. Castellsague, X., Albero, G., Cleries, R., et al.: HPV and circumcision: a biased, inaccurate and misleading meta-analysis. J. Infect. **55**, 91–93 (2007)
81. Gray, R.H.: Infectious disease: Male circumcision for preventing HPV infection. Nat. Rev. Urol. **6**, 298–299 (2009)
82. Weaver, B.A., Feng, Q., Holmes, K.K., et al.: Evaluation of genital sites and sampling techniques for detection of human papillomavirus DNA in men. J. Infect. Dis. **189**, 677–685 (2004)
83. Smith, J.S., Backes, D.M., Hudgens, M.G., et al.: Prevalence and risk factors of human papillomavirus infection by penile site in uncircumcised Kenyan men. Int. J. Cancer **126**, 572–577 (2009)
84. Giuliano, A.R., Lazcano, E., Villa, L.L., et al.: Circumcision and sexual behavior: factors independently associated with human papillomavirus detection among men in the HIM study. Int. J. Cancer **124**, 1251–1257 (2009)
85. Nielson, C.M., Schiaffino, M.K., Dunne, E.F., et al.: Associations between male anogenital human papillomavirus infection and circumcision by anatomic site sampled and lifetime number of female sex partners. J. Infect. Dis. **199**, 7–13 (2009)
86. Dickson, N.P., Ryding, J., van Roode, T., et al.: Male circumcision and serologically determined human papillomavirus infection in a birth cohort. Cancer Epidemiol. Biomarkers Prev. **18**, 177–183 (2009)
87. Lu, B., Wu, Y., Nielson, C.M., et al.: Factors associated with acquisition and clearance of human papillomavirus

infection in a cohort of US men: a prospective study. J. Infect. Dis. **199**, 362–371 (2009)
88. Katelaris, P.M., Cossart, Y.E., Rose, B.R., et al.: Human papillomavirus: the untreated male reservoir. J. Urol. **140**, 300–305 (1988)
89. Aynaud, O., Ionesco, M., Barrasso, R.: Penile intraepithelial neoplasia – specific clinical features correlate with histologic and virologic findings. Cancer **74**, 1762–1767 (1994)
90. Daling, J.R., Madeleine, M.M., Johnson, L.G., et al.: Penile cancer: importance of circumcision, human papillomavirus and smoking in in situ and invasive disease. Int. J. Cancer **116**, 606–616 (2005)
91. Dillner, J., von Krogh, G., Horenblas, S., et al.: Etiology of squamous cell carcinoma of the penis. Scand. J. Urol. Nephrol. **205**(Suppl), 189–193 (2000)
92. Reddy, C.R., Devendranath, V., Pratap, S.: Carcinoma of penis: role of phimosis. Urology **24**, 85–88 (1984)
93. Velazquez, E.F., Bock, A., Soskin, A., et al.: Preputial variability and preferential association of long phimotic foreskins with penile cancer: an anatomic comparative study of types of foreskin in a general population and cancer patients. Am. J. Surg. Pathol. **27**, 994–998 (2003)
94. Dennis, E.J., Heins, H.C., Latham, E., et al.: The carcinogenic effect of human smegma: an experimental study. I. Preliminary report. Cancer Epidemiol. Biomarkers Prev. **9**, 671–680 (1956)
95. Heins Jr., H.C., Dennis, E.J.: The possible role of smegma in carcinoma of the cervix. Am. J. Obstet. Gynecol. **76**, 726–733 (1958)
96. Pratt-Thomas, H.R., Heins, H.C., Latham, E., et al.: Carcinogenic effect of human smegma: an experimental study. Cancer **9**, 671–680 (1956)
97. Reddy, D.G., Baruah, I.K.: Carcinogenic action of human smegma. Arch. Pathol. **75**, 414 (1963)
98. Schoeberlein, W.: Bedeutung und Haeufigkeit von Phimose und Smegma (Significance and frequency ofr phimosis and smegma) (Translated by Kasper, J.P., 1997; edited by Bailis, S.A., 1997). Muench Med. Wschr. **7**, 373–377 (1966)
99. Madsen, B.S., van den Brule, A.J., Jensen, H.L., et al.: Risk factors for squamous cell carcinoma of the penis–population-based case-control study in Denmark. Cancer Epidemiol. Biomarkers Prev. **17**, 2683–2691 (2008)
100. Haneke, E.: Skin diseases and tumors of the penis. Urol. Int. **37**, 172–182 (1982)
101. Sayed, E.I., Viraben, R., Bazex, J., et al.: Carcinome verruqueux du penis. Nouv. Dermatol. **12**, 112–113 (1993)
102. Pietrzak, P., Hadway, P., Corbishley, C.M., et al.: Is the association between balanitis xerotica obliterans and penile carcinoma underestimated? BJU Int. **98**, 74–76 (2006)
103. Nasca, M.R., Innocenzi, D., Micali, G.: Association of penile lichen sclerosus and oncogenic human papillomavirus infection. Int. J. Dermatol. **45**, 681–683 (2006)
104. Fernando, J.J., Wanas, T.M.: Squamous carcinoma of the penis and previous recurrent balanitis: a case report. Genitourin. Med. **67**, 153–155 (1991)
105. zur Hausen, H.: Herpes simplex virus in human genital cancer. Int. Rev. Exp. Pathol. **25**, 307–326 (1983)
106. Bailis, S.A.: Circumcision – The debate goes on. Pediatrics **105**, 682 (2000)
107. Ozsahin, M., Jichlinski, P., Weber, D.C., et al.: Treatment of penile carcinoma: to cut or not to cut? Int. J. Radiat. Oncol. Biol. Phys. **66**, 674–679 (2006)
108. Zouhair, A., Coucke, P.A., Jeanneret, W., et al.: Radiation therapy alone or combined surgery and radiation therapy in squamous-cell carcinoma of the penis? Eur. J. Cancer **37**, 198–203 (2001)
109. Opjordsmoen, S., Waehre, H., Aass, N., et al.: Sexuality in patients treated for penile cancer; patient's experience and doctor's judgement. Br. J. Urol. **73**, 554–560 (1994)
110. Adami, H.O., Kuper, H., Andersson, S.O., et al.: Prostate cancer risk and serologic evidence of human papilloma virus infection: a population-based case-control study. Cancer Epidemiol Biomarkers Prev **12**, 872–875 (2003)
111. Correa, P.: Is prostate cancer an infectious disease? Int. J. Epidemiol. **34**, 197–198 (2005)
112. Dennis, L.K., Dawson, D.V.: Meta-analysis of measures of sexual activity and prostate cancer. Epidemiology **13**, 72–79 (2002)
113. Dillner, J., Knekt, P., Boman, J., et al.: Sero-epidemiological association between human-papillomavirus infection and risk of prostate cancer. Int. J. Cancer **75**, 564–567 (1998)
114. Fernandez, L., Galan, Y., Jimenez, R., et al.: Sexual behaviour, history of sexually transmitted diseases, and the risk of prostate cancer: a case-control study in Cuba. Int. J. Epidemiol. **34**, 193–197 (2005)
115. Hayes, R.B., Pottern, L.M., Strickler, H., et al.: Sexual behaviour, STDs and risks for prostate cancer. Br. J. Cancer **82**, 718–725 (2000)
116. Oliver, J.C., Oliver, R.T., Ballard, R.C.: Influence of circumcision and sexual behaviour on PSA levels in patients attending a sexually transmitted disease (STD) clinic. Prostate Cancer Prostatic Dis. **4**, 228–231 (2001)
117. Radhakrishnan, S., Lee, A., Oliver, T., et al.: An infectious cause for prostate cancer. BJU Int. **99**, 239–240 (2007)
118. Ross, R.K., Shimizu, H., Paganini-Hill, A., et al.: Case-control studies of prostate cancer in blacks and whites in southern California. J. Natl. Cancer Inst. **78**, 869–874 (1987)
119. Taylor, M.L., Mainous 3rd, A.G., Wells, B.J.: Prostate cancer and sexually transmitted diseases: a meta-analysis. Fam. Med. **37**, 506–512 (2005)
120. Balis, V., Sourvinos, G., Soulitzis, N., et al.: Prevalence of BK virus and human papillomavirus in human prostate cancer. Int. J. Biol. Markers **22**, 245–251 (2007)
121. Schlaberg, R., Choe, D.J., Brown, K.R., et al.: XMRV is present in malignant prostatic epithelium and is associated with prostate cancer, especially high-grade tumors. Proc. Natl. Acad. Sci. USA **106**, 16351–16356 (2009)
122. Stark, J.R., Judson, G., Alderete, J.F., et al.: Prospective study of *Trichomonas vaginalis* infection and prostate cancer incidence and mortality: Physicians' Health Study. J. Natl. Cancer Inst. **101**, 1406–1411 (2009)
123. Apt, A.: Circumcision and prostatic cancer. Acta Med. Scand. **178**, 493–504 (1965)
124. Ewings, P., Bowie, C.: A case-control study of cancer of the prostate in Somerset and east Devon. Br. J. Cancer **74**, 661–666 (1996)
125. Ravich, A., Ravich, R.A.: Prophylaxis of cancer of the prostate, penis, and cervix by circumcision. N Y State J. Med. **51**, 1519–1520 (1951)

126. Alderson, M.: Occupational Cancer. Butterworths, London (1986)
127. Morris, B.J., Waskett, J., Bailis, S.A.: Case number and the financial impact of circumcision in reducing prostate cancer. BJU Int. **100**, 5–6 (2007)
128. Drain, P.K., Halperin, D.T., Hughes, J.P., et al.: Male circumcision, religion, and infectious diseases: an ecologic analysis of 118 developing countries. BMC Infect. Dis. **6**, 172 (110 pp.) (2006)
129. Barrasso, R., De Brux, J., Croissant, O., et al.: High prevalence of papillomavirus associated penile intraepithelial neoplasia in sexual partners of women with cervical intraepithelial neoplasia. N. Engl. J. Med. **317**, 916–923 (1987)
130. Zelkowitz, R.: Cancer. HPV casts a wider shadow. Science **323**, 580–581 (2009)
131. Amarante, M.K., Watanabe, M.A.: The possible involvement of virus in breast cancer. J. Cancer Res. Clin. Oncol. **135**, 329–337 (2009)
132. Lawson, J.S., Gunzburg, W.H., Whitaker, N.J.: Viruses and human breast cancer. Future Microbiol. **1**, 33–51 (2006)
133. Hennig, E.M., Suo, Z., Thoresen, S., et al.: Human papillomavirus 16 in breast cancer of women treated for high grade cervical intraepithelial neoplasia (CIN III). Breast Cancer Res. Treat. **53**, 121–135 (1999)
134. Widschwendter, A., Brunhuber, T., Wiedemair, A., et al.: Detection of human papillomavirus DNA in breast cancer of patients with cervical cancer history. J. Clin. Virol. **31**, 292–297 (2004)
135. Kan, C.Y., Iacopetta, B.J., Lawson, J.S., et al.: Identification of human papillomavirus DNA gene sequences in human breast cancer. Br. J. Cancer **93**, 946–948 (2005)
136. Lawson, J.S., Kan, C.Y., Iacopetta, B.J., et al.: Are some breast cancers sexually transmitted? Br. J. Cancer **95**, 1708 (2006)
137. Heng, B., Glenn, W.K., Ye, Y., et al.: Human papilloma virus is associated with breast cancer. Br. J. Cancer **101**, 1345–1350 (2009)
138. Lawson, J.S., Glenn, W.K., Heng, B., et al.: Koilocytes indicate a role for human papilloma virus in breast cancer. Br. J. Cancer **101**, 1351–1356 (2009)
139. Tseng, C.J., Pao, C.C., Lin, J.D., et al.: Detection of human papillomavirus types 16 and 18 mRNA in peripheral blood of advanced cervical cancer patients and its association with prognosis. J. Clin. Oncol. **17**, 1391–1396 (1999)
140. Chen, A.C., Keleher, A., Kedda, M.A., et al.: Human papillomavirus DNA detected in peripheral blood samples from healthy Australian male blood donors. J. Med. Virol. **81**, 1792–1796 (2009)
141. Herrero, R.: Human papillomavirus (HPV) vaccines: limited cross-protection against additional HPV types. J. Infect. Dis. **199**, 919–922 (2009)
142. Garland, S.M., Hernandez-Avila, M., Wheeler, C.M., et al.: Quadrivalent vaccine against human papillomavirus to prevent anogenital diseases. N. Engl. J. Med. **356**, 1928–1943 (2007)
143. de Kok, I.M.C.M., van Ballegooijen, M., Habbem, J.D.F.: Cost-effectiveness analysis of human papillomavirus vaccination in the Netherlands. J. Natl. Cancer Inst. **101**, 1083–1092 (2009)
144. Brisson, M., Van de Velde, N., Boily, M.C.: Economic evaluation of human papillomavirus vaccination in developed countries. Public Health Genom. **12**, 343–351 (2009)
145. Choi, Y.H., Jit, M., Gay, N., et al.: Transmission dynamic modelling of the impact of human papillomavirus vaccination in the United Kingdom. Vaccine **28**, 4091–4102 (2010)
146. Cherpes, T.L., Meyne, L.A., Krohn, M.A., et al.: Risk factors for infection with herpes simplex virus type 2: role of smoking, douching, uncircumcised males, and vaginal flora. Sex. Transm. Dis. **30**, 405–410 (2003)
147. Tobian, A., Serwadda, D., Quinn, T., et al.: Trial of male circumcision: prevention of HSV-2 in men and vaginal infections in female partners, Rakai, Uganda. 15th Conference on Retroviruses and Opportunistic Infections, Boston, abstract 28LB (2008)
148. Brankin, A.E., Tobian, A.A., Laeyendecker, O., et al.: Aetiology of genital ulcer disease in female partners of male participants in a circumcision trial in Uganda. Int. J. STD AIDS **20**, 650–651 (2009)
149. Castellsague, X., Peeling, R.W., Franceschi, S., et al.: *Chlamydia trachomatis* infection in female partners of circumcised and uncircumcised adult men. Am. J. Epidemiol. **162**, 907–916 (2005)
150. Turner, A.N., Morrison, C.S., Padian, N.S., et al.: Male circumcision and women's risk of Incident chlamydial, gonococcal, and trichomonal Infections. Sex. Transm. Dis. **35**, 689–695 (2008)
151. Cherpes, T.L., Hillier, S.L., Meyn, L.A., et al.: A delicate balance: risk factors for acquisition of bacterial vaginosis include sexual activity, absence of hydrogen peroxide-producing lactobacilli, black race, and positive herpes simplex virus type 2 serology. Sex. Transm. Dis. **35**, 78–83 (2008)
152. Gray, R.H., Kigozi, G., Serwadda, D., et al.: The effects of male circumcision on female partners' genital tract symptoms and vaginal infections in a randomized trial in Rakai, Uganda. Am. J. Obstet. Gynecol. **200**, e1–e7 (2009)
153. Joint United Nations Programme on HIV/AIDS. The HIV/AIDS Situation in Mid 1996: Global and Regional Highlights. United Nations, Geneva (UNAIDS fact sheet) (1996)
154. Fink, A.J.: A possible explanation for heterosexual male infection with AIDS. N. Engl. J. Med. **314**, 1167 (1986)
155. Fischbacher, C.M.: Circumcision of newborn boys. Lancet **353**, 669–670 (1999)
156. Siegfried, N., Muller, M., Volmink, J., et al.: Male circumcision for prevention of heterosexual acquisition of HIV in men. Cochrane Database Syst. Rev. CD003362 (2003)
157. Weiss, H.A., Quigley, M.A., Hayes, R.J.: Male circumcision and risk of HIV infection in sub-Saharan Africa: a systematic review and meta-analysis. AIDS **14**, 2361–2370 (2000)
158. Weiss, H.A., Halperin, D., Bailey, R.C., et al.: Male circumcision for HIV prevention: from evidence to action? (Review). AIDS **22**, 567–574 (2008)
159. McCoombe, S.G., Short, R.V.: Potential HIV-1 target cells in the human penis. AIDS **20**, 1491–1495 (2006)
160. Szabo, R., Short, R.V.: How does male circumcision protect against HIV infection? Br. Med. J. **320**, 1592–1594 (2000)

161. Cameron, B.E., Simonsen, J.N., D'Costa, L.J., et al.: Female to male transmission of human immunodeficiency virus type 1: risk factors for seroconversion in men. Lancet **ii**, 403–407 (1989)
162. Bailey, R.C.: Male circumcision as an effective HIV prevention strategy: current evidence. 8th Conference on Retroviruses and Opportunistic Infections, Chicago, S22, 2001. http://www.retroconference.org//requested_lectures.cfm?ID=383& mode =send
163. Kaizu, M., Weiler, A.M., Weisgrau, K.L., et al.: Repeated intravaginal inoculation with cell-associated simian immunodeficiency virus results in persistent infection of nonhuman primates. J. Infect. Dis. **194**, 912–916 (2006)
164. O'Farrell, N., Morison, L., Moodley, P., et al.: Association between HIV and subpreputial penile wetness in uncircumcised men in South Africa. J. Acquir. Immune Defic. Syndr. **43**, 69–77 (2006)
165. O'Farrell, N., Chung, C.K., Weiss, H.A.: Foreskin length in uncircumcised men is associated with subpreputial wetness. Int. J. STD AIDS **19**, 821–823 (2008)
166. Alanis, M.C., Lucidi, R.S.: Neonatal circumcision: A review of the world's oldest and most controversial operation. Obstet. Gynecol. Surv. **59**, 379–395 (2004)
167. Patterson, B.K., Landy, A., Siegel, J.N., et al.: Susceptibility to human immunodeficiency virus-1 infection of human foreskin and cervical tissue grown in explant culture. Am. J. Pathol. **161**, 867–873 (2002)
168. Miller, C.: Localization of simian immunodeficiency virus-infected cells in the genital tract of male and female rhesus macaques. J. Reprod. Immunol. **4**, 331–339 (1998)
169. Fischetti, L., Barry, S.M., Hope, T.J., et al.: HIV-1 infection of human penile explant tissue and protection by candidate microbicides. AIDS **23**, 319–328 (2009)
170. Wawer, M.J., Reynolds, S.J., Serwadda, D., et al.: Might male circumcision be more protective against HIV in the highly exposed? An immunological hypothesis. AIDS **19**, 2181–2182 (2005)
171. Peters, B., Whittall, T., Babaahmady, K., et al.: Effect of heterosexual intercourse on mucosal alloimmunisation and resistance to HIV-1 infection. Lancet **363**, 518–524 (2004)
172. Donoval, B.A., Landay, A.L., Moses, S., et al.: HIV-1 target cells in foreskins of African men with varying histories of sexually transmitted infections. Am. J. Clin. Pathol. **125**, 386–391 (2006)
173. Turville, S.G., Cameron, P.U., Handley, A., et al.: Diversity of receptors binding HIV on dendritic cell subsets. Nat. Immunol. **3**, 975–983 (2002)
174. Boggiano, C., Littman, D.R.: HIV's vagina travelogue. Immunity **26**, 145–147 (2007)
175. Hladik, F., Sakchalathorn, P., Ballweber, L., et al.: Initial events in establishing vaginal entry and infection by human immunodeficiency virus type-1. Immunity **26**, 257–270 (2007)
176. de Witte, L., Nabatov, A., Pion, M., et al.: Langerin is a natural barrier to HIV-1 transmission by Langerhans cells. Nat. Med. **13**, 367–371 (2007)
177. Schwartz, O.: Langerhans cells lap up HIV-1. Nat. Med. **13**, 245–246 (2007)
178. Kigozi, G., Wawer, M., Ssettuba, A., et al.: Foreskin surface area and HIV acquisition in Rakai, Uganda (size matters). AIDS **23**, 2209–2213 (2009)
179. Byakika-Tusiime, J.: Circumcision and HIV infection: assessment of causality. AIDS Behav. **12**, 835–841 (2008)
180. O'Farrell, N.: Enhanced efficiency of female-to-male HIV transmission in core groups in developing countries. Sex. Transm. Dis. **28**, 84–91 (2001)
181. Powers, K.A., Poole, C., Pettifor, A.E., et al.: Rethinking the heterosexual infectivity of HIV-1: a systematic review and meta-analysis. Lancet **8**, 553–563 (2008)
182. Boily, M.C., Baggaley, R.F., Wang, L., et al.: Heterosexual risk of HIV-1 infection per sexual act: systematic review and meta-analysis of observational studies. Lancet Infect. Dis. **9**, 118–129 (2009)
183. Gilbert, M.T., Rambaut, A., Wlasiuk, G., et al.: The emergence of HIV/AIDS in the Americas and beyond. Proc. Natl. Acad. Sci. USA **104**, 18566–18570 (2007)
184. Telzak, E.E., Chiasson, M.A., Bevier, P.J., et al.: HIV-1 seroconversion in patients with and without genital ulcer disease. Ann. Intern. Med. **119**, 1181–1186 (1993)
185. US Centers for Disease Control and Prevention: HIV/AIDS surveillance report: cases of HIV infection and AIDS in the United States and dependent areas, 2005, vol. 17. Revised edition [cited]. http://www.cdc.gov/hiv/topics/surveillance/resources/reports/2005report/default.htm (2007)
186. Centers for Disease Control and Prevention, HIV/AIDS Surveillance Reports [cited]. http://www.cdc.gov/hiv/topics/surveillance/resources/reports/
187. Xu, X., Patel, D.A., Dalton, V.K., et al.: Can routine neonatal circumcision help prevent human immunodeficiency virus transmission in the United States? (Review). Am. J. Mens Health **3**, 79–84 (2009)
188. Warner, L., Ghanem, K.G., Newman, D.R., et al.: Male circumcision and risk of HIV infection among heterosexual African American men attending Baltimore sexually transmitted disease clinics. J. Infect. Dis. **199**, 59–65 (2009)
189. Sullivan, P.S., Kilmarx, P.H., Peterman, T.A., et al.: Male circumcision for prevention of HIV transmission: what the new data mean for HIV prevention in the United States. PLoS Med. **4**(e223), 1162–1166 (2007)
190. Macdonald, A., Humphreys, J., Jaffe, H.W.: Prevention of HIV transmission in the United Kingdom: what is the role of male circumcision? Sex. Transm. Infect. **84**, 158–160 (2008)
191. Gray, R.H., Quinn, T.C., Serwadda, D., et al.: The ethics of research in developing countries. N. Engl. J. Med. **343**, 361–362 (2000)
192. Halperin, D., Bailey, R.: Male circumcision and HIV infection: 10 years and counting. Lancet **354**, 1813–1815 (1999)
193. Wamai, R.G., Weiss, H.A., Hankins, C., et al.: Male circumcision is an efficacious, lasting and cost-effective strategy for combating HIV in high-prevalence AIDS epidemics: Time to move beyond debating the science. Future HIV Ther. **2**, 399–405 (2008)
194. Mastro, T., Satten, G., Nopkesorn, T., et al.: Probability of female-to-male transmission of HIV-1 in Thailand. Lancet **343**, 204–207 (1994)
195. Reynolds, S.J., Shepherd, M.E., Risbud, A.R., et al.: Male circumcision and risk of HIV-1 and other sexually transmitted infections in India. Lancet **363**, 1039–1040 (2004)
196. Talukdar, A., Khandokar, M.R., Bandopadhyay, S.K., et al.: Risk of HIV infection but not other sexually transmitted

diseases is lower among homeless Muslim men in Kolkata. AIDS **21**, 2231–2235 (2007)
197. Dandona, L., Dandona, R., Kumar, G.A., et al.: Risk factors associated with HIV in a population-based study in Andhra Pradesh state of India. Int. J. Epidemiol. **37**, 1274–1286 (2008)
198. Munro, H.L., Pradeep, B.S., Jayachandran, A.A., et al.: Prevalence and determinants of HIV and sexually transmitted infections in a general population-based sample in Mysore district, Karnataka state, southern India. AIDS **22**(suppl 5), S117–S125 (2008)
199. Madhivanan, P., Krupp, K.: Doesn't the public have the right to know that male circumcision protects against HIV? Indian J. Med. Ethics **6**, 5–6 (2009)
200. Li, P.S., Lü, N.Q., Cheng, Y., et al.: The need for high-quality training and surgical standards for adult male circumcision in China (Article in Chinese). Zhonghua Nan Ke Xue **15**, 390–394 (2009)
201. Périssé, A.R., Schechter, M., Blattner, W.: Association between male circumcision and prevalent HIV infections in Rio de Janeiro, Brazil. J. Acquir. Immune Defic. Syndr. **50**, 435–437 (2009)
202. Short, R.V.: New ways of preventing HIV infection: thinking simply, simply thinking. (Review). Philos. Trans. R. Soc. Lond. B Biol. Sci. **361**, 811–820 (2006)
203. Al-Mutairi, N., Joshi, A., Nour-Eldin, O., et al.: Clinical patterns of sexually transmitted diseases, associated sociodemographic characteristics, and sexual practices in the Farwaniya region of Kuwait. Int. J. Dermatol. **46**, 594–599 (2007)
204. Orroth, K.K., Freeman, E.E., Bakker, R., et al.: Understanding the differences between contrasting HIV epidemics in east and west Africa: results from a simulation model of the Four Cities Study. Sex. Transm. Infect. **83**(suppl 1), i5–i16 (2007)
205. Schmid, G.P., Buve, A., Mugyeny, P., et al.: Transmission of HIV-1 infection in sub-Saharan Africa and effect of elimination of unsafe injections. Lancet **363**, 482–488 (2004)
206. Baeten, J.M., Richardson, B.A., Lavreys, L., et al.: Female-to-male infectivity of HIV-1 among circumcised and uncircumcised Kenyan men. J. Infect. Dis. **191**, 546–553 (2005)
207. Gray, R.H., Kiwanuka, N., Quinn, T., et al.: Male circumcision and HIV aquisition and transmission: cohort studies in Raiki, Uganda. AIDS **14**, 42371–42381 (2000)
208. Quinn, T.C., Wawer, M.J., Sewankambo, N., et al.: Viral load and heterosexual transmission of human immunodeficiency virus type 1. N. Engl. J. Med. **342**, 921–929 (2000)
209. Makumbi, F.E., Gray, R.H., Wawer, M., et al.: Male post-coital penile cleansing and the risk of HIV-acquisition in rural Rakai district, Uganda. 4th International AIDS Society Conference, Sydney (2007) (late-breaker abstract)
210. Agot, K.E., Ndinya-Achola, J.O., Kreiss, J.L., et al.: Risk of HIV-1 in Kenya. A comparison of circumcised and uncircumcised men. Epidemiology **15**, 157–163 (2004)
211. Bailey, R.C., Neema, S., Othieno, R.: Sexual behaviors and other HIV risk factors in circumcised and uncircumcised men in Uganda. J. Acquir. Immune Defic. Syndr. **22**, 294–301 (1999)
212. Johnson, K., Way, A.: Risk factors for HIV infection in a national adult population: evidence from the 2003 Kenya Demographic and Health Survey. J. Acquir. Immune Defic. Syndr. **42**, 627–636 (2006)
213. Kelly, R., Kiwanuka, N., Wawer, M.J., et al.: Age of male circumcision and risk of HIV infection in rural Uganda. AIDS **13**, 399–405 (1999)
214. Urassa, M., Todd, J., Boerma, J.T., et al.: Male circumcision and susceptibility to HIV infection among men in Tanzania. AIDS **11**, 73–80 (1997)
215. Brown, J.E., Micheni, K.D., Grant, E.M., et al.: Varieties of male circumcision: a study from Kenya. Sex. Transm. Dis. **28**, 608–612 (2001)
216. Nnko, S., Washija, R., Urassa, M., et al.: Dynamics of male circumcision practices in Northwest Tanzania. Sex. Transm. Dis. **28**, 214–218 (2001)
217. Diseker, R.A., Lin, L.S., Kamb, M.L., et al.: Fleeting foreskins: the misclassification of male circumcision status. Sex. Transm. Dis. **28**, 330–335 (2001)
218. Risser, J.M., Risser, W.L., Eissa, M.A., et al.: Self-assessment of circumcision status by adolescents. Am. J. Epidemiol. **159**, 1095–1097 (2004)
219. Auvert, B., Taljaard, D., Lagarde, E., et al.: Randomized, controlled intervention trial of male circumcision for reduction of HIV infection risk: the ANRS 1265 trial. PLoS Med. **2**(e298), 1112–1122 (2005)
220. Kim, D.S., Lee, J.Y., Pang, M.G.: Male circumcision: a South Korean perspective. BJU Int. **83**(suppl 1), 28–33 (1999)
221. Bailey, R.C., Moses, S., Parker, C.B., et al.: Male circumcision for HIV prevention in young men in Kisumu, Kenya: a randomised controlled trial. Lancet **369**, 643–656 (2007)
222. Desai, K., Boily, M.C., Garnett, G.P., et al.: The role of sexually transmitted infections in male circumcision effectiveness against HIV-insights from clinical trial simulation. Emerg. Themes Epidemiol. **3**, 19 (16 pp.) (2006)
223. Mills, E., Cooper, C., Anema, A., et al.: Male circumcision for the prevention of heterosexually acquired HIV infection: a meta-analysis of randomized trials involving 11, 050 men. HIV Med. **9**, 332–335 (2008)
224. Siegfried, N., Muller, M., Deeks, J.J., et al.: Male circumcision for prevention of heterosexual acquisition of HIV in men. Cochrane Database Syst. Rev. CD003362 (38 pp.) (2009)
225. Bailey, R.C., Moses, S., Parker, C.B., et al.: The protective effect of male circumcision is sustained for at least 42 months: results from the Kisumu, Kenya Trial. In: XVII International AIDS Conference, Mexico City, 2008
226. Tobian, A.A., Quinn, T.C.: Herpes simplex virus type 2 and syphilis infections with HIV: an evolving synergy in transmission and prevention. Curr. Opin. HIV AIDS **4**, 294–299 (2009)
227. Stephenson, J.: New HIV prevention strategies urged: averting new infections key to controlling pandemic. J. Am. Med. Assoc. **292**, 1163–1164 (2004)
228. Todd, J., Grosskurth, H., Changalucha, J., et al.: Risk factors influencing HIV infection incidence in a rural African population: a nested case-control study. J. Infect. Dis. **193**, 458–466 (2006)
229. Boily, M.C., Desai, K., Masse, B., et al.: Incremental role of male circumcision on a generalised HIV epidemic through its protective effect against other sexually transmitted infections: from efficacy to effectiveness to population-level impact. Sex. Transm. Infect. **84**(Suppl 2), i28–i34 (2008)

230. Johnson, K.E., Sherman, M.E., Ssempiija, V., et al.: Foreskin inflammation is associated with HIV and herpes simplex virus type-2 infections in Rakai, Uganda. AIDS **23**, 1807–1815 (2009)
231. Watson-Jones, D., Weiss, H.A., Rusizoka, M., et al.: Effect of herpes simplex suppression on incidence of HIV among women in Tanzania. N. Engl. J. Med. **358**, 1560–1571 (2008)
232. Zhu, J., Hladik, F., Woodward, A., et al.: Persistence of HIV-1 receptor-positive cells after HSV-2 reactivation is a potential mechanism for increased HIV-1 acquisition. Nat. Med. **15**, 886–892 (2009)
233. Auvert, B., Lissouba, P., Cutler, E., et al.: Association of oncogenic and nononcogenic human papillomavirus with HIV incidence. J. Acquir. Immune Defic. Syndr. **53**, 111–116 (2010)
234. Shelton, J.D., Halperin, D.T., Wilson, D.: Has global HIV incidence peaked? Lancet **367**, 1120–1122 (2006)
235. White, R.G., Glynn, J.R., Orroth, K.K., et al.: Male circumcision for HIV prevention in sub-Saharan Africa: who, what and when? AIDS **22**, 1841–1850 (2008)
236. Auvert, B., Marseille, E., Korenromp, E.L., et al.: Estimating the resources needed and savings anticipated from roll-out of adult male circumcision in Sub-Saharan Africa. PLoS ONE **3**, e2679 (8 pp.) (2008)
237. Cohen, J.: HIV/AIDS. Prevention cocktails: combining tools to stop HIV's spread. Science **309**, 1002–1005 (2005)
238. Williams, B.G., Lloyd-Smith, J.O., Gouws, E., et al.: The potential impact of male circumcision on HIV in Sub-Saharan Africa. PLoS Med **3**(e262), 1032–1040 (2006)
239. Kahn, J.G., Marseille, E., Auvert, B.: Cost-effectiveness of male circumcision for HIV prevention in a South African setting. PLoS Med. **3**(e517), 2349–2358 (2006)
240. Nagelkerke, N.J., Moses, S., de Vlas, S.J., et al.: Modelling the public health impact of male circumcision for HIV prevention in high prevalence areas in Africa. BMC Infect. Dis. **7**, 16 (15 pp.) (2007)
241. Gray, R.H., Li, X., Kigozi, G., et al.: The impact of male circumcision on HIV incidence and cost per infection prevented: a stochastic simulation model from Rakai, Uganda. AIDS **21**, 845–850 (2007)
242. Bollinger, L.A., Stover, J., Musuka, G., et al.: The cost and impact of male circumcision on HIV/AIDS in Botswana. J. Int. AIDS Soc. **12**, 7 (2009)
243. Londish, G.J., Murray, J.M.: Significant reduction in HIV prevalence according to male circumcision intervention in sub-Saharan Africa. Int. J. Epidemiol. **37**, 1246–1253 (2008)
244. Krieger, J.N., Bailey, R.C., Opeya, J., et al.: Adult male circumcision: results of a standardized procedure in Kisumu District, Kenya. BJU Int. **96**, 1109–1113 (2005)
245. Auvert, B., Kahn, J.G., Korenromp, E., et al.: Cost of the roll-out of male circumcision in sub-Saharan Africa. 7th International AIDS Society Conference, WEAC105 (2007)
246. World Health Organization and UNAIDS: New data on male circumcision and HIV prevention: policy and programme implications [cited]. http://who.int/hiv/mediacentre/MCrecommendations_en.pdf (2007)
247. Sahasrabuddhe, V.V., Vermund, S.H.: The future of HIV prevention: control of sexually transmitted infections and circumcision interventions. Infect. Dis. Clin. N. Am. **21**, 241–257 (2007)
248. Manning, S.E., Thorpe, L.E., Ramaswamy, C., et al.: Estimation of HIV prevalence, risk factors, and testing frequency among sexually active men who have sex with men, aged 18–64 years–New York City, 2002. J. Urban Health **84**, 212–215 (2007)
249. McKinney, C.M., Klingler, E.J., Paneth-Pollak, R., et al.: Prevalence of adult male circumcision in the general population and a population at increased risk for HIV/AIDS in New York City. Sex. Transm. Dis. **35**, 814–817 (2008)
250. Kreiss, J.K., Hopkins, S.G.: The association between circumcision status and human immunodeficiency virus infection among homosexual men. J. Infect. Dis. **168**, 1404–1408 (1993)
251. Buchbinder, S.P., Vittinghoff, E., Heagerty, P.J., et al.: Sexual risk, nitrite inhalant use, and lack of circumcision associated with HIV seroconversion in men who have sex with men in the United States. J. Acquir. Immune Defic. Syndr. **39**, 82–89 (2005)
252. Fankem, S.L., Wiysonge, C.S., Hankins, C.A.: Male circumcision and the risk of HIV infection in men who have sex with men. Int. J. Epidemiol. **37**, 353–355 (2008)
253. Millett, G.A., Ding, H., Lauby, J., et al.: Circumcision status and HIV infection among Black and Latino men who have sex with men in 3 US cities. J. Acquir. Immune Defic. Syndr. **46**, 643–650 (2007)
254. Millett, G.A., Flores, S.A., Marks, G., et al.: Circumcision status and risk of HIV and sexually transmitted infections among men who have sex with men: a meta-analysis. JAMA **300**, 1674–1684 (2008)
255. Sanchez, J., Lama, J.R., Peinado, J., et al.: High HIV and ulcerative sexually transmitted infection incidence estimates among men who have sex with men in Peru: awaiting for an effective preventive intervention. J. Acquir. Immune Defic. Syndr. **51**(Suppl 1), S47–S51 (2009)
256. Templeton, D.J., Jin, F., Mao, L., et al.: Circumcision and risk of HIV infection in Australian homosexual men. AIDS **23**, 2347–2351 (2009)
257. Lane, T., Raymond, H.F., Dladla, S., et al.: High HIV prevalence among men who have sex with men in Soweto, South Africa: results from the Soweto Men's Study. AIDS Behav. **13**, 7 Aug (9 pp.) (2009)
258. Guanira, J., Lama, J., Goicochea, P., et al.: How willing are gay men to "cut off" the epidemic? Circumcision among MSM in the Andrean region. 4th International AIDS Society Conference on HIV Pathogenesis, Treatment and Prevention, Sydney, Australia, WEAC102 (2007)
259. Anderson, J., Wilson, D., Templeton, D.J., et al.: Cost-effectiveness of adult circumcision in a resource-rich setting for HIV prevention among men who have sex with men. J. Infect. Dis. **200**, 1803–1812 (2009)
260. Short, R.V.: The HIV/AIDS pandemic: New ways of preventing infection in men. Reprod. Fert. Dev. **16**, 555–559 (2004)
261. Turner, A.N., Morrison, C.S., Padian, N.S., et al.: Men's circumcision status and women's risk of HIV acquisition in Zimbabwe and Uganda. AIDS **21**, 1779–1789 (2007)
262. Weiss, H.A., Hankins, C.A., Dickson, K.: Male circumcision and risk of HIV infection in women: a systematic review and meta-analysis. Lancet Infect. Dis. **9**, 669–677 (2009)

263. Baeten, J.M., Donnell, D., Inambo, M., et al.: Male circumcision and risk of male-to-female HIV-1 transmission: a multinational prospective study. 5th International AIDS Society Conference, Cape Town, South Africa, LBPEC06
264. Chersich, M.F., Rees, H.V.: Vulnerability of women in southern Africa to infection with HIV: biological determinants and priority health sector interventions. AIDS **22**(suppl 4), S27–S40 (2008)
265. Cassell, M.M., Halperin, D.T., Shelton, J.D., et al.: Risk compensation: the Achilles' heel of innovations in HIV prevention? Br. Med. J. **332**, 605–607 (2006)
266. Mattson, C.L., Campbell, R.T., Bailey, R.C., et al.: Risk compensation is not associated with male circumcision in Kisumu, Kenya: a multi-faceted assessment of men enrolled in a randomized controlled trial. PLoS ONE **3**, e2443 (9 pp.) (2008)
267. Agot, K.E., Kiarie, J.N., Nguyen, H.Q., et al.: Male circumcision in Siaya and Bondo Districts, Kenya: prospective cohort study to assess behavioral disinhibition following circumcision. J. Acquir. Immune Defic. Syndr. **44**, 66–70 (2007)
268. Mehta, S.D., Gray, R.H., Auvert, B., et al.: Does sex in the early period after circumcision increase HIV-seroconversion risk? Pooled analysis of adult male circumcision clinical trials. AIDS **23**, 1557–1564 (2009)
269. Bailey, R.C., Muga, R., Poulussen, R., et al.: The acceptability of male circumcision to reduce HIV infections in Nyanza Province, Kenya. AIDS Care **14**, 27–40 (2002)
270. Kebaabetswe, P., Lockman, S., Mogwe, S., et al.: Male circumcision: an acceptable strategy for HIV prevention in Botswana. Sex. Transm. Infect. **79**, 214–219 (2003)
271. Lagarde, E., Dirk, T., Puren, A., et al.: Acceptability of male circumcision as a tool for preventing HIV infection in a highly infected community in South Africa. AIDS **17**, 89–95 (2003)
272. Rain-Taljaard, R.C., Lagarde, E., Taljaard, D.J., et al.: Potential for an intervention based on male circumcision in a South African town with high levels of HIV infection. AIDS Care **15**, 315–327 (2003)
273. Westercamp, N., Bailey, R.C.: Acceptability of male circumcision for prevention of HIV/AIDS in sub-Saharan Africa: a review. AIDS Behav. **11**, 341–355 (2007)
274. Krieger, J.N., Bailey, R.C., Opeya, J.C., et al.: Adult male circumcision outcomes: experience in a developing country setting. Urol. Int. **78**, 235–240 (2007)
275. Halperin, D.T., Fritz, K., McFarland, W., et al.: Acceptability of adult male circumcision for sexually transmitted disease and HIV prevention in Zimbabwe. Sex. Transm. Dis. **32**, 238–239 (2005)
276. Rennie, S., Muula, A.S., Westreich, D.: Male circumcision and HIV prevention: ethical, medical and public health tradeoffs in low-income countries. J. Med. Ethics **33**, 357–361 (2007)
277. Karim, Q.A.: Prevention of HIV by male circumcision. Effective but integration with existing sexual health services remains the biggest challenge. Br. Med. J. **335**, 4–5 (2007)
278. Meissner, O., Buso, D.L.: Traditional male circumcision in the Eastern Cape–scourge or blessing? S. Afr. Med. J. **97**, 371–373 (2007)
279. World Health Organization/UNAIDS: Male circumcision: global trends and determinants of prevalance, safety and acceptability. http://whqlibdoc.who.int/publications/2007/9789241596169_eng.pdf. World Health Organization, Geneva (42 pp.) (2008)
280. Madhivanan, P., Krupp, K., Chandrasekaran, V., et al.: Acceptability of male circumcision among mothers with male children in Mysore, India. AIDS **22**, 983–988 (2008)
281. Stemple, L.: Health and human rights in today's fight against HIV/AIDS. AIDS **22**(suppl 2), S113–S121 (2008)
282. Clark, P.A., Eisenman, J., Szapor, S.: Mandatory neonatal male circumcision in Sub-Saharan Africa: medical and ethical analysis. Med. Sci. Monit. **12**, RA205–RA213 (2007)
283. Griffith, D., Bellows, B., Potts, M.: Cut to the chase: quickly achieving high coverage male circumcision. J. Epidemiol. Community Health **61**, 612 (2007)
284. Potts, M., Prata, N., Walsh, J., et al.: Parachute approach to evidence based medicine. Br. Med. J. **333**, 701–703 (2006)
285. Halperin, D.T., Steiner, M.J., Cassell, M.M., et al.: The time has come for common ground on preventing sexual transmission of HIV. Lancet **364**, 1913–1915 (2004)
286. Ferrante, P., Delbue, S., Mancuso, R.: The manifestation of AIDS in Africa: an epidemiological overview. J. Neurovirol. **11**(suppl 1), 50–57 (2005)
287. Donovan, B., Ross, M.W.: Preventing HIV: determinants of sexual behaviour (review). Lancet **355**, 1897–1901 (2000)
288. Yahya-Malima, K.I., Matee, M.I., Evjen-Olsen, B., et al.: High potential of escalating HIV transmission in a low prevalence setting in rural Tanzania. BMC Publ. Health **7**, 103 (10 pp.) (2007)
289. Anderson, J.E., Wilson, R., Doll, L., et al.: Condom use and HIV risk behaviors among US adults: data from a national survey. Fam. Plann. Perspect. **31**, 24–28 (1999)
290. Sanchez, T., Finlayson, T., Drake, A., et al.: Human immunodeficiency virus (HIV) risk, prevention, and testing behaviors–United States, National HIV Behavioral Surveillance System: men who have sex with men, November 2003-April 2005. MMWR Surveill. Summ. **55**, 1–16 (2006)
291. Jadack, R.A., Yuenger, J., Ghanem, K.G., et al.: Polymerase chain reaction detection of Y-chromosome sequences in vaginal fluid of women accessing a sexually transmitted disease clinic. Sex. Transm. Dis. **33**, 22–25 (2006)
292. Beckman, L.J., Harvey, S.M., Tiersky, L.A.: Attitudes about condoms and condom use among college students. J. Am. Coll. Health **44**, 243–249 (1996)
293. Kang, M., Rochford, A., Johnston, V., et al.: Prevalence of *Chlamydia trachomatis* infection among 'high risk' young people in New South Wales. Sex. Health **3**, 253–254 (2006)
294. Caballero-Hoyos, R., Villasenor-Sierra, A.: [Socioeconomic strata as a predictor factor for constant condom use among adolescents] (Spanish). Rev. Saúde Pública **35**, 531–538 (2001)
295. Tapia-Aguirre, V., Arillo-Santillan, E., Allen, B., et al.: Associations among condom use, sexual behavior, and knowledge about HIV/AIDS. A study of 13,293 public school students. Arch. Med. Res. **35**, 334–343 (2004)
296. Slaymaker, E.: A critique of international indicators of sexual risk behaviour. Sex. Transm. Infect. **80**(Suppl 2), ii13–ii21 (2004)
297. Padian, N.S., van der Straten, A., Ramjee, G., et al.: Diaphragm and lubricant gel for prevention of HIV acquisition in

southern African women: a randomised controlled trial. Lancet **370**, 251–261 (2007)
298. Potts, M., Halperin, D.T., Kirby, D., et al.: Public health. Reassessing HIV prevention. Science **320**, 749–750 (2008)
299. Van Howe, R.: Circumcision and HIV infection: review of the literature and meta-analysis. Int. J. STD AIDS **10**, 8–16 (1999)
300. Moses, S., Nagelkerke, N.J.D., Blanchard, J.F.: Commentary: analysis of the scientific literature on male circumcision and risk for HIV infection. Int. J. STD AIDS **10**, 626–628 (1999)
301. O'Farrell, N., Egger, M.: Commentary: circumcision in men and the prevention of HIV infection: a 'meta-analysis' revisited. Int. J. STD AIDS **11**, 137–142 (2000)
302. Low, N., Broutet, N., Adu-Sarkodie, Y., et al.: Global control of sexually transmitted infections. Lancet **368**, 2001–2016 (2006)
303. UNAIDS: Safe, voluntary, informed male circumcision and comprehensive hiv prevention programming: guidance for decision-makers on human rights, ethical & legal considerations. http://data.unaids.org/pub/Manual/2007/070613_humanrightsethicallegalguidance_en.pdf (2007)