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Chapter

Male Circumcision and Infection

Ruth Mielke

Abstract

Worldwide, male circumcision is done for religious or cultural reasons, and to a lesser degree for medical indications. Newborn male circumcision is associated with fewer genitourinary infections in younger males. In the current decade, a substantial body of research suggests that male circumcision is effective as a prophylactic measure against HIV and other sexually transmitted infections. The compelling HIV reductions in 3 African randomized control trials in circumcised men have prompted use of male circumcision as a key part of HIV prevention in developing nations. More recently, the use of male circumcision as a public health measure in developed nations is a topic of international discussion.

Keywords: male circumcision, sexually transmitted infections, sexually transmitted diseases, HIV, urinary tract infection, HPV

1. Introduction

Historically, male circumcision has been done for religious/cultural reasons and to a lesser degree, for medical indications. Contemporary discussion of male circumcision relates to its utility as a public health measure – specifically in the prevention of genitourinary and sexually transmitted infections. Male circumcision was suggested to prevent sexually transmitted infection as early as the 1850s [1] and broadly as a "sanitary measure" in 1914 [2]. However, when three large randomized controlled trials in sub-Sahara Africa reported that male circumcision reduced the risk of acquiring HIV infection in males by as much as 60%, [3–5] attention to its health benefits became a world-wide discussion. In 2007, the World Health Organization (WHO), and the Joint United Nations Programme on HIV/AIDS (UNAIDS), announced that male circumcision was integral to comprehensive HIV prevention [6, 7].

Most professional organizations in developed nations do not recommended routine use of newborn male circumcision but recognize its use in disease prevention. The American Urological Association, Canadian Paediatric Society, Canadian Urological Association and Royal Australasian College of Physicians recognize a benefit for some boys in high-risk populations [8–11]. However, the Centers for Disease Control supports infant and later age MC and the American Academy of Pediatrics endorses newborn MC; e.g. "current evidence indicates that the health benefits of newborn male circumcision outweigh the risks, and the benefits of newborn male circumcision justify access to this procedure for those families who choose it" [12, 13].

This chapter will discuss the impact of male circumcision in the context of the health promotion and health prevention specific to genitourinary and sexually transmitted infections.

2. Physiology of the foreskin

Male circumcision involves cutting and removing all or part of the foreskin, or prepuce, from the glans penis. To understand the rationale for the use of male circumcision (MC) in prevention of infections, it is important to understand the function and physiology of the foreskin. At birth, the glans penis and inner foreskin share a common, fused mucosal epithelium called the balano-preputial lamina (BPL). Much like the membrane that fuses the fingernail to the finger, it acts as "living glue". 'The extent of this fusion is such that the foreskin can only be retracted in 4% of newborn boys resulting in physiologic phimosis; natural inability to separate the foreskin. As the penis grows in the first 3–4 years of the boy's life, the foreskin gradually separates from the glans when smegma, epithelial debris produced by sebaceous glands, accumulates under the foreskin [14]. By age 10 most boys have a retractable foreskin, and by age 17, natural separation of the foreskin from the glans penis is complete [15] (**Figure 1**).

2.1 Uncircumcised

There are divergent viewpoints on the purpose and function of the foreskin. MC opponents view the keratinized squamous epithelium that covers the penile shaft and the foreskin in the uncircumcised penis as having protective functions. Beyond being epithelial debris, smegma is a natural emollient that protects and lubricates the glans. One author's suggestion that the inner foreskin contains apocrine glands that secrete substances e.g. lysozymes and cytokines with antibacterial properties [16] has not been verified in biochemical research. It is contended that neonatal male circumcision not only removes tissue containing fine-touch receptors but interferes with the natural separation process. This may lead to subsequent sensory imbalance and risk of injury and tears that make the circumcised penis less hygienic and more prone to infection [17].

2.2 Circumcised

The alternate view is that the biochemical and structural properties of the intact foreskin result in increased acquisition of HIV and other STIs. During intercourse, the foreskin slides backward and exposes the inner mucosal surface with its high density of target cells for HIV, Langerhans cells, CD4+ cells, and macrophages - providing an entry point for pathogens. Lymphoid areas of mucosal surfaces are primary sites for HIV infection. Foreskin tissue has been identified as both having abundant HIV target cells and susceptibility to trauma because of its thinly keratinized surface [18]. Structurally, the folding of the foreskin on the non-erect

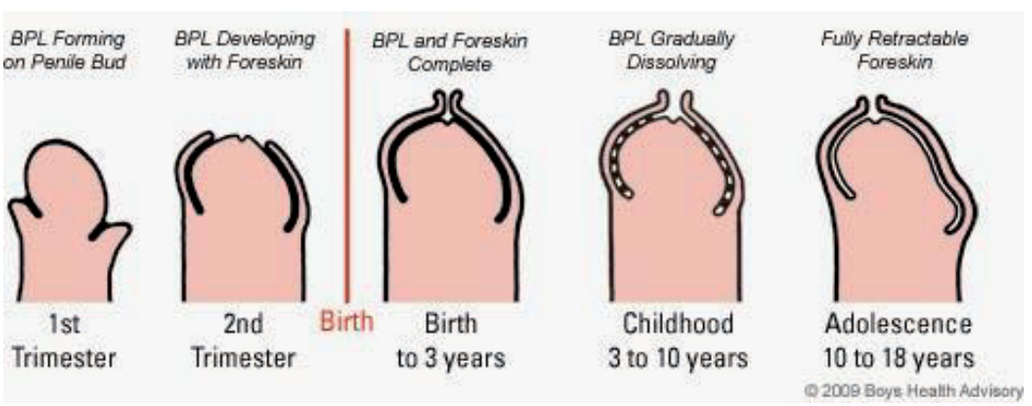


Figure 1.
Physiologic changes in the male foreskin and balano-preputial lamina (BPL) over time.

uncircumcised penis creates a sub-preputial space which is eliminated on the erect penis. By removing the foreskin surgically, this space is eliminated thereby removing the reservoir for HIV, human papilloma virus (HPV), and other pathogens [19–21]. In theory, removal of the foreskin HIV reduces target cells, eliminates the sticky medium for viruses, exposes the more keratinized penile shaft and eliminates the sub-preputial space which collectively diminishes pathogen exposure.

3. Urinary tract infection

Urinary tract infection (UTI) is one of the more common bacterial infections in children with 1–3% of children experiencing one UTI in early childhood [22, 23]. The strongest risk factors are renal tract abnormalities, which are relatively rare [24]. Common risk factors are female gender, young age, and uncircumcised state in boys [22, 25, 26]. A population study in Australia (N = 2856), conducted over 12.8 years in which most males (80.7%) were uncircumcised, reported the prevalence of UTI as twice (5.3%) in girls than in boys (2.1%) [25]. An epidemiologic study of 596 cases of childhood UTI in Sweden, where circumcision is uncommon, reported the prevalence of UTI by 11 years of age to be 3.0% for girls and 1.1% for boys. [23] Other sex differences observed by were that the prevalence of UTI was highest during the first month of life and then decreased more rapidly in boys than in girls [23, 27]. As the uncircumcised foreskin may support the growth of pathogenic bacteria at the meatus [28], this decline in UTI prevalence in boys likely occurred because of the physiologic retraction of the prepuce over time [16].

3.1 Current research

The associations of MC and UTI in older studies were limited due to having samples with disproportionately larger groups of circumcised boys and generally, because of being single studies of observational, non-experimental design. More robust evidence of the disease prevention potential of MC with respect to UTI has come about from more recent multi-study reviews [26, 29]. One of these, a meta-analysis of 22 studies (21 observational and one randomized controlled trial of 70 participants) examined lack of circumcision as a risk factor for UTI and reported a lifetime relative risk of UTI as 3.7 times higher than that in uncircumcised males. Stratified for age, the risk of UTI was 9.91 greater for those aged 0–1 year; 6.56 greater for those aged 1–16 years; and 3.41 for those older than 16 years, in uncircumcised males [26]. These results are consistent with the known decline of UTIs in males as they mature, but also suggest that the effect of MC in UTI prevention is most evident in infants and younger boys.

3.2 High-risk populations

Recurrent UTIs are the principal cause of permanent kidney tissue scarring in children, so interventions that reduce frequency of UTIs are needed to prevent short and long-term morbidity. Vesicoureteral reflux (VUR), an abnormal retrograde or "back" flow of urine from the bladder to the upper urinary tract, is the most common abnormality of the urinary tract in children and is found in 30–40% of children with UTI [30]. In children with VUR, risk of UTI recurrence increases to 10 and 30% [31]. One review of 12 studies (one RCT, 4 cohort studies, and 7 case-control studies) used a meta-analysis to assess the effect of MC on UTI, and then estimated the degree of benefit in normal boys compared to those with (a) recurrent UTI and (b) VUR, who have increased risk of UTI. Male circumcision was associated with a significantly reduced risk (87%) of UTI [31]. However, given the low risk of UTI in normal boys (1%) they estimated that

the number of MC needed to prevent one UTI was 111. However, in higher risk boys, the number of MC needed to treat those with recurrent UTIs was reduced to 11 and for those with VUR to 4 [31]. This suggests that use of MC particularly in higher risk groups of boys is an intervention to reduce UTI, subsequent renal scarring and loss of renal reserve.

Prenatal hydronephrosis (fetal urinary tract dilatation), is one of the most common congenital urological anomalies, and is reported in 1–2% of all pregnancies [32]. Prenatal identification of high-grade hydronephrosis has been associated with VUR and 3-fold increase in UTIs, so such findings may warrant consideration of early infant male circumcision [33]. Genetics has increasing importance in identifying those at risk for recurrent UTI. Genes have been identified that cause inefficient bacterial clearance and greater susceptibility to UTIs [34]. Syndromes in which there are genital tract anomalies, most prominently, vesicoureteral reflux, may increase the risk for recurrent UTI [24, 32, 33]. Early infant male circumcision (EIMC) may be warranted in boys who are at risk for recurrent UTIs based on prenatal findings.

4. Sexually transmitted infections

Worldwide, more than 1 million sexually transmitted infections (STIs) are acquired daily [35, 36]. Organisms causing STIs are bacterial, protozoal, and viral. Those with bacterial (chlamydia, gonorrhea, syphilis) or protozoal (trichomonas) causes are treatable while those caused by viruses (herpes simplex, human papilloma, HIV) are not [36, 37]. Each year, 376 million new infections are caused by chlamydia, gonorrhea, syphilis and trichomonas and more than 500 million persons experience genital infections from herpes simplex virus (HSV) [36, 38] (**Figure 2**). Most STIs have no symptoms or only mild symptoms that may not be recognized as an STI. Further, STIs such as HSV type 2 and syphilis increase the risk of HIV acquisition. Longer term, STIs can have serious reproductive health consequences beyond the immediate impact of the infection such as infertility, mother-to-child transmission and genitourinary cancers. Moreover, people with sexually transmitted infections often experience stigma, stereotyping, vulnerability, shame and gender-based violence [35].

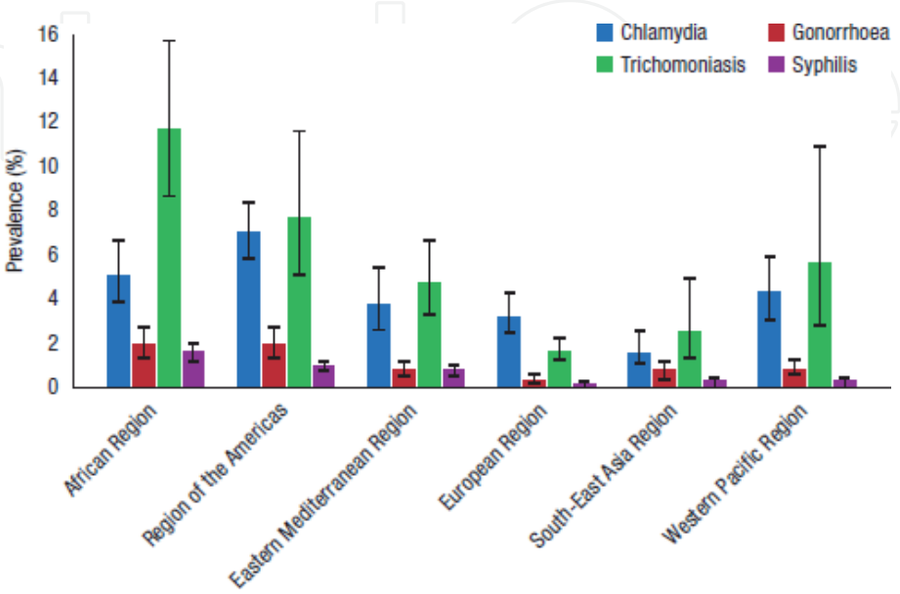


Figure 2.
Estimated prevalence of chlamydia, gonorrhea, trichomoniasis and active syphilis in women aged 15–49 years by WHO region, 2009–2016 Source: WHO Report on global sexually transmitted infection surveillance, 2018.

4.1 HIV

The health burden of HIV infections is greatest in developing countries where HIV is more prevalent, and treatment is least available. **Figure 3** shows geographic extremes ranging from 0.1% to nearly 5% in Africa. Of the 39.3 million persons living with HIV worldwide, nearly 70% live in Sub-Saharan Africa [39]. Of those, adolescent girls and women account for a disproportionate percentage (59%) of new HIV infections among adults aged 15 and older. This contrasts with other parts of the world, where men account for 63% of the new adult HIV infections. Globally, there were almost 90,000 more new HIV infections among men than women in 2017 [40]. Therefore, reaching more men with HIV treatment but more proactively, with preventive measures such as circumcision, is critical to breaking cycles of HIV transmission and reducing HIV incidence among young women. If fewer men acquire HIV because of male circumcision, this will benefit women by reducing exposure to HIV-infected men.

4.1.1 Heterosexual transmission

The potential of male circumcision to protect from heterosexual HIV infection was first suggested in 1986 [41]. Subsequently, a rich body of research done in developing countries has emerged focusing on the relationship between male circumcision and heterosexual HIV acquisition in men. In a review of (1) biological evidence, (2) observational study data supported by high-quality meta-analyses, and the (3) results of three well-recognized randomized clinical trials [3–5] (**Table 1**) and high-quality meta-analyses [42, 43] from 1999 to 2011, all of the highest quality studies; Grades 1 and 2 (meta-analyses and randomized control trials) favored MC in terms of reducing HIV risk as did the vast majority of the Grades 3 and 4 (case-control/observational studies and expert opinion) studies [44].

A more recent meta-analysis evaluated the effect of male circumcision on HIV acquisition for HIV (−/+) males and HIV (−) females during heterosexual behavior. The analysis of fifteen studies (4 RCTs and 11 prospective cohort) reported strong evidence that male circumcision was associated with reduced HIV acquisition for HIV (−)

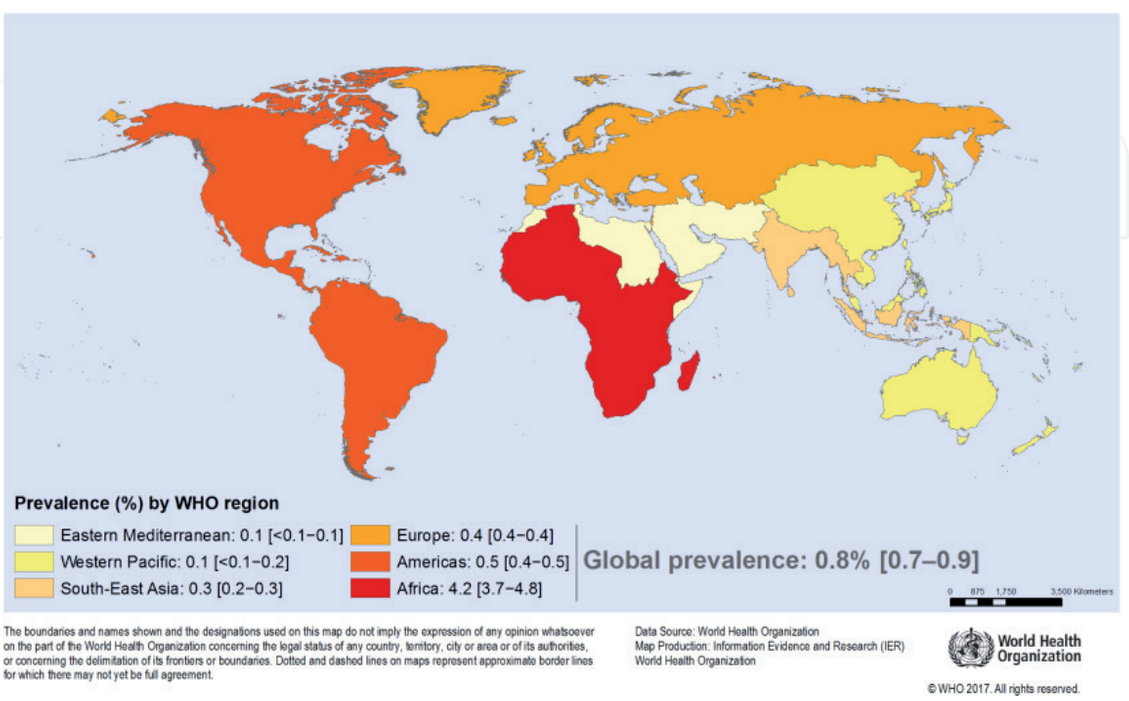


Figure 3.
Prevalence of HIV among adults aged 15 to 49, 2016 by WHO region.

Male circumcision and HIV and STI acquisition in men and transmission to female partners			
	Ratio (95% confidence interval) by study location[a]		
	Uganda	South Africa	Kenya
	N = 4996	N = 3274	N = 2784
Male protection benefit			
HIV	0.43 (0.24–0.75)[b]	0.40 (0.24–0.68)[b]	0.47 (0.28–0.78)[b]
High-risk HPV	0.65 (0.46–0.90)[c]	0.68 (0.52–0.89)[c]	
HSV-2	0.72 (0.56–0.92)[d]	0.66 (0.32–1.12)[b]	
Syphilis	1.10 (0.75–1.65)[d]		
Neisseria gonorrhoeae		0.87 (0.60–1.26)[c]	0.95 (0.68–1.34)[b]
Chlamydia trachomatis		0.56 (0.32–1.00)[e]	0.87 (0.65–1.16)[b]
Trichomonas vaginalis		0.53 (0.28–1.02)[e]	0.77 (0.44–1.36)[b]
GUD	0.53 (0.43–0.64)[c]		
Female protection benefit			
HIV	1.49 (0.62–3.57)[d]		
Bacterial vaginosis (any)	0.60 (0.38–0.94)[c]		
Bacterial vaginosis (severe)	0.39 (0.24–0.64)[c]		
Trichomonas vaginalis	0.52 (0.05–0.98)[c]		
GUD	0.78 (0.63–0.97)[c]		
High-risk HPV	0.72 (0.60–0.85)[c]		

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Abbreviations: GUD, genital ulcer disease; HIV, human immunodeficiency virus; HPV, human papillomavirus; HSV-2, herpes simplex virus type 2; STI, sexually transmitted infection.
[a]*Data shown are from 3 randomized controlled trials by Gray et al. [5], Auvert et al. [3], and Bailey et al. [4], that presented the effect of male circumcision on HIV/STI acquisition in men, 2 RCTs and a secondary analysis related to the Ugandan study on effect of MC in HIV (−/+) men on female partners by Wawer et al. [46], MC effect on HPV acquisition in female partners by Wawer et al. [60], and a MC effect on female partner STI acquisition by Gray et al. [85]. All ratios are adjusted (except for South African HSV-2 and Kenyan bacterial STIs) and represent an intention-to-treat analysis.*
[b]*The ratio expressed is an incidence rate ratio.*
[c]*The ratio expressed is a prevalence risk ratio.*
[d]*The ratio expressed is a hazard ratio.*
[e]*The ratio expressed is an odds ratio.*

Table 1.
Male circumcision and HIV and STI acquisition in men and transmission to female partners.

males during sexual intercourse with females (70% protective effect) but no difference was detected in HIV acquisition for HIV (−) females between the circumcised and uncircumcised groups [45]. One of the RCTs that evaluated the effect of MC in HIV (+) and (−) men on their female partners was stopped early in that MC did not prevent female HIV infection in either group [46]. Although the women in the studies did not experience individual protective benefit of HIV from partners with MC, the reduction of HIV in men with MC is important from a population reduction perspective.

A study of heterosexual men in a Baltimore, Maryland (United States) reported that 1096 (2.7%) of clinic visits yielded positive HIV test results. Among 394 visits by patients with known HIV exposure, circumcision was significantly associated with lower HIV prevalence (10.2 vs. 22.0%) [87]. This suggests that MC may have a role in HIV prevention in resource rich countries as well.

The optimal time for MC is when the man is HIV (−) but there may be benefit in HIV (+) men as well. WHO/UNAIDS have recommended that MC not be denied to

HIV-infected men who request the procedure (unless there are medical contraindications) to reduce stigma but also as MC can reduce acquisition of HPV in men and syphilis and herpes in their female partners [47–49]. Further, including all males in voluntary medical male circumcision programs, irrespective of HIV status, results in greater population uptake as higher risk HIV (−) males who may otherwise avoid programs due to fear of being tested for HIV will be more likely to participate [50]. In an RCT of HIV-positive men in Uganda, MC did not reduce HIV transmission to women over a period of 2 years [48]. However, the higher rate of HIV transmission in couples who initiated intercourse soon after MC compared to those who waited until healing occurred, underscores the importance of delaying intercourse until the MC wound is healed.

Therefore, MC protects men from HIV infection in areas where prevalence of HIV (e.g. sub-Saharan Africa) is high, is largely due to heterosexual transmission, and where access to antivirals is low. Male circumcision does not appear to decrease HIV acquisition in their female partners on an individual level but decreasing new HIV infections overall will ultimately reduce the HIV burden in the population overall.

4.1.2 Homosexual transmission

The case for MC as a preventive measure is less compelling in areas where HIV acquisition is largely due to men who have sex with men. In developed countries, where HIV prevalence overall is low, most HIV are cases are related to homosexual transmission e.g. in the United States, 66%, [51, 52]. Further, developed countries have access to antivirals for prevention as well as for treatment of HIV infection which keep prevalence of new infections and AIDs mortality low. One review of 20 observational studies (N = 71,693), reported that the pooled effect estimate for HIV acquisition in homosexual men was not statistically significant. However, when subgroups were analyzed, the results of 7 studies of men reporting an insertive role were statistically significant for a 27% reduction in HIV acquisition in contrast to the 3 studies of men reporting a receptive role [53]. However, a more recent meta-analysis by Sharma et al. that examined the impact of sexual roles among homosexual men reported that MC did not definitively have a protective effect among predominantly insertive homosexual men or receptive men but acknowledged that there were a small number of studies reporting the effect of sexual role on HIV acquisition [54].

More broadly, the Sharma et al. meta-analysis of 49 studies was conducted to assess MC as a method to prevent HIV acquisition in homosexual and/or heterosexual men. The overall pooled risk ratio (RR) for both homosexual and heterosexual men was 0.58 (95% CI 0.48–0.70), suggesting that MC was associated with a reduction in HIV risk. Heterosexual men had a greater risk reduction (72%) compared with 20% for homosexual men. However, there was significant heterogeneity among the studies and less than 6% of total subject count was from randomized controlled trials [54]. Although the study suggests that MC was effective in reducing HIV risk for both heterosexual and homosexual men, the effect was dramatically lower in homosexual men.

Male circumcision represents one of very few proven HIV prevention strategies particularly in high prevalence areas, such as sub-Saharan Africa where transmission is largely related to heterosexual contact. It is less clear whether voluntary male medical circumcision programs, such as those employed in Africa would be as beneficial in developed nations. In the United States, HIV prevalence is comparatively low and most new HIV infections are attributed to men having sex with men. Theoretically, certain groups in the United States,

e.g. African-American and Hispanic men with higher risk of HIV infections could benefit but this impact would be much less profound [12]. In addition, the reality that individuals may identify as either homosexual or heterosexual but are bisexually active further confounds the potential effect of MC on homosexual transmission of HIV.

4.2 Human papilloma virus

Human papillomavirus (HPV) has been established as the leading cause of invasive cervical cancer in women and is associated with anogenital warts and cancers in men and women [55]. Of the 100+ strains of HPV; about 40 affect the anogenital areas. HPV strains are classified as either low-risk (causes benign lesions) or high-risk (causes malignancies). Oncogenic high-risk strains (e.g. HPV types 16 and 18) cause most of the HPV-related cancers and pre-cancers, while the low-risk strains cause genital warts or mild Pap test abnormalities. Most sexually active persons will contract HPV infection at some time in their lives but in most cases, the infection will be asymptomatic and clear spontaneously. Risk factors associated with HPV infection include, increased exposure to the virus via multiple partners, decreased condom usage, history of other STIs, tobacco usage, and for women, having sex with an uncircumcised partner [56].

4.2.1 HPV in women

More than 290 million women have human papillomavirus (HPV) infection [57]. Worldwide, cervical cancer is the fourth most frequent cancer in women and fourth leading cause of death in women. In developing countries, cervical cancer ranks second (breast cancer is first) in incidence and mortality. Approximately 90% of deaths from cervical cancer occur in low- and middle-income countries where women do not have access to pap testing and HPV vaccine [58, 59]. Absent of such health resources, MC in their partners provides a means of HPV prevention and exposure reduction for women.

A challenge to ascertaining associations between a woman's HPV risk and her partner's circumcision status is the reality that she may have numerous partners in her lifetime. A study of HPV and cervical cancer in women with only one male partner demonstrated HPV infection of 5.5% in circumcised versus 19.6% of uncircumcised men [19]. Therefore, the procedure of MC itself removes a reservoir for viruses, such as HPV, thus reducing exposure over the long-term.

As the precursor of cervical cancer, reducing high-risk HPV transmission is a critical part of disease prevention. Decreased prevalence of high-risk HPV was found in an RCT of Ugandan women whose long-term partners were circumcised immediately compared with women with partners who were circumcised 24 months after enrollment [60] (**Table 1**). The significant reduction (28%) in high-risk HPV that was observed in women whose partners were circumcised earlier suggests that MC has a role in reducing HPV exposure to women in areas where HPV vaccine is not readily available.

A systematic review by Grund et al. analyzed data from 60 studies on the influence MC on women's health outcomes [47]. In the cervical cancer and cervical dysplasia groups, there were no RCTs, but the quality of the studies was graded using the Newcastle-Ottawa scale for non-randomized studies. All but one of the studies reported a highly protective effect of MC related to cervical cancer (in the exception study only 11% of the men were circumcised) [61]. In the same review, four of the five cases reviewed also showed that MC was highly protective of cervical dysplasia and moderately protective of HPV infection. In developed countries,

access to HPV vaccination along with early identification and treatment of cervical dysplasia is a well-established part of preventive health care for women. In resource poor countries without such preventive care programs, the protective effect of MC on cervical dysplasia and cancer offers a critical means of preventing morbidity and mortality in women.

4.2.2 HPV in men

HPV is the most common STI in the world. More attention has been on HPV infection in women because of its association with cervical cancer. In men, manifestations of HPV infection range from genital warts and mild dysplasia (low-risk strains) to rarely, anogenital cancers (high-risk strains). Two of the African trials [3, 5] (**Table 1**) reported that MC was associated with an estimated 33% reduced occurrence of high-risk HPV virus in men. Two reviews and meta-analyses analyzed the effect of male circumcision on genital HPV infection in men. Albero et al. (21 studies; N = 14,382) reported that MC was associated with a 43% reduction in both low- and high-risk strains of HPV and in two studies (RCTs), 33% reduction in high-risk HPV. However, no associations were found in the acquisition of new HPV infections, genital HPV clearance, or genital warts [62]. Larke et al. (27 studies; N = 10,779) also reported that MC was associated with modest (25%) HPV reduction but no evidence of an association with genital warts [63]. However, Larke et al. reported 33% increased HPV clearance after MC which is important when considering that diminishing viral load in men reduces exposure to their female partners.

Penile cancer is rare—globally with 0.84 cases per 100,000 person-years [64]. High-risk HPV infection has a considerable role in penile cancer, but with less consistency than in cervical cancer. In contrast to cervical cancer, in which HPV is responsible for nearly all cases, HPV infection is associated with penile cancer from 55 to 82% of the time [65]. In a study of HIV-positive men in Uganda, MC reduced the prevalence and incidence of multiple HR-HPV infections. Multiple HR-HPV infections were found in 22.4% of subjects in the intervention (MC) group and in 42.5% of those in the control (no MC) group demonstrating 47% efficacy [48]. Therefore, male circumcision may provide a direct benefit for HIV-positive men by preventing penile HR-HPV infection and thus potentially averting penile cancer. In addition, it is possible that circumcision of HIV-infected men may protect female partners from infection and potentially from cervical neoplasia.

5. Other sexually transmitted infections

Male circumcision has a role in the acquisition of other sexually transmitted infections. Although MC has not been directly associated with decreases in HIV transmission to female partners [5] (**Table 1**) it is still important to understand whether MC affects ulcerative sexually transmitted infections such as HSV type 2 [66–68] and syphilis [67, 69] both of which are associated with an increased risk of HIV.

5.1 Herpes simplex virus

Infection with the herpes simplex virus (HSV) is due to herpes simplex virus type 1 (HSV-1) or herpes simplex virus type 2 (HSV-2). HSV-1 is mainly transmitted by oral contact to cause infection in or around the mouth (oral herpes). HSV-2 is almost exclusively sexually transmitted, causing infection in the genital or anal area (genital herpes) [70]. HSV infection is highly stigmatized and negatively impacts relationships. However, more critical is its potential for

perinatal transmission, resulting newborn morbidity and mortality [71–73] and its well-documented relationship with HIV.

Perinatal transmission mostly occurs during delivery from mothers with herpes simplex virus HSV-1 or HSV-2 genital infection. If contracted, 60% of newborns will die without treatment [73]. In a first estimate of global neonatal herpes infection, Looker et al. reported 14,000 neonatal herpes cases annually and that most neonatal herpes cases occurred in Africa, due to high maternal HSV-2 infection and high birth rates. HSV-1 contributed more cases than HSV-2 in the Americas, Europe, and Western Pacific [72]. Therefore, understanding the relationship between MC and HSV transmission is important as circumcision may afford important benefit in terms of reductions in HSV infections, particularly in female partners in their childbearing years.

HSV-2 is a leading cause of genital ulcer disease worldwide, but prevalence by global region differs [71]. Looker et al. reported that Africa had the highest prevalence (32%), followed by the Americas (14%), with Africa contributing most to the global totals due to combined large population and high prevalence. Despite their lower prevalence, South-East Asia (8%) and Western Pacific (8%) also contributed large numbers infected to the global totals due to their large population numbers [38].

Women are more likely to acquire HSV-2 than men and certain ethnicities are at greater risk. For instance in the United States, the prevalence of HSV-2 in adults is 12.1%; but affects women (15.9%) more so than men (8.2%) and is highest among non-Hispanic black persons (34.6%) [74]. In Africa, HSV-2 prevalence in men ranged from 5.9 to 39.8% while in women, from 29.2% (rural women) to 79.9% (sex workers) [75].

Two of the African RCTs reported that MC was associated with HSV-2 reductions of 28 and 34% in men [3, 5] (**Table 1**). Subsequently, a large meta-analysis (N = 49) supported this original finding with respect to HSV reductions in men in that MC diminished risk of HSV-2 by 15% and genital ulcers (often due to HSV-2) by 20% [54]. There are fewer reports of the relationship between MC and HSV infections in the female partners. However, in the Grund et al. systematic review of MC and women's health outcomes, the direction of the evidence in the six studies (including one RCT) was highly protective of HSV-2 [47]. Five of the studies were in developing countries and one was in the U.S. suggesting greater global generalizability.

The HIV epidemic in sub-Saharan Africa is known to be fueled by HSV-2 consequently directing attention on the prevalence and transmission of HSV-2 in in recent years [68, 75]. Abu-Rabbad et al. estimated that in areas of high HSV-2 prevalence, such as Kisumu, Kenya, more than a quarter of incident HIV infections may have been attributed directly to HSV-2 [68]. Therefore, the role of MC in reducing HSV-2 transmission has the potential for short-term benefit along with long-term influence in perinatal health promotion and disease prevention.

5.2 Syphilis

Syphilis can cause neurological, cardiovascular and dermatological disease in adults, and stillbirth, neonatal death, premature delivery or severe disability in infants [36]. Women of childbearing age are a particularly vulnerable population. During pregnancy, the immunosuppression of pregnancy increases risk of syphilis acquisition and if untreated or undertreated, there is great risk for adverse infant consequences. In 2016, 988,000 pregnant women worldwide were infected with syphilis, resulting in over 350,000 such adverse outcomes including 200,000 stillbirths and newborn deaths [76].

The interaction between syphilis and HIV is complex and continues to be studied [69]. The World Health Organization has identified dual elimination of HIV and syphilis as a global health priority [77]. In the early stages of syphilis, painless

genital sores (chancres or ulcers) facilitate transmission of HIV infection sexually. Conversely, the immunocompromised state of HIV infection makes syphilis acquisition more likely. In developed countries, homosexual (men having sex with men) are the largest affected group [78, 79]. However, recent increases in congenital syphilis in developed [78] and developing countries warrant attention to the learning the potential value of MC in prevention of syphilis acquisition in women as well.

Several reviews have studied the influence of MC and syphilis. Weiss et al. studied risk of three ulcerative STIs (syphilis, chancroid, and genital herpes) and reported that of the syphilis studies (N = 14), there was substantial reduction of syphilis (33%) in men; however, this was limited by significant heterogeneity between the studies. The reduced risk of HSV-2 infection was of borderline statistical significance and MC was associated with lower risk of chancroid in six of seven studies [80]. More recently, a large review (N = 60) of studies assessed the association between MC and women's health outcomes included six studies on syphilis acquisition [47]. All the studies were in developing countries; there were no RCTs. The results were that MC was highly protective; all studies reported a reduction in syphilis with one reporting no cases of syphilis in the treatment (MC) group [81].

Partners PrEP Study Team followed 4716 HIV sero-discordant couples, of whom roughly 50% of the men were circumcised. During the follow-up period (~ 2·75 years), MC was associated with significantly fewer cases of syphilis by 42% in men compared with uncircumcised men and was most protective for HIV (+) men as demonstrated by 62% reduction. Further, MC male circumcision reduced overall female partner syphilis incidence by 59%; by 75% in the HIV (−) women and a 48% HIV (+) women. Thus, MC was strongly associated with reductions in syphilis acquisition in both men and their female partners. This suggests that MC decreases syphilis acquisition even in HIV discordant couples and should be an option for HIV (+) men in countries employing voluntary medical male circumcision to reduce syphilis [77, 82].

5.3 Genital ulcerative disease

Genital ulcerative disease (GUD) is associated with an increased risk of HIV acquisition and transmission. The ulcer results from various sexually transmitted infections but the ulcer's disruption of the skin tissue promotes co-infection by other viruses and bacteria. In the United States most genital ulcers are due to HSV or syphilis. Less prevalent infectious causes include chancroid (*Haemophilus ducreyi*), granuloma inguinale (*Klebsiella granulomatis*), and lymphogranuloma venereum [83].

Lymphogranuloma venereum (LGV) is a sexually transmitted infection caused by certain chlamydia trachomatis strains. LGV is common in certain areas of Africa, Southeast Asia, India, the Caribbean, and South America. It is rare in developed countries, but in the last 10 years has been increasingly recognized in North America, Europe, and the United Kingdom as causing rectal infections among men who have sex with men [84]. In the Ugandan RCT, MC reduced the risk of genital ulcer disease (GUD) in men by 50% [5] (**Table 1**).

5.4 Gonorrhea, chlamydia, trichomonas, and bacterial vaginosis infections

These bacterial STIs cause cervicitis, urethritis, vaginitis and genital ulceration, and some may also infect the rectum and pharynx. Chlamydia and gonorrhea are associated with serious short- and long-term conditions such as pelvic inflammatory disease, ectopic pregnancy, infertility, chronic pelvic pain and arthritis. They also can be transmitted to the newborn infant during pregnancy or delivery [36].

The three African RCTs also reported associations between MC and gonorrhea, chlamydia, trichomonas, and bacterial vaginosis (**Table 1**). The South African trial reported reductions with borderline statistical significance in male acquisition of chlamydia (44%) and trichomonas (47%) in men with MC [3]. The Kenyan study results suggested reductions in chlamydia and trichomonas, but neither was statistically significant [4]. Neither study reported an association between MC and gonorrhea in men. Gray reported statistically significant reductions in bacterial vaginosis (any severity) (40%), severe bacterial vaginosis (61%) and trichomonas (48%) in females whose partners had MC [85].

Grund et. al's review of the impact of MC on women's health outcomes reported high quality evidence that MC was protective of chlamydia, that effect was moderately generalizable, and inclusive of studies from Africa, Americas, Asia, Europe and the U.S. In contrast, low consistency evidence was found for MC and female acquisition of trichomonas, bacterial vaginosis, and gonorrhea [47].

6. Summary and conclusions

Three African trials of male circumcision in HIV-negative men showed that circumcision reduced male acquisition of HIV by 50–60%. As a result, male

Male Circumcision and Infection - Information to Share
1. Consider factors associated with decision making Health benefits and risks of elective neonatal, adolescent, or adult medically performed male circumcision should be considered in consultation with medical providers while considering factors associated with decision-making around male circumcision, including religion, societal norms and social customs, hygiene, aesthetic preference, and ethical considerations.
2. Provide information to sexually active adolescent and adult males regardless of circumcision status All sexually active adolescent and adult males should consider using other proven HIV and STI risk-reduction strategies such as reducing the number of partners, correct and consistent use of male latex condoms, and HIV preexposure or postexposure prophylaxis
3. Provide information to uncircumcised sexually active adolescent and adult males Prior to sharing information about medically performed male circumcision, uncircumcised sexually active adolescent and adult males should be assessed to determine their HIV risk behaviors, HIV infection status, and the gender of their sexual partner(s). These assessments will inform the discussion with men about the risks and benefits of medically performed male circumcision.
3A. Provide information to uncircumcised adolescent and adult males who are heterosexually and bisexually active (i.e., men who have sex with women)
3A-1. Assess the patient's risk of acquiring HIV through heterosexual sex: • Review the patient's HIV risk behavior • Assess condom use practices, consistency of use, and barriers to use • Inform heterosexually and bisexually active adolescent and adult males that males at high risk of HIV exposure during heterosexual sex include HIV uninfected males in sexual relationships with: o An HIV-infected woman (i.e., in an HIV discordant couple) o One or more females who are at high risk for HIV (this includes commercial sex workers, females who inject drugs, and females in defined geographic locations with a prevalence of HIV >1.0%); o Multiple female partners
3A-2. Regardless of assessed risks in 3A-1, all uncircumcised adolescent and adult males who engage in heterosexual sex should be informed about the significant, but partial, efficacy of male circumcision in reducing the risk of acquiring HIV and some STIs through heterosexual sex, as well as the potential harms of male circumcision. • Male circumcision reduces, but does not eliminate, the risk of acquiring HIV and some STIs during penile-vaginal sex. In clinical trials, medically performed male circumcision reduced the incidence of genital ulcer disease (GUD) by 48% and the prevalence by 47% and reduced the prevalence of HR-HPV by 23%–47% among circumcised men. • Male circumcision has not been shown to reduce the risk of HIV during receptive anal sex. • Male circumcision has not been shown to reduce the risk of STIs during anal sex. • The effect of male circumcision on reducing the risk of HIV and STI transmission during oral sex has not been evaluated • Male circumcision has not been shown to reduce the risk of HIV transmission to female partners. However, in clinical trials, medically performed male circumcision reduced the prevalence of GUD by 22%, HR-HPV by 28%, T. vaginalis by 48%, and bacterial vaginosis by 40% among female partners. • Male circumcision has been shown to reduce the risk of urinary tract infections in males aged 0–1 years by 90%, in males aged 1–16 years by 85%, and in males >16 years by 71%. • During adulthood, uncircumcised males are more likely than circumcised males to experience invasive penile cancer. • After circumcision, men should not have sex until their health care provider has documented wound healing.

Male Circumcision and Infection - Information to Share (continued)
3B. Provide information to men who have sex with men (exclusively) • Male circumcision reduces the risk of men acquiring HIV and other STIs during penile-vaginal sex, but no definitive statements can be made about whether male circumcision reduces the risk of MSM acquiring HIV and other STIs during penile-anal sex. • Data pooled across several observational studies indicate that among MSM who practice mainly or exclusively insertive anal sex, circumcision was associated with a decreased risk of acquiring a new HIV infection for the insertive partner; however, numbers of MSM in clinical trials are not enough to make a definitive conclusion. • It is biologically plausible that MSM who practice mainly insertive anal sex may experience a reduction in the risk for acquiring HIV and STIs like that among heterosexuals in clinical trials during penile-vaginal sex; among men who practice mainly or exclusively receptive-anal sex, male circumcision does not provide a biologically plausible benefit for a similar reduction in risk.
4. Provide information to parents of male newborns, children, or adolescents Health benefits and risks of elective neonatal, pediatric, or adolescent male circumcision should be considered in consultation with medical providers. Ideally, discussions about neonatal circumcision should occur prior to the birth of the child. Ultimately, whether to circumcise a male neonate or child is a decision made by parents or guardians on behalf of their newborn son or dependent child.
4A. Parents and guardians should be informed about the medical benefits and risks of neonatal, pediatric, or adolescent medically performed male circumcision • During infancy, circumcised infants are less likely than uncircumcised infants to experience urinary tract infections (UTIs); an estimated 7% of infant males presenting with fever in outpatient clinics and emergency rooms had UTIs, including 20% of uncircumcised febrile infants and 2% of circumcised febrile infants aged younger than 3 months of age • 32% of uncircumcised males compared with 9% of circumcised males will experience a UTI in their lifetime, suggesting that circumcision is associated with a 23% absolute decreased lifetime risk of UTI • Although most UTIs are treatable, serious complications may occur when UTIs are not diagnosed, recurrent, difficult to treat, or left untreated. Such complications may include sepsis, pyelonephritis, and renal scarring and have been associated with an increased risk for long-term consequences, including hypertension, build-up of kidney waste products (uremia), and end-stage renal disease • 8% of annual HIV diagnoses in the United States are among persons with infection attributed to heterosexual contact. STIs are very common, with human papilloma virus (HPV) infection of the anus or genitals occurring in many sexually active persons, although HPV vaccination is highly effective against many serotypes. • Current risks for either HIV or other non-HIV STIs may not remain constant in the future and the future risk for any individual neonate, child, or adolescent cannot be definitively defined at the time that a circumcision decision is made.

Figure 4.
Male circumcision and infection - information to share adapted from "information for providers to share with male patients and parents regarding male circumcision and the prevention of HIV infection, sexually transmitted infections, and other health outcomes" - division of HIV/AIDS prevention National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention Centers for Disease Control and Prevention.

circumcision is now a recommended strategy for HIV prevention in men in developing nations. By reducing the number of new infections in the population, the resource burden of HIV treatment is lessened, and fewer women and babies are exposed to HIV infection. Nearly 15 million voluntary medical male circumcisions (VMMC) have been performed for HIV prevention in 14 countries of eastern and southern Africa during the decade since WHO and UNAIDS recommended VMMC to be a component of HIV prevention intervention [7, 49]. Swaziland was the first country to introduce national early infant male circumcision (EIMC) into VMMC programming for HIV prevention [86]. It is estimated that these VMMCs will avert over half a million new HIV infections through 2030.

Although MC has not been directly associated with decreases in HIV transmission to female partners, MC has health promotion benefits for women. High-consistency evidence exists that male circumcision protects women against cervical cancer, cervical dysplasia, herpes simplex virus type 2, chlamydia, and syphilis. Even in HIV infected men and women, MC appears to have a role in reducing co-infection with syphilis and STIs such as chlamydia and gonorrhea.

To date, there are no formal programs for MC, whether for VMMC or EIMC in developing countries. However, health care workers in developed and developing countries alike must be prepared to counsel parents that choosing EIMC could have protective benefits ranging from UTIs in infancy to STIs in adulthood. In addition, health care workers must be able to counsel sexually active adolescent and adult males not only on safe sex practices, but that MC may be an option to promote their health or that of their partner [12, 87] (**Figure 4**).

World-wide, male circumcision is an important component in the arsenal of tools to prevent disease. It does not replace but strengthens established approaches to prevent and treat infection e.g. avoidance of risky sexual behaviors, condom use, anti-viral/antibiotic medications, and vaccinations. The role of male circumcision to diminish infections, whether urinary tract or STIs, conserves health resources for those with unpreventable illness and more broadly, can play a role in increasing the health of the population overall.

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