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Effects of HIV Voluntary Medical Male Circumcision Programs on Sexually Transmitted Infections

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Abstract

Purpose of review: Evidence of the protective effect of voluntary medical male circumcision (VMMC) against HIV is well established. However, evidence of the protective effect of VMMC against other sexually transmitted infections (STIs) has been inconsistent or scarce across different populations and settings. This review summarizes the current evidence on the effect of VMMC for HIV prevention on acquisition and transmission of other STIs in heterosexual men, women and men who have sex with men (MSM).

Recent findings: Recent findings continue to strongly support the protective effect of male medical circumcision against acquisition and transmission of herpes simplex virus type 2 (HSV-2), human papillomavirus (HPV) and syphilis infections in heterosexual men and women, and bacterial vaginosis and trichomoniasis in women. There is emerging evidence on the protective effect of VMMC against acquisition of hepatitis B and *Mycoplasma genitalium* infections in heterosexual men, and HSV-2, HPV and syphilis in MSM.

Summary: Evidence on the protective effect of VMMC against acquisition and transmission of common sexually transmitted infections is available for heterosexual men and women but more evidence is required for MSM. This review supports policy recommendations for the protective benefits of VMMC against STIs.

Keywords

Voluntary medical male circumcision; sexually transmitted infections

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Conflicts of interest

We have no conflicts of interest to report.

Introduction

Three landmark randomized controlled trials (RCTs) in Africa demonstrated that voluntary medical male circumcision (VMMC) reduces the risk of female-to-male HIV transmission by 60%. In 2007, the World Health Organization (WHO) endorsed VMMC as a key HIV prevention strategy for high HIV and low circumcision prevalence settings [1]. Since 2008, over 27 million VMMC procedures have been performed in 15 priority countries in eastern and southern Africa, with a target to reach 90% of males between ages of 10 and 29 years by 2021 [1]. The landmark RCTs subsequently found risk reduction benefits of VMMC on other sexually transmitted infections (STIs). Over the past decade, additional evidence has emerged on the effectiveness of VMMC on STI prevention. However, the effectiveness varies across different pathogens, populations and settings.

The evolution of evidence on effectiveness of VMMC on STI prevention

The preventive effect of male circumcision on STIs was first described around the 1850s. However, the focus on its medical benefits heightened after the landmark RCTs in the mid-2000s [2]. Since then, evidence on the preventive effect of circumcision on STIs has emerged for most STIs. The early RCTs showed risk reduction benefits of VMMC for herpes simplex virus (HSV), syphilis and human papillomavirus (HPV) in heterosexual men [3]. To date, several studies have supported the early findings and unveiled evidence of the potential protective effect of VMMC against additional STIs in heterosexual men, women and MSM, resulting in policy recommendations by WHO and US Centers for Disease Control that VMMC is beneficial for prevention of STIs [1,4,5]. This review outlines the most recent evidence on the effectiveness of VMMC on different STIs in heterosexual men, women and MSM in an era of VMMC scale-up.

Genital ulcerative disease (GUD)

GUD is strongly associated with HIV infection. VMMC reduces the risk of acquiring GUD in men by 47% (prevalence risk ratio = 0.53 (95% CI: 0.43, 0.64) [2]. The most common ulcerative infections are HSV-2, syphilis and chancroid (Table 1).

Herpes Simplex Virus Type 2 (HSV-2)

HSV infections are very common globally. HSV type 1 infections are primarily transmitted through oral-to-oral contact but oral-to-genital transmission is becoming common [2]. HSV-2 is largely transmitted sexually and is the leading cause of GUD with an estimated 491.5 million people aged 15 – 49 years living with HSV-2 in 2016 – and is strongly associated with HIV infection [6].

More consistent evidence has emerged since the early RCTs that strongly supports VMMC's protective effect against HSV-2 acquisition in heterosexual men. Two early RCTs reported HSV-2 acquisition risk reductions of 28% and 34% in Uganda and South Africa, respectively [2]. Later, a meta-analysis of 49 studies reported a 15% risk reduction [2]. Recently, a HIV incidence surveillance cohort (HIPPS cohort) of over 10,000 households in South Africa found VMMC was protective against acquisition of HSV-2 (aOR=0.66,

95%CI: 0.50 to 0.86) [7]. In the same study, partner circumcision was protective against acquisition of HSV-2 in women (aOR=0.71, 95% CI: 0.53, 0.95) [7]. In a recent systematic review of 82 publications, the odds of acquiring HSV-2 in women with uncircumcised partners were two to six times higher compared to women with circumcised partners [8]. The protective benefit in women can be through direct protection of HSV-2 acquisition from an infected partner. In a RCT of HIV serodiscordant couples in which the HIV infected partner was HSV-2 infected, the risk of HSV-2 acquisition among women with uncircumcised partners was nine times higher than women with circumcised partners (HR 8.91, 95% CI: 1.17, 67.85) [9]. On the other hand, the protective benefit in women can be secondary to reduced prevalence of HSV-2 infection in men. In the Kenya AIDS Indicator Survey, the prevalence of HSV-2 in circumcised men versus uncircumcised men was 24.0% and 38.8% (P<0.001), respectively [10]. The HSV-2 prevalence was lower in women with circumcised partners (39.4%) compared to those with uncircumcised partners (77.4%) (P<0.001). Among MSM, a recent meta-analysis of 58 studies showed that VMMC reduced the odds of acquiring HSV by 16% (OR=0·84, 95% CI: 0·75, 0·95) [11].

In summary, there is strong evidence supporting the protective effect of VMMC against HSV-2 in heterosexual men, women and MSM.

Syphilis (*Treponema pallidum*)

The global burden of syphilis among 15–49 year-old men and women in 2016 ranged from 0.1% to 1.6% - the largest burden in Africa [12]. In 2018, prevalence among pregnant women ranged from 1% to 10% [12]. Syphilis can cause dermatological, neurological and cardiovascular disease in adults, and stillbirth, neonatal death, premature delivery or severe disability in infants; it is also strongly associated with HIV infection [12].

Evidence is strong on the protective effect of VMMC against syphilis. Recent data show that VMMC reduces the risk of acquiring syphilis by 33% – 42% in men [2]. Several studies [2,8] have reported VMMC's protective effect against acquisition of syphilis in women - up to 75% incidence reduction in women with circumcised partners compared to women with uncircumcised partners [8]. Among MSM, a recent systematic review reported three studies with significant protective effect of VMMC against syphilis; however, in the meta-analysis, the odds of syphilis did not differ between circumcised versus uncircumcised MSM (OR=0.94, 95%CI: 0.75, 1.11) [11].

In summary, evidence of the protective effect of VMMC against syphilis is strong in heterosexual men and women and weak in MSM. Further research among MSM is required.

Chancroid (*Hemophylus Ducreyi*)

Hemophylus Ducreyi causes painful necrotizing genital ulcers that may be associated with inguinal lymphadenopathy. Like other ulcerative genital infections, chancroid is associated with HIV infection [13]. The prevalence of chancroid has decreased tremendously from a high of about 70% to 0% in some settings [13]. We are not aware of any recent studies on the effect of VMMC on chancroid in men. This could partly be due to its low prevalence in most settings. An early systematic review reported four of seven studies that found reduced

risk of chancroid in circumcised men (individual study RRs: 0.13 – 0.66) [14], while a meta-analysis in 2012 found no protective effect [15]. We are not aware of any studies on this subject in women or MSM.

In summary, evidence on the protective effect of VMMC against chancroid in scarce and mixed.

Mechanisms of action for GUD

The inner foreskin mucosa, which is exposed due to retraction during sexual intercourse, has a high concentration of inflammatory cells such as target cells, Langerhans cells, CD4+ cells and macrophages that are entry points for pathogens [2,6,11]. Also, the inner mucosa is highly susceptible to micro-abrasions during sexual intercourse due to its thin keratinized lining resulting in increased susceptibility to pathogens [2,4,6]. VMMC reduces the pathogen entry points and micro-abrasions in men thereby reducing the risk of acquisition [11]. This protective effect in men potentially trickles down to women with circumcised partners. However, because syphilitic ulcers may occur widely in the genitalia, the protective effect of VMMC on syphilis may be reduced because syphilis can be transmitted through other modes like direct skin-to-skin contact [6]. Chancroid lesions frequently occur on the external and internal surfaces of the foreskin. Despite the mixed evidence on VMMC's effect on chancroid, the anatomical location may make VMMC more protective against chancroid than other GUD pathogens [14].

The protective benefits of circumcision are more pronounced in heterosexual men than MSM. Circumcision has been shown to provide a direct protective benefit to MSM who practice insertive and not receptive anal intercourse. Further, some argue that the anatomical and biological environment of the rectum make it more prone to acquisition of STIs [11].

Cervical, urethral and vaginal infections

The most common vaginal infections are *Trichomonas vaginalis and,* bacterial vaginosis; the most common cervical or urethral infections are *Neisseria gonorrhea, Chlamydia trachomatis* and *Mycoplasma genitalium* (Table 1).

Bacterial vaginosis

Bacterial vaginosis (BV) is a syndrome caused by a shift in the vaginal flora leading to overgrowth of other bacteria. It is very common among women worldwide with prevalence ranging from 8% – 75% - the highest prevalence in Africa. BV is associated with preterm delivery, low birth weight and increased risk of HIV infection [8]. A recent systematic review reported a protective effect of VMMC against BV including results from a RCT - reduced risk of acquiring BV in women after partner circumcision (PRR = 0.60, 95% CI: 0.38, 0.94) [8].

In summary, there is strong evidence supporting the protective effect of VMMC against bacterial vaginosis in women.

Trichomoniasis *(Trichomonas vaginalis)*

Trichomonas vaginalis causes acute urogenital infections such as urethritis and vaginitis and rarely, cervicitis. Trichomoniasis may also cause pharyngeal and rectal infections. Its pooled global prevalence in 2016 in women and men was 5.3% and 0.6%, respectively [12].

A few studies have explored this topic in men. Earlier, a RCTs found borderline significant protective trends [2]. Recently, protective association (OR=0.49, 95%CI: 0.26, 0.90) between VMMC and trichomoniasis were found in bivariable analysis but not in multivariable analysis [7]. A recent review reported a 48% reduction in trichomoniasis prevalence in women with circumcised partners compared to women with uncircumcised partners (PRR = 0.52 (95% CI: 0.05, 0.98)), and a 18% ($P = 0.004$) reduced risk of acquiring trichomoniasis in women with circumcised partners in 7 African countries [8]. We are not aware of any studies in MSM.

In summary, evidence on the protective effect of VMMC against *Trichomonas vaginalis* is strong in women but inconclusive and inconsistent for heterosexual men and not available for MSM. Further research is warranted in heterosexual men and MSM.

Chlamydia (*Chlamydia trachomatis*)

Chlamydia trachomatis is a cervical infection that can cause serious acute or chronic conditions such as pelvic inflammatory disease, chronic pelvic pain, ectopic pregnancy, infertility, arthritis, and pharyngeal and rectal infections [2]. Chlamydia can be transmitted from mother to child in utero or during delivery. The pooled global prevalence in 15–49 year-old women and men in 2016 was 3.8% and 2.7%, respectively [12].

Among men, an early RCT reported borderline significant protective trends (OR=0.53, 95% CI: 0.32, 1.00) while, a recent study observed increased risk (aOR= 1.56, 95%CI: 1.0 to 2.43) of acquiring chlamydia among circumcised men [7]. Among women, a recent systematic review found two studies with protective effect and four studies with no protective effect [8] while no protective association has been reported among MSM (OR=0.99, 95% CI: 0.86, 1.14) [11].

In summary, evidence on the protective effect of VMMC against chlamydia in heterosexual men and women is mixed and unsupported in MSM. Further research is warranted.

Gonorrhea (*Neisseria gonorrheae*)

Neisseria gonorrheae causes disease and complications similar to chlamydia trachomatis. Gonorrhea can also be transmitted from mother to child in utero or during delivery. The pooled global prevalence in 15–49 year-old women and men in 2016 was 0.9% and 0.7%, respectively [12].

Two early RCTs found no protective association between VMMC and gonorrhea in men [2]. Subsequent studies also found no association [7]. Recently, circumcised Tanzanian men were less likely (OR=0.52, 95%CI: 0.37, 0.74) to report gonorrhea than uncircumcised men;

however, this study was prone to reporting bias [16]. Among women, most early studies found no association except for a study in India that found that women with circumcised partners had no gonorrhea compared to 7.1% of women with uncircumcised partners [8]. Among MSM, a recent meta-analysis found no protective association (OR=0.96, 95%CI: 0.85, 1.09) [11].

In summary, evidence is mixed on the protective effect of VMMC on gonorrhea in heterosexual men and women and unsupported for MSM.

Mycoplasma genitalium

Mycoplasma genitalium is an emerging cause of non-gonococcal non-chlamydial urethritis in men and cervicitis in women. It is associated with infertility, preterm birth and pelvic inflammatory disease. Its prevalence varies widely across settings ranging from 1% to 30% [17].

Few studies exist on this subject. In the HIPPS cohort, VMMC was protective (aOR=0.53, 95%CI: 0.32 to 0.88) against *M. genitalium* acquisition in men, detected using multiplex PCR [7]. A recent systematic review reported no protective association from one study in women [8]. We are not aware of any studies among MSM.

In summary, data is scarce; nonetheless, protective evidence is minimal in heterosexual men while no evidence is available for women and MSM. Further research is required.

Mechanisms of action: Trichomoniasis and Bacterial vaginosis

Trichomonas is a protozoan that can survive occasionally in the warm moist environment under the foreskin, amplifying transmission exposure [2,5,6,13]. Bacteria that resides under the foreskin is commensurate with the bacterial overgrowth of BV in the vagina [14].

Mechanisms of action: gonorrhea, chlamydia and *Mycoplasma genitalium*

Gonorrhea, chlamydia and *Mycoplasma genitalium* are mucosal infections, that directly infect the urethra or cervix during or soon after the sex act, which would minimize the effect of circumcision on transmission.

Other STIs

Due to data availability, we will only discuss the effect of VMMC on human papillomavirus and Hepatitis B infections (Table 1).

Human papillomavirus (HPV)

Human papillomavirus is the leading cause of cervical cancer in women and is strongly associated with anogenital warts and cancers in men and women. HPV has over 200 strains, of which 40 are associated with anogenital disease and about 14 are high-risk strains for anogenital cancers, particularly types 16 and 18. HPV is transmitted sexually and the most become infected shortly after sexual debut [18]. Approximately 290 million women have

HPV infection worldwide [2] and more than 80% of sexually active men and women will acquire HPV infection by the age of 45 years [19].

Among men, early studies have reported about 25% to 45% risk reduction (33% for high-risk HPV) for HPV acquisition [2]. To date, evidence of this preventive effect remains consistent [16,20]. In women, several studies have demonstrated strong protective effect of VMMC against HPV acquisition and cervical cancer [2,3,16,20]. A recent systematic review reported a reduced incident risk ratio for high-risk HPV of 0.72 (95% CI: 0.60, 0.85) for women with circumcised partners compared to those with uncircumcised partners [8]. Among MSM, only one of eleven studies found a protective association (OR = 0.71, 95% CI: 0.51, 0.99) between VMMC and penile HPV infection among HIV-infected MSM [11].

In summary, strong evidence exists supporting the preventive effect of VMMC on HPV in heterosexual men and women while evidence is limited for MSM. Further research is warranted among MSM.

Mechanism of action

The vulnerability of the foreskin mucosal surface to micro-abrasions plays an important role in HPV transmission. This vulnerability to HPV also apply to the cervical transformation zone in women [8].

Hepatitis B

Hepatitis B is a sexually, parenterally or vertically transmitted viral infection of the liver that can cause acute or chronic disease leading to cirrhosis and liver cancer in a minority of patients. WHO estimated that 257 million people were living with chronic hepatitis B infection globally in 2015, resulting to 887,000 deaths. Transmission is mostly through direct contact with blood or other bodily fluids but sexual transmission may occur, especially in unvaccinated heterosexual persons with multiple sex partners and MSM [21].

In the HIPPS cohort, VMMC was protective against acquisition of hepatitis B in men (aOR=0.53, 95%CI: 0.30, 0.95) [7]. We are not aware of any studies in women. Among MSM, no protective effect was found in a recent meta-analysis [11].

In summary, minimal data is available on this subject. While there is emerging evidence of some protective effect in heterosexual men, more research is required.

Conclusion

Our review was based on available recent data largely from observational and cross-sectional studies (Table 1). Recent RCTs, specifically designed to evaluate the effect of VMMC on STIs, are scarce. This may limit the strength of the evidence on the effect of VMMC for the different STIs. However, since we reviewed recent data in heterosexual men, women and MSM, our review offers the most recent data on this topic and is likely informative to other researchers and policy makers.

The evidence of the protective effect of VMMC for most common STIs is well established in heterosexual men and women but poorly established in MSM. There is emerging evidence that VMMC is not only protective against genital ulcerative infections but may also be protective against several other sexually transmitted infections and in a broader patient population. This review supports policy recommendations for the protective benefits of male medical circumcision against STIs. Further research should concentrate on the effect of VMMC against sexually transmitted infections where evidence is mixed and among MSM.

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Key points

Early studies demonstrated the preventive effect of VMMC mainly for genital ulcerative infections.

Recent studies have provided more, consistent and strong evidence to support the early studies in a broader patient population.

There is emerging evidence that VMMC may have preventive benefits for more STIs, including those that cause genital discharge symptoms and rarer STIs.

Table 1:

Summary of recent findings on the protective effect of circumcision against sexually transmitted infections

Pathogen	Heterosexual men (Citation)	Women (Citation)	MSM (Citation)
Genital Ulcerative Infections			
Herpes simplex virus type 2	Strong (4)	Strong (4, 5)	Strong (6)
Syphilis (Treponema pallidum)	Strong (2)	Strong (2, 5)	Weak (6)
Chancroid (Hemophilus ducreyi)	Mixed*	No studies found	No studies found
Cervical, Urethral and Vaginal Infections			
Bacterial vaginosis	Not applicable	Strong (2, 5)	Not applicable
Trichomonas vaginalis	Weak (4)	Strong (5)	No studies found
Chlamydia trachomatis	Mixed (4)	Mixed (2, 5)	No protective effect (6)
Neisseria gonorrhea	Mixed (2, 3, 14)	Mixed (5)	No protective effect (6)
Mycoplasma genitalium	Weak (4)	No protective effect (5)	No studies found
Other STIs			
Human papillomavirus	Strong (2, 13, 17)	Strong (2, 3, 5, 13, 17)	Weak (6)
Hepatitis B	Weak (4)	No studies found	No protective effect (6)

All citations are from a time period between January 2019 and June 2020

*Data from studies earlier than January 2019