Background, Methods, and Synthesis of Scientific Information Used to Inform "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"

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CONTENTS

INTRODUCTION

Male circumcision is the surgical removal of some or all of the foreskin (or prepuce) from the penis.[1] Medically attended circumcisions performed by health care professionals are voluntary, elective procedures that are preceded by an informed consent process. Male circumcision may also be performed as part of religious or cultural rites. Circumcision is a very common procedure; it has been estimated that approximately 30% of the world's male population is circumcised.[2] In the United States, overall rates of newborn male circumcision rose throughout much of the twentieth century largely due to changing cultural norms, increased rates of childbirths in hospitals, and a perception that male circumcision was more hygienic.[3] Personal decisions about circumcision are influenced by information about the preventive health benefits, safety, and risks of the procedure, as well as ethical, religious, cultural, familial, and economic considerations. Until recently, prevention of human immunodeficiency virus (HIV) infection was unlikely to factor in the decision to circumcise a male newborn or child, although other preventive health benefits of male circumcision may have been considered.

Study results indicate that male circumcision reduces the risk of male HIV acquisition through penile-vaginal sex. Results from randomized controlled trials (RCTs) provide the strongest level of evidence; however, we describe data from both RCTs and observational studies. Observational studies are often conducted instead of RCTs because of cost considerations and other barriers, and these studies may be the only feasible methodology in some cases for studying particular health outcomes, such as cancer. The results of 3 RCTs of voluntary male circumcision involving more than 10,000 HIV-negative men in settings in sub-Saharan Africa with predominantly heterosexual HIV transmission demonstrated 50%–60% reductions in HIV incidence[4-6] in the study population. Statistically significant reductions in the following infections among circumcised heterosexual men were also demonstrated in RCTs: (1) incidence and prevalence of genital ulcer disease (GUD),[6,7] (2) incidence of herpes simplex virus type 2 (HSV-2),[8,9] (3) prevalence[8,10,11] and incidence[12,13] of high-risk oncogenic human papillomavirus (HR-HPV), (4) prevalence of *Trichomonas vaginalis (T. vaginalis)*,[14] and (5) prevalence of *Mycoplasma genitalium (M. genitalium).*[15] Statistically significant reductions in the following infections among female sexual partners of circumcised men were also demonstrated in RCTs: (1) prevalence of GUD,[16] (2) prevalence of HR-HPV,[17] (3) prevalence of *T. vaginalis,*[16] and (4) prevalence of bacterial vaginosis (BV).[16] RCTs also provided evidence of increased clearance of HR-HPV infection among circumcised heterosexual men and their female sexual partners.[13] Observational studies indicate that male circumcision is likely to reduce rates of other sexually transmitted infections (STIs),[18,19] including syphilis,[20] in men and their female partners, and indicated other health benefits as well, such as reduced risk of penile[21-30] and cervical[31] cancer and reduced rates of infant urinary tract infections (UTIs).[32-37] Risks potentially associated with male circumcision include surgical adverse events (AEs),[1,4-6,38-56] adverse effects on sexual sensation and function,[57-70] and behavioral risk compensation[5,71-86] (increased risk behavior because of perception of decreased risk). In February 2007, the World Health Organization (WHO) and the Joint United Nations Programme on HIV/AIDS (UNAIDS) jointly recommended that male circumcision be recognized as an additional important

intervention to reduce heterosexual acquisition of HIV infection among men in settings with high HIV prevalence and low male circumcision rates.[87]

When describing the generalizability of the results of the African RCTs to the United States, there are both inherent limitations and strengths to be considered. In the United States, the prevalence of HIV is generally much lower than that in sub-Saharan Africa, and most persons living with diagnosed HIV infection are men who have sex with men. In 2014, there were an estimated 955,081 persons living with diagnosed HIV infection in the United States[88] compared with 25.8 million people living with HIV infection in Sub-Saharan Africa.[89] In 2014, 53% of persons living HIV infection in the United States are men who have sex with men[88] while women account for greater than half of persons living with HIV infection in sub-Saharan Africa.[89] In the absence of randomized clinical trials among men who have sex with men (MSM), meta-analysis of observational studies indicates that male circumcision did not reduce the risk of HIV acquisition among MSM overall, however, circumcision was protective for men who reported practicing mainly unprotected insertive anal intercourse compared to those who practiced mainly receptive anal intercourse.[90]

Despite these overall differences, the results of African trials are likely to have application to HIV prevention efforts in the United States. Although the United States differs epidemiologically from regions targeted by the WHO/UNAIDS recommendations and the sub-Saharan African areas in which the RCTs were conducted, there are geographic areas and subpopulations in the United States with HIV prevalence comparable to that of sub-Saharan African countries. For example, the prevalence of diagnosed HIV infection among all black or African American adult and adolescent males in San Francisco in 2012 (5,553.5/100,000 or 5.6%)[91] was similar to that among adults aged 15–49 years living in Kenya in 2014 (5.3%).[92] The predominant mode of sexual HIV acquisition among men in the United States is by penile-anal sex among men who engage in male-to-male sexual contact, but 8% of the estimated annual diagnoses of HIV infection in the United States are attributed to female-to-male sexual transmission.[93] Based on evidence from the African trials, uncircumcised heterosexual men living in areas with high HIV prevalence are likely to experience the most public health risk-reduction benefit from elective male circumcision. Although most men in the United States are circumcised, non-Hispanic black and Mexican-American men have lower rates of circumcision compared to non-Hispanic white men.[94] and African-American and Hispanic men have higher rates of diagnosis of HIV-infection compared with white, non-Hispanic men.[95] In the absence of RCT data for MSM related to male circumcision, CDC cannot make definitive statements about whether male circumcision can reduce the risk of acquiring HIV and other STIs in this population. In a meta-analysis of pooled data from observational studies among MSM who practiced mainly or exclusively insertive anal sex, circumcision was associated with a statistically significant decrease in acquiring new HIV infections,[90] and one oncogenic HPV type[96] (HPV-16). Data from observational studies are considered less robust compared with data from RCTs; however, it is biologically plausible that MSM who practice mainly or exclusively insertive anal sex may experience a reduction in the risk for acquiring HIV and STIs similar to the reduction found in RCTs among heterosexuals practicing penile-vaginal sex.

Male circumcision is another strategy or option in the portfolio of biomedical interventions to prevent acquisition of HIV infection, along with condoms, HIV testing, HIV postexposure prophylaxis, HIV pre-exposure prophylaxis, and antiretroviral treatment of HIV-positive persons. Diverse interventions are critical as no one intervention is likely to prevent all HIV transmissions. For example, the overall effectiveness of condoms in reducing heterosexual HIV transmission is reported to be 80%.[97] Also, using such strategies in combination rather than in isolation would likely enhance their overall prevention effect.[98,99]

This document presents the methods to gather, synthesize, and interpret data on the preventive health benefits, safety, and risks of medical male circumcision. It also describes the acceptability of, provider attitudes towards, access to, and cost-effectiveness of male circumcision and related ethical considerations. The data examined are mainly in the context of the United States, but data from other countries are included to inform the U.S. experience, particularly where data are lacking for the United States or for comparison purposes. This background document was used to inform the development of an informational document for providers sharing information with male patients and parents regarding the role of male circumcision as a strategy for preventing HIV and other adverse health outcomes.[a] CDC has developed an informational document to help ensure that providers will now have this information and be able to discuss with persons considering undergoing male circumcision or parents of newborn boys considering male circumcision for their infants to have the best possible public health information to guide those decisions. Social, cultural, religious, and ethical considerations are other factors associated with decision-making.

METHODS TO GATHER, SYNTHESIZE, AND INTERPRET EVIDENCE

A 2-day symposium to obtain input on the potential role of medically attended male circumcision in preventing transmission of HIV infection in the United States was held on April 26–27, 2007. It was a face-to-face meeting of external partners and a broad range of subject matter experts, including clinicians, academicians, and public health practitioners to obtain input on the potential role of male circumcision in preventing transmission of HIV in the United States.[100] A systematic Medline search—including the PubMed database and using the MeSH terms "male circumcision" or "circumcision" and "HIV"—was conducted for the symposium, and relevant literature describing male circumcision for the prevention of HIV along with policy statements regarding male circumcision, were distributed to participants in advance of the meeting. Views on the benefits of male circumcision, as well as risks and adverse effects, were presented by meeting participants. Participants examined scientific evidence to assess the relevance of male circumcision to the HIV burden in the United States, and explored other factors including potential cost-effectiveness, cultural, ethical and safety concerns, and integration of male circumcision with existing prevention methods. The questions posed to the participants, the resulting working group proposals, and names of participants in this symposium have been previously described.[100]

[a] The draft informational document was available for public comment at http://www.regulations.gov. Locate document by entering docket no. "CDC-2014-0012" in search window.

For this document, a systematic literature review was conducted to assess the association of male circumcision with medical benefits and AEs. All studies of outcomes of male circumcision published during 1950 through the end of October 2015 in Medline, Embase, and Cochrane Library, as well as citation lists were included. Systematic reviews were conducted for the following outcomes related to medically attended male circumcision: HIV acquisition and transmission (female-to-male, male-to-female, and male-to-male); other STIs; penile cancer; cervical cancer; infant UTIs; risks and AEs; sexual function and penile sensation. We conducted a broad search of all articles containing the MeSH terms "male circumcision" or "circumcision" and then conducted crosstab searches of the following terms: "HIV," "STIs," "STDs," "cancer," "malignancy," "urinary tract infection," "risks," "benefits," "sexual function," and "penile sensation." Our inclusion criteria included studies published in English that presented original data, including RCTs, cohort studies, case-control studies, cross-sectional studies, case series and case reports. Any studies cited that were published prior to 1950 were used to provide a historical perspective. Study design was classified according to guidelines for collecting scientific data in reports published in the *Guide to Community Preventive Services (the Guide).*[101] The quality of evidence was assessed according to strength of association, consistency of findings across studies and the methodologic rigor of study designs.[101-103] Because they reduce spurious causality and bias, RCTs were considered the most rigorous method for determining whether a cause-effect relationship existed between a treatment and an outcome.

Our review of the literature published during January 1950 through October 2015 also used PubMed to conduct a broad, non-systematic narrative review of articles that included the terms "male circumcision" or "circumcision" focused on articles relevant to the *Considerations related to male circumcision in the United States* section*,* because this section did not evaluate clinical outcomes. Articles published in English that included information about acceptability, cost-effectiveness, risk compensation, policy issues, and ethical issues related to male circumcision were reviewed. Data through 2014 were included to describe HIV trends in the United States.

In formulating the informational document, available evidence from the literature review was considered together with input on the potential role of male circumcision in preventing HIV transmission made at the 2007 symposium[100] and the numerous comments from the public that were received and reviewed. The 2007 symposium consisted of a two-day consultation with stakeholders. Working groups consisting of stakeholders summarized data and discussed the use of male circumcision for prevention of HIV and other sexually transmitted infections among heterosexual men, MSM, and newborn males. The drafted background document and informational document were reviewed by subject matter experts whose input was incorporated. The revised background document and informational document were posted in a Federal Register Notice for public comment. Numerous comments were reviewed and incorporated. The final drafts of the background document and informational document were sent to subject matter experts for review and their comments were incorporated. A subcommittee of CDC's Public Health Ethics Committee (PHEC) reviewed the informational document and provided guidance on ethical issues related to elective male circumcision. The developers of these guidelines disclose that they have no financial interests or other

competing interests related to male circumcision. The informational document will be updated as needed based on the availability of relevant significant new information.

SUMMARY OF EVIDENCE

Effect of Male Circumcision on Health Outcomes

This section describes the evidence of biological plausibility of male circumcision on reducing the acquisition of HIV and other STIs, and includes a summary of results of RCTs, observational studies, and meta-analyses. It also describes study results about the frequency of penile and prostate cancers among circumcised men, cervical cancer in female partners of circumcised men, UTIs in circumcised infants, and other associated health risks, including effect on sexual function and penile sensation.

Biological Plausibility

The foreskin can serve as a portal of entry for STIs (including HIV), lending biological credibility to the role of circumcision in preventing STI and HIV acquisition through insertive sexual intercourse.[104,105] The likely mechanism of increased susceptibility associated with an intact foreskin involves both histopathological and anatomic factors,[106] as well as the interaction between HIV and other STIs.

Compared to the dry external skin surface of the glans penis and the penile shaft, the inner surface of the foreskin is less keratinized. This may allow easier access to the epithelial cells of the epidermis and dermis (in which STIs such as HPV and HSV-2 replicate) as well as access to target cells for HIV infection.[104,107] Some laboratory studies have shown foreskin tissue to be more susceptible to HIV infection than keratinized epithelium.[108,109] However, in another study of rhesus macaques, although more HIV-1 virions were observed on the inner foreskin compared with the glans tissue, a larger proportion of virions were seen penetrating uncircumcised glans tissue and to greater mean depths than inner foreskin tissue of cadaveric specimens.[110] More virions were also visualized on the inner foreskin than outer foreskin at 24 hours of culturing, suggesting that both the inner foreskin and glans epithelia may serve as sites for HIV transmission in uncircumcised men.[110] The inner foreskin surface has been found to contain a higher density of HIV target cells, such as Langerhans cells close to the skin surface,[111-114] and in men with a history of recent STIs, the number of target cells in the prepuce was increased.[112] The fact that the size of foreskins excised from 965 men enrolled in the Rakai Community Cohort Study[115] significantly correlated with HIV incidence rates may be explained by the hypothesis that surface area would be associated with more resident HIV immune cells such as Langerhans cells, CD4+ T cells, CD8+ T cells, and macrophages and therefore greater rates of HIV transmission.[116] However, the precise role of Langerhans cells is not fully understood.[117-119] A study of the inner foreskin of healthy Peruvian males who have sex with males or transgender females at elevated risk for HIV infection, found evidence of subclinical changes that may support an inflammatory state in the inner foreskin, including an increased density of target cells for HIV infection such as CCR5+ and CD4+CCR5+ cells in the inner compared with outer foreskin.[120]

Because the inner surface of the foreskin is lightly keratinized, it may be relatively susceptible to traumatic epithelial disruptions during intercourse, providing a portal of entry for pathogens.[104] Furthermore, the foreskin retracts away from the glans and over the shaft of the penis during intercourse, which exposes this surface to the body fluids of the sex partner.[111] It has been postulated that the foreskin may serve as a reservoir for various pathogens, particularly HIV and anaerobic bacteria, since the micro-environment in the preputial sac between the unretracted foreskin and the glans penis may be conducive to their survival, thereby increasing contact time of these infectious agents with penile tissues. The anoxic microenvironment of the preputial sac may support pro-inflammatory anaerobes that can activate Langerhans cells to present HIV to CD4 cells in draining lymph nodes.[121] Circumcision has been associated with a significant decrease in total bacterial load in the coronal sulcus of male adults, particularly that of anaerobes, and a minor increase in aerobes.[122] A significant decrease in bacterial colonization of the glans penis, including that of uropathogenic bacteria, has also been reported in circumcised boys compared with uncircumcised boys.[123] Investigators determined that uncircumcised compared to circumcised males had higher rates of "wetness" around the glans or coronal sulcus and that higher degrees of "wetness" were associated with higher rates of HIV infection.[124] Among male attendees at a sexually transmitted disease (STD) clinic in Durban, South Africa, men with any level of penile wetness compared to men with no wetness had HIV seroprevalences of 66.3% and 45.9%, respectively.[124] Langerhans cells and CD4+T cells in the inner foreskin are significantly more responsive to certain inflammatory cytokines than those in the outer foreskin. This may suggest that immune cells of the inner foreskin more easily respond to infectious and other exposures resulting in increased viral susceptibility of the inner foreskin.[116,125]

HIV infection and other STIs, which independently may be more likely in uncircumcised men, interact synergistically to increase acquisition risk.[126-130] Infection with ulcerative STIs such as HSV-2 has been associated with increased risk of HIV infection in observational studies;[128,131,132] this risk was 3-fold in a recent meta-analysis.[133] In the South African trial, the authors estimated that approximately 28% of incident HIV cases were attributable to HSV-2 seropositivity or acquisition.[9] Proposed mechanisms of increased susceptibility include breaches in the mucosal barrier and increased susceptibility of tissue due to inflammation, or increasing HIV target cells associated with inflammation.[107] Synergistically, HIV seropositivity may increase the risk for new STIs,[128,134] although some studies have failed to find such an association.[135]

Male Circumcision and the Risk of HIV Infection Acquisition

Male acquisition of HIV infection from female partners

Three RCTs have been undertaken in sub-Saharan Africa to determine whether circumcision of adult males will reduce their risk for HIV infection (Table 1).[4-6] The randomized, controlled follow-up in all 3 studies was stopped early when interim analyses demonstrated that circumcision by a clinician significantly reduced male participants' risk of HIV infection. The control group was then offered circumcision, as it was determined to be unethical not to offer them circumcision. In intention-to-treat (ITT) analyses, men who had been randomly assigned to the circumcision group had a 60% (South Africa), 53% (Kenya), and 51% (Uganda) lower incidence of HIV infection

compared to men assigned to the group to be circumcised at the end of the study. In all 3 studies, some of the men who had been assigned to be circumcised did not undergo the procedure, and vice versa. Non-compliance with assigned study group may mean that the ITT analyses underestimated the potential benefit of circumcision. When the data were reanalyzed to account for these crossovers in an as-treated (AT) analysis, men who had been circumcised had 76% (South Africa), 60% (Kenya), and 55% (Uganda) reductions in risk of HIV infection compared to those who were not circumcised.[4-6] However, it should be noted that AT analyses may be considered biased.

The Ugandan RCT included male participants aged 15 years or older.[6] Among all men aged 15–49 years, there was a 51% lower HIV incidence at 24 months of follow-up in circumcised compared to uncircumcised males. The reduction in HIV acquisition rate did not vary significantly by age group.

The protective effect of male circumcision appears to be remain over time. In a rigorous meta-analysis of the ITT data of the 3 RCTs, the overall relative risk reduction of acquiring HIV was 50% at 12 months and 54% at 21 or 24 months following circumcision.[136] During 4.79 years of trial surveillance of participants in the Rakai randomized trial of male circumcision, investigators found that the overall HIV incidence was 0.50/100 person-years and 1.93/100 person-years in circumcised men and uncircumcised men, respectively. The corresponding effectiveness was 73% [95% confidence interval (CI) = 55%–84%]) after adjusting for sociodemographic characteristics during the last trial visit and time-dependent sexual behavior at post-trial follow-up.[81] The HIV prevention effectiveness in the post-trial observational study was not statistically significantly different to that of the AT effectiveness of circumcision observed during the randomized trial. At 72 months of post-trial follow-up in Kisumu, Kenya, the cumulative 72-month HIV incidence was 4.8% among circumcised men and 11.0% among uncircumcised men with an overall efficacy of 58% (adjusted hazard ratio [aHR] 0.42 [95% CI = 0.26–0.66])[137] similar to a 60% reduction at 24 months.[5]

International observational studies also indicate that male circumcision is associated with lower rates of HIV,[138,139] although some cross-sectional studies conducted in general populations have failed to find an association between circumcision status and HIV-1.[140-142] A systematic review and meta-analysis of 28 studies that focused on heterosexual transmission of HIV in Africa was published in 2000.[138] It included 19 cross-sectional studies, 5 case-control studies, 3 cohort studies, and 1 partner study. In the overall pooled unadjusted analysis, a substantial protective effect of male circumcision on risk for HIV infection was noted, with a 48% reduction in risk for HIV infection among circumcised men compared to uncircumcised men (pooled risk ratio (RR) = 0.52 [95% CI = 0.40–0.68; $P < 0.001$]). In 3[143-145] of 5 studies that were adjusted for other factors, including history of current or previous GUD, an additional 1%–6% risk for HIV infection was noted which suggested a greater protective effect of male circumcision against HIV in populations with more prevalent GUD. After adjusting for confounding factors in the population-based studies, the relative risk for HIV infection was 44% lower in circumcised men compared with uncircumcised men. The strongest association was seen in men who were most likely to be exposed to HIV, such as patients at STD clinics, for

whom the adjusted relative risk was 71% lower in circumcised men compared with uncircumcised men.

Prior to the completion of RCTs, another review was conducted that included stringent assessment of 10 potential confounding factors and was stratified by study type or study population.[139,146] The review included 37 studies,[139] with 18 studies (1 cohort, 16 cross-sectional, and 1 case-control) conducted in the general population and 19 studies (4 cohort, 12 cross-sectional, and 3 case-control) conducted in high-risk populations. Most of the studies were from Africa. Of the 37 studies included in the review,[139] the 18 studies conducted in general populations had inconsistent results, whereas the 19 studies conducted in high-risk populations found a consistent, substantial protective effect, which increased with adjustment for confounding. Of the 18 studies in the general population, the single cohort study showed a benefit of male circumcision (Odds ratio [OR] 0.58 [95% CI 0.36–0.96]), the case-control study found no significant difference (OR 1.90 [95% CI 0.50–7.20]), and the 16 cross-sectional studies had varying results including 10 studies that indicated a beneficial effect of male circumcision and 6 that indicated a harmful effect (ORs ranging from 0.21–1.73). Of the 8 cross-sectional studies with statistically significant findings, 6 indicated a benefit and 2 indicated harm. The 1 large prospective cohort study conducted in the general population which included 5,507 HIV-negative Ugandan men, and 187 HIV-negative men in discordant relationships, showed a significant protective effect, with 42% lower risk of acquisition of HIV infection among circumcised men compared with uncircumcised men.[147] Among serodiscordant couples, in a substudy of this cohort, none of 50 circumcised men with HIV-infected female partners seroconverted, whereas there were 40 incident cases among 137 uncircumcised men with HIV-infected female partners.[147,148] The 19 studies conducted in high-risk populations in this review[139] found a consistent, substantial protective effect and were in better agreement than the 18 studies in the general population. All 4 cohort studies indicated a beneficial effect from male circumcision, including 3 with statistically significant results with point estimates from crude odds ratios (ORs) varying from 0.10 to 0.39. Eleven of the 12 cross-sectional studies indicated a benefit of male circumcision, including 8 which were statistically significant with ORs of 0.10 to 0.66. Of the 5 cross-sectional studies reporting adjusted ORs, these ranged from 0.20–0.59. Among the 3 case-control studies in high-risk populations, all indicated a protective effect of circumcision on HIV status, including 2 that were statistically significant with ORs of 0.37 and 0.88.

More recent meta-analyses have been conducted that include RCTs in addition to observational and case-control studies. One meta-analysis of 13 studies, including 3 RCTs, found a 58% reduced risk of HIV infection among circumcised men (overall risk ratio [RR] 0.42 [95% CI = 0.33–0.53]) and determined that the studies met criteria for causality between lack of circumcision and HIV-1 infection.[149] In a meta-analysis of 15 studies, including 4 RCTs and 11 prospective cohort studies, male circumcision was associated with 70% reduction in the risk for HIV acquisition (pooled adjusted risk ratio [aRR] 0.30 [95% CI = 0.24–0.38]).[150]

Several studies have examined the association of male circumcision in reducing HIV acquisition in the context of other STI infections. For example, in an RCT studying the

role of GUD and HSV-2 in the protection against HIV associated with male circumcision in Rakai, Uganda, male circumcision significantly reduced the risk of HIV acquisition in HSV-2 seronegative men (incidence rate ratio [IRR] 0.34 [95% CI = 0.15–0.81]).[151] There were 11.2% and 8.6% reductions in HIV acquisition mediated by reductions in symptomatic GUD (95% CI = 5.0–38.0) and HSV-2 incidence (95% CI = 1.2–77.1), respectively. In Kenya, male medical circumcision did not affect HSV-2 incidence and GUD, and HSV-2 infection, in turn, did not have an impact on the protective effect of male medical circumcision against HIV.[7] In RCTs, male circumcision has also been associated with reductions in prevalent infection with HR-HPV,[8,10,11,17] *T. vaginalis,*[14,16] BV,[16] or *M. genitalium,*[15] and reductions in incident infection with HR-HPV.[12,13]

Ecologic studies also demonstrate a strong association between lack of male circumcision and HIV infection at the population level. Although links between male circumcision, culture, religion, and risk behavior likely account for some of the differences in HIV infection prevalence, the countries in Africa and Asia with prevalence of male circumcision of less than 20% have HIV-infection prevalence several times as high (seroprevalence range: 0.24–25.84) than countries in those regions where more than 80% of men are circumcised (seroprevalence range: 0.03–11.64).[152] Based on data from an HIV transmission model fitted to data from the Four Cities Study, which included 2 cities in sub-Saharan Africa with relatively low HIV prevalence (Cotonou and Yaoundé) and 2 with high HIV prevalence (Kisumu and Ndola), investigators concluded that differences in rates of male circumcision likely played an important role in differing rates of HIV transmission across Africa.[153]

The question of whether resumption of sexual intercourse soon after adult male circumcision affected HIV risk was examined in a combined analysis of data from 3 RCTs limited to HIV-negative men who were randomized to and underwent circumcision.[154] Early sex (intercourse < 42 days after circumcision) was reported by 3.9% of participants in Kenya, 5.4% in Uganda, and 22.5% in South Africa. In all 3 trials, early resumption of sex was reported more often among men who were married or living as married. These same factors associated with early resumption of sex were also identified in a literature review of 11 publications.[155] In pooled analyses of the 3 RCTs, circumcised men reporting early sex did not have higher HIV infection rates at the 3- or 6-month follow-up visit than circumcised men who did not have early sex.[154]

In a prospective cohort study in Rakai, Uganda, the effect of male circumcision on the plasma HIV viral load of 111 HIV-positive, HAART-naïve men with complete follow-up was studied. After male circumcision, compared to baseline, there was not a statistically significant increase in HIV plasma viral load, even after controlling for CD4 count.[156] In this study, men with higher baseline $\log_{10}$ plasma viral load were significantly more likely to experience a reduction in mean $\log_{10}$ plasma viral load after undergoing circumcision.

The RCTs[4-6] in Africa and numerous observational studies[138,157] have demonstrated that male circumcision reduces the risk for female-to-male transmission of HIV. Careful consideration is required to apply these findings to the U.S. context, given differences in HIV risk groups.[158,159] In contrast to the sub-Saharan African countries where the RCTs were conducted, the United States has low prevalence of HIV infection (0.47%),[160] with

HIV infection concentrated among men who have male-to-male sexual contact (men who have sex with men [MSM] and men who have sex with men and women) rather than men who have sex exclusively with women.[161-163] In 2014, there were an estimated 44,784 new diagnoses of HIV in the United States and 6 dependent areas.[93] While no RCTs have been conducted in the United States, a similar magnitude of risk-reduction benefit of circumcision would likely apply to U.S. men engaged in penile-vaginal sex. However, the population effect would be less pronounced in the United States compared to sub-Saharan Africa due to the smaller proportion of cases among men of heterosexually acquired HIV infection in the United States.

Few U.S. studies have evaluated the effect of male circumcision for preventing heterosexually acquired HIV infection. Two published observational studies have reported on the association between circumcision and the risk of HIV infection in the United States among male patients attending STD clinics.[130,164] The first study suggests that being uncircumcised might be associated with increased HIV risk, but the finding was limited by small sample size and was not statistically significant. The more recent study was a cross-sectional evaluation conducted among heterosexual African American men attending STD clinics in Baltimore, with an overall HIV seroprevalence of 3%.[164] Among approximately 40,000 visits by patients with unknown HIV exposure, male circumcision was not associated with reduced HIV prevalence. However, among 394 visits by men who had female sexual partners known to be infected with HIV, male circumcision was significantly associated with a 51% reduced relative prevalence of HIV infection (10.2% among circumcised men vs 22.0% among uncircumcised men).

HIV infection transmission from circumcised men to female partners

Studies on the effect of male circumcision on HIV transmission from male partners to female partners have shown mixed results. Some observational studies suggest a benefit; a randomized prospective study failed to demonstrate one. In a study of serodiscordant couples in Uganda in which the male partner was HIV infected and the female partner was initially HIV negative, the infection rates of the female partners differed by male circumcision status and viral load of their male partners. If the HIV viral load in the blood of the male partner was < 50,000 copies/mL, and the man was uncircumcised, the rate of HIV transmission was 9.6 per 100 person-years; if the man was circumcised, there was no HIV transmission.[147] For all male partners, regardless of viral load, the male-to-female transmission rate from circumcised men was somewhat lower than that from uncircumcised men, but this was not statistically significant. In another study of heterosexual serodiscordant couples from 7 sites in eastern Africa and 7 sites in southern Africa, in which the HIV-infected partner was also infected with HSV, 1,096 couples included a male as the HIV-infected partner. Adjusting for HIV-1 concentration in male partner plasma, female partners of circumcised men retained a not statistically significant 40% reduced risk of HIV-1 acquisition compared to those with partners of uncircumcised men (Hazard ratio [HR] 0.60 [95% CI = 0.31–1.16, $P = 0.13$], for genetically-linked events). After excluding follow-up time occurring after male partners initiated antiretroviral therapy, the risk of HIV acquisition decreased by a not statistically significant 47% (HR 0.53 [95% CI = 0.26–1.07, $P = 0.07$], for genetically-linked events).[165] Other observational studies have evaluated the effect of male circumcision on HIV risk to women without limiting the participants to serodiscordant couples. In a

prospective study among 2,471 HIV-uninfected women in Tanzania, having an uncircumcised husband was associated with a significantly increased risk of HIV acquisition (aRR 3.60 [95% CI = 1.12–11.59]).[166] Similarly, in a cross-sectional case-control study of 4,404 women in Kenya, having a regular sex partner who was uncircumcised was associated with an odds ratio (OR) of 2.9 (95% CI = 2.0–4.2) of being HIV infected.[167] However, another observational study from Uganda found that after adjustment for other risk factors, male circumcision of the primary sex partner was not associated with a woman's risk for HIV infection.[168]

Finally, an RCT in Rakai, Uganda, among HIV-infected men failed to demonstrate benefit to female partners. In this trial, 922 uncircumcised, HIV-infected men were randomly assigned to immediate or delayed circumcision. HIV-negative female partners were concurrently enrolled.[169] Overall, 18% of women in the intervention group and 12% of women in the control group acquired HIV during follow-up (HR 1.58 [95% CI = 0.68–3.66]). In a subanalysis not specified in the protocol, early resumption of sexual relations following male circumcision was significantly associated with higher risk for HIV acquisition among female participants, with a rate ratio versus control of 3.50 (95% CI = 1.14–10.76). These results suggest an increased risk for HIV acquisition when early resumption of sex occurs after male circumcision. However, among couples in the immediate male circumcision arm who delayed resumption of sex until after wound healing, there was no significant difference in HIV incidence relative to uncircumcised controls (rate ratio 1.2 [95% CI = 0.39–3.73]). In a study of HIV shedding from male circumcision wounds in Rakai among 223 HIV-infected men,[170] compared to baseline, the proportion of men shedding increased significantly after male circumcision at 1 week (prevalence rate ratio [PRR] 1.87 [95% CI = 1.12–2.14]), 2 weeks (PRR 3.16 [95% CI = 1.94–5.13]), and 3 weeks (PRR 1.98 [95% CI = 1.19–3.28]), decreased by 6 weeks (PRR 0.27 [95% CI = 0.09–0.83]), and continued to be suppressed at 12 weeks (PRR 0.19 [95% CI = 0.06–0.64]). Detectable HIV shedding was positively correlated with HIV plasma viral load > 50,000 copies/ml compared with plasma viral load < 400, having unhealed wounds compared with having healed wounds, and not receiving antiretroviral HIV therapy compared with having undetectable plasma viral load related to receiving antiretroviral HIV therapy.

A systematic review and meta-analysis of the evidence for a direct effect of male circumcision on the risk of women becoming infected with HIV identified 19 epidemiological analyses from 11 study populations.[171] The meta-analysis of data from the 1 RCT and 6 longitudinal analyses showed little evidence that male circumcision directly affects the risk of HIV acquisition in women (RR 0.80 [95% CI = 0.53–1.36]).

More recent estimates of the effect of male circumcision on male-to-female transmission were calculated using 2 mathematical models representing the HIV epidemics in Zimbabwe and Kisumu, Kenya, based on 4 trials of circumcision among adults and new observational data of HIV transmission from men who were in stable partnerships and who were circumcised at younger ages. According to these models, it is estimated that male circumcision may confer a 46% reduction in the rate of male-to-female HIV transmission.[172]

Whether or not circumcision of HIV-infected men directly reduces HIV risk for their female partners, male circumcision of HIV-negative men offers a benefit to women by contributing to a decline in the overall prevalence of HIV in the male population, and thus fewer HIV-infected sexual partners.[173]

Male acquisition of HIV and other STIs from male partners

HIV transmission. The RCTs demonstrating HIV risk reduction associated with male circumcision were conducted in settings in which most HIV transmission is through heterosexual sex and apply to men engaging mainly in insertive penile-vaginal sex.[4-6] Only 6 (0.2%) trial participants reported having had male-to-male sexual relations in the 1 RCT in which this history was collected.[5] To date, the data on male circumcision and rates of HIV acquisition among men who have male-to-male sexual contact have been limited to observational studies.[90,174-187] No prospective trial of male circumcision for reducing HIV risk among MSM has been conducted, although such studies have been proposed.[188]

Some observational studies have shown higher rates of HIV acquisition among uncircumcised MSM compared with circumcised MSM. Among a convenience sample of 387 MSM receiving social and clinical services geared to MSM at local drop-in centers in India, men who self-reported being circumcised had 83% lower odds of prevalent HIV infection (adjusted odds ratio [aOR] 0.17 [95% CI = 0.07–0.46]) than men who self-reported being uncircumcised.[185] When controlling for the number of male sex partners and having had unprotected sex with an HIV-positive partner, circumcision was associated with 2-fold decreased odds of prevalent HIV infection (adjusted odds ratio [aOR] 0.5; 95% CI = 0.25–1.0) in a vaccine preparedness cohort followed from April 1995 through May 1997.[189] Self-reported circumcised status was associated with 2-fold decreased odds of prevalent HIV infection (aOR 0.5 [95% CI = 0.25–1.0]) in a cross-sectional survey of MSM in Seattle in the early 1990s,[190] and the odds of being HIV infected were 5-fold lower among circumcised men in a cross-sectional survey of MSM in Soweto in 2008 (aOR 0.2 [95% CI = 0.1–0.2]).[180]

However, other observational studies have failed to show a benefit (or risk) of male circumcision. In a cross-sectional survey of black and Latino MSM in New York City, Los Angeles, and Philadelphia, there was no evidence that being circumcised was protective against HIV infection, even among men who had reported engaging in insertive unprotected anal intercourse (UAI) but not receptive UAI.[191] Also, in a retrospective analysis of male circumcision status and risk for HIV among MSM participants in a vaccine trial, no association was found, even among primarily insertive partners.[192] Similarly, no association was found in a study of MSM in Seattle,[178] or in an Australian study of MSM.[176] However, a subsequent prospective study of MSM in Australia did report a significantly reduced HIV infection risk in circumcised men who reported engaging primarily in insertive UAI (HR 0.11 [95% CI = 0.03–0.80]).[193] The authors noted that because more infections were associated with receptive UAI, lack of male circumcision may have accounted for only 9% of the infections in the study overall. A study of Andean men reported that circumcision was not protective overall, but men who reported mainly insertive anal intercourse, defined as ≥60% of insertive acts with

their recent male partners, experienced a nonstatistically significant 69% reduction in the risk of HIV acquisition (RR 0.31 [95% CI = 0.06–1.51]) compared with those who reported < 60% of insertive acts.[194]

The presumed mechanism of decreased HIV acquisition among circumcised men engaging in penile-vaginal sex is decreased HIV entry and infection through target cells on the foreskin. Thus, if there is an HIV prevention benefit to circumcision for MSM, the benefit is likely be associated with insertive acts. Furthermore, the relative risk of HIV infection per sex act may be higher for insertive penile-anal sex than for penile-vaginal sex due to higher HIV RNA concentrations in rectal secretions relative to vaginal or cervical secretions.[195] The risk of HIV acquisition among MSM engaging in penile-anal sex is, however, greater for the anal receptive partner than for the insertive partner.[196,197] Additionally, relatively few MSM are exclusively insertive. Many or most MSM practice both insertive and receptive UAI, but the subject has not been well studied. Among 205 HIV-positive MSM surveyed in the United States, approximately half of men self-identified as versatile partners (men who practice both insertive and receptive anal sex) and the remaining half equally split, with one-quarter predominantly engaging in insertive anal intercourse and one-quarter predominantly engaging in receptive anal intercourse.[198] In a survey of UAI among 4,295 MSM participating in an observational cohort in 6 cities in the United States, 16.7% were exclusively insertive, 9.6% were exclusively receptive, and 63% were versatile.[199] The proportion of MSM who reported being versatile and who were predominantly insertive was not reported in this study. In another study, substantial proportions of partners who self-identified as predominantly insertive also reported practicing receptive anal intercourse.[200]

A Cochrane review conducted in 2011, which included 21 observational studies[b] and 71,693 participants from mainly Western countries, but also included 1 study each from India, Taiwan, and South Africa, demonstrated that there is a potential benefit of male circumcision in prevention of HIV transmission among MSM; however, the evidence did not support making a recommendation for male circumcision in this population.[90] More specifically, the overall pooled effect estimate for HIV acquisition, which included 20 studies and 65,784 participants, was not statistically significant (OR 0.86 [95% CI = 0.70–1.06]) and showed significant heterogeneity (I^2 = 53%). However, there were differing results in subpopulations based on having an insertive versus receptive role in MSM sexual relations. The results were statistically significant among 3,465 men in 7 studies reporting an insertive role (OR 0.27 [95% CI = 0.17–0.44, I^2 = 0%]), but were not significant among 1,792 men in 3 studies reporting a receptive role (OR 1.20 [95% = CI 0.63–2.29, I^2 = 0%]). The overall quality of evidence based on the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system was low.[201] Thus, while there is biological plausibility and evidence from some studies to suggest a reduced risk for HIV infection in circumcised men as compared with uncircumcised men engaging in insertive anal sex with an HIV-infected male partner, other well-conducted observational studies do not indicate a protective effect, either in

[b] Locations of studies included in Cochrane analysis ((United States [11 studies], Canada [3 studies], Caribbean (1 study), South America (3 studies), Europe (4 studies), Australia (2 studies), Asia (3 studies) and South Africa (1 study).

predominately insertive MSM or overall among MSM. Because of the greater risk posed by receptive anal sex, the role of male circumcision as a public health intervention to prevent HIV transmission among MSM appears limited based on current data.

After the Cochrane review, studies evaluating the association of male circumcision and HIV infection among MSM who practice mainly or exclusively insertive anal intercourse have had mixed results. In a cross-sectional study of 1,155 MSM in China, after adjusting for demographic covariates, number of lifetime male sexual partners and anal sex role, male circumcision confirmed by examination was associated with 85% lower odds of prevalent HIV infection (aOR 0.15 [95% CI = 0.04–0.65]) for men who reported practicing predominantly insertive anal sex compared with uncircumcised men who reported practicing predominantly receptive anal sex or being versatile.[183] In contrast, in a survey of MSM in Chongqing, China who practiced mainly or exclusively insertive anal intercourse, the prevalence of HIV infections did not differ significantly when comparing men who self-reported being circumcised with those who self-reported being uncircumcised.[187] Similarly, among a convenience sample of 1,521 white MSM in Britain who predominantly or exclusively engaged in insertive UAI, men who self-reported being circumcised were not significantly less likely to be HIV seropositive compared with men who self-reported being uncircumcised (aOR 0.79 [95% CI = 0.43–1.44]).[202] This lack of association was also seen when limiting the comparison to 400 circumcised and uncircumcised MSM who practiced insertive UAI exclusively (aOR 0.84[95% CI = 0.25–2.81]).[202] A meta-analysis of data from 15 studies that examined the strength of the association between male circumcision among MSM and HIV and other STIs; little overall effect on HIV infection was revealed.[182] Among a total of 53,567 MSM participants, 52% of whom were circumcised, the overall weighted odds of being HIV-positive was slightly less than 1 among circumcised MSM versus uncircumcised MSM (OR 0.95 [95% CI = 0.81–1.11]). There was also no significant association when stratified by study type (e.g., cross-sectional, prospective) or when limited to MSM who reported engaging exclusively in insertive anal sex. However, in 3 studies completed before the introduction of highly active antiretroviral therapy, male circumcision was protective against HIV (OR 0.47 [95% CI = 0.32–0.69]).

Because of the potential that engaging in receptive UAI would dilute whatever risk-reduction benefit might be associated with being circumcised while engaging in insertive UAI, an RCT study among MSM who practice predominantly or exclusively insertive UAI would aid efforts to obtain more definitive answers regarding the benefit of male circumcision among this population.

STI acquisition. A 2011 Cochrane review found that male circumcision was not significantly associated with the following STIs in MSM: syphilis (34,999 men, 8 studies; OR 0.96, 95% CI = 0.82–1.13, $I^2 = 0\%$), HSV-1 (2 studies, 2,740 participants; OR 0.90 [95% CI = 0.53–1.52, $I^2 = 0\%$]), or HSV-2 (5 studies; 10,285 participants; OR 0.86 [95% CI = 0.62–1.21, $I^2 = 0\%$]).[90]

A U.S. Internet-based survey with 26,257 respondents also found that circumcision status did not significantly predict HIV serostatus or most STI diagnoses (syphilis, gonorrhea, chlamydia, HPV). Being uncircumcised was predictive of HSV-2 diagnosis in this study;

however, condom use mediated this relationship, as circumcision was associated with higher rates of condom use.[203]

An observational study of MSM in Australia found that male circumcision was not associated with prevalent or incident HSV-1, HSV-2, self-reported genital warts, or incident urethral gonorrhea or chlamydial infection.[204] Being circumcised was associated with a significantly reduced risk of incident (HR 0.35 [95% CI = 0.15–0.84]) but not prevalent (OR 0.71 [95% CI = 0.35–1.44]) syphilis. Among 637 HIV-positive men in a cohort study in Barcelona, Spain, including 450 MSM, 187 heterosexuals, 143 circumcised men, and 494 uncircumcised men, prevalent HPV infection was not associated with circumcision status with the exception of decreased prevalence of HPV-51, a high-risk HPV subtype among circumcised compared with uncircumcised men (1% vs 4%, OR 0.2 [95% CI = 0.10–0.90, $P = 0.048$]).[205] Based on data from 2 community-based cohort studies of 1,990 circumcised and 998 uncircumcised Australian MSM, among men who practiced predominantly insertive anal intercourse, male circumcision was associated with a 57% reduction in acquisition of HPV-16 among men who practiced predominantly insertive anal intercourse (HR 0.43 [95% CI = 0.21–0.80, $P = 0.021$]).[96]

Male Circumcision and Other Health Conditions

In addition to studies of male circumcision related to HIV acquisition, the following sections review other studies exploring the association between male circumcision and other health conditions such as STIs (other than HIV) in heterosexual men and women, penile and prostate cancer, cervical cancer in female partners of circumcised men, UTIs in infants, and other associated health risks, including effect on sexual function and penile sensation.

Sexually transmitted infections (STIs)

Male circumcision has been shown to reduce the risk for other STIs in addition to HIV.[6-8,10-20] The effect of male circumcision on susceptibility to other STIs has been assessed in a number of observational studies in men who have sex with women.[206,207] Results from these studies have been mixed but suggest that male circumcision is associated with lower risk for some STIs. More recent data from the RCTs of male circumcision provide evidence that circumcision is significantly associated with decreased prevalence[6] and incidence[7] of GUD, decreased incidence of HSV-2,[8,14] decreased prevalence,[8,10,11] decreased incidence,[12,13] and increased clearance[13] of HR-HPV, and decreased prevalence of *T. vaginalis*[14] and *M. genitalium*[15] in circumcised heterosexual men (Table 2). Data from RCTs also provide evidence that circumcision in men is significantly associated with reductions in prevalence of GUD,[16] HR-HPV,[17] *T. vaginalis*,[16] and BV,[16] and increased clearance of HR-HPV[17] among their female sexual partners. The trials did not provide evidence of any association between male circumcision status and gonorrhea,[14,208] chlamydial infection,[14,208] genital discharge,[6] or dysuria.[6] In the 2 circumcision trials in which it was assessed, no association was found with syphilis.[7,8] However, in a prospective cohort study of HIV-serodiscordant couples enrolled in a trial of HIV preexposure prophylaxis (PrEP), syphilis was strongly associated with lack of male circumcision in men overall, in HIV-negative men, in their female sexual partners overall, and in both their HIV-negative and HIV-positive female sexual partners.[20] Syphilis had also been strongly associated with lack of male circumcision in

observational studies.[207] While a systematic review and meta-analysis concluded that based on studies of general populations, circumcision was not significantly associated with the risk of individual STIs,[209] the review was found to have several critical methodological flaws.[210]

Although rarely fatal, STIs other than HIV are among the most common communicable diseases in the United States, and interventions that prevent STIs would result in substantial reductions in morbidity and cost of health services. Most STIs are asymptomatic and the most prevalent STIs are not reportable in the United States; thus, the incidence of these infections must be estimated. The most recent estimate is that 19.7 million new STIs were acquired in the United States in 2008, including infections with *Trichomonas vaginalis* (1.1 million), HPV (14.1 million), *Chlamydia trachomatis* (2.9 million), HSV-2 (776,000), *Neisseria gonorrhoeae* (820,000), and *Treponema pallidum* (55,400).[211] Data on male circumcision and STIs in MSM are summarized in the Male-to-Male transmission section.

Rates of STIs differ in the United States compared to sub-Saharan Africa. Thus, it is important to assess the magnitude of the incremental benefit of male circumcision on HIV infection due to its protective effect against other STIs. In a dynamic stochastic model, it was concluded that the protection of male circumcision against STIs contributes little to the overall effect of circumcision on HIV.[212] Analyses of the RCTs confirmed this result,[9,151] which suggests that differing rates of other STIs should not be a major concern in generalizing the HIV prevention results of the RCTs from one setting to another.

Genital Ulcer Disease (GUD). Male circumcision is associated with a reduction of HSV-2[6-13,15-20] and GUD[6,7] in randomized controlled trials and a reduction of GUD due to syphilis[18] or chancroid[19] in observational studies.

GUD (various types). There is evidence of an association of reduction in GUD with male circumcision in 2 RCTs.[7,16] In the Kenyan RCT, male circumcision was associated with a reduction in GUD (RR 0.52 [95% CI = 0.37–0.73]).[7] This reduction occurred regardless of HSV-2 status. Male circumcision significantly reduced symptomatic GUD in HSV-2-seronegative men (PRR 0.51 [95% CI = 0.43–0.74]), HSV-2-seropositive men (PRR 0.66 [95% CI = 0.51–0.69]), and in HSV-2 seroconverters (PRR 0.48 [95% CI = 0.30–0.79]).[7] In the Ugandan RCT, male circumcision was also associated with a reduction in GUD (PRR 0.53 [95% CI = 0.43–0.64]) in men[6] and in their female partners (adjusted prevalence rate ratio [aPRR] 0.78 [95% CI 0.61–0.99]).[16]

Herpes Simplex Virus (HSV-2). HSV-2 infection is often asymptomatic but can cause genital ulcers. Compelling evidence of the protective effect of male circumcision on HSV-2 acquisition is available from 2 of 3 RCTs.[8,14] In the South African trial, IRR for acquisition of HSV-2 through 21 months of follow-up was 0.66 (95% CI = 0.39–1.12) for the intervention arm in the ITT analysis, and 0.55 (95% CI = 0.32–0.94) for circumcised men in the AT analysis.[14] In the Uganda RCT, among 1,684 interventions and 1,709 control participants who were HSV-negative at baseline, the adjusted HR in the intervention group for HSV-2 infection was 0.72 (95% CI = 0.56–0.92) at 24 months

in the ITT analysis.[8] In these 2 clinical trials, circumcised men were approximately 30% to 45% less likely to become infected with HSV-2 over 21 to 24 months of observation. In addition, investigators estimated the probability of HSV-2 per-sex-act female-to-male transmission per sex act in South Africa, and found that there was a positive correlation between HIV and HSV-2 infections and that male circumcision had a protective effect on HSV-2 acquisition by males.[213] From the RCT in Kisumu, Kenya, which included 1,391 men assigned to the circumcision arm and 1,393 men assigned to the delayed circumcision arm, male circumcision was not associated with the cumulative incidence of HSV-2 through 24 months of follow-up (overall HSV-2 incidence = not reported; circumcised:uncircumcised point estimates 5.8/100 person years and 6.1 per 100 person years, respectively; RR = 0.94 [95% CI = 0.70–1.25])[7] or 72 months of follow-up (overall HSV-2 incidence = 33.5%; circumcised:uncircumcised point estimates 33.5% and 32.7%, respectively; crude HR 0.89 [95% CI = 0.73-1.09]).[214] Investigators from the Kenyan study and others hypothesized that the reason that results from the Kisumu RCT were inconsistent with the South African and the Ugandan RCTs may have been due to location of lesions, test performance, higher prevalence of HSV-2 infection, and greater risk of exposure for younger men in Kisumu.[7,214,215] For example, 37% of clinically detected genital ulcers were on the penile shaft rather than the foreskin mucosa in Kisumu; however, similar data were not reported for the other 2 RCTs. Also, the sensitivity and specificity of the Kalon test for detecting HSV-2 were higher in Kampala, Uganda (95% and 88%, respectively), compared to Kisumu, Kenya (92% and 79%, respectively).[215-217] However, a re-analysis of the Kenya data using various Kalon index optical density cut-off values to vary the specificity did not find a protective effect of male circumcision against HSV-2.[218] In the Uganda RCT, female partners of circumcised HSV-2-positive males did not have significantly lower HSV-2 acquisition compared to partners of their uncircumcised male counterparts (IRR = 0.85 [95% CI = 0.44–1.67, P = 0.62]).[219]

Observational studies have provided mixed results.[18,19,71,73,82] In an early review of 6 observational studies, 2 found male circumcision was protective against HSV-2 and 4 found no association with HSV-2.[206] In a subsequent review of 10 observational studies related to HSV-2 serostatus, 6 studies found a reduced relative risk associated with male circumcision status, and the difference was statistically significant for 2 of the studies.[207] Compared to uncircumcised men, circumcised men had a summary estimated relative risk for HSV-2 infection of 0.88 (95% CI = 0.77–1.01). In a cross-sectional observational study of men in rural Tanzania, those circumcised before sexual debut were less likely to be HIV seropositive compared with uncircumcised men (aOR 0.50 [95% CI = 0.25–0.97]), and were also less likely to be HSV-2 infected (aOR 0.67 [95% CI = 0.57–0.80]) or have genital ulcer syndrome in the past 12 months (aOR 0.69 [95% CI = 0.47–1.00]).[82] In a population-based observational survey in Kisumu, Kenya, conducted to estimate baseline male circumcision status and attitudes associated with male circumcision, circumcision status was not associated with HIV/HSV-2 infection.[220] Observational data from a cross-sectional study in the United States have not shown an association between male circumcision status and HSV-2 infection. In an evaluation conducted by the National Health and Nutrition Examination Surveys (NHANES) of 3,850 U.S. adolescent and adult males aged 14–49 years who reported having had sex, there was no association

between self-reported circumcision status and HSV-2 infection, after controlling for potential confounders such as age, race/ethnicity, and sexual behaviors.[221]

Treponema pallidum. Syphilis, caused by *T. pallidum,* classically presents as a painless genital ulcer. A review of 11 studies in which genital ulcers were due either to chancroid or syphilis found statistically significant decreases in risk of GUD among circumcised men.[206] In addition, of 14 studies that have assessed the association between male circumcision and a serologic diagnosis of syphilis, 13 found a reduction in risk associated with male circumcision, and the difference was statistically significant in 4 studies.[207] A summary estimate of relative risk for syphilis was 0.69 (95% CI = 0.50–0.94) for circumcised men versus uncircumcised men.

While there was no prevention benefit from male circumcision against syphilis acquisition in 2 of the randomized trials of male circumcision interventions,[7,8] a benefit was reported in a prospective cohort study of HIV discordant couples enrolled in an RCT related to HIV PrEP.[20] In the Uganda RCT of male circumcision, syphilis was detected in 50 of 2,083 subjects (2.4%) in the intervention group, compared with 45 of 2,143 subjects (2.1%) in the control group (crude HR 1.14 [95% CI = 0.77–1.75, $P = 0.50$]; aHR 1.10 [95% CI = 0.75–1.65, $P = 0.44$]).[8] Circumcised men were less likely to report genital ulcers; however, nearly all genital ulcers with an identified etiology were attributed to herpes virus infection and not syphilis. At the 24-month follow-up visit in the Kenya RCT of male circumcision, only 13 men had developed syphilis among 2,714 men who did not have syphilis at enrollment. Of the 13 men who developed syphilis, 6 were uncircumcised and 7 were circumcised.[7] Incident syphilis did not differ by circumcision status in this trial: 0.4/100 person-years circumcised men versus 0.3/100 person-years uncircumcised men (RR 1.23 [95% CI 0.41–3.65]). Because of the small numbers of incident syphilis in this trial, no conclusions about the association between circumcision status and incident syphilis were drawn. During a median of 2.75 years of prospective follow-up of 4,716 HIV-1 serodiscordant Kenyan and Ugandan couples in an RCT of pre-exposure prophylaxis, male circumcision was associated with reductions in incident syphilis of 42% in men overall (aHR 0.58 [95% CI = 0.37–0.91]) and 62% in HIV-infected men (aHR 0.38 [95% CI = 0.18–0.81]).[20] HIV-uninfected men experienced no statistically significant reductions in incident syphilis associated with circumcision (aHR 0.64 [95% CI = 0.36–1.11]).[20] In this same trial, male circumcision was associated with reductions in incident syphilis of 59% in women overall (aHR 0.41 [95% CI = 0.25–0.69]), 75% reduction in HIV-negative women (aHR 0.25 [95% CI = 0.08–0.76)], and 48% reduction in HIV-positive women (aHR 0.52 [95% CI = 0.27–0.97]).[20]

Haemophilus ducreyi. *H. ducreyi,* the organism that causes chancroid, is now uncommon in the United States. Only 1 observational study was found that included serologic diagnosis, so a review included 6 other studies that were based on clinical diagnosis.[207] Six studies found a reduced relative risk for circumcised males versus uncircumcised males, which was statistically significant in 4[222-225] studies. Relative risks varied widely, and no summary relative risk was estimated due to variability in study design.

Other STIs. Male circumcision is associated with a reduction of high risk HPV infections in RCTs. Mixed results for other STIs, such as trichomoniasis, are included and described in this section.

Human Papilloma Virus (HPV). HPV is generally an asymptomatic infection, but oncogenic or high-risk HPV (principally genotypes 16, 18, 31, and 33) are believed to be responsible for 100% of squamous cervical cancers, 90% of anal cancers, and 40% of cancers of the penis, vulva and vagina.[226] Penile squamous carcinoma (caused by carcinogenic HPV subtypes) has been strongly and consistently associated with lack of male circumcision[206] (see the *Penile Cancers* section). Cervical cancer has been associated with lack of circumcision in male partners of women in several case-control studies[227] (see the *Cervical Cancer* section).

HPV prevalence. Two meta-analyses of 21[228] and 23[229] studies evaluated the potential association of male circumcision and HPV infection and included mainly cohort studies, cross-sectional studies, and RCTs[8,10,11] published through 2010. The meta-analysis of 21 studies included 8,046 circumcised and 6,336 uncircumcised men,[228] but the other meta-analysis of 24 studies did not report the total number of circumcised men and uncircumcised men.[229] Both meta-analyses concluded that male circumcision was significantly associated with reduced odds of prevalent genital HPV infection overall (OR 0.57 [95% CI= 0.42-0.77][228], (OR 0.57 [95% CI=0.45-0.77].[229]

The RCTs, which were conducted in Uganda[8,10] and South Africa,[11] studied circumcision and prevalent HPV. In the Uganda RCT, the overall prevalence of HPV of any risk type was similar at baseline in both arms prior to the circumcision intervention, but lower in the circumcision arm at the 24-month follow-up visit (RR 0.70 [95% CI = 0.53–0.91]).[8] The overall prevalence of any high-risk HPV genotypes at the 24-month follow up visit in Uganda was also lower among circumcised men who were both HIV-negative and HSV-2 seronegative at baseline (aRR 0.65 [95% CI = 0.46–0.90])[8] and among HIV-positive circumcised men (RR 0.77 [95% CI = 0.62–0.97])[10] compared with that among uncircumcised men in the control arms. In the South African RCT, the overall prevalence of any urethral high-risk HPV genotype at the 21-month follow-up visit was lower among circumcised men compared with that among uncircumcised men in both the ITT and AT analyses (ITT analysis: aPRR 0.68 [95% CI = 0.52–0.89]; AT: aPRR 0.62 [95% CI = 0.47–0.80]).[11] Circumcised men in the Ugandan RCT also had a lower prevalence of multiple high-risk HPV genotypes at the 24-month follow-up (RR 0.53 [95% CI = 0.33–0.83]) than uncircumcised men.[10]

Among 15,162 men and women aged 16–74 years enrolled in the third National Survey of Sexual Attitudes and Lifestyles (Natsal-3) in Britain, circumcised men were less likely than uncircumcised men to have any HPV-type (aOR 0.26 [95% CI = 0.13–0.50]), high-risk-HPV[c] (aOR 0.14 [95% CI = 0.05–0.40]), and possible high-

[c] High-risk-HPV was defined as being positive for genotype (s) 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 and/or 68; possible high-risk-HPV was defined as being positive for genotype(s) 26, 53, 66, 70, 73 and/or 82.

risk-HPV (aOR 0.24 [95% CI = 0.06–0.94]) detected in their urine.[230] A multi-national longitudinal cohort study of HPV in 1,424 circumcised men and 2,545 uncircumcised men from Brazil, Mexico and the United States found no overall association between male circumcision and prevalent genital HPV infections (adjusted prevalence rate ratio [aPRR] 0.96 [95% CI = 0.91–1.01]) or prevalent genital oncogenic HPV infections (aPRR 0.95 [95% CI = 0.87–1.03]) in men, and a negative association with certain non-oncogenic HPV infections (aPRR 0.85 [95% CI = 0.76–0.95]).[231] However, _an important limitation of the study was the lack of specificity of study results by site of penile swabbing for HPV sampling. Because results for HPV samples taken from the glans penis, coronal sulcus, penile shaft, and scrotum were combined into an aggregate result for each patient, results for samples taken from the glans penis, an area hypothesized to be more likely protected by male circumcision, could not be distinguished from results for samples taken from other sites.

HPV incidence or acquisition. A meta-analysis of 23 articles found that male circumcision was associated with decreased HPV incidence and that the effect of male circumcision on reducing prevalent HPV infection was stronger at the glans/corona and urethra compared with penile areas more distal to the foreskin.[229] The incidence of high risk HPV genotypes in relation to circumcision was also studied in the Uganda and Kenya RCTs. At the 24-month follow-up visit, among HIV-positive men in the Uganda trial, there were no significant differences between circumcised men and uncircumcised men in the incidence of high-risk HPV genotypes overall (RR 0.74 [95% CI = 0.54–1.01]) or of single high-risk HPV genotypes (RR 1.00 [95% CI = 0.65–1.53]), but incidence of multiple high-risk HPV genotypes was lower among circumcised men (RR 0.40 [95% CI = 0.19–0.84]). At the 24-month follow up visit among HIV-negative men in the Uganda trial, circumcised men had lower incidences of high-risk HPV genotypes overall (RR 0.67 [95% CI = 0.51–0.89]) and of multiple high-risk HPV genotypes (RR 0.45 [95% CI = 0.28–0.73]) compared with uncircumcised men, but the two groups had a similar incidence of single high-risk HPV genotypes (RR 0.89 [95% CI = 0.60–1.30]).[12] In the Uganda trial, in a mixed population of HIV-negative men and HIV-positive men, the overall HPV incidence was lower among circumcised men than uncircumcised men (adjusted incidence rate ratio [aIRR] 0.70 [95% CI = 0.55–0.89]).[232]At the 6-month follow up visit among men in the Kenya trial, circumcised men had lower incidences of single high-risk HPV genotypes HPV-16 (HR 0.32 [95% CI = 0.20–0.49]) and HPV-18 (HR 0.34, [(95% CI = 0.21–0.54]) than uncircumcised men.[13]

In a multi-national study of 1,469 circumcised men and 2,564 uncircumcised men, male circumcision was not significantly associated with overall incident HPV infection (aHR 1.08 [95% CI 0.91–1.27]).[233] In a cohort study of 359 circumcised and 118 uncircumcised university students from Seattle, Washington who underwent testing for 37 alpha HPV genotypes from 3 genital sites (shaft/scrotum, glans, and urine), rates of acquiring clinically relevant HPV genotypes (high-risk genotypes plus HPV-6 and HPV-11) did not differ by circumcision status, although there was a higher likelihood of detecting infections at all 3 sites versus at only 1 site among uncircumcised men than among circumcised men.[234]

HPV clearance. Two meta-analyses concluded that male circumcision was not significantly associated with HPV clearance.[228,229] Clearance of high-risk HPV genotypes were also studied in both the Uganda and Kenya trials. In Uganda, overall clearance of HPV genotypes was similar in both study arms among HIV-positive men only (RR 1.09 [95% CI = 0.94–1.27]),[10] but clearance was higher among circumcised men compared with uncircumcised men in the analysis restricted to HIV-negative men (aRR 1.39 [95% CI = 1.17–1.64])[12] and in the analysis of a mixed population of HIV-positive and HIV-negative men (aRR 1.48 [95% CI = 1.26–1.74]).[232] Similarly, at the 6-month follow-up visit among men in the Kenya trial, circumcised men had lower persistence of HPV-16 with high viral load (RR 0.36 [95% CI = 0.18–0.72]) and HPV-18 with high viral load (RR 0.34 [95% CI = 0.13–0.86]) than uncircumcised men.[13]

In the Uganda RCT, when analysis was restricted to results at the 24-month follow-up visit only among men infected with one of 6 selected high-risk HPV genotypes (16, 18, 31, 33, 35,and 52), circumcised men had a lower viral load associated with HPV infections acquired after enrollment compared with uncircumcised men, but the same association was not seen with HPV infections persisting from enrollment.[235] This may help to explain why, at the 24-month follow-up visit, HPV-infected women who were partners of circumcised men in the Uganda RCT had a lower prevalence of high risk HPV DNA load (PRR 0.78 [95% CI = 0.65–0.94]) compared with HPV-infected women who were partners of uncircumcised men, particularly for incident high-risk HPV (PRR 0.66 [95% CI = 0.50–0.87]), but not for persisting high-risk HPV (PRR 1.02 [95% CI = 0.83–1.24]) from the time of enrollment.[17]

In a multi-national longitudinal cohort study of 1,469 circumcised men and 2,564 uncircumcised men, in which samples from different penile collections sites such as the glans and shaft were pooled together for each participant, male circumcision was associated with shorter clearance for oncogenic HPV-33 and longer clearance for oncogenic HPV-16, and HPV-51.[233]

T. vaginalis Trichomoniasis, caused by the parasite *T. vaginalis,* is believed to be the most common curable STI in the United States. The infection is generally asymptomatic in men but can cause severe cervicitis, vaginal discharge and labial itching and irritation in women, and may increase susceptibility to HIV.[236] The association of *T. vaginalis* and male circumcision had not been previously studied in any major observational studies. In the South African RCT, the effect of male circumcision on *T. vaginalis* infections was measured by polymerase chain reaction (PCR) from urine specimens.[14] Circumcised men were less likely to have a prevalent trichomonas infection (1.7%) than were uncircumcised men (3.1%), with statistical significance in the AT analysis (aOR 0.47 [95% CI = 0.25–0.92]) and borderline statistical significance in the ITT group (aOR 0.53 [95% CI = 0.32–1.02]). However, in the Kenya trial, which measured *T. vaginalis* by culture in participants' urine and urethral discharge, no significant association between male circumcision status and trichomonas infection was found.[208] The Uganda RCT assessed trichomonas infections in female partners. The prevalence of *T. vaginalis* was found to be about half as high among the HIV-negative wives of married participants who were

circumcised (5.9%) compared with HIV-negative wives of participants who were uncircumcised (11.2%) (aPRR 0.52 [95% CI = 0.05–0.98]).[16]

Mycoplasma genitalium. *M. genitalium* causes male urethritis, including persistent or recurrent urethritis[237] and cervicitis and pelvic inflammatory disease in women.[238,239] Nucleic acid amplification testing (NAAT) is the easiest method to diagnose *M. genitalium* infection, but there is no diagnostic test for *M. genitalium* approved by the FDA.[240] In a cross-sectional study of 526 men enrolled in the Kenya RCT, circumcised men had half the odds of being infected with *M. genitalium* (aOR 0.54 [95% CI = 0.29–0.99]) compared with circumcised men.[15] In the Uganda RCT, 437 female partners of circumcised men did not have a significantly different *M. genitalium* prevalence compared with 394 female partners of uncircumcised men either in the ITT analysis (aPRR 0.93 [95% CI = 0.43–2.03]) or the AT analysis (aPRR 1.00 [95% CI = 0.46–2.18]).[241] Among 1,850 men aged 16–74 years enrolled in Britain's Natsal-3, being circumcised compared with not being circumcised was not significantly associated with the detection of *M. genitalium* in urine samples in the crude (OR 1.90 [95% CI = 0.62–5.87]) or adjusted analyses (aOR 0.61 [95% CI = 0.18–2.09]).[230]

Chlamydia trachomatis. *C. trachomatis* causes urethritis in men and cervicitis and pelvic inflammatory disease in women. Before accurate tests were available, chlamydial infection in men was often diagnosed syndromically as "non-gonococcal urethritis" after exclusion of gonorrhea by Gram stain. Of 8 observational studies of non-gonococcal urethritis, 2 found that male circumcision was protective, 3 found that it increased risk, and 3 found no association.[206] In women, 1 cross-sectional study found chlamydial infection among female partners of circumcised men to be 5.6-fold lower than among partners of uncircumcised men (OR 0.18 [95% CI = 0.05–0.58]), as tested by the presence of antibodies to *C. trachomatis*.[242] In another cross-sectional study, *C. trachomatis* infection was not associated with circumcision status of the partner (HR 1.25 [95% CI = 0.96–1.63).[243] In the Uganda trial, there was no association between male circumcision and self-reported urethritis or discharge in men or women,[6,16] and in the Kenya trial, no association was found between laboratory-confirmed *C. trachomatis* infection and the male circumcision status of trial participants.[208] However, the South African trial showed a borderline significant association in the ITT analysis (aOR 0.56 [95% CI = 0.32-1.00]) between *C. trachomatis* infection among male participants in the circumcision intervention arm (2.1%) and control arm (3.6%); this association was not statistically significant in the AT analysis (aOR 0.75 [95% CI = 0.42–1.32]).[14] Among 15,162 men and women aged 16–74 years enrolled in the Natsal-3 in Britain, circumcised men were less likely than uncircumcised men to have *C. trachomatis* detected in their urine sample (aOR 0.09 [95% CI = 0.01–0.77]) but were as likely to report a prior history of *C. trachomatis* (aOR 1.06 [95% CI = 0.73–1.52]).[230]

Neisseria gonorrhoeae. Gonorrhea is caused by the bacterium *N. gonorrhoeae* and can lead to urethritis in men and cervicitis and pelvic inflammatory disease in women. Of 7 observational studies, 5 found statistically significant decreases in risk in circumcised men and 2 found no association with circumcision status.[206] However, no

association has been demonstrated in prospective trials. In the Uganda RCT, there was no association between male circumcision and self-reported urethritis or discharge in men or women.[6] In the South Africa trial, the prevalence of gonorrhea, tested by polymerase chain reaction in first void urine, was similar in the male circumcision (10.0%) and the control (10.3%) groups.[14] Similarly, in the Kenya trial, no association between male circumcision status and gonorrhea was found.[208]

Bacterial vaginosis (BV). BV, a clinical syndrome where anaerobic bacteria, *G. vaginalis*, Ureaplasma, and Mycoplasma replace hydrogen-peroxide-producing Lactobacillus in the vagina, may occasionally produce vaginal discharge or malodor, but is most often asymptomatic.[240] BV can be diagnosed by gram stain or clinical diagnostic criteria.[244] In the Uganda RCT, male circumcision was associated with reduced risk in the prevalence of any BV (aPRR 0.60 [95% CI 0.38–0.94]) and of severe BV (PRR 0.39 [0.24–0.64]) in female partners.[16]

Penile and prostate cancers

Penile cancer is rare in developed countries, accounting for < 1% of malignancies among men.[245] Observational studies have found that among men diagnosed with penile cancer, only a small percentage were circumcised.[21-24] Aside from circumcision status, penile cancer is associated with a history of HPV infection[31,246] and certain lifestyle choices such as smoking,[247,248] poor hygiene,[249] and multiple sex partners.[250] In one meta-analysis, key risk factors for penile cancer included phimosis (8 studies), smegma (4 studies), balanitis (4 studies), and high-risk HPV types (10 studies), and these risk factors were more prevalent in uncircumcised than circumcised men.[26] Invasive penile cancer is very rare in circumcised men. The lifetime risk for a U.S. male of ever being diagnosed with penile cancer is 1 in 1,437.[29] During 1982–2005, the overall incidence of penile cancer was higher in England and Wales (1.44 per 100,000 man-years) than in Australia (0.80 per 100,000 man-years) and the United States (0.66 per 100,000 man-years).[251] It is hypothesized that the lower rates of male circumcision in England and Wales compared with the United States and Australia may partly explain the differing penile cancer rates.[251] In a retrospective analysis of 89 cases of invasive penile cancer diagnosed from 1954 through 1997, 98% were in uncircumcised men; of 118 cases of carcinoma in situ, 84% were in uncircumcised men.[27] In a retrospective review of 5 studies with 592 cases of invasive penile cancer in the United States, none of the cases were in men who had been circumcised in infancy.[24] It has been suggested that the protective effect of male circumcision may be by preventing phimosis.[252] In a population-based case-control study, the authors found that men not circumcised during childhood were at increased risk of invasive (OR 2.3 [95% CI = 1.3–4.1]), but not in situ (OR 1.1 [95% CI = 0.6–1.8]) penile carcinoma.[253] Among uncircumcised men, phimosis was strongly associated with invasive penile cancer (OR 11.4 [95% CI = 5.0–25.9]). Racial/ethnic distribution of penile cancer in the United States reflects the varying prevalence of male circumcision. In an analysis of penile cancer among 6,539 U.S. men identified through population-based registries during 1995-2003, Hispanic men had the highest age-adjusted incidence (6.58 per million), followed by blacks (4.02 per million) and whites (3.9 per million).[25]

The lifetime risk of prostate cancer among men in the United States during 2008–2010 was about 15%.[254] Prostate cancer represented the second highest age-adjusted invasive cancer incidence rate in the United States during 2012[255] and was also one of the leading causes of cancer death among men, with 27,682 men dying from prostate cancer in 2013.[256] Infection with STIs has been associated with the development of prostate cancer in some studies[257-260] but not others.[261-263] In 1 meta-analysis, an increased risk of prostate cancer was associated with a history of any STI (OR 1.5 [95% CI = 1.3–1.7]).[264] Risk factors for STIs have also been associated with prostate cancer, including earlier age of first sexual activity[265] and a greater number of sexual partners.[261,266] A meta-analysis of the association between male circumcision and prostate cancer based on 7 reports from case-control studies published during 1971–2014 did not show a significant association between prostate cancer and circumcision in the overall analysis (OR 0.88, $P = 0.19$), but it did show significantly reduced risk in the following subgroups of published studies: those conducted after PSA testing became available (OR 0.83, $P = 0.03$), population-based studies (OR 0.84, $P = 0.05$), studies that collected data by personal interview (OR 0.83, $P = 0.03$), and studies including black race as a variable (OR 0.59, $P = 0.02$).[267] In an ecologic study evaluating the relationship between male circumcision prevalence and the prostatic carcinoma mortality rate in 85 countries, investigators reported that countries with male circumcision prevalence exceeding 80% had significantly higher prostate cancer mortality than countries with circumcision prevalence ranging from 0%–19% (aOR 1.82 [95% CI = 1.14–2.91]) or 20%–80% (aOR 1.80 [95% CI = 1.16–1.78]).[268] In a population-based case-control study in Montreal, Canada, among 1,590 men with prostate cancer and 1,680 population controls, circumcision was associated with lower rates of prostate cancer in men aged ≥ 36 years (OR 0.55 [95% CI = 0.30–0.98])[28] and the largest reduction in rates of prostate cancer associated with circumcision was seen in black men (OR 0.40 [95% CI = 0.19–0.86]).[28] Circumcision before first sexual intercourse was associated with a 15% reduction in risk of prostate cancer compared to that of uncircumcised men or those circumcised after first sexual intercourse in a combined analysis using pooled data from 1,754 cases and 1,645 controls from 2 population-based case-control studies; prevalence of prostate cancer for circumcised men and uncircumcised men was 64.9% and 69.0%, respectively (OR 0.85 [95% CI = 0.73–0.99]).[30]

Cervical cancer in female partners of circumcised men

In a meta-analysis of male circumcision status and cervical cancer in female partners, data from 7 case-control studies were pooled.[227] Circumcision was associated with significantly less HPV infection in men. In an analysis restricted to monogamous women, there was a nonsignificant reduction in the odds of having cervical cancer among women with circumcised partners (OR 0.75 [95% CI = 0.49–1.14]). When the couples with men with ≤ 5 lifetime partners (40% of the study population) were excluded, the odds of cervical cancer in female partners of circumcised men were significantly reduced compared with female partners of uncircumcised men (OR 0.42 [95% CI = 0.23–0.79]).

Urinary tract infection (UTI) in males

Studies have consistently demonstrated decreased incidence of UTIs among circumcised boys compared with uncircumcised boys.[32-37] A multicenter prospective study of 1,025

febrile infants aged < 2 months found that 9.0% of the fevers were attributable to UTIs. Of the uncircumcised male infants, 21.3% had UTIs compared with 2.3% of the circumcised male infants.[36] A large cohort study including all births (n=427,698) in U.S. Army hospitals worldwide during 1975–1984 demonstrated an increase in the total number of UTIs among male infants as the circumcision rate declined over time.[35]

In a meta-analysis including 22 studies and over 336,000 males, the relative risk for UTI was higher for uncircumcised boys compared with circumcised boys in all 3 age groups studied: 0–1 year (RR 9.9 [95% CI = 7.5–13.1]); 1–16 years (RR 6.6 [95% CI = 3.3–13.2]), and > 16 years (RR 3.4 [95% CI = 0.9–12.7]).[37] Based on this meta-analysis, it is estimated that a 23.3% higher proportion of uncircumcised males (32.1% [95% CI = 15.6–49.8]) experience a UTI in their lifetime compared with circumcised males (8.8% [95% CI = 4.15–13.2]) (RR 3.7 [95% CI = 1.2–11.8]).[37] In a meta-analysis of 18 studies and 22,919 children mainly from the United States, the pooled prevalence of UTI in infants presenting with fever in outpatient clinics and emergency departments was 7.0% (95% CI = 5.5–8.4), but was as high as 20.1% (95% CI = 16.8–23.4) among febrile uncircumcised males aged < 3 months compared with 2.4% (95% CI = 1.4–3.5) among febrile circumcised males aged < 3 months and with 7.8% (95% CI = 6.6–8.9) among both febrile and afebrile older children aged < 19 years[269] Another systematic review[33] which included 12 studies and over 400,000 children, concluded that male circumcision was associated with a significantly reduced risk of UTI (OR 0.13 [95% CI = 0.08–0.20, P < 0.001]).

Among infants hospitalized for UTIs in Canada, the annual rate of UTIs necessitating hospitalization was 0.70% for uncircumcised infants versus 0.18% for circumcised infants (P < 0.0001).[34]

As a result of decreasing the likelihood of UTIs in infants overall, neonatal circumcision reduces the likelihood of associated serious complications of UTIs in infants, including sepsis, pyelonephritis, and renal scarring. Such complications have been associated with the increased potential for long term consequences including hypertension, uremia, and end stage renal disease.[270]

Other health conditions

The presence of a foreskin has been associated with various penile dermatoses, including psoriasis, infections (e.g., molluscum and candidiasis), lichen sclerosis and seborrheic dermatitis.[271] Balanitis, inflammation of the glans penis, or balanoposthitis, the inflammation of the glans and the prepuce, are painful conditions that occur more frequently in uncircumcised males.[272-274] In a retrospective cohort study of boys, the total frequency of complications (balanitis, irritation, adhesions, phimosis, paraphimosis) was higher among uncircumcised boys than circumcised boys (14% vs 6%), but most conditions were minor.[274] A prospective longitudinal study of over 500 boys in New Zealand found the adjusted rates of penile conditions in infants aged < 1 year to be 5% and 1% (P < 0.01) in circumcised and uncircumcised boys, respectively. These conditions included phimosis, penile inflammation, inadequate circumcision, and post-circumcision infection. However, among children aged 1–8 years, the collective adjusted rates in circumcised boys and uncircumcised boys in the study were 7% and 17% (P <

0.01), respectively. The majority of these problems were for penile inflammation including balanitis, meatitis, and inflammation of the prepuce.[272] A separate study of penile hygiene in the United States found that subjects who retracted the foreskin when bathing were less likely to have smegma accumulation, inflammation, phimosis, or adhesions than those who did not. Significant correlations were also found between early instructions concerning hygiene and the type of hygiene practiced, which suggests that good hygiene can offer some of the advantages of circumcision.[275]

Health Conditions for Which Male Circumcision Is Indicated

Specific medical conditions for which male circumcision is indicated include phimosis, paraphimosis, and balanoposthitis. Phimosis is a narrowing of the preputial orifice can lead to an inability to retract the foreskin over the glans, and can be categorized as physiological phimosis or pathological phimosis.[276] Physiological phimosis occurs when there is non-retractable foreskin or preputial adherence to the glans, which occurs in babies and young boys.[277] Physiological phimosis is a normal part of penile development, and foreskin separation from the glans occurs over time, usually within the first 3 to 4 years of life by physical maturity without intervention.[276] It is estimated that the prevalence of physiological phimosis decreases from 96% at birth, to 50% at age 1 year, to 10% at age 3 years, to 6%–8% at age 7 years, to 1% at age 16 years.[278] Pathological phimosis occurs when there is a failure to retract the foreskin due to distal scarring of the prepuce and may occur as a result of balanitis xerotica obliterans (a progressive inflammatory dermatological condition), recurrent balanoposthitis, or after forceful prepuce retraction.[276,279-281] In addition to difficulty in retracting the foreskin, pathological phimosis may result in pain on urination or erection, urinary retention, UTI, renal stones, dermatological infections localized to the area of phimosis, sexual dysfunction, and tearing of the foreskin.[276,282] Pathologic phimosis is rare before the first 5 years of life, peaks before puberty, and has been estimated to be present in 0.8%–1.5% of boys in Liverpool, England, by their 17th birthday.[276] In the absence of a response to topical steroids, or when the child is not a candidate for steroid use, male circumcision is the definitive treatment.

Paraphimosis is the entrapment of a retracted foreskin behind the coronal sulcus. Because paraphimosis may constrict blood flow leading to tissue damage and gangrene, it is considered a medical emergency.[283,277] Male circumcision may also be indicated for recurrent balanitis (also known as balanoposthitis), a swelling (inflammation) of the foreskin and head of the penis, if the condition does not respond to conservative medical treatment.

A study of 25,718 admissions for male circumcision in Western Australia that excluded neonatal circumcisions at birth found the rate of circumcision (per 1,000 person-years) decreased from 5.51 at ages 0–4 years to 0.39 at ≥ 15 years.[284] Most male circumcisions were for phimosis, and some of the circumcisions may have been unnecessarily done for non-retractable foreskins or preputial adhesions. The rate of male circumcision for balanoposthitis was 0.44 at ages 0–4 years and decreased to 0.04 at ≥ 15 years.

Safety and Risks Associated with Male Circumcision

In the United States, reported rates of complications in large studies of medically attended male circumcision in the neonatal period, including infants from birth to age 1 month, are approximately 0.2%,[39,285 41] (note: complication rates reported as 0.19%,[285] 0.22%,[39] and 0.2%[41]) and vary by type of study, setting, operator, and surgical technique. Similarly, the reported rate of complications of medically attended male circumcisions occurring at any age in the United States is 0.23%.[40] In a comprehensive risk-benefit analysis of infant male circumcision based on reviews of the literature and meta-analyses, it is estimated that over a lifetime, benefits exceed risks by a factor of 100:1.[286] Based on a meta-analysis of 22 studies, most of which were conducted in the United States, it is estimated that 32.1% (95% CI = 15.6–49.8) of uncircumcised men compared with 8.8% (95% CI = 4.15–13.2) of circumcised men will experience a UTI in their lifetime, suggesting that lack of circumcision is associated with a 23.3% increased risk of UTI during a man's lifetime.[37]

The most common complications reported have been bleeding and infection, which are usually minor and easily managed.[1,39,41,285] Other reported complications, including wound dehiscence, unsatisfactory cosmesis, skin bridges, urinary retention, meatal stenosis, chordee, retained Plastibell devices that require surgical removal, "concealed" (or "buried") penis, major bleeding, injury to the urethra due to fistula, surgical mishap, and severe infection are rare[287] and may occur after discharge from the hospital. More severe bleeding episodes may be a sign of an undiagnosed coagulation disorder and underscore the need to conduct routine preoperative laboratory screening for such disorders, include questions about family history of prolonged bleeding or bleeding disorders, and have institutional protocols for circumcising infants with bleeding disorders, including therapy for treating prolonged bleeding after male circumcision.[52,53,55,288-290] In a study of 130,475 circumcised neonates, 0.18% had hemorrhagic complications, 0.04% suffered injury to the penis, and 0.0008% had cellulitis; the overall complication rate was 0.22%.[39] A similar AE rate of 0.19% was observed in a retrospective cohort of 100,157 circumcised neonates, including local infection, bacteremia, hemorrhage, surgical trauma, and UTI.[285] In a smaller study, complications were associated with 4% of 361 neonatal male circumcisions (hemorrhage, infection, surgical revision) and 13% of 230 circumcisions performed after the neonatal period (adhesions, poor hygiene, meatitis, surgical revisions).[291] A recent meta-analysis of 16 prospective studies from diverse settings worldwide that evaluated complications following neonatal and infant male circumcision found that median frequency of severe AEs was 0% (range 0–2%). The median frequency of any complication was 1.5% (range 0–16%). Medically attended male circumcision performed on children tended to be associated with more complications (median frequency 6%; range 2–14%) than for neonates and infants.[292]

In a study using data from a large longitudinal healthcare reimbursement dataset in the United States, investigators estimated the incidence of AEs during 2001–2010 attributable to male circumcision and assessed whether AE rates differed by the age range when male circumcision was performed (i.e., aged < 1 year, 1–9 years, or ≥ 10 years).[40] Among 1,400,920 circumcised males, circumcision was performed in 95.3% male infants

aged < 1 year, in 2.0% of males aged 1–9 years, and in 2.7% of males aged ≥ 10 years. Among males aged ≥ 10 years, 22.9% were aged 10–18 years. The overall estimated crude and adjusted incidences of probable AEs were 0.31% (95% CI = 0.30–0.32) and 0.23% (95% CI = 0.21–0.24), respectively. When estimated by age group, the incidence of probable AEs was 0.40%, 9.06%, and 5.31% for males aged < 1 year, 1–9 years, and ≥ 10 years, respectively. The incidence of AEs was 10–20-fold higher for males in older age groups compared with infants. The highest incidence rate differences (IRDs) of AEs among circumcised newborn males compared to uncircumcised newborns included incomplete circumcision or penile adhesions resulting in correctional procedures [1,887 AE/million male circumcisions (PMMC)],[d] bleeding [998.24 AE/PMMC],[e] and inflammation of the penis [168.36 AE/PMMC].[f] In comparing incidence rates of probable AEs between circumcised males aged 1–9 years and circumcised neonates aged < 1 year, the highest IRDs included incomplete circumcision, penile adhesions, or other abnormalities resulting in correctional procedures [2,947 AE/PMMC][g], bleeding [8,398 AE/PMMC][h], and inflammation of the penis [6,421 AE/PMMC].[i] Finally, in comparing incidence rates of probable AEs between circumcised males aged > 9 years and circumcised neonates aged < 1 year, the highest IRDs included incomplete circumcision, penile adhesions, or other abnormalities resulting in correctional procedures [29,460 AE/PMMC],[j] inflammation [17,575 AE/PMMC],[k] bleeding [7,346 AE/PMMC],[l] and wounds [2,944.7 AE/PMMC].[m]

Meatal stenosis may be a complication of surgery. In a prospective study, meatal stenosis was documented in 24 of 239 (7.3%) circumcised boys aged > 3 years but no uncircumcised boys.[293] However, the study population was not clearly defined, and the diagnosed cases were not independently confirmed. In addition, the investigator reported that the low number of uncircumcised boys in the study resulted in a lack of power to

[d] Highest IRDs included repair incomplete circumcision [919 AE/PMMC], and lysis or excision of penile post-circumcision adhesions [757 AE/PMMC]

[e] Highest IRDs included intraoperative bleeding [896.23 AE/PMMC], and hemorrhage control [107.21 AE/PMMC]

[f] Highest IRDs included edema of the penis [1,116.59 AE/PMMC], and other inflammatory disorders of the penis/ cellulites of the penis [68.0 AE/PMMC]

[g] Highest IRDS included division of penile adhesions [42,034 AE/PMMC], repair of incomplete circumcision [30,389 AE/PMMC], lysis or excision of penile adhesion [12,573 AE/PMMC], and other repair of penis [15,968 AE/PMMC within 365- day window post-circumcision and 15,795 AE/PMMC within 1,200-day window post-circumcision]

[h] Highest IRDs included intraoperative bleeding [7,498.3 AE/PMMC], and hemorrhage control [807.76 AE/PMMC].

[i] Highest IRDs included edema of the penis [2,605 AE/PMMC] and other inflammatory disorders of the penis/cellulitis of the penis [3,816 AE/PMMC].

[j] Highest IRDs included division of penile adhesions [12,395 AE/PMMC], other repair of penis [9,864 within the 356-day window post- circumcision and 9,719 within the 1,200-day window post-circumcision, repair of incomplete circumcision [3,388 AE/PMMC], and lysis or excision of penile post-circumcision adhesions [2,576.8 AE/PMMC].

[k] Highest IRDs included edema of penis [4,163 AE/PMMC] and other inflammatory disorders of the penis/cellulitis of the penis [4,163 AE/PMMC].

[l] Highest IRDs included intraoperative bleeding [6,756.0 AE/PMMC] and hemorrhage control [569.38 AE/PMMC].

[m] Included open wound of penis without mention of complications [2,944.7 AE/PMMC]

demonstrate a significant association between circumcision status and meatal stenosis. A study among 3,125 boys aged 6–12 years in Tehran, Iran, demonstrated a much lower rate of meatal stenosis of 0.9%.[294]

Results from studies have implicated male circumcision in methicillin-resistant *Staphylococcus aureus* (MRSA) outbreaks. A case-control study of 2 outbreaks in 11 otherwise healthy male infants at a well infant nursery in a hospital in Los Angeles, California, identified circumcision as a potential risk factor. However, in no case did MRSA infections involve the circumcision site, anesthesia injection site, or the penis, and MRSA was not found on any of the circumcision equipment or anesthesia vials tested.[44] In a review of published MRSA outbreaks, it was hypothesized that MRSA infections and circumcision might be associated.[295]

Minimizing pain is an important consideration for the procedure. Appropriate use of analgesia is considered standard of care for male circumcision at all ages and can substantially control pain.[38] In one study, 93.5% of neonates circumcised in the first week of life with appropriate analgesia gave no indication of pain on an objective, standardized neonatal pain rating system.[38] In a review of 14 studies of analgesia in neonatal circumcision, most showed that a combined pharmacological and non-pharmacological approach is best to maximally reduce pain, such as dorsal penile nerve block combined with other therapies including acetaminophen and nonnutritive sucking or 2.5% lidocaine/2.5% prilocaine cream and acetaminophen.[296] In a study of 112 men ranging in age from 15 to 82 years in Edinburgh, Scotland, pain was reported to be mainly mild to moderate after circumcision under general anesthesia with intraoperative penile block. Pain was rarely severe and occurred mostly after circumcision-related complications.[56]

Because of their rarity, rates of severe complications are difficult to document. In a review article, data from a myriad of sources were compiled, including personal correspondence, to estimate the following rates of AEs per circumcisions performed in the United States: excessive bleeding requiring ligature, 1 per 4,000; bleeding requiring transfusion, 1 per 20,000; severe infection requiring parenteral antibiotics, 1 per 4,000; subsequent surgery (e.g., for skin bridges), 1 per 1,000; repair of traumatic injury, 1 per 15,000; and loss of entire penis, less than 1 per 1,000,000.[273] There were 3 deaths due to male circumcision during 1954–1989.

A study from a large longitudinal healthcare reimbursement dataset in the United States estimated the incidence rate difference (IRD) (subtracting out the background rate of AEs in uncircumcised newborns) for potential serious AEs to range from a low of 0.76 persons (95% CI = 0.10–5.43) with stricture of male genital organ PMMC to a high of 703.23 persons (95% CI = 659.22–750.18) with repair of incomplete circumcision PMMC.[40] Four amputations of the penis (incidence = 3.87 per million) occurred in uncircumcised newborns and 3 partial amputations of the penis (incidence = 2.29 per million) circumcised newborns (IRD [circumcised–uncircumcised] = -1.58 [95% CI = 6.16–3.02]).

In a study of 1,239 infant male circumcisions using the Mogen clamp in Western Kenya, the overall AEs rate was 2.7%.[297] Most AEs were mild or moderate and treated

conservatively. One severe AE involving excision of a small piece of the lateral aspect of the glans penis was documented. AEs were more common in babies who were aged ≥ 1 month, resulting in the conclusion that infant male circumcision is optimally conducted within the first month of life.

Complication rates for medically attended adult male circumcisions were well documented in the 3 African clinical trials. The complications were of similar magnitude and severity, and most commonly were pain, bleeding, infection and unsatisfactory cosmesis and the complication rate ranged from 2% to 4%.[43] In Kenya, the rate of complications was 1.7% and the most common complications included bleeding and infection.[5] In South Africa, 3.8% of trial participants experienced complications; the most common complications were pain (31.7%), bleeding (15.0%), swelling or hematoma (16.7%), and problems with appearance (15.0%).[4] In Uganda, moderate to severe complications (those requiring any treatment) were reported in 3.6% of procedures, all of which resolved with treatment.[6] There were no reported deaths or long-term sequelae.

In an observational follow-up study of males aged ≥ 12 years who underwent voluntary male medical circumcision (VMMC) between November 2008 and March 2010 in 16 clinics in Nyanza Province, Kenya, the AE rate among clinic system participants during the intra-operative period was 0.1% and post-operative period was 2.15%.[42] The rate increased to 7.5% among participants under active surveillance. Providers performing 100 or more procedures compared to those who performed fewer than 100 procedures were 63% and 39% less likely to perform a procedure resulting in an AE in both a clinic-based passive surveillance system and among a randomly selected subset of clinic participants followed through a home-based active surveillance system (involving an in-depth interview), respectively, and had a shorter duration of male circumcision procedures (15.5 vs 24.0 minutes, respectively). Those performing > 100 procedures achieved an AE rate of 0.7% and 4.3% in the clinic-based passive and home-based active surveillance systems, respectively.[42]

In Uganda, it was determined that the mean time to complete male circumcision surgery was 40 minutes for the first 100 procedures and 25 minutes for the subsequent 100 procedures.[298] The rate of moderate and severe AEs ranged from 8.8% for the first 19 unsupervised procedures after training, 4.0% for the next 20–99 procedures, and 2.0% for the last 100. All AEs were found to resolve with medical management. Investigators concluded that >100 circumcisions needed to be completed to achieve optimum duration of surgery and that the first 20 procedures after completing training should be supervised.

Effect of Male Circumcision on Sexual Function and Penile Sensation

The foreskin is a highly innervated structure[299] and some authors have expressed concern that its removal may compromise sexual sensation or function.[59] However, in one survey of 123 men following medical circumcision in the United States, men reported improved sexual satisfaction and no change in sexual activity, despite decreased erectile function and penile sensation.[67] Furthermore, a small survey conducted in the United States among 15 men before and after circumcision found no statistically significant difference in sexual function or sexual satisfaction.[300] Other studies conducted among men after adult

circumcision have found that relatively few men report that there is a decline in sexual functioning after circumcision; most report either improvement or no change.[62,64,301,302]

A systematic review of the literature of the histological correlates of penile sensitivity and sexual pleasure concluded that circumcision results in increased "access of genital corpuscles to sexual stimuli" and that exposure of the glans, rather than lack of prepuce may be the most important factor in penile sensitivity and sexual pleasure.[69] Results from 2 other systematic literature reviews refute the assertion that circumcision compromises sexual sensation or function.[58,303] A systematic review and meta-analysis based on results from studies reporting original data evaluated the relationship between male circumcision and sexual function, sensitivity, and satisfaction and included 40,473 men of which 19,542 were uncircumcised and 20,931 were circumcised.[303] The authors of this systematic review used the Scottish Intercollegiate Guidelines Network grading system to grade the quality of the articles.[303] Of the 36 publications, 2 were classified as high quality RCTs, and 34 were case-control or cohort studies. Of the 34 case-control or cohort studies, 11 were classified as high quality, 10 were classified as well-conducted, and 13 were classified as low quality. The results from high quality RCTs and high quality or well-conducted case-control or cohort studies indicated that circumcision was not associated with an overall compromise on "penile sensitivity, sexual arousal, sexual sensation, erectile function, premature ejaculation, ejaculatory latency, orgasm difficulties, sexual satisfaction, pleasure, or pain during penetration."[303] Ten of 13 lower quality studies found compromises in ≥ 1 parameter(s);[303] however, several critical flaws have been reported in at least 1 of these studies.[304] In another systematic review and meta-analysis including 10 studies and 9,317 circumcised men and 9,423 uncircumcised men, there were no significant associations between male circumcision and sexual desire, dyspareunia, premature ejaculation, ejaculation latency time, erectile dysfunction, or orgasm difficulties.[58] Despite that no such differences were detected in 2 large, well-designed RCTs included in this systematic review, the authors suggest that more studies are needed in diverse settings over longer study periods to further elucidate this topic.[58]

Three of 4 additional studies not included in the systematic reviews and meta-analyses described above also failed to find that circumcision reduces sexual function or satisfaction.[65,66,305,68] Results from a survey about erectile function and sexual quality of life conducted in Cottbus, Germany among 2,499 men, including 167 circumcised men, indicated that male circumcision was not significantly associated with erectile dysfunction or sexual satisfaction.[65] Investigators included 35 survey items from the International Index of Erectile Function version 6[306] (IIEF-6) and reported that this study represented the largest survey worldwide on male erectile dysfunction using the IIEF-6 as a validated instrument.[65] In a cross-sectional survey in Lusaka, Zambia, of 478 men (242 circumcised and 236 uncircumcised) who responded to the IIEF-5 questionnaire, circumcised men had higher average erectile function scores ($P < 0.001$) and percentage of participants with normal erectile function ($P < 0.05$) and lower prevalence of erectile dysfunction (56% and 68%, respectively) ($P < 0.05$) compared with uncircumcised men.[305] Among 6,293 men surveyed through Britain's Natsal-3, 20.7% of whom were circumcised, there was no association between male circumcision and being in the lowest quintile of scores for the Natsal-SF (indicator of poorer sexual function) (aOR 0.95 [95% CI = 0.76–1.18]).[66] Among 62 men in Portugal participating in telephone surveys using

questions from 3 validated scales, including the IIEF, about sexual habits and dysfunction before and after circumcision, male circumcision was associated with increased frequency of erectile dysfunction (9.7% [before circumcision] vs. 25.8% [after circumcision]; $P = 0.002$)), and delayed orgasm (11.3% [before] vs. 48.4% [after]; $P < 0.001$), and symptomatic improvement in patients with pain with intercourse (50.0% [before] vs. 6.5% [after]); $P < 0.001$).[68]

CONSIDERATIONS RELATED TO MALE CIRCUMCISION IN THE UNITED STATES

Policy decisions regarding male circumcision need to be considered in light of several factors. These factors include the domestic HIV burden, rates of male circumcision in the United States, acceptability of both adult male and newborn male circumcision in the United States and abroad, risk compensation, policy issues, and cost-effectiveness, while addressing ethical concerns.

HIV Infection in the United States

The epidemiology of HIV in the United States differs considerably from that of regions targeted by the WHO/UNAIDS recommendations and the sub-Saharan African areas of Kenya,[5] Uganda,[6] and South Africa,[4] where the RCTs were conducted.[87] The overall prevalence of HIV infection (0.47%)[160] is considerably lower in the United States than in other nations such as Kenya (6.0%), Uganda (7.4%) and South Africa (19.1%), where the male circumcision clinical trials were conducted.[92] Most sexual transmission in the United States occurs among men who engage in male-to-male sexual contact, whereas in sub-Saharan Africa, transmission is predominantly through heterosexual sex. It should be noted, however, that HIV prevalence is high in some U.S. communities (for example, 2.5% of all adults and adolescents in Washington, DC)[307] and social networks.[308] In an analysis of surveillance data from 12 urban areas, overall HIV prevalence was between 1%–2% in 4 cities (Miami [Miami-Dade County], Florida [1.2%]; Philadelphia, Pennsylvania [1.4%]; New York, New York [1.3%], and Tampa, Florida [1.4%]), between 2%–3% in 4 cities (Atlanta, Georgia [2.0%], Baltimore, Maryland [2.4%], San Francisco [City and County][2.0%], and Washington, District of Columbia [2.7%]) and nearly 4% in one (Fort Lauderdale, Florida [3.998%]).[309] Prevalence was 1%–4% among blacks in all areas and was 1%–2.2% for Hispanics in 5 areas. Heterosexual contact accounted for about 20% of HIV infections among men in the metropolitan statistical areas (MSAs) of Washington, D.C.-Virginia-Maryland-West Virginia, Baltimore-Towson, Maryland, and Miami, Florida (Miami-Dade County), and 33.8% in the MSA of Philadelphia, Pennsylvania-New Jersey-Delaware-Maryland.

New HIV diagnoses in the United States and 6 dependent areas, including American Samoa, Guam, the Northern Mariana Islands, Puerto Rico, the Republic of Palau, and the U.S. Virgin Islands, are predominantly in males; adult and adolescent males who engage in male-to-male sex represent the largest risk group. An estimated 44,784 HIV diagnoses were made in 2014, of which 81% were in adult or adolescent males; 8% of HIV diagnoses were in adult or adolescent males who acquired HIV heterosexually, and 69% were in adult or adolescent males who acquired HIV through male-to-male sexual contact

(66% male-to-male sexual contact alone, 3% male-to-male sexual contact and injection drug use [IDU]).[93] In addition, it is estimated that among persons living with diagnosed HIV infection in the United States in 2013, 75% were adult or adolescent males, 8% were adult or adolescent males who acquired HIV infection heterosexually, and 58% were adult or adolescent males who acquired HIV infection through male-to-male sexual contact (52.2% male-to-male sexual contact alone, 5.4% male-to-male sexual contact and IDU).[93] As noted earlier, there are few data showing a benefit of male circumcision on the risk of HIV associated with penile-anal sex or oral sex between men, and thus the benefit of circumcision among MSM is uncertain.

In the United States, because an estimated 8% of HIV diagnoses in 2014 and 8% of persons living with HIV in 2013 were among adult and adolescent males with infection attributed to heterosexual contact,[93] circumcision can play a role in preventing HIV among men who engage in unprotected heterosexual vaginal sex, especially in communities where prevalence of HIV infection among women is high or among men with multiple sex partners. The potential benefit of male circumcision as an intervention to prevent HIV infection among men who have sex with women depends upon the likelihood of HIV exposure among such men, and thus, upon the prevalence of HIV among their female sex partners.

The applicability of newly proven HIV prevention practice like male circumcision across racial/ethnic groups is a critical consideration. Of the HIV diagnoses among non-Hispanic whites, non-Hispanic blacks, and Hispanics or Latinos in the United States in 2014, the highest rates of diagnosis per 100,000 population occurred in black adult or adolescent males (94.0) and black adult or adolescent females (30.0).[93] The overall estimated rate of HIV diagnosis among adult or adolescent males in the United States and 6 dependent areas in 2014 was 27.5 per 100,000 population. Overall, 8% of all estimated HIV diagnoses in 2014 in the United States and 6 dependent areas were among adult or adolescent males with infection attributed to heterosexual contact and the proportions attributed to heterosexual contact among adult or adolescent males was 11% among Blacks or African Americans, 7% among Hispanics or Latinos, and 4% among whites.[93] In the United States during 2014, the rate of diagnoses of HIV infection for black women (30.0 per 100,000) was 5 times that for Hispanic or Latino women (6.5 per 100,000) and 18 times the rate for white women (1.7 per 100,000).[93]

Rates of Male Circumcision in the United States

The United States differs from some regions of sub-Saharan Africa in that most American men are already circumcised, including 80.5% of men and adolescents aged 14-59 years in the United States during 2005-2010.[94] The practice of circumcising male newborns for reasons unrelated to religious beliefs was introduced to the United States in the late 1800s,[3] and by the 1940s, an increasing proportion of male children in the United States were born in hospitals and circumcised shortly after birth.[310] The percentage of newborns who were circumcised annually reached 80% after World War II, peaked in the mid-1960s, and has decreased by 28% to 58% in 2010. In 2002, approximately 1.2 million newborn boys were circumcised prior to discharge from the hospital.[311] In 1996,

an estimated 142,000 male circumcision procedures were performed beyond the neonatal period; of these, 49,000 were in persons older than 15 years.[312]

Four nationally representative surveys have examined the prevalence of circumcision among U.S. males: 2 among newborns prior to discharge from the hospital, 1 among adult men, and 1 among adolescent males and adult men. According to the National Hospital Discharge Survey (NHDS), 65% of newborn boys born in hospitals were circumcised in 1999, and the overall proportion of newborns circumcised was stable from 1979 to 1999.[313] The proportion of black newborns who were circumcised during this period rose from 58% to 64%, while the proportion of white newborns who were circumcised remained stable at 66%. Significant differences in rates of male circumcision exist by region. While the proportion of newborns born in the Midwest who were circumcised increased over this 20-year period from 74% to 81%, the proportion of newborns born in the West who were circumcised decreased over the same period, from 64% to 37%.[313] From 2000 to 2007, newborn male circumcision rates in the NHDS declined from 63% to 56% (CDC unpublished data). In another hospital discharge survey with different methodology (Healthcare Cost and Utilization Project [HCUP] National Inpatient Sample [NIS]), the rate of circumcision performed during newborn male delivery hospitalizations increased significantly from 48% in 1988–1991 to 61% in 1997–2000[314] and declined from 61% in 2000 to 57% in 2010.[315] Male circumcision was more common among newborns born to families of higher socioeconomic status, in patients with private insurance or belonging to a health maintenance organization, and among those born in the Northeast and Midwest. On multivariate analysis, black newborns were slightly more likely and newborns of other races much less likely to undergo male circumcision than whites.[314] These surveys document male circumcisions performed in hospitals and billed or coded in discharge diagnoses, but do not ascertain male circumcisions which were not billed or coded, were performed outside of hospitals (e.g., circumcision conducted in religious ceremonies), or were performed after delivery hospitalization.

In a series of national probability samples in which random samples of adults living in U.S. households were surveyed during 1999–2004 as part of the NHANES, the overall prevalence of male circumcision among adult males in the United States was 79% and varied by race or ethnicity (88% in non-Hispanic white men, 73% in non-Hispanic black men, 42% in Mexican Americans, and 50% in men of other races and ethnicities).[221]

Similarly, in a follow-up study, data from the NHANES 2005–2010 were used to estimate the prevalence of male circumcision among men and adolescents aged 14–59 years in the United States. The overall estimated prevalence of male circumcision in this population was 80.5% and also varied by race or ethnicity (90.8% in non-Hispanic whites, 75.7% in non-Hispanic blacks, and 44% in Mexican Americans). The estimated circumcision prevalence calculated retrospectively by birth cohort among men and adolescents increased from 65.7% in the 1946–1949 birth cohort to a high of 83.3% in the 1960–1969 birth cohort, and decreased to 76.2% in the 1990–1996 birth cohort.[316]

In a study of NHDS during 1979–2010, the prevalence of newborn circumcision declined from 64.5% to 58.3% over this time period, with the highest prevalence of neonatal

circumcision of 65.9% in 1981 and lowest prevalence of 55.4% in 2007. [286] This decrease in the prevalence of circumcision in newborns in the United States was accompanied by an increase in the proportion of Hispanics in Western states,[316] and the withdrawal of Medicaid coverage in 18 states.[286] Hispanics typically have a lower prevalence of male circumcision compared with the overall U.S. population.

Using 2010 MarketScan claims data, investigators reported that 156,247 circumcisions were performed in privately insured boys aged 0–18 years, including 93.6% in neonates (aged ≤ 28 days) and 6.4% in postneonates (aged > 28 days).[317] Investigators estimated a neonatal circumcision rate of 65.7%. The proportion of circumcisions having a nonmedical indication was 81.6% among neonates and 25.1% among postneonates. The proportion of circumcisions having phimosis as the indication in neonates and postneonates was 7.9% and 66.3%, respectively. Of postneonatal circumcisions, 46.6% were performed in infant males aged < 1 year.

During 1993–2009, data on newborn male circumcision procedures during hospitalizations from the HCUP indicated that the percentage of newborn hospital stays during which a male newborn circumcision was performed increased from 55.3% in 1993 to a high of 62.7% in 1999, and then decreased to a low of 54.5% in 2009.[318] The decrease in percentage of newborn hospital stays during which a male newborn circumcision was performed after 1999 coincided with the release of a statement in 1999 by the American Academy of Pediatrics (AAP) indicating that the evidence of medical benefits from circumcisions was not compelling enough to warrant routine newborn circumcision.[319] The AAP has since changed its policy stance indicating that the medical benefits of neonatal circumcision outweigh the risks.[320]

Acceptability

Acceptability of adult male circumcision in the United States

It is not well understood whether American men and male adolescents at higher risk for heterosexual acquisition of HIV would be willing to undergo circumcision for partial HIV prevention, nor whether parents would be willing to have their newborns circumcised for the purpose of reducing risk of possible future HIV infection. In a consumer survey assessing the acceptability of male circumcision as an HIV prevention intervention among adult males in the continental United States, investigators mailed surveys to a random sample of 19,996 potential respondents of approximately 340,000 households.[321] Among the 789 uncircumcised men with completed survey responses, 13.1% reported they would be likely or very likely to get circumcised if their health care provider told them it would reduce their risk of becoming HIV infected, including 15% of heterosexual men and 13% of MSM.[321] In contrast, in an analysis of data collected from MSM interviewed at gay pride events in 2006, over half of uncircumcised MSM and 70% of uncircumcised black MSM indicated that they would be willing to be circumcised if the procedure were proven to reduce risk of HIV among MSM.[322] Willingness was associated with black race (OR 3.4 [95% CI = 1.3–9.8]), non-injection drug use (OR 6.1 [95% CI = 1.8–23.7]) and the perception that male circumcision reduces the risk of penile cancer (OR 4.7 [95% CI = 2.0–11.9]). Post-surgical pain and wound infection were the most commonly reported concerns about male circumcision in that study.

Based on a retrospective review of medical records of 500 male patients from an STD clinic in southern Florida, the proportion of men who were circumcised was 27% overall, 17% among Hispanics, and 36% among non-Hispanics.[323] In the same clinic, among a convenience sample of 39 Hispanic male and female patients during 2009, 53% of male respondents indicated that they would be willing to be circumcised. In a follow-up study by the same investigators, after receiving information about biomedical prevention strategies in the form of a pamphlet or brief video, the most preferred HIV prevention strategies among 97 male and female patients attending the STD clinic included male condoms (34%), PrEP (18%), microbicides (18%), male circumcision (14%), and female condoms (14%).[324]

Adult and adolescent male circumcision could potentially have the largest impact on HIV acquisition in populations in which a low percentage of males are circumcised and there is a high risk for HIV transmission through penile-vaginal sex. As noted above, among racial/ethnic groups, Hispanic men have the lowest rates of circumcision and higher rates of heterosexually acquired HIV than white men, while black men have the highest risk of heterosexually acquired HIV infection. Further research regarding acceptability of male circumcision in these populations is needed.

Acceptability of adult male circumcision in sub-Saharan Africa

More research on the acceptability of adult male circumcision has been conducted in sub-Saharan Africa in countries where HIV prevalence is high and male circumcision is practiced less frequently. The studies discussed below addressed facilitators and barriers to male circumcision. While some of the facilitators and barriers may be culturally specific to sub-Saharan Africa, others are universal in nature and help inform the U.S. discussion.

A review of 13 articles concerning male circumcision in 9 sub-Saharan African countries found that a median of 65% of uncircumcised men reported willingness to be circumcised, but there was a wide range of acceptability by country (from 29% in Uganda in 1997 to 81% in Swaziland in 2006).[325] In a later study, the range of acceptability of male circumcision among uncircumcised men in 4 districts in Uganda in 2008 was reported to be 40%–62%.[326] Factors that increased acceptability of male circumcision in the studies from the review article and other studies include the perception of improved hygiene,[326-334] protection from HIV and other STIs,[220,326,327,330-334] increased sexual pleasure,[326,327,330-334] acceptance of procedure by female partner,[335] and improved ease of condom use.[327,328]

Barriers to male circumcision include concerns about the pain associated with surgery,[327,328,330,331,336] religious and cultural beliefs,[328,330-333,337] the cost of surgery,[327,330,337] complications from surgery,[326,327,329,331] lack of access to health care,[327] concerns about contracting HIV during the procedure,[326] need for financial assistance during the recovery period to help maintain family income,[326] and beliefs about resulting changes in penile size, sensation, or performance.[333]

The beliefs of women also have an impact on the acceptability of male circumcision, and their beliefs differ by country.[325] There are several reasons why women report that they

prefer that their male partners be circumcised. Some women reported that they believed that it is easier for men to maintain good hygiene if they are circumcised,[327,330,331,333] some reported believing that male circumcision decreases their own risk of acquiring STIs,[327,331-333] some reported preferring circumcised sex partners and some believed that men enjoy sex more if they are circumcised.[330,332,333] In the Ugandan RCT, of 455 female partners of men circumcised as adults, 2.9% reported less sexual satisfaction after their partners were circumcised, 57.3% reported no change, and 39.8% reported an improvement.[338]

Acceptability of newborn male circumcision in the United States

Newborn circumcision has generally been well accepted in the United States, as evidenced by the rates of parents choosing to circumcise their newborn sons. Parents have typically made the decision based more on social concerns or perceptions of improved hygiene rather than medical reasons.[291,339] A 1999 survey among parents of young boys found that those whose sons were uncircumcised were generally less satisfied with the decision than those who had chosen to circumcise their sons, and these parents of uncircumcised sons felt that they had not received adequate information.[340]

It is not clear whether more information on potential health benefits and risks of male circumcision would influence parents' decisions, particularly among racial/ethnic groups that do not typically elect to have their sons circumcised. In a survey of new parents, 76% responded that they probably or definitely would want circumcision for their male children and few participants' attitudes changed after reading an AAP policy summary or after reading about the results of the RCTs on HIV and HPV risk reduction.[341]

However, in a more recent telephone survey of nearly 10,000 respondents across the continental United States, sampled through random digit dialing, 88% of respondents said that they would definitely or probably circumcise a newborn son, including 65% who "definitely would" and 23% who "probably would"; 53% of all respondents (including those who said they would definitely have their sons circumcised) stated that they would be more willing to consider circumcision for a male newborn child based on information provided about potential future HIV risk reduction.[321] Approximately one-third of those who probably would not circumcise a newborn son responded that they were more likely to circumcise as a result of the information of a partial HIV protective effect later in life. Greater odds of not being inclined to circumcise a newborn son were associated with individuals of Hispanic ethnicity and other race/ethnicity compared with non-Hispanic whites; uncircumcised men and men with unknown circumcision status compared with females; individuals receiving postgraduate education compared with individuals with no more than a high school education; individuals living in the South and West compared to the Midwest; and those who were not or only somewhat confident in the safety of routine childhood vaccines compared with those who were confident or very confident in vaccine safety.

In an STD clinic in southern Florida, among a convenience sample of 39 Hispanic male and female patients during 2009, most respondents expressed a preference for circumcising their children (male respondents [84%], female respondents [80%]) and

reported that the best age to conduct male circumcision was during the first month of life (male respondents [63%], female respondents [75%]).[323]

In a study about attitudes and decision making about infant male circumcision in a predominantly Hispanic population in New York City, the parental decision in favor of circumcising a male infant was associated with parents who came from a culture and family that believed in circumcision and who believed that it was not too risky.[342]

Investigators studying whether presence of state Medicaid coverage for infant male circumcision was associated with male circumcision rates in the United States, found that the average rate of male circumcision was 55.9% and states with Medicaid coverage for routine male circumcision had, on average, male circumcision rates that were 24 percentage points higher than states without such coverage. Hospitals with higher percentages of Hispanic patients also had lower circumcision rates.[343] As of 2012, coverage for male circumcision through the Medicaid program is denied in 18 states.[344]

Acceptability of newborn male circumcision in sub-Saharan Africa

Although some of the issues related to acceptability of newborn male circumcision in sub-Saharan Africa may be culturally specific to this region, others are universal in nature and help inform the discussion of male circumcision in the United States. In addition, some of the culturally specific issues of sub-Saharan Africans may continue to influence decision making around male circumcision even after migrating to the United States. In Uganda, willingness of men to have their sons circumcised ranged from 60%–86%, depending on geographic region.[326] A higher proportion of circumcised (96%–100%) compared to uncircumcised men (59%–79%) were likely to have their sons circumcised. Women's support of a son's circumcision ranged from 49%–95%, based on geographic region. To prevent HIV or provide for a "healthier future" was the most common reason for willingness to support a son's circumcision. Concerns about male circumcision included cost, pain associated with surgery, perception that circumcision would signify a religious conversion, lack of information about male circumcision, or that it would encourage their children to engage in risky sexual activity. Household survey participants and healthcare workers preferred male circumcision during infancy or childhood (0–9 years) compared to adolescence (10–17 years) or adulthood (≥ 18 years).[326] In Zimbabwe, acceptability of early infant male circumcision was high among most ethnic groups; concerns included issues related to safety, questionable motivations behind free service provision by health care providers, handling of the discarded foreskin, separation of traditional circumcision from the adolescent initiation process, and female nursing of an infant's wound (which would be considered taboo).[345] In Botswana, among mothers who were interested in circumcision, protecting the infant from future infections such as HIV and hygiene were the main reasons expressed for circumcising their infants, while the child's comfort or safety during the procedure and timing of the procedure at too young an age were concerns voiced by those not interested in the procedure.[346] Among 129 grandparents and parents participating in focus group discussions in Lusaka, Zambia, most participants felt there were benefits for HIV prevention associated with circumcision, as well as advantages to conducting circumcisions at a young age.[347] Among these same focus group participants, barriers to neonatal circumcision included concerns about pain and cultural identity. Factors associated with allowing infant males

to be circumcised among parents participating in a case-control study at 5 government hospitals in Nyanza Province, Kenya differed by gender.[348] Among mothers, having a husband (infant's father) who was circumcised or agreeing with the husband (infant's father) about the infant male circumcision facilitated infant male circumcision. Among fathers, being circumcised and agreeing with the mother about infant male circumcision were factors associated with conducting infant male circumcision. The primary decision makers were found to be fathers in 66% of instances.

Provider attitudes and practices regarding male circumcision in the United States

Although many medical societies have addressed neonatal male circumcision,[320,349-351] few systematic data are available regarding provider attitudes and practices. In a nationally representative, self-administered cross-sectional electronic survey of 1500 physicians (510 family or general practitioners, 490 internists, 250 pediatricians, and 250 obstetricians/gynecologists) conducted in 2008, 33% of respondents thought that the medical benefits outweighed the risks of newborn male circumcision, while 34% thought the benefits and risks were equal, 18% believed that the benefits did not justify the risks, and 15% reported not knowing whether or not the medical benefits of newborn male circumcision outweighed the risks.[352] Overall, 39% of physicians reported being somewhat or very familiar with data from the male circumcision RCTs. Being supportive of newborn male circumcision was not associated with familiarity with African male circumcision trial results. Nevertheless, 22% (n = 327/1,500) of physicians in this study reported not understanding the risks and benefits of newborn male circumcision well enough to counsel parents and 40% (n = 504/1,250) reported not understanding the risks and benefits well enough to counsel adult men, suggesting the need for more education of physicians regarding the latest male circumcision research in order to feel comfortable counseling adult men or parents of newborn male infants.[353]

A study of health care provider overall knowledge of infant male circumcision and knowledge of male circumcision reduction in HIV acquisition was conducted among 92 health care providers, including 37 obstetricians, 28 pediatricians, and 27 family practitioners in an urban medical center in Chicago, Illinois.[354] Health care providers scored high on knowledge items related to AE rates, the concepts that male circumcision protects against phimosis and UTIs and does not prevent hypospadias demonstrated but scored lower for knowledge items related to the concepts that male circumcision protects against cervical cancer, GUD, BV, and reduced HIV acquisition. Pediatricians demonstrated greater knowledge of overall infant male circumcision and obstetricians demonstrated greater knowledge of male circumcision related to HIV acquisition.

Study results from interviews of a nonrandom sample of key informants and health care practitioners serving the Hispanic community in Miami, including physicians, nurses, and other allied health professionals illustrated differing attitudes based on gender and highlighted the importance of supporting health care workers in any efforts to counsel clients around male circumcision and its role as an HIV prevention strategy.[355] The acceptability of male circumcision among male health care providers was associated with acceptability of American Pediatric Association guidelines, and personal circumcision. Some male health care providers expressed skepticism regarding health benefits for sexually transmitted disease or HIV risk reduction. Female providers expressed the

importance of parental financial burden, lack of information, and low acceptability among Hispanic men.

Cost-Effectiveness

The medical costs of male circumcision must also be accounted for in considering the role of circumcision for HIV prevention in any setting. While male circumcision has been shown to be a cost-saving HIV prevention intervention in sub-Saharan Africa,[356,357] the calculus is different in the United States, where the costs of performing male circumcision as well as HIV treatment costs are higher, and the risk of HIV infection is lower. Another important factor driving the cost-effectiveness is the length of time between the intervention and when the benefits are experienced. The value of these benefits is discounted over decades for newborn male circumcision, but over a shorter period for adult male circumcision.

One cost-utility analysis of male circumcision in the United States reported that circumcision increased incremental costs by $828 per patient and resulted in an incremental 15.30 well-years lost per 1,000 males. However, like most other cost-effectiveness analyses of male circumcision in the United States, it was conducted prior to publication of the RCTs that reported benefits of circumcision to prevent HIV[4-6] and focused on costs and benefits of related conditions other than HIV;[358] cost-effectiveness increased if the procedure was cost-free, pain-free, and had no immediate complications. One evaluation of a large health maintenance organization database found the expected lifetime cost of male circumcision was small, compared with larger expected benefits.[359] Much of the benefit of neonatal male circumcision in that analysis derived from pre-empting the need for post-neonatal circumcision, which is substantially more costly. Two other studies published in 1991, which did not include an HIV prevention benefit, estimated that both costs and benefits were too small to play a substantial role in the decision whether to perform the procedure.[360,361]

A model estimating the impact of newborn circumcision on a U.S. male's lifetime risk of HIV from heterosexual contact showed that circumcision reduced the 1.9% absolute lifetime risk by 15.7% overall, by 20.9% for black males, 12.3% for Hispanic males and 7.9% for white males.[362] The number of circumcisions needed to prevent 1 HIV infection was 298 for all males, and ranged from 65 for black males to 1,231 for white males. Newborn male circumcision was a cost-saving HIV prevention intervention overall, as well as for black and Hispanic males. The net cost of newborn male circumcision per quality-adjusted life-year (QALY) saved was $87,792 for white males. Results were most sensitive to the discount rate, male circumcision efficacy in preventing acquisition of HIV, and cost. The main analysis did not take into account secondary prevention (i.e., HIV cases prevented among partners of circumcised males), the benefits of male circumcision in preventing other STIs, AEs, and possible reduction in HIV risk from male-to-male sexual contact.

A population-based model of the effect of adult male circumcision in MSM indicated that over 20 years, circumcision could very slightly reduce (< 1%) the number of new HIV cases among MSM (CDC, unpublished data). Although there are no conclusive data demonstrating a protective effect for MSM, the model assumed 50%–60% protection

from HIV for circumcised men engaging in insertive sex. The net costs of the procedure were less than $50,000 per QALY saved, which is considered a conservative threshold for cost-effectiveness. The model included the prevention of secondary cases of HIV. The reduction in new cases of HIV was small because the chief source of HIV infection among MSM is receptive anal sex and the model assumed no circumcision-related protection for receptive acts.

Investigators evaluated the reduction in infections associated with male circumcision and resulting health care costs associated with continued decreases in male circumcision rates. They estimated that if male circumcision rates continue to decrease in the United States, such decreases would likely be associated with increased infection prevalence and resulting increased medical expenditures for men and women. For example, a reduction in the male circumcision rate to 10%, a rate similar to that in Europe, would result in an increase in lifetime health care costs by $407 per male and $43 per female, and in an increase in net expenditure per annual birth cohort of $505 million. The projected increase in HIV infections would be responsible for 78.9% of increased costs.[363]

Investigators conducting a cost-effectiveness analysis for MSM in Australia similarly found that male circumcision could be cost effective or cost saving in some scenarios, although a relatively small percentage of HIV infections would be prevented by circumcision of MSM and the associated cost was high relative to other HIV prevention programs.[364] They estimated that 2%–5% of HIV infections per year would be averted and that 118–338 male circumcisions would be required to prevent one HIV infection. Circumcising all MSM, all MSM aged 35–44 year old years, and all MSM who practice only insertive penile-anal sex were all cost-effective strategies compared to not circumcising any MSM.

A number of mathematical modeling studies have found that male circumcision would be an effective prevention tool in sub-Saharan Africa. Using mathematical modeling, UNAIDS, WHO, and the South African Centre for Epidemiological Modelling and Analysis (SACEMA) estimated that male circumcision among heterosexual men in areas with a low prevalence of male circumcision and a high HIV prevalence would be very beneficial; 5 to 15 male circumcisions would need to be performed to avert 1 HIV infection.[365] The estimated costs to avert 1 HIV infection would range from US$150 to US$900 using a 10-year time span. Investigators conducting a cost and impact study in Botswana estimated that US$689 per HIV infection and 70,000 HIV infections through 2025 could be averted by scaling-up adult and neonatal circumcision to reach 80% coverage by 2012, at a total net cost of US$47 million between 2012 and 2025.[366]

In a cost-effectiveness study of male circumcision over a lifetime in Rwanda, an African country with an adult HIV prevalence of 3%, infant male circumcision was found to be less expensive per procedure than adolescent and adult male circumcision (US$15 instead of US$59) and was determined to be cost-saving despite the calculation that savings from an infant circumcision would require up to 52 years to be realized, which is the life expectancy at birth in Rwanda. Adult male circumcision was neither cost-saving nor highly cost-effective when considering only the direct benefit for the circumcised man.[367] A compartmental epidemic model simulating the population-level impact of various male

circumcision programs on heterosexual transmission in Soweto, South Africa, incorporated both gender-specific negotiation strategies related to condom use with the male circumcision program. Investigators determined that even modest programs offering circumcision would result in significant benefits and estimated that a 5-year prevention program in which an additional 10 percent of uncircumcised males undergo circumcision annually, would prevent 13% of expected new HIV infections over a 20-year period.[368]

Other Considerations

Risk compensation

The possibility that men may alter their risk behavior and engage in riskier sex practices following circumcision may undermine the preventive health benefits of male circumcision.[84,369] In addition, it is possible that generalized dissemination of public health information regarding male circumcision may introduce complacency and greater risk behavior among men circumcised early in life, such as the period during infancy through young adulthood.

In general, however, risk compensation was not observed among circumcised participants in the majority of RCTs.[5,74,77,370] A meta-analysis of secondary outcomes measuring sexual behavior for the Kenyan and the Ugandan trials found no significant differences in risky sexual behavior between circumcised and uncircumcised men,[136] and in a sub-sample of men in the Kenyan trial, a detailed longitudinal sexual risk assessment indicated no statistically significant differences in sexual risk propensity scores or in incident infections of gonorrhea, chlamydial infection, or trichomoniasis by male circumcision status.[371] A similar result for the RCT conducted in Kenya found no significant difference in risk behavior between circumcised and uncircumcised men over 12 months of follow-up.[5] More recently, during 4.79 years of trial surveillance of participants in the Rakai randomized trial of male circumcision, there was no evidence of significant self-selection or behavioral risk compensation based on male circumcision status.[77,81] However, in the South African RCT, during 2002–2005, the mean number of sexual contacts was statistically significantly greater for circumcised men compared to uncircumcised men at the visits during months 4–12 (5.9 vs 5.0, $P < 0.001$) and at the visits during months 13–21 (7.5 vs. 6.4, $P = 0.0015$), although the number of partners did not increase.[81]

Results of observational studies that compared high-risk sexual behavior in circumcised men and uncircumcised men were mixed. In a population-based observational survey conducted to estimate baseline male circumcision status and attitudes associated with male circumcision in Kisumu, Kenya, some respondents expressed a concern that circumcised men might engage in riskier sex or might become more promiscuous due to misperceptions about the degree of protection provided by male circumcision.[220] However, in this same study, circumcision status was not associated with increased high-risk sexual behavior or lifetime number of sexual partners.[72,220] Similarly, in Uganda, in a mixed-method study using survey and focus group methodology, some respondents also expressed a concern that circumcised men might engage in riskier sex or might become more promiscuous due to misperceptions about the degree of protection provided by male circumcision. However, the RCT failed to find evidence of this.[326] A cross-sectional

survey of 1,257 sexually active men aged 15 years or older in Botswana found that circumcision was not significantly associated with condom use; 15% of circumcised men compared to 12% of uncircumcised men did not use condoms. Lack of condom use was significantly associated with religious beliefs, low level of education, marriage, drunkenness, and misconceptions regarding antiretroviral therapy.[86] During 2007–2008, in a cross-sectional survey of 7,300 young men aged 15–34 years in 20 rural communities in Tanzania, the prevalence of male circumcision was 40.6%. Circumcised men compared with uncircumcised men were more likely to report having ever used a condom (aOR 2.62 [95% CI = 2.32–2.95]).[82] Among 304 HIV-uninfected circumcised men surveyed in Cape Town, South Africa, men who were aware that circumcision offers protection against HIV compared to those who were not aware were more likely to agree that risk compensation might occur in association with male circumcision (RR1.19 [95% CI = 1.06–1.32, $P < 0.01$]), perceived lower risk of HIV infection when circumcised (RR 1.15 [95% CI = 1.11–1.12, $P < 0.01$]) and were more likely to report unprotected vaginal sex acts (RR 1.08 [95% CI = 1.04–1.12, $P < 0.01$]). Those who were more likely to agree that risk compensation might occur in relation to male circumcision were also more likely to be diagnosed with a chronic STI (OR 1.64 [95% CI = 1.06–2.53, $P < 0.05$]).[372] In a cross-sectional national survey in Uganda, while circumcised men, when compared with uncircumcised men, had higher odds of engaging in non-marital sex (aOR 1.26 [95% CI = 1.05–1.52]) and of reporting ≥ 4 multiple life-time partners (aOR 1.46 [95% CI = 1.27–1.67]), circumcised men also had lower odds of non-use of condoms with a non-marital partner (aOR 0.79 [95% CI = 0.63–0.98]).[78] Another study in Cape Town, South Africa, found risk compensation among women, but not men, who were informed of the HIV-protective effects of male circumcision.[373]

To date, there are few data to predict possible patterns of risk compensation in U.S. males. In one national survey of 4,892 U.S. men, 82% of circumcised and uncircumcised men agreed that even if being circumcised does reduce a man's risk for HIV infection through heterosexual sex, because circumcision is not fully protective against HIV infection, additional risk reduction measures are needed.[321] Among 6174 men interviewed about circumcision status and sexual behaviors as part of the NHANES during 1999–2004, no significant differences were noted in sexual behaviors among U.S. men according to their circumcision status, including mean age at sexual initiation, percent who ever had a male partner, and median number of lifetime sex partners.[221] In a consumer survey assessing the acceptability of male circumcision for both adult men and newborn males as an HIV prevention intervention and the potential for risk compensation in the continental United States, among 4,310 male respondents, 17.7% strongly agreed, agreed, or were neutral about the idea that men who are circumcised do not have to worry about the risks associated with not using a condom during sex or having more sex partners.[321] Among high-risk heterosexual men, defined as those who reported having had > 1 sexual partner or a new sexually transmitted infection in the past 12 months, the odds of potential risk compensation were higher among (1) non-Hispanic blacks and men of other race/ ethnicity compared to non-Hispanic whites, (2) men reporting an annual household income < $60,000 compared to > $60,000, (3) men who were never married or widowed/divorced/separated compared to married men, (4) men who agreed that they have little control over the things that happen to them compared with men who disagreed that they have little control , and (5) men aged > 45 years compared with men aged 18–

34.[321] Among a convenience sample of men attending 2 publicly funded sexually transmitted disease clinics in Louisville, Kentucky and Cincinnati, Ohio, men who self-reported being uncircumcised compared with those who self-reported being circumcised, were less likely to report unprotected vaginal sex in the past 3 months (60.5% and 82.9%, respectively; $P < 0.001$), using condoms for 50% or fewer of the sex acts occurring in the past 3 months (38.1% and 52.9%, respectively; $P = 0.02$), or having a recent STD in the past 3 months (11.8% and 25.4%, respectively; $P = 0.01$).[85]

Policy considerations regarding reimbursement

Until recently, most U.S. medical societies have adopted relatively neutral stances regarding the practice of routine neonatal male circumcision. In 1999, the American Medical Association stated: "Virtually all current policy statements from specialty societies and medical organizations do not recommend routine neonatal circumcision, and support the provision of accurate and unbiased information to parents to inform their choice."[349] The AAP statement on neonatal male circumcision from that year, reaffirmed in 2005, concluded that "[data demonstrate] potential medical benefits … however, these data are not sufficient to recommend routine neonatal circumcision."[319] Similar neutral statements were issued by the American Academy of Family Physicians[374] and the American Urological Association (AUA).[375] The AUA states that "when circumcision is being discussed with parents and informed consent obtained, medical benefits and risks, and ethnic, cultural, religious, and individual preferences should be considered. The risks and disadvantages of circumcision are encountered early whereas the advantages and benefits are prospective."

However, in the wake of the male circumcision clinical trial results from Africa, the AUA has modified their recommendation to say that, "While the results of studies in African nations may not necessarily be extrapolated to men in the United States at risk for HIV infection, the American Urological Association recommends that circumcision should be presented as an option for health benefits (but)… should not be offered as the only strategy for risk reduction."[376] In 2012, after the AAP's Taskforce on Circumcision reviewed the latest evidence, the AAP updated its stance and concluded that new evidence indicates the preventive health benefits of newborn male circumcision outweigh the risks and that the benefits of newborn male circumcision justify access to this procedure for families who choose it.[320,377]

In a study assessing insurance coverage and reimbursement for routine newborn and adult male circumcision in 2009, investigators reported that private insurance offered broader coverage compared with state Medicaid programs for routine neonatal male circumcision, and both public and private insurance plans offered only sparse coverage for adult male circumcision.[378] In 2009, based on data from HCUP, private insurance and Medicaid were the leading primary payers of hospital stays involving circumcision procedures in male newborns, having paid for 57.4% and 35.3% of such hospital stays, respectively.[318] Based on an analysis of MarketScan claims data from 2010, the average payment for circumcisions covered by private insurance was $285 for neonatal circumcision and $1,885 for postneonatal circumcision.[317] In 2 studies, reimbursement by Medicaid or private insurance for the costs of neonatal male circumcision were associated with higher circumcision rates in hospitals compared to states which disallow Medicaid

reimbursement or where patients did not have private insurance coverage.[314,343] In a study using hospital discharge data from the 2000–2010 Nationwide Inpatient Sample, circumcision incidence decreased significantly from 61.3% in 2000 to 56.9% in 2010 and overall remained higher for newborn hospitalizations covered by private insurance compared with Medicaid (66.9% vs 44.0%).[315] During this same period, the proportion of male newborn hospitalizations with Medicaid coverage increased from 36.0% in 2000 to 50.1% in 2010.[315] In one retrospective study of rates of neonatal and early childhood male circumcision conducted from 1977–2001 limited to 2 hospitals in the Midwest, insurance coverage was not correlated with rates of neonatal male circumcision.[379]

Investigators in Louisiana and Florida, 2 states that no longer cover elective circumcision under Medicaid programs, studied the impact of lack of such coverage on nonneonatal circumcision. In Louisiana, among boys aged ≤ 5 years, the average annual number and expense of neonatal circumcision significantly decreased in 2005, the year during which Medicaid coverage was eliminated for elective circumcision.[380] However, the number of "medically indicated" circumcisions began a steady increase during 2006–2010, and in 2010, expenditures for circumcision reached the same levels as those in 2002, before the loss of Medicaid coverage. Investigators estimated that the percentage of expenditures related to nonneonatal circumcisions would increase from 43% in 2002 to 96% in 2015 of all circumcision spending. In Florida, during 2003–2008, publicly funded circumcision procedures increased more than 6-fold compared with those covered by private insurance; this included a significant increase in the number of nonneonatal circumcisions and a doubling in the cost of nonneonatal circumcisions.[381]

Ethical Considerations

Ethical issues, in addition to medical benefits and risk, must be considered before making recommendations related to male circumcision. A subcommittee of CDC's PHEC composed of CDC staff and external (i.e., non-governmental) consultants from academia and a center for ethics was consulted in October 2009 to review the ethical considerations related to elective male circumcision in the United States. The ethical principles of beneficence (maximizing benefit and minimizing harm, both at the individual and societal level); autonomy (respect for individual values and choices); and justice (the obligation to fairly distribute risks, burdens and benefits, to minimize stigmatization, and to make decisions in a transparent fashion) were considered. Of particular importance were ethical questions related to parental decision-making on behalf of a newborn boy, targeting populations at high risk for HIV, and medical reimbursement for the procedure.

The subcommittee concluded that newborns cannot provide informed consent and so must rely on their parents or caretakers to determine and act in their best interests, raising the issue of autonomy in discussions of circumcision of male newborns. The subcommittee took into account varying opinions about the decision-making process, including that the decision about whether to be circumcised should be made by individuals when they are old enough to make their own informed decisions. It has been pointed out that a man with a foreskin can elect to be circumcised but a man circumcised as a newborn cannot easily reverse that decision.[382,383] Others argue that it is a choice that parents should be able to make on behalf of their male children because of the strong

evidence showing that the procedure is beneficial and the risks are minimal if performed competently.[384-386] Parents are generally given the authority to make decisions, such as vaccination, for their minor children based on their evaluative consideration of the child's best interests. Appropriately, this consideration takes into account social, cultural, and religious perspectives, as well as objective, scientific information about preventive health benefits and risks. Thus, in the opinion of the PHEC subcommittee, both a decision to circumcise and a decision to not circumcise are legitimate decisions, and either decision is an appropriate exercise of parental authority on behalf of a minor child.

There are advantages and disadvantages to performing male circumcision at various stages of life. The procedure is simpler, safer, and less expensive for neonates and infants than for adolescents and adults. However, the newborn has no ability to participate in the decision. Furthermore, although there is evidence of reduced UTIs among male infants who have been circumcised, the benefit of the protective effect against STIs, including HIV, is delayed for many years, not accruing until the child becomes sexually active. It is possible that new, less invasive interventions (e.g., effective topical microbicides or vaccines) may be developed in the intervening years.[385] Delaying male circumcision until adolescence or adulthood obviates concerns about violation of autonomy. However, performing the procedure after sexual debut would result in missed opportunities for prevention of HIV infection.[385,387] In the United States, previous sexual intercourse was reported among 32% of males aged 15 to 17 years and 65% of males aged 18 to 19 years.[388] Uptake of the procedure after the neonatal period is also likely to be lower due to the increased cost, greater likelihood of complications, and other barriers to male circumcision at a later age. The PHEC subcommittee concluded that the disadvantages associated with delaying male circumcision would be ethically compensated to some extent by the respect for the integrity and autonomy of the individual.

The prevalence of HIV infection in the United States is not as high as in sub-Saharan Africa, and most men do not acquire HIV through penile-vaginal sex. Targeting recommendations for adult male circumcision to men at elevated risk for heterosexually acquired HIV infection would be more cost effective than offering routine adult male circumcision. Men may be targeted according to sexual practices or an elevated prevalence of HIV within a geographic region or race/ethnicity group. However, some groups at high risk for HIV infection may also be more likely to be members of certain racial or ethnic groups, thus leading to the perception that men are being targeted because of their ethnic/racial status rather than their risk for HIV infection. Furthermore, recommendations to increase rates of male circumcision in the United States to reduce male acquisition of heterosexually acquired HIV infection may result in stigmatization of uncircumcised men or groups of men who are not routinely circumcised should they choose to not undergo circumcision. Conversely, targeting populations at high risk may raise questions about distributive justice, if persons in groups that are not targeted do not have equal access to the procedure.[385] The PHEC subcommittee concluded that programs incorporating male circumcision should be undertaken with sensitivity to the beliefs and practices of communities affected, and potential participants must be provided with an accurate explanation of potential risks and benefits, as well as assurances of protection of their best interests and informed choice.[384,385,389]

The PHEC subcommittee also noted that lack of health care insurance for some groups and lack of coverage for male circumcision by Medicaid in some states raises issues of distributive justice, and because data demonstrate that male circumcision has the potential to reduce the risk of HIV infection and other adverse health conditions, the procedure should be made available to all who want it.

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APPENDIX

Abbreviations Used in This Report

AIDS	acquired human immunodeficiency syndrome
AAFP	American Academy of Family Physicians
AAP	American Academy of Pediatrics
ACOG	American College of Obstetrics and Gynecology
AE	adverse event
AMA	American Medical Association
aHR	adjusted hazard ratio
aIRR	adjusted incidence rate ratio
aOR	adjusted odds ratio
aPRR	adjusted prevalence rate ratio
aRR	adjusted risk ratio
AT	as treated
AUA	American Urological Association
BV	bacterial vaginosis
CDC	Centers for Disease Control and Prevention
CI	confidence interval
GRADE	Grading of Recommendations Assessment, Development and Evaluation
GUD	genital ulcerative disease
HCUP	Healthcare Cost and Utilization Project
HIV	human immunodeficiency virus
HPV	human papillomavirus
HR	hazard ratio
HR-HPV	high-risk human papilloma virus
HSV	herpes simplex virus
IDU	injection drug user
IRD	incidence rate difference
IRR	incidence rate ratio
ITT	intention-to-treat
MMWR	Morbidity and Mortality Weekly Report
MRSA	methicillin-resistant *Staphylococcus aureus*

MSA	metropolitan statistical area
MSM	men who have sex with men
NATSAL-3	third National Survey of Sexual Attitudes and Lifestyles
NIS	National Inpatient Sample
NHANES	National Health and Nutrition Examination Surveys
NHDS	National Hospital Discharge Survey
PHEC	Public Health Ethics Committee
OR	odds ratio
PMMC	per million male circumcisions
PRR	prevalence rate ratio
QALY	quality-adjusted life-year
RCT	randomized controlled trial
RR	risk ratio
SACEMA	South African Centre for Epidemiological Modelling and Analysis
STD	sexually transmitted disease
STI	sexually transmitted infection
UNAIDS	Joint United Nations Programme on HIV/AIDS
US	United States
UTI	urinary tract infection
VMMC	voluntary male medical circumcision
WHO	World Health Organization

TABLES

Table 1. Reduction in risk of male HIV acquisition and male circumcision in randomized controlled trials

Reference	Setting	Number and age range of HIV-negative participants enrolled	Adverse events related to surgery (%), among HIV-negative participants	Cumulative HIV infection events/cumulative person-years of follow-up (incidence per 100 person-years)		Modified intention-to-treat analysis		Per protocol (as-treated) analysis	
				Intervention	Control	IRR (95% CI)	Efficacy*	IRR (95% CI)	Efficacy*
Auvert†	Orange Farm, South Africa	3,128 men aged 18–24 years	54/1,495 (3.6%)	20/2,354 (0.85)	49/2,339 (2.11)	0.40 (0.24–0.68)	60%	0.24 (0.14–0.44)	76%
Gray§	Rakai, Uganda	4,996 men aged 15–49 years	178/2,328 (8%) (3.6% moderate or severe)	22/3,352 (0.66)	45/3,392 (1.33)	0.49 (0.28–0.84)	51%	0.45 (0.25–0.78)	55%
Bailey¶	Kisumu, Kenya	2,784 men aged 18–24 years	24 (in 23 persons) / 1,334 (1.7%)	22/1,391(2.1)	47/1,393 (4.2)	0.47 (0.28–0.78)	53%	0.40 (0.23–0.68)	60%

IRR = incidence rate ratio

***** Reduction in HIV incidence

† **Source:** Auvert B, Taljaard D, Lagarde E, Sobngwi-Tambekou J, Sitta R, Puren A. Randomized, controlled intervention trial of male circumcision for reduction of HIV infection risk: The ANRS 1265 Trial. *PLoS Med* 2005;2(11):e298.

§ **Source:** Gray RH, Kigozi G, Serwadda D, et al. Male circumcision for HIV prevention in men in Rakai, Uganda: a randomized trial. *Lancet* 2007;369:657–666.

¶ **Source:** Bailey RC, Moses S, Parker CB, et al. Male circumcision for HIV prevention in young men in Kisumu, Kenya: a randomized controlled trial. *Lancet* 2007;369:643–665.

Table 2. Summary of evidence on the risk of STI associated with male circumcision status in heterosexual populations

Etiology	Population	Type of study	Location, duration of follow-up, STI outcome measure	Result	Measure of association
HSV-2	Men	RCTs	Uganda (24-month follow-up; HSV-2 incidence)	Significant association	aHR 0.72, 95% CI 0.56–0.92[8]
			South Africa (21-month follow-up; HSV-2 seroincidence)	No significant association in intention to treat analysis (ITT)	IRR 0.66, 95% CI 0.39–1.12[9]
				Significant association in as-treated (AT) analysis	IRR 0.55, 95% CI 0.32–0.94[9]
			Kenya (24-month follow-up; HSV-2 incidence)	No significant association	RR 0.94, 95% CI 0.70–1.25[7]
			Kenya (72-month post-trial follow-up; HSV-2 incidence)	No significant association	HR 0.89, 95% CI 0.73–1.09[214]
		Observational studies		No significant association in meta-analysis	Summary RR 0.88, 95% CI 0.77–1.01[207]
	Women (female partners of HSV-2–positive males)	RCTs	Kenya (24-month follow-up; HSV-2 incidence)	No significant association	IRR 0.85, 95% CI 0.44–1.67[219]
HR HPV—**HR-HPV prevalence**	Men	RCTs	Uganda (24-month follow-up)	Significant association among men who were HIV-negative and HSV-2–negative at baseline	aRR 0.65, 95% CI 0.46–0.90[8]
			Uganda (24-month follow-up)	Significant association among HIV-positive men	RR 0.77, 95% CI 0.62–0.97[10]
			Uganda (24-month follow-up; prevalence of multiple HR-HPV genotypes)	Significant association	RR 0.53, 95% CI 0.33–0.83[10]
			South Africa (21-month follow-up; prevalence of urethral HR-HPV)	Significant association (ITT analysis)	aPRR 0.68, 95% CI 0.52–0.89[11]
			South Africa (21-month follow-up; prevalence of urethral HR-HPV)	Significant association (AT analysis)	aPRR 0.62, 95% CI 0.47–0.80[11]
		Observational studies	Britain (prevalence of HR-HPV in urine)	Significant association	aOR 0.14, 95% CI 0.05–0.40[230]
			Brazil, Mexico, and U.S. (multinational study)	No significant association	aPR 0.95, 95% CI 0.87–1.03[231]
			Barcelona, Spain (prevalence of single HR-HPV = HPV-51)	Significant association	OR 0.2, 95% CI 0.1–0.9[205]
	Women (female sexual partners of males enrolled in study)	RCTs	Uganda (24-month follow-up; prevalence of HR-HPV DNA viral load)	Significant association	PRR 0.78, 95% CI 0.65–0.94[17]

Etiology	Population	Type of study	Location, duration of follow-up, STI outcome measure	Result	Measure of association
HR-HPV Incidence	Men	RCTs	Uganda (24-month follow-up; incidence of HR-HPV genotypes overall)	No significant association in HIV-positive men	RR 0.74, 95% CI 0.54–1.01[12]
			Uganda (24-month follow-up; incidence of single HR-HPV genotypes)	No significant association in HIV-positive men	RR 1.00, 95% CI 0.65–1.53[12]
			Uganda (24-month follow-up; incidence of multiple HR-HPV genotypes in HIV-positive men)	Significant association	RR 0.4, 95% CI 0.19–0.84[12]
			Uganda (24-month follow-up; incidence of HR-HPV genotypes overall in HIV-negative men)	Significant association	RR 0.67, 95% CI 0.51–0.89[12]
			Uganda (24-month follow-up; incidence of multiple HR-HPV genotypes in HIV-negative men)	Significant association	RR 0.45, 95% CI 0.28–0.73[12]
			Uganda (24-month follow-up; incidence of single HR-HPV genotypes in HIV-negative men)	No significant association	RR 0.89, 95% CI 0.60–1.30[12]
			Kenya (6-month follow-up; incidence of a single HR-HPV genotype [HPV-16])	Significant association in men overall	HR 0.32, 95% CI 0.20–0.49[13]
			Kenya (6-month follow-up; incidence of a single HR-HPV genotype [HPV-18])	Significant association in men overall	HR 0.34, 95% CI 0.21–0.54[13]
		Observational studies	Australia (incidence of single HR-HPV genotype: HPV-16)	Significant association	HR 0.43, 95% CI 0.21–0.8[96]
			Seattle, Washington (incidence of clinically relevant HPV types [HR-HPV genotypes + types 6 and 11])	No significant association	HR 0.9, 95% CI 0.7–1.2[234]
HR-HPV clearance	Men	RCTs	Kenya (6-month follow-up; persistence of a single HR-HPV genotype [HPV-16] with high viral load)	Significant association in men overall	RR 0.36, 95% CI 0.18–0.72[13]
			Kenya (6-month follow-up; persistence of a single HR-HPV genotype [HPV-18] with high viral load)	Significant association in men overall	RR 0.34, 95% CI 0.13–0.86[13]
		Longitudinal cohort studies	Southern Florida, U.S.; Cuernavaca, Mexico; Sao Paulo, Brazil (multinational study)	Significant association (higher clearance of single HR-HPV genotype, HPV-33)	$P = 0.02$[233]
				Significant association (lower clearance of single HR-HPV genotype, HPV-16)	$P < 0.001$[233]
				Significant association (lower clearance of single HR-HPV genotype, HPV-51)	$P = 0.02$[233]
	Women (female sexual partners of males enrolled in study)	RCTs	Uganda (24-month follow-up; prevalence of HR-HPV DNA viral load for incident HR-HPV infections)	Significant association	PRR 0.66, 95% CI 0.50–0.87[17]
			Uganda (24-month follow-up; prevalence of HR-HPV DNA viral load for persistent HR-HPV infections)	No significant association	PRR 1.02, 95% CI 0.83–1.24[17]

Etiology	Population	Type of study	Location, duration of follow-up, STI outcome measure	Result	Measure of association
Trichomoniasis (*T. vaginalis)*	Men	RCTs	Kenya (24-month follow-up; *T. vaginalis* incidence)	No significant association	IRR 0.77, 95% CI 0.44–1.36[208]
			South Africa (21-month follow-up; *T. vaginalis* prevalence)	No significant association in ITT analysis	aOR 0.53, 95% CI 0.32–1.02[14]
				Significant association in AT analysis	aOR 0.47, 95% CI 0.25–0.92[14]
	Women (female sexual partners of males enrolled in study)	RCT	Uganda (12-month follow-up; T. vaginalis prevalence)	Significant association	aPRR 0.55, 95% CI 0.34–0.89[16]
Syphilis	Men	RCTs	Uganda (circumcision RCT; 24-month follow-up; syphilis incidence)	No significant association	aHR 1.10, 95% CI 0.75–1.65[8]
			Kenya (circumcision RCT; 24-month follow-up; syphilis incidence)	No significant association (Note: only 13 men developed syphilis [6 uncircumcised men, 7 circumcised men]; numbers too small to draw definitive conclusion about association between circumcision and syphilis	RR 1.23, 95% CI 0.77–1.75[7]
		Prospective Cohort Study	Kenya and Uganda (HIV preexposure prophylaxis RCT; syphilis incidence):	Significant association, men overall	aHR 0.58, 95% CI 0.37–0.9[20]
				Significant association, HIV-positive men	aHR 0.38, 95% CI 0.18–0.81[20]
				No significant association, HIV-negative men	aHR 0.64, 95% CI 0.36–1.11[20]
		Observational studies (meta-analysis)		Significant association	Summary RR 0.69, 95% CI 0.50–0.94[207]
	Women (female HIV serodiscordant sexual partners of males enrolled in study)	Prospective Cohort Study	Kenya and Uganda (HIV preexposure prophylaxis RCT; syphilis incidence)	Significant association, women overall	aHR 0.41, 95% CI 0.25–0.69[20]
				Significant association, HIV-positive women	aHR 0.52, 95% CI 0.27–0.97[20]
				Significant association, HIV-negative women	aHR 0.25, 95% CI 0.08–0.76[20]

Etiology	Population	Type of study	Location, duration of follow-up, STI outcome measure	Result	Measure of association
Chlamydial infection	Men	RCTs	Kenya (24-month follow-up; chlamydia incidence)	No significant association	IRR 0.87, 95% CI 0.65–1.16[208]
			South Africa (21-month follow-up; chlamydia prevalence)	Borderline significant association in the ITT analysis	aOR 0.56, 95% CI 0.32–1.00[14]
				No significant association in the AT analysis	aOR 0.75, 95% CI 0.42–1.32[14]
			Uganda (24-month follow-up) (prevalence of self-reported genital discharge or dysuria)	No significant association	PRR 0.84, 95% CI 0.63–1.11[6] PRR 0.97, 95% CI 0.77–1.21[6]
		Cross-sectional studies	Great Britain, national British survey (*C. trachomatis* prevalence in urine samples)	Significant association	aOR 0.09, 95% CI 0.01–0.72[230]
			Great Britain, national British survey (self-report of previous history of *C. trachomatis* infection)	No significant association	aOR 1.23, 95% CI 0.81–1.86[230]
	Women (female sexual partners of males enrolled in study)	RCTs	Uganda (24-month follow-up; prevalence of self-reported genital discharge or dysuria)	No significant association	PRR 0.99, 95% CI 0.89–1.12[16] PRR 0.97, 95% CI 0.75–1.21[16]
		Cross-sectional studies		Mixed results:	
			Thailand, Philippines, Brazil, Colombia, Spain (multinational case-control study, *C. trachomatis* seroprevalence)	Significant association	OR 0.18, 95% CI 0.05–0.58[242]
			Uganda, Zimbabwe, Thailand (multinational prospective cohort study; *C. trachomatis* incidence)	No significant association	HR 1.25, 95% CI 0.96–1.63[243]
Gonorrhea (*N. gonorrhea*)	Men	RCTs	Kenya (24-month follow-up, *N. gonorrhea* incidence)	No significant association	IRR 0.95, 95% CI 0.68–1.34[208]
			South Africa (21-month follow-up, *N. gonorrhea* prevalence)	No significant association in ITT analysis	aOR 0.94, 95% CI 0.69–1.29[14]
				No significant association in AT analysis	aOR 1.02, 95% CI 0.74–1.40[14]
			Uganda (24-month follow-up; prevalence of self-reported genital discharge or dysuria)	No significant association	PRR 0.84, 95% CI 0.63–1.11[6] PRR 0.97, 95% CI 0.77–1.21[6]
	Women (female sexual partners of males enrolled in study)	RCTs	Uganda (24-month follow-up; prevalence of self-reported genital discharge or dysuria)	No significant association	PRR 0.99, 95% CI 0.89–1.12[16] PRR 0.97, 95% CI 0.75–1.21[16]
Chancroid (*H. dureyi*)	Men	RCTs		Not assessed	
		Observational studies		Lower risk of chancroid in 6 out of 7 studies (mostly assessed by clinical exam)	No summary RR due to heterogeneity; Individual study RRs: 0.12 to 1.11[207]

Etiology	Population	Type of study	Location, duration of follow-up, STI outcome measure	Result	Measure of association
Mycoplasma genitalium (M. genitalium)	Men	RCT	Kenya (6-month follow-up; *M. genitalium* prevalence)	Significant association	aOR 0.54, 95% CI 0.29–0.99[15]
		Observational study	Great Britain, national British study	No significant association (*M. genitalium* prevalence)—crude	OR 1.90, 95% CI 0.62–5.87[230]
				No significant association (*M. genitalium* prevalence)—adjusted	aOR 0.61, 95% CI 0.18–2.09[230]
	Women (female sexual partners of males enrolled in study)	RCT	Uganda (24-month follow-up; *M. genitalium* prevalence)	No significant association in ITT analysis	aPRR 0.93, 95% CI 0.43–2.03[241]
				No significant association in AT analysis	aPRR 1.00, 95% CI 0.46–2.18[241]
Syndromes					
GUD	Men	RCTs	Uganda (24-month follow-up; GUD prevalence)	Significant association	PRR 0.53, 95% CI 0.43–0.64[6]
			Kenya (24-month follow-up; GUD incidence)	Significant association	RR 0.52, 95% CI 0.37–0.73[7]
	Women (female sexual partners of males enrolled in study)	RCT	Uganda (24-month follow-up; GUD prevalence)	Significant association	aPRR 0.78, 95% CI 0.61–0.99[16]
BV	Women (female sexual partners of males enrolled in study)		Uganda (12-month follow-up)	Significant association with any BV (prevalence)	aPRR 0.60, 95% CI 0.38–0.94[16]
				Significant association with severe BV (prevalence)	PRR 0.39, 95% CI 0.24–0.64[16]
Genital discharge	Men	RCT	Uganda (24-month follow-up; genital discharge prevalence)	No significant association	PRR 0.84, 95% CI 0.63–1.11[6]
	Women (female sexual partners of males enrolled in study)	RCT	Uganda (24-month follow-up; genital discharge prevalence)	No significant association	PRR 0.99, 95% CI 0.89–1.12[16]
Dysuria	Men	RCT	Uganda (24-month follow-up; dysuria prevalence)	No significant association	PRR 0.97, 95% CI 0.77–1.21[6]
	Women (female sexual partners of males enrolled in study)	RCT	Uganda (24-month follow-up; dysuria prevalence)	No significant association	PRR 0.97, 95% CI 0.75–1.21[16§§]

aHR = adjusted hazard ratio; aOR = adjusted odds ratio; aPRR = adjusted prevalence rate ratio; aRR = adjusted risk ratio; AT = as-treated; BV = bacterial vaginosis; CI = confidence interval; GUD = genital ulcer disease; HPV = human papillomavirus; analysis; HR = hazard ratio; HR-HPV = high-risk human papillomavirus genotype; HSV = herpes simplex virus; IRR = incidence rate ratio; ITT = intention-to-treat; OR = odds ratio; *P* = P-value PRR = prevalence rate ratio; RCT = randomized controlled trial; RR = risk ratio; STI = sexually transmitted infection