Public health initiative: male circumcision for prevention of HIV in sub-Saharan African countries

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Public Health Initiative:

Male Circumcision for Prevention of HIV in sub-Saharan African Countries

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Dedication

I would like to thank my family, classmates and friends…..it is finally over. No more complaining from me. Thank you for letting me vent my frustrations the last couple years.
Acknowledgements

Thank you, Professor Peterson, for your time and effort you have invested in this paper. I have always appreciated your endless editing and suggestions.

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Introduction

Globally there are an estimated 39.5 million people infected with Human Immunodeficiency Virus (HIV). While there has been significant coverage of HIV in the lay press and medical community, there were still 4.3 million people newly infected with HIV throughout the world in 2006. There were also 2.9 million deaths directly attributed to HIV and the Acquired Immunodeficiency Syndrome (AIDS) (UNAIDS, 2006b). In recent years, numerous prevention programs and increased access to medical treatment comprise some of the efforts to combat this epidemic. While much has been done in technologically advanced countries, slowing or stopping both the spread and mortality associated with the disease has been elusive in certain parts of the world.

The global HIV incidence rate is believed to have peaked at the end of last century. HIV prevalence appears to have also reached a plateau, though this can be misleading; due to both the decrease in HIV incidence and a corresponding rise in AIDS related mortality (UNAIDS, 2006b). Due to population growth and effective antiretroviral therapy, the total number of people living with HIV and AIDS continues to rise (UNAIDS, 2006a). However, HIV rates vary greatly in different regions of the world. Sub-Saharan Africa continues to have ownership of the largest burden of the HIV/AIDS epidemic. Sub-Saharan Africa accounts for a staggering 24.7 million people infected with HIV (approximately two-thirds of the global total), while accounting for about 10% of the world’s population (UNAIDS, 2006b; University of California San Francisco, Center for HIV Information, 2007). Of the total 2.9 million HIV/AIDS deaths in 2006, almost 75% (2,175,000 deaths) occurred in sub-Saharan Africa. In 2006, there were more new HIV infections in sub-Saharan Africa than all other regions of the world combined (UNAIDS, 2006b).
Background – HIV and AIDS

Many myths and rumors still surround the transmission of HIV. While homosexual intercourse (men having sex with men) and IV drug use are two relevant methods of transmission, unprotected vaginal intercourse accounts for the vast majority of HIV infections globally (UNAIDS, 2006a; Hansasuta & Rowland-Jones, 2001). The most widely accepted model for transmission of HIV is based on infection of the genital tract of rhesus monkeys with simian immunodeficiency virus (SIV), the monkey-equivalent of HIV (Spira et al., 1996; Miller, 1998). Once monkeys become inoculated with SIV intravaginally, the virus targets Langerhans’ cells in the vaginal mucosa. The infected Langerhans’ cells then fuse with nearby CD4 T cells and migrate to deeper tissues. In just a few days after introduction of the virus, SIV is already disseminated systemically via the lymph nodes (Szabo & Short, 2000). The same sequence of cellular events likely occurs with SIV infection into the penile urethra of male monkeys (Miller).

In lymph nodes, Langerhans’ cells come into contact with T cells, which then generate an immune response to the antigen (Hansasuta & Rowland-Jones, 2001). CCR5, a chemokine receptor, acts as a co-receptor for the HIV virus. Upon activation, some T cells then secrete chemokines, which bind to CCR5 and block infection with HIV by competing with the virus (Abbas & Lichtman, 2003). DC-SIGN (dendritic cell-specific intercellular adhesion molecule-3-grabbing nonintegrin), another HIV-specific co-receptor, has also been described to be co-expressed with CD4+ and CCR5 on dendritic cells in the foreskin (Atashili, 2006). When bound to DC-SIGN, the virus is able to live outside the cell for several days and thus able to survive the trip to T cell rich areas of lymph nodes. Current thinking proposes that DC-SIGN then plays its role in activating the waiting T cell population. This mechanism provides HIV with a reservoir of highly susceptible T cells where it can preferentially replicate and then gain
access to systemic lymphoid tissue (Hansasuta & Rowland-Jones). Once HIV has become established in lymphoid tissues, there is extensive viral replication. This is reflected in the very high peak plasma viral load that occurs 6-15 days after onset of clinical symptoms (Daar, Moudgil, Meyer, & Ho, 1991; Clark et al., 1991). Initial symptoms often present as an acute antiretroviral syndrome and usually appear days to weeks after primary HIV infection (Kahn & Walker, 1998). This acute antiretroviral syndrome manifests most often nonspecifically with fever, and any/all of the following: headache, fatigue, arthralgias, myalgias, vomiting, diarrhea, cutaneous rash, inguinal lymphadenopathy, and oral candidiasis/thrush. These clinical symptoms last from a few days to weeks, although typically, the duration is less than 14 days (Vanhems et al., 1999). A patient presenting with these nonspecific symptoms poses a great challenge to health care workers when determining the presence of symptomatic illness due to an acute HIV infection. High viral loads during the acute antiretroviral syndrome make the host most infectious at this time (Quinn et al., 2000; Jacquez, Koopman, Simon, & Longini, 1994). In fact, the strongest predictor of human HIV infectivity is the viral load in the plasma (Kovacs et al., 2001). Statistical models propose the risk of HIV transmission is increased 100-1000 times during this primary HIV infection (Jacquez, Koopman, Simon, & Longini).

In adult men, more than 90% of HIV infections are acquired through vaginal intercourse. (Bailey, Plummer, & Moses, 2001) In sub-Saharan Africa, heterosexual intercourse is the predominant mode of HIV transmission (Weiss, Quigley, & Hayes, 2000). Therefore, most men who are HIV positive have acquired the virus through the penis. Researchers have investigated how HIV enters the penis, and what makes a man who is uncircumcised more susceptible to HIV acquisition. A keratinized, stratified squamous epithelium covers the penile shaft and outer surface of the foreskin. The keratinized skin provides a protective barrier against HIV
transmission. During heterosexual intercourse, the foreskin is pulled back down the shaft of the penis, allowing the entire inner surface of the foreskin to be exposed to vaginal secretions, providing a large surface area for HIV transmission to occur (Szabo & Short, 2000). The inner mucosal surface of the foreskin is not keratinized (Barreto, Caballero, & Cubilla, 1997), therefore lacking the inherent protective barrier. The inner foreskin is also rich in Langerhans’ cells (Hussain & Lehner, 1995), which as mentioned earlier, possess HIV-specific receptors on their surfaces and are likely to be the initial point of entry for HIV into the penis of an uncircumcised man (Szabo & Short).
Background - Sub-Saharan African Countries

As stated earlier, sub-Saharan Africa is the global epicenter of the HIV and AIDS epidemic. In recent years, only one country in sub-Saharan Africa has shown evidence of a decline in adult HIV prevalence (UNAIDS, 2006a). While trends in HIV prevalence in some individual nations of sub-Saharan Africa appear stable, it is likely due to new infections of HIV nearly equaling the continually high rate of people dying of AIDS in the same region (UNAIDS, 2006b). In the country of South Africa, HIV data gathered in the extensive prenatal clinic surveillance system suggest that HIV prevalence is still increasing (UNAIDS, 2006b). Furthermore, the 2006 Global AIDS Epidemic Update states that prevalence of HIV among women attending prenatal clinics in South Africa has increased 35% in just six years (UNAIDS, 2006b). In the country of South Africa alone, approximately 5.5 million people were living with HIV in 2005 (UNAIDS, 2006a).

It is also evident that increasing numbers of South Africans are now dying from AIDS. South Africa’s latest official mortality data demonstrate that total deaths from all causes have increased by 79% from 1997 to 2004 (Statistics South Africa, 2006). For women ages 25 to 34, death rates from natural causes has increased by 500% from 1997 to 2004, and the death rates of males ages 30 to 44 has doubled in the same timeframe. A large proportion of the rising trend in death rates is directly attributable to HIV/AIDS (Anderson & Phillips, 2006).

In the face of these grim statistics, a national survey of South Africans found that many believe they are at no risk of acquiring HIV infection. Of the participants taking an HIV test for the first time in the national survey, approximately 13% were found to be HIV-positive. Until that time, most participants had declined HIV testing. The same survey found half of the HIV positive people had reported they were at no risk of acquiring HIV (Shisana, 2005).
This means that approximately two million South Africans living with HIV are unaware of their HIV-positive status and believe they face no risk of HIV infection. This unawareness and a lack of sufficient preventative measures have led to continued unavoidable transmission of HIV. Since HIV testing in South Africa is rarely performed, HIV-positive South Africans only become aware of their status once symptomatic illness is present (UNAIDS, 2006b). So, the non-specific symptoms experienced during the primary HIV infection present a very arduous task in diagnosing HIV and otherwise symptoms may not be present for years (as HIV progresses to AIDS) (Hansasuta & Rowland-Jones, 2001).

Kenya is another sub-Saharan African country in East Africa where 1.3 million people are currently living with HIV/AIDS (UNAIDS, 2006b). There still exists a serious epidemic in this country even with a reduction in HIV prevalence. National adult HIV prevalence fell from 10% in the late 1990s to about 6% in 2005 (Ministry of Health Kenya, 2005; UNAIDS, 2006a). These numbers are due mostly to the reduction in prevalence of HIV infections in pregnant women (Cheluget, Marum, & Stover, 2006). There has been a 25% reduction in HIV prevalence in pregnant Kenyan women (UNAIDS, 2006b).

Uganda is very similar to Kenya when discussing its own HIV/AIDS epidemic. In 2005, approximately one million people were living with HIV in Uganda (UNAIDS, 2006b). Uganda also shows a decrease in prevalence of HIV among pregnant women, thus stabilizing the epidemic overall in this country. An increase in AIDS deaths also contributes to this stabilization (Kirungi et al., 2006). The national adult HIV prevalence was 6.7% in 2005 (Ministry of Health Uganda & ORC Macro, 2006). Recent data suggests there has been an increase in HIV infections in rural Uganda. Prevalence in adult men grew from just 5.6% in 2000 to 6.5% in 2004 (Shafer, L. A., Biraro, S., Kamali, A., Grosskurth, H., Kirungi, W.,
Madraa, E., et al., 2006). National surveys conducted repeatedly during the years from 1992 to 2005 show a reduction in high risk sexual behavior in Kenya in both young men and women. However, there was found to be an increase in this behavior in the young women of Uganda (UNAIDS, 2006b). While there is a reduction in HIV prevalence in Kenya and Uganda, these countries still possess certain population groups that remain high risk for acquiring HIV. This will be discussed at length later in this paper.

Data show that patients who are both diagnosed with HIV and treated very early in the disease process are able to recover or retain HIV-specific cell counts needed to maintain an effective immune response (Oxenius et al., 2000; Rosenberg et al., 1997). However, treatment for HIV and AIDS in sub-Saharan Africa is also less available than in most parts of the world (UNAIDS, 2006b). Current research indicates early antiretroviral treatment given during the primary HIV infection provides the best chance at preserving immune function (Hansasuta & Rowland-Jones, 2001). Antiretroviral therapy in sub-Saharan Africa is available to less than one quarter of those suffering from the disease. While work has been done to increase access to treatment in this region, the need for antiretroviral therapy is still dramatically overwhelming resources (UNAIDS, 2006b). As recently as 2002, the South African government policy regarding HIV consisted entirely of providing condoms, safe-sex counseling, and voluntary HIV testing after counseling. Thus, no antiretroviral treatment was provided to the millions who were already infected. Beginning in 2004, a small amount of antiretroviral treatment became available, only at specific government health centers (Department of Health, Republic of South Africa, 2004). The number of CD4+ T cells in a human’s blood gradually declines when HIV goes untreated. When the CD4+ count falls below 200/mm³, a person becomes susceptible to
infections and other diseases characteristic of AIDS, the end stage of HIV disease (National Institute of Allergy and Infectious Diseases, 2005).

In every region across the globe, more adult women than men have HIV. In sub-Saharan Africa, there are 14 HIV infected women for every 10 infected men. Spanning all age groups, 59% of sub-Saharan people living with HIV in 2006 were women (UNAIDS, 2006b). Among adults, the age cohort of 15 to 24 years accounted for 40% of new HIV infections in 2006. Due to this statistic, and the knowledge that HIV is spread most commonly through sexual intercourse, one sees the need to further investigate sexual behavior trends of this group of people. In 2001, the United Nation’s Declaration of Commitment on HIV/AIDS outlined a goal of reducing HIV prevalence by 25% in young people in the most-affected countries (like South Africa) by 2005. Outcomes unfortunately revealed a continual increase in HIV infection levels in the young people of three sub-Saharan countries (including South Africa) (UNAIDS, 2006b).

The 2006 AIDS Epidemic Update provides the most current and comprehensive picture regarding the demographics and other factors affecting the spread of HIV. This report serves to highlight the need for targeted prevention strategies in areas of the world where the arena of HIV prevention has yet to make an impact on HIV transmission. There exists certain population groups affected by HIV and AIDS which posses certain attributes making themselves and their behavior more high risk. In sub-Saharan Africa, one group of special concern is uncircumcised heterosexual men. While male circumcision is regularly practiced in some parts of Africa, many ethnic groups in eastern and southern Africa do not traditionally practice male circumcision (Bongaarts, Reining, Way, & Conant, 1989; Moses et al., 1990). Most of Uganda, western Kenya, and South Africa are included in this area of non-circumcision (Weiss, Quigley, & Hayes, 2000).
Cochrane Review: Circumcision in Reducing HIV Infection in Men

The Cochrane Review assessed the likelihood that use of circumcision, as an intervention, would reduce transmission of HIV infection in men. In total, 35 observational studies were included in this review. Twenty-five of the studies were cross-sectional surveys performed at a single time point and participants were tested for HIV at the same time risk factors were obtained. There were five cohort incidence studies which followed a group known to be HIV-negative over a period of time and identified new cases of HIV by repeat testing. Four studies were case-control designs in which investigators compared the prevalence of risk factors in two groups of subjects known to be HIV-negative and positive. Sixteen of the studies were conducted in general population settings and 19 were conducted in high-risk settings (where HIV infection rate is either known to be high or conditions exist in this population which are conducive to the spread of HIV). It is also important to mention, in all of these observational studies, multiple risk factors for HIV infection were investigated but without a specific focus on the role of circumcision. Each study’s results were given odds ratios, which allowed the comparison of results between the different types of observational studies.

Of the studies conducted in general population settings, one cohort study, 14 cross-sectional studies and one case-control study were identified. The single cohort study, with 5,516 subjects, indicated a decreased risk of HIV infection with circumcision. The case-control study (containing 51 subjects) found no significant decrease in HIV transmission in circumcised men. Of the 14 cross-sectional studies, eight studies’ findings supported a decreased risk in HIV transmission with circumcision while six studies pointed towards an increased risk. Of the eight which supported the benefits of circumcision, four had statistically significant results.
Four cohort studies, 12 cross-sectional studies and three case-control studies were conducted within high-risk population groups. Two of the four cohort studies had statistically significant results and all four supported a decreased risk of HIV infection with circumcision. Results from eleven of the twelve cross-sectional studies showed a decreased risk of HIV infection with circumcision with eight of the studies having statistically significant results. The three case-control studies performed within the high-risk settings supported the protective effect of circumcision on HIV infection and two of the studies had statistically significant results. This led to the three recent randomized, controlled intervention trials.
The ANRS 1265 Trial was conducted within a semi-urban region near the city of Johannesburg, South Africa to test the hypothesis that male circumcision may provide protection against HIV infection in men. Participants were informed that the impact of male circumcision on acquisition of HIV and other sexually transmitted infections is unknown. Intervention group participants were offered circumcision within one week, while the control group was asked to wait until the end of the study before being circumcised.

Three follow-up visits took place at the end of months 3, 12, and 21. At each of these visits, including the first screening visit, all participants answered a face-to-face questionnaire, provided a blood sample, had a genital exam, and underwent an individual sexually transmitted infections and prevention counseling session. The participants were also encouraged to attend voluntary counseling and testing (VCT) in a public clinic or in a center funded by the study. An ELISA screen and two ELISA confirmatory tests were used when testing for HIV. Samples that were positive on all three ELISAs were regarded as “positive” and all others as “negative.” For each period of follow-up, the following sexual behavior covariates were considered: any at-risk behavior (at least one sexual contact without use of a condom), having a spousal partner, the number of non-spousal partners, the number of sexual contacts, and having at least one relationship with only one sexual contact. Also, health-seeking behavior was defined as having at least one visit to a clinic for a genital problem during the twelve months prior to the visit. Investigators also analyzed the impact of a six-week period of abstinence following circumcision, in order for healing to occur.

A total of 3,274 men volunteered to participate in this study, with 146 being found HIV positive at randomization (0.045%). During the first 14 months of the trial, 20 of the
intervention participants and 49 of the control participants acquired HIV. This corresponds to incidence rates of 0.85 per 100 person years (0.55 – 1.32) in the intervention group and 2.1 per 100 person years (1.6 – 2.8) in the control group with 95% CI. The rate ratio for HIV infection for the intervention group compared with the control group was 0.40 (0.24 – 0.68), \( p = 0.00059 \). This rate ratio corresponds to a protection by circumcision of 60% against HIV infection. The trial was stopped prematurely (mean follow-up of 18.1 months) before all subjects had completed the trial (it was originally scheduled to last 21 months) because the investigators felt it unethical to continue based on the significant risk reduction associated with circumcision.

Forty-two days (exactly six weeks) was the median interval between circumcision and first sexual contact reported by the sexually experienced participants of the intervention. When reducing the M1 – M3 period by 42 days in the intervention group, the rate ratio was 0.43 (0.26 – 0.73), \( p = 0.0016 \), a value close to the rate ratio obtained in the intention-to-treat analysis which was 0.40 (0.24 – 0.68), \( p = 0.00059 \). The authors analyzed this forty-two day period for changes in the rate ratio of obtaining HIV. The rate ratio changed from 0.38 to 0.43. This minute change illustrates that the six-week period of abstinence plays only a minor role, if any in explaining the effects of circumcision found in this study.

Of the sexual behavior factors analyzed, the high-risk or riskier behaviors were higher in the intervention group than in the control group. Yet, the intervention group still had a lower number of clinic visits for genital problems in the first twelve months of follow-up (4.7% versus 7.2% in the control group). These results illustrate the protective effect of circumcision cannot be attributed to the change in sexual behavior because high-risk behaviors were found to be higher in the intervention group (those who were circumcised). In addition, when adjusting for
potential confounders, like different sexual behaviors, there was a very minimal effect on protection that circumcision provides against HIV acquisition.
Kisumu, Kenya: Randomized Controlled Intervention Trial

A second randomized, controlled, intervention trial was conducted in Kisumu, the capital city of western Kenya. Kisumu is home to many inhabitants who identify themselves as Luo, an ethnic group that does not traditionally practice circumcision. About 10% of Luo adult men are circumcised (Buve et al., 2000). As with the South African trial, participants who met the Kenyan trial criteria were randomly assigned to either the intervention (circumcision) or control (delayed circumcision) group. Participants assigned to the intervention group were scheduled for circumcision that day or shortly thereafter. Participants in the control group were asked to remain uncircumcised until the end of the trial, when they would be offered the chance to be circumcised if they wished.

Study participants received HIV counseling and testing, genital examinations, and were interviewed about sexual activity at months 1, 3, 6, 12, 18, and 24. (Two rapid HIV tests were performed, if double positive or discordant results, blood was drawn and sent for two ELISA tests). More thorough follow-up also occurred during the visits at months 6, 12, 18, and 24 when blood and urine samples were collected for STD testing. Also at these visits, the risk of HIV infection was assessed by examining sexual function and behavioral factors through an extensive questionnaire.

After recruitment and randomization, 2,784 men, ages 18 to 24 years entered the trial with 98% of these men identifying themselves as Luo. The median length of follow-up in this study was 24 months. During the study, 22 participants in the intervention group and 47 participants in the control group were found to be HIV positive. Once final calculations and data adjustment for error was completed, the 2-year HIV incidence in the intervention group was 1.9% (95% CI 1.0 – 2.7) versus 4.1% (95% CI 2.9 – 5.3) in the control group (p = 0.0031). This
corresponds to a risk ratio of 0.41 (0.24 – 0.70) or a reduction in the risk of acquiring HIV by 59% (30 – 76). Investigators also adjusted the data for individuals who did not adhere to the randomization assignments, the as-treated analysis, and found the risk ratio of circumcision to be 0.45 (95% CI 0.27 – 0.76). When this adjustment was combined to adjustments made for exclusion of the four subjects previously discussed, the risk ratio of circumcision was found to be 0.40 (0.23 – 0.68). This value is equivalent to a 60% (32 – 77) protective effect of circumcision against HIV prevention. The Kenyan investigators state the 60% protective effect most likely represents a more accurate estimate of treatment effect; this value compares circumcised HIV-negative men to uncircumcised HIV-negative men after trial randomization.

The Kenyan investigators chose five behavioral factors to analyze changes in HIV risk behavior in the intervention group. Overall, participants in the control group (uncircumcised men), practiced safer sexual behaviors. Researchers found a larger proportion of circumcised men reporting riskier sexual behavior, though the differences were found to be small and not statistically significant.
Rakai, Uganda: Randomized Controlled Intervention Trial

This study recruited 4,996 men ages 15 to 49 years in the Rakai district of Uganda. Like the South African and Kenyan trials, study participants agreed to HIV testing and health counseling upon enrollment in the study. The men were then randomly assigned to the intervention group (circumcision) or to the control group (those offered circumcision at the end of the study). All participants in the trial returned for recheck visits at 1, 6, 12, and 24 months. At each follow-up visit, participants answered questions about sexual risk behaviors, potential symptoms of STDs, any illnesses or hospitalizations, and received genital exams. Blood and urine samples and two penile swabs were collected for HIV, HPV and other STD testing. Each visit also included HIV and general health counseling.

The Ugandan trial was halted prior to the predetermined study time due to the efficacious results (statistically significant \( \alpha = 0.05 \)) seen with preliminary analyses of the data. Since the trial ended early (44% of men in both groups completed 24 months), the analysis for the entire 24 months is heavily weighted with the data collected during the first 12 months of the study. HIV incidence was estimated per 100 person-years and time from enrollment was accumulated up to the 24-month follow-up visit. The data presented is based on what was collected up to the end of the trial and represents 73% of total anticipated person time.

In the modified intention-to-treat analysis, the HIV incidence for 24 months was 0.66 cases per 100 person-years in the circumcised group and 1.33 cases per 100 person-years in the uncircumcised group. This data was adjusted to reflect 24 months of follow-up time. These values equate to an estimated intervention efficacy of 51% (95% CI 16 –72, \( p = 0.006 \)). When assigning person-time according to the actual circumcision status of the men, an incidence of 0.61 cases per 100 person-years in the intervention group and 1.35 cases per 100 person-years on
the control group were found. These values reflect an as-treated efficacy of 55% (95% CI 22 – 75, p = 0.002).

Ugandan researchers found the rates of HIV acquisition were lower among circumcised men in all sociodemographic, risk factor and STD symptom characteristics examined. It was found that circumcision reduced HIV acquisition irrespective of studied behavioral characteristics (non-marital partners, condom use, and consumption of alcohol before sexual intercourse) among the sexually active men.

Investigators also wished to assess behavioral disinhibition after circumcision, so sexual risk factors were assessed at each follow-up visit. Consistent condom use was slightly higher in the circumcised men at the first six month follow-up visit. Number of sexual partners, non-marital relationships, and condom use were very similar between the intervention and control groups at the 12 and 24 month follow-up visits. Researchers state, “There is no consistent or substantial evidence of behavioral disinhibition after circumcision in the study population (Gray et al., 2007).”
Discussion

When analyzing the results from the Cochrane Review, one notices the consistency between different observational studies that were conducted in the high-risk population settings. All studies on high-risk populations supported the potential protective effect of male circumcision on HIV acquisition in heterosexual men, while results for the general population were mixed. The association between male circumcision and protection against HIV acquisition was strongest in groups at high-risk for HIV infection. This review is instrumental in the discussion of HIV prevention because it found that men who had already been circumcised had lower rates of HIV infection than uncircumcised men. The Cochrane Review set the groundwork for investigators in randomized and controlled intervention trials to then test male circumcision as an effective intervention tool in preventing transmission of HIV/AIDS.

Randomized and controlled intervention trials, are regarded as the best method of assessing healthcare interventions (in this instance, circumcision). With these trials, one is able to directly compare intervention and non-intervention groups, so the only differences between the two groups could be due to the effects of the circumcision (the intervention), or chance (Kleijnen, Gotzsche, Kunz, Oxman, & Chalmers, 1997). Results from the observational studies discussed are also very helpful, as they examine evidence from many different populations and may include other factors regarding HIV transmission. However, it is imperative to mention that circumcision did not occur as part of any of the observational studies and it is likely that most of the study participants had been circumcised in childhood (due to religious and cultural practices prevalent in those regions of study). It is also important to mention that the observational studies were not designed to compare circumcised and non-circumcised men, where as, this was the main objective of the randomized, controlled intervention trials.
The three randomized, controlled intervention trials reviewed have many similarities. Each study examined the effect an intervention (male circumcision) had on the acquisition of HIV in young males in sub-Saharan Africa. In addition, each study was conducted in a region of sub-Saharan Africa where male circumcision is not traditionally practiced. Once the men in each study were randomly assigned to the intervention or control groups, they were followed for roughly two years (South Africa – 21 months, Kenya – 24 months, Uganda – 24 months). All three studies were stopped prematurely due to ethical considerations, since preliminary data from each study demonstrated overwhelmingly protective effects of the intervention being studied (circumcision). The men in each of the control groups were given the opportunity to undergo circumcision once the study was concluded. The primary outcome of the three trials was remarkably consistent; with the South African and Kenyan trials demonstrating a protective effect of 60% and the Ugandan trial finding a similar protective effect of 55% against HIV acquisition. Very low rates of adverse events or complications related to the circumcision were found in the studies.

When analyzing the data collected regarding sexual behavior in the intervention and control groups, mixed results were reported in these studies. Ugandan researchers found no substantial evidence of “behavioral disinhibition” after circumcision in the intervention group. While one might argue circumcision promotes riskier sexual behaviors and a false sense of safety or protection against HIV, the Ugandan researchers found no evidence of circumcised males adopting high-risk sexual behaviors more frequently than those who remained uncircumcised. This differs from South African trial results, which reveal an inclination toward riskier behavior. While Kenyan researchers documented an overall reduction in risk behaviors in both intervention and control groups from the start of the trial to follow-up completion, they found a greater
proportion of men in the intervention group (circumcised men) reporting riskier sexual behaviors. The proportion was small and not statistically significant. The Kenyan researchers propose this overall reduction can be attributed to initial counseling and voluntary HIV testing offered to participants. This may serve as a reminder to public health policy makers, demonstrating that if male circumcision is implemented as a way to reduce the spread of HIV, a strong emphasis should be placed on health education about practicing safer sex. Male circumcision is only partial protection against HIV acquisition.

These trials were the first to directly examine and then overwhelmingly support the efficacy of circumcision’s benefits in reducing HIV transmission. They also provide the first experimental evidence to demonstrate that any surgery can be used effectively to prevent an infectious disease. The results of these trials are consistent with the observational results previously discussed from the 35 surveys included in the Cochrane Review.

Now the scientific community has three randomized, controlled intervention trials, conducted in three different locations in sub-Saharan Africa. Since each trial has shown very similar efficacy, one may say the results can be generalized to other population groups and areas where the spread of HIV is uncontrolled. These studies provide compelling data supporting male circumcision as a public health initiative in sub-Saharan Africa.

All trials also demonstrate that the protective effect of male circumcision is unchanged when controlling for various sexual behaviors. In other words, these factors played at most a minimal role in explaining the protective effect of circumcision against HIV acquisition. A number of direct anatomic factors are involved in circumcision, which may explain the protective effect seen in these studies. One potential effect is the keratinization of the glans penis that occurs when it is no longer protected by the non-keratinized foreskin. Without having the
susceptible inner mucosal surface of the foreskin, a circumcised male has more surface area of keratinized penis. This appears to provide a much stronger barrier to HIV infection than seen in the uncircumcised male (McCoombe & Short, 2004; Patterson et al., 2002). Secondly, without the foreskin, there is a decrease in the life expectancy of HIV on the penis after sexual contact with an HIV positive partner. When the total surface area of the penis is reduced (by removing the foreskin), HIV has fewer target cells, like Langerhans’ cells and macrophages, to encounter; the numbers of target cells used for HIV entry are reduced when the foreskin is removed. When the foreskin is removed, the risk of acquiring other STDs is also decreased, which in turn reduces the risk of HIV transmission. Many studies exist which strongly suggest that the presence of a pre-existing STD, like genital ulcers, increases the risk of acquiring HIV. A person who has a pre-existing STD who is not infected with HIV is more susceptible to acquiring the virus (Cameron & Simonsen, 1989; Fleming & Wasserheit, 1999). One such study found that the chance of HIV transmission is increased by up to ten times in a person who is already infected with an STD (Chakraborty et al., 2001). Also, the highly vascular frenulum in an uncircumcised man is very susceptible to trauma during intercourse and lesions produced by STDs commonly occur here. Therefore, circumcision further reduces the risk of HIV infection by removing a site that has previously been found to increase acquisition of any STD (Fleming & Wasserheit).

These trials strongly support the idea that circumcision should be recognized as an efficacious means to decrease HIV transmission to males, especially males who are at high risk. When looking at each study’s overwhelming efficacy, one realizes that women could also be indirectly affected, and therefore also the infants born to these women. If men are made less susceptible to HIV transmission, and fewer men acquire the disease, fewer women would then be exposed to HIV during sexual contact. Furthermore, vertical transmission from mother to
infant could also then be reduced. Thus, circumcision’s beneficial effects may potentially be extrapolated to benefit entire populations.

The authors of all three RCTs propose male circumcision as an effective and safe intervention tool to prevent the spread of HIV in areas where transmission is primarily due to heterosexual intercourse and where most males are not already circumcised. The implications of these studies come at a crucial time in HIV research and prevention as no vaccine or microbicides are currently available. While antiretroviral therapy is available to some, treatment under World Health Organization guidelines have had only a small impact on the spread of HIV (Auvert, Males, Puren, Taljaard, & Careal, 2004). According to all investigators in the studies discussed, the protective effect of male circumcision against acquiring HIV is high. This degree of protection (between 55 and 60% in all three RCTs) is equivalent to what would be achieved by a vaccine of high efficacy (Auvert et al., 2005). However, until a vaccine against HIV is developed and becomes available globally, male circumcision (especially in high risk populations) could be considered as a primary public health intervention tool. Finally, male circumcision is an inexpensive procedure that only needs to be performed once (as opposed to some multi-vaccination series) and can be performed at any time during life.

Using the 55 to 60% protective effect male circumcision provides, simulation models predict as many as two million new HIV infections and 300,000 deaths in sub-Saharan Africa could be prevented over the next ten years and 3.7 million and 2.7 million, respectively, over the next twenty years (Williams et al., 2006). Suggesting high acceptability of male circumcision, Ugandan researchers reported that 80% of eligible control participants who had remained uncircumcised and had completed the 24 months of follow-up wished to be circumcised at the end of the Ugandan trial. From a review of 13 informational surveys conducted in nine sub-
Saharan countries, the median proportion of uncircumcised men willing to become circumcised was 65%. In addition, 69% of women were in favor of their partners being circumcised and over three out of four parents (71% of men and 81% of women) were willing to have their sons circumcised. These results make a compelling argument for implementing the intervention of circumcision as the success depends largely on the acceptance of this practice where it has traditionally not been implemented (Westercamp & Bailey, 2007).

One limitation of these studies is the relatively short period of follow-up. Of the three studies, 24 months is the longest period of follow-up (range 12 to 24 months). All studies were stopped prematurely by their respective Data Safety and Monitoring Boards due to what they felt were overwhelmingly beneficial findings of intervention (circumcision). Due to the relatively short periods of follow-up, these trials were unable to study the longer-term (greater than 24 months) effects male circumcision may have on acquiring HIV infection.

Acknowledging the risks of any surgical procedure is imperative and male circumcision is not without risks. The Ugandan trial reported a rate of 4% of adverse events related to the procedure, and this was comparable with South African (3.6%) and Kenyan (1.5%) trial rates. Pain, wound infections and disruption, and bleeding were the most common adverse events listed in all of the studies. Postoperative follow-up, sterile equipment and appropriate facilities, and well-trained healthcare providers are essential considerations when planning the implementation of male circumcision.
Conclusion

Male circumcision is defined as the surgical removal of all or part of the foreskin of the penis (Siegfried, 2003). This procedure has been performed for centuries, for various reasons such as: medical procedures, religious beliefs, and cultural practices. Today, male circumcision could also be implemented as a way to reduce transmission of one of the most devastating diseases of our time: HIV. The spread of HIV through heterosexual intercourse is well established throughout the world, including sub-Saharan Africa. Current prevention strategies and delivery of antiretroviral therapy are making little headway in this region of the world. In sub-Saharan Africa, where rates of HIV infection show no signs of decline, male circumcision may prove to be the most useful tool in reducing HIV transmission.

To date, all three randomized, controlled intervention trials that studied the effect(s) male circumcision has on HIV acquisition through heterosexual intercourse overwhelmingly support male circumcision as a means to prevent HIV transmission in sub-Saharan Africa. While more work at the national and global levels will need to be completed before circumcision can be implemented as a means to prevent HIV, evidence is now available for the global AIDS community: male circumcision has repeatedly been shown to be an effective tool in reducing HIV acquisition. In addition to circumcision, global AIDS organizations and health care workers still must place emphasis on risk behavior modification and safe sex practices in these affected countries. Future research should investigate the best practice to implement large-scale circumcision public health initiatives in sub-Saharan Africa.
Reference List


Abstract

Objective: To investigate the Cochrane review and three recent randomized, controlled intervention trials (RCTs) which studied male circumcision as an intervention to prevent HIV transmission in sub-Saharan African countries.

Method: PubMed and MEDLINE searches were completed for literature on HIV/AIDS and circumcision. The searches resulted in finding the Cochrane Review, three recent RCTs along with other sources dealing with the main focus of this paper.

Results: All three RCTs reviewed that examined the effect(s) male circumcision has on HIV acquisition through heterosexual intercourse overwhelmingly support male circumcision as a means to prevent HIV transmission in sub-Saharan Africa. The degree of protection is between 55 and 60% (efficacy equal to many disease vaccines).

Conclusion: Male circumcision is the first example of a surgical procedure preventing an infectious disease. With minimal costs or risks, male circumcision proves to be a viable public health initiative to reduce HIV incidence in sub-Saharan African countries.