Essay

Male Circumcision for HIV Prevention

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Abstract

As the impervious HIV/AIDS epidemic continues to ravage the regions of the world, with an estimated 33.4 million people battling the human immunodeficiency virus (HIV), there is an unprecedented need to heap on HIV prevention methods. Male circumcision is one of such preventive measures. This paper critically reviews the evidence that adult male circumcision is efficacious in HIV prevention, while exploring its feasibility and acceptability in sub-Saharan Africa. This is a critical analysis of the literature. Relevant citations were selected after a search of EMBASE and MEDLINE using the terms HIV/AIDS and circumcision. Biological and various observational studies suggest reduced HIV acquisition risk in circumcised men. This is consolidated by additional evidence from three randomized controlled trials in sub-Saharan Africa. There is strong evidence that safe male circumcision in HIV prevention is feasible, effective and acceptable; hence could be added to the arsenal of HIV prevention packages in high-incidence settings. However, to maximize infections-averted, a much broader evidence base is called for in terms of optimal ways of improving behavioural change and operational management.

Keywords: HIV; circumcision; prevention.

Introduction

The HIV/AIDS pandemic rages on with an estimated 33.4 million people living with the virus, of whom some 2 million have died (WHO/UNAIDS 2008). With predominantly heterosexual HIV transmission, Sub-Saharan Africa bears the brunt of the pandemic; accounting for 67% of all people living with HIV/AIDS, and 75% of AIDS-related deaths (WHO/UNAIDS 2008). Consequently, the devastatin1.5g social, health, and economic impact has never been greater, nor the need for a vaccine/cure more urgent.

However, with the elusive hope of a vaccine/cure, the onus is on preventive strategies. Hence, efforts are unprecedentedly geared towards finding new preventative measures, as additions to the arsenal of existing ones. Male circumcision is one of the new prevention methods; more relevant in countries of Sub-Saharan Africa with heterosexual epidemics and low rates of male circumcision (Weiss, Quigley and Hayes, 2000).

Male circumcision is the surgical removal of some or whole of the foreskin (prepuce) from the penis (Alanis & Lucidi 2004). The precise biological rationale behind the protective effect of male circumcision against HIV infection is unknown. However, various proposed biological mechanisms evolve around the anatomy of the foreskin. The soft mucosal surface of the inner foreskin is highly prone to micro tears during sexual intercourse, which facilitates HIV entry (Bailey et al. 2001). Similarly, the inner foreskin is highly vulnerable to ulcerative sexually transmitted diseases (Weiss et al. 2006) which increase susceptibility to HIV. Further, the damp, warm sub-preputial space favours survival and proliferation of micro-organisms. This may be accentuated by poor penile hygiene (O'Farrell et al 2006). Moreover, the mucosal surface of the inner foreskin has a high density of Langerhans cells (the main HIV target cells) and a minimal overlying protective layer of keratin; which makes it highly receptive to the virus (Patterson et al. 2002; McCoombe and Short 2006).

Various observational and experimental studies have also shown compelling evidence that male circumcision is efficacious against heterosexual HIV acquisition. This review primarily evaluates the studies on which the evidence is based, with a focus on sub-Saharan Africa over the last two decades. Secondarily, it examines the acceptability of male circumcision as a public health tool in traditionally non- circumcising countries of sub-Saharan Africa.

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Overview of the Evidence

Observational studies

A possible protective effect of male circumcision on the risk of HIV acquisition was first opined in the mid 1980s (Fink, 1986), although this was speculative. Since then, this effect has been examined in a plethora of observational studies including ecological, cross-sectional and case-control studies.

Ecological studies

Some of the ecological studies have demonstrated that HIV prevalence in Africa is inversely correlated with the level of male circumcision practices. In a study of the geographical pattern of HIV prevalence in Africa, Moses et al (1990) found low HIV prevalence in areas with high rate of male circumcision practices. This corroborates the finding from a prior ecological study in Africa by Bongaarts et al. (1989). However, the studies may have been fraught with lack of control for confounding factors: sexual risk behaviour, religion, culture; the use of crude indices of HIV prevalence; and old anthropological data of male circumcision. Similar findings on the mappings of HIV prevalence in Africa resulted from a study by Halperin and Bailey (1999). Countries like Zimbabwe, Botswana and Zambia with low circumcision practices (<20%) have high HIV prevalence, while countries with high rates of male circumcision (>80%) e.g. Cameroon, Gabon and Ghana, have low HIV prevalence. Like the other ecological studies, the inadequate control for confounding factors leaves little ground for the validity of the finding.

Furthermore, the inverse correlation of HIV prevalence with circumcision rates was confirmed in a large community-based, multi-site study by Auvert and colleagues (2001). The authors conducted a random household survey on sexually active men aged 15-49 years in four Sub-Saharan African cities with contrasting HIV prevalence. The survey entailed testing for HIV and other sexually transmitted infections (STIs), genital examination to verify circumcision status, and interviews on socio-demographic characteristics and sexual behaviours. In two of the cities, Cotonou, in Benin, and Yaoundé, in Cameroon, where HIV prevalence was low (approximately 4%), nearly all the men were circumcised. The other two cities in eastern and southern Africa (Kisumu, Kenya and Ndola, Zambia) with HIV prevalence rates of 22% and 26% respectively, had low circumcising populations. The authors found male circumcision to be a major predictor of the heterogeneity in HIV prevalence in Sub-Saharan Africa. Another explanatory factor was sexually transmitted

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infections. A conceivable weakness of this study, however, is limitation in the validity of self-reported data on sexual behaviours.

Studies in the general population

A cross-sectional study in a population-based cohort in Rakai district of Uganda, also reported a significant protective effect of circumcision (adjusted OR 0·39, 95% CI 0·29–0·53), but only in those circumcised before age 21 years (Kelly et al 1999). This finding is at variance with that obtained in a study conducted by Quigley and colleagues (1997) in Tanzania, which found significant protective effect of circumcision against HIV infection only in those circumcised at age 15 years or more. This variation implies that age at circumcision is a likely confounder of the protective effect of circumcision on HIV infection. A criticism that runs across these two studies by Kelly et al and Quigley et al respectively is the self-reporting of circumcision status by the participants. This may have led to misclassification of circumcision status, with subsequent bias of the findings (Diseker et al 2001). Moreover, participants who have had sexual relations before circumcision may have flawed the findings.

Another cross-sectional study of circumcised and uncircumcised men in Kigali, Rwanda, found a significant protective effect of male circumcision on HIV infection in Muslims (crude RR 0.79 ; 95 CI 0.02-1.20) as opposed to the weak association noted in Christians (crude RR 0.79; 95 CI 0.50-1.23) (Seed et al 1995). This study is limited by the confounding of religion.

Studies in High-risk population

In contrast to the above studies carried out in the general population, some of the observational studies have investigated protective effect of male circumcision against HIV susceptibility among high-risk populations.

In a cohort study conducted on 746 Kenyan trucking company employees, the incidence of HIV infection was significantly lower in circumcised men (2.5 per 1000 person-years) than in uncircumcised men (5.9 per 1000 person-years). The effects were even stronger after controlling for potential confounders (adjusted rate ratio 0.25; 95% confidence interval 0.1-0.5) (Lavreys et al 1999). A similar trend was observed in the incidence of genital ulcer disease (GUD) in circumcised men (6·5 per 1000 person-years) compared to uncircumcised men (15·2 per 1000 person-years) following adjustment for confounders. This suggests that the protective effect of male circumcision

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on HIV acquisition could be partially attributed to the protective effect of circumcision against ulcerative STIs. This study may have been susceptible to bias due to low power to analyse the association within the uncircumcised stratum (only 13% of the participants were circumcised) when adjusting for confounders. Here lies the inability to separate the effect of ethnicity from circumcision. In addition, the substantial loss to follow-up may have biased the result.

However, intact foreskin has been shown to increase susceptibility to HIV acquisition independently of ulcerative STIs. In a study population of men with GUD from clientele of STI clinics in Nairobi, Tyndall et al (1996) claimed a 5·3-fold (95%, CI 2·3–13·1) increased risk of HIV seroconversion in favour of uncircumcised men with GUD. There are two reservations about the findings of this study. First, there may have been population bias since the samples were derived from STI clinics, which may not be reflective of the general population. This may also be the cause of the second limitation, that the generalisability may be limited.

Nonetheless, the synergistic effect of the two risk factors namely - lack of circumcision and GUD, has a direct correlation with the HIV seroconversion status. Cameron et al (1989) conducted a longitudinal study on 370 HIV-seronegative Nairobi male STI patients, after they had sex with HIV-seropositive female sex workers (with high HIV infection rates). After the 2 week follow-up, the authors estimated that 2.5% of circumcised men without GUD became seroconverted as opposed to the 52% of uncircumcised men with GUD. By extension, 13.4% of circumcised men with GUD seroconverted as opposed to 29% of uncircumcised men without GUD – meaning that lack of circumcision played a far greater role than GUD in potentiating HIV seroconversion. This study is fraught with methodological limitations. Given the higher number of circumcised men lost to follow-up, selection bias may have occurred. In addition, the inadequate follow-up of two weeks may have led to a considerable proportion of missed seroconversions – culminating in further bias, not least if this varied in the circumcised and the uncircumcised strata of the study.

Partner studies

Similar strong association between circumcision status and seroconversion was also noted in partner studies. In Rakai, Uganda, an elegant partner study was conducted by Gray and colleagues (2000) on male partners of HIV-positive women in regular sexual relationships (discordant couples). The authors found that 29% of 137 of uncircumcised men (incidence rate 16·7 per 100 person-years),

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and none of 50 circumcised men seroconverted over a period of 4-years (p<0.001). In the same cohort population, Quinn et al (2000) analysed HIV incidence in 224 discordant couples of HIV infected men and their HIV-negative female partners and found that the incidence of HIV infection was 5·2 per 100 person-years in women with circumcised partners, and 13·2 per 100 person-years in women with uncircumcised partners. This was only a statistically significant effect when the viral load in the infected male partner was below 50,000 copies per milliliter, thus suggesting that the combination of circumcision and lower viral loads reduces male-to-female transmission. However, the effects of religion and circumcision could not be delineated in this study thus complicating its generalisability to the whole population.

Summarily, though the evidence from observational studies in support of male circumcision as an effective HIV prevention measure is compelling, inadequate control for potential confounding cannot be overemphasized. Moreover, not all the observational studies found a protective effect of male circumcision on HIV acquisition. A cross-sectional study by Auvert et al (2001) in Carletonville, South Africa, found no effect of circumcision on HIV serostatus (OR 1·6, 95% CI 0·7–3·2) .On the other hand, a study by Chao et al (1994) found a positive correlation between the HIV serostatus of pregnant women in Rwanda and the circumcised status of their partners. These two studies, however, may have been biased by the self-reporting of sexual behaviours.

Compelling results with no proof of causality in the observational studies provided rationale for randomised trials of male circumcision to prevent HIV infection .

Randomised controlled trials (RCT's)

In stark contrast to the substantial number of observational studies, there is paucity of randomized controlled trials (RCTs) to determine the efficacy of male circumcision in reducing heterosexual HIV acquisition. Three RCTs were conducted in areas with low rate of male circumcision and high prevalence of HIV. Specifically, they were conducted in South Africa, Uganda, and Kenya by Auvert et al (2005), Gray et al (2007) and Bailey et al (2007) respectively.

In 2005, Auvert et al. reported the outcome of the study in South Africa conducted on 3,274 uncircumcised, HIV-negative men. Immediate (at study entry) and delayed circumcision (at the end of the study) were offered to the intervention group and the control group respectively. Interim statistical analysis showed that 20 of the circumcised cohort (incidence rate 0.85 per 100 person-

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years) and 49 of the uncircumcised group (2.1 per 100 person-years) became HIV infected. Adjustment for crossover effects gave a 61% protective effect of circumcision against HIV. The trial was stopped prematurely by the study's Data Safety Monitoring Boards (DSMB) due to the overwhelmingly positive findings. The study, however, has various methodological limitations. First, generation of the randomization sequence was not detailed. Second, inadequate allocation concealment in this study may have caused selection bias. Third, short duration of follow up in this study may have left little ground to explore the efficacy of male circumcision in HIV prevention. Fourth, the study did not control for non-sexual causes of HIV transmission; 23 out of the 69 HIV seropositive men contracted the virus from non-sexual causes, in which case, male circumcision will not be protective. Lastly, contamination may have occurred as some of the participants did not adhere to the arm they were randomly assigned to - 10.3% of men in the circumcised group had been circumcised outside the trial before the end of the study. A virtue of this study though, is that the sample was representative of the population, hence the result is generalisable.

The Ugandan study by Gray et al. also reported a substantial efficacy of male circumcision against HIV acquisition of 51-60%. In the study, 4,996 uncircumcised, HIV-negative men were randomly allocated to a control group and an intervention group. While the intervention group was offered immediate circumcision (study entry), the control group was offered delayed circumcision (at the end of the study after 24 months). The study was also stopped on the recommendation of study's Data Safety Monitoring Boards (DSMB) due to the significant protective effect of circumcision against HIV infection; and men in the control group were offered male circumcision intervention. The Ugandan trial demonstrated HIV seroconversion rate of 0.66 cases per 100 person-years (22 cases) in the intervention group and a seroconversion rate of 1.33 cases per 100 person-years in the delayed circumcision group (45 cases). In this study, possible bias in the self-reporting of sexual behaviours, inadequate control for non-sexual means of HIV transmission and short duration of follow-up may have flawed the findings.

Moreover, in 2007, Bailey and colleagues reported the outcome of the Kenyan trial in Kisumu. Of the 2,784 uncircumcised, HIV-negative male participants, half were circumcised during the trial, and the other half, at the end of the trial. This study was also stopped prematurely because of the overwhelming evidence that male circumcision is markedly protective against HIV acquisition. 22 men (2.1% 95 CI 1.2-3.0) in the circumcised arm of the study as opposed to 47 men (4.2% 95 CI

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3.0-5.4) in the control arm of the cohort had HIV infection. The protective effect of male circumcision was 53% (95 CI 22-72) while with adjustment of crossover effects, protection effects increased to 60%. Bailey et al however, acknowledged that there may have been shortcomings in their findings. Blinding to the intervention could not be achieved with the medical personnel, but the non medical staff were blinded - though some of the participants divulged their circumcision status. There may have been possible bias in the self-report of sexual behaviours; which could be underreported or over reported. Further, generalisability of this study could be limited. In addition, short duration of follow up is another limitation to this study. However, results of the long-term follow up from the Kenyan study has blunted the claim that short duration of follow up may have led to the overestimation of the effects. At 42 month follow-up, the protective effect was 64% (Bailey et al 2008).

In summary, the results of the three large studies are compelling and remarkably consistent; all showing that circumcision has a protective effect of 50-60% against heterosexual acquisition of HIV infection. Interestingly, this is also consistent with the meta-analysis of observational studies by Weiss et al (2000). In this context, this finding excels the results of trials for other HIV preventive strategies e.g. cellulose sulfate microbicide (Weiss et al 2008)

Acceptability of male circumcision as a public health tool in the fight against HIV in sub-Saharan Africa

Following the compelling evidence that male circumcision is efficacious in heterosexual HIV prevention, from the observational studies and randomized clinical trials, UNAIDS/WHO (2007) endorsed male circumcision as an additional preventive strategy for HIV in regions of heterosexual epidemics and low rates of male circumcision. However, the effectiveness of male circumcision depends on individual uptake and the community acceptance of the procedure.

Thirteen studies in nine Sub-Saharan African countries which were executed to explore the level of acceptability of male circumcision, yielded considerable positive results. The study designs of the studies involved open-ended questions asked in group discussions. Alternatively, close-ended questions were asked during one-on-one interviews. Men were asked about their circumcision preference for themselves and their sons, and women, for their husbands and sons. The acceptance

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rates ranged from 29% in Uganda (Bailey et al 1999) to 87% in Swaziland (Tsela and Halperin 2006). Variance in acceptability rates largely dependent on how the questions were asked, clear understanding of the questions by the participants, information session on the health benefits and risks of HIV. A cross-sectional study conducted in 9 geographical representative locations in Botswana yielded a 60% acceptance rate which increased to 80% after a one hour information session on the health benefits of circumcision. Moreover in Malawi, where 32 focus group discussions were conducted with 159 men and 159 women aged 16–80 years, acceptance rates varied by region. A similar acceptability study conducted by Lukobo and Bailey (2007) in Zambia, showed a reasonable acceptability rate similar to what obtained in Kenya, Zimbabwe, South Africa and Tanzania, where approximately 45 to 70% of uncircumcised men wanted to be circumcised.

Barriers to circumcision in most of the studies include bleeding, cost, and pain; while facilitators include hygiene, reduced risk of HIV or other STI, religion, medical conditions, and enhanced sexual pleasure (Westercamp and Bailey 2007). The geographical restrictions of these studies suggest limited generalisability, while participants understanding and interviewers subjective interpretation of the respondents answer may have caused further bias. The acceptability rates in most of these studies highlighted the potential of the procedure as a population-level intervention in the fight against HIV.

Conclusions

Due to the overriding influence of culture, religion, socio-economic status etc, on the practice of male circumcision in disparate countries, a holistic approach to its implementation as a public health tool for HIV prevention is important to maximize the benefit. There should be broad community engagement, with adherence to medical ethics and human rights principles. Trained providers, in clinical settings, should do the procedure at affordable costs.

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