Original Article

Male Circumcision and Risk of HIV Transmission from Male to Women

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Abstract

Male circumcision has proved to be protective for male to male HIV transmission. The effect of male circumcision on female partner's HIV status is still uncertain from previous studies. This systematic review aimed to assess whether circumcision status of an HIV-infected male changes the risk of HIV transmission to his female sexual partner. We analyzed findings from one randomized controlled trial and 4 cross sectional study and found no significant evidence in support of our hypothesis that male circumcision prevents HIV transmission in female. Due to high methodological and clinical heterogeneity, meta-analysis was not done. Qualitative synthesis revealed lack of existing good quality study to address this question. Four of five studies reported no association between male circumcision and HIV transmission. One cohort study reported protective effect of male circumcision on their female partner's HIV. Only one subpopulation of RCT (resume to sexual activity before wound healing) reported increased HIV transmission in female whose male partner is circumcised. Effect of male circumcision on HIV transmission is still blurred. Large scale randomized trial is needed to answer this question. Until then, the prevention programs should also emphasize other measures of HIV transmission.

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Introduction

Human immunodeficiency virus (HIV) is one of the leading causes of infectious-disease-related death. Globally, two million people is detected as newly infected each year and of them, 1.2 million die of HIV[1]. Transmission of HIV by sexual, parenteral, and vertical routes can be prevented by interventions like condom use, needle exchange programs, and antiretroviral treatment of pregnant women[2]. Antiretroviral treatment of HIV infected person not only reduce the viral load of the individual but also reduce the risk of transmission of the infection to their sexual partners. Unfortunately, about half of HIV infected persons are unaware of their HIV status[3,4] and thus other preventive measures remain important for controlling the epidemic. 70% people who has HIV infection are from sub-Saharan Africa1 where heterosexual transmission drives the HIV epidemic[5] access to condoms is limited[4] and at-risk women may have limited autonomy to choose condom as contraceptive method and protect themselves against HIV-infected male partners[6] which signifies the importance of other measures which can prevent male to female HIV transmission. Significant evidence supports a role of male circumcision in reducing HIV transmission to circumcised men from HIV infected sexual partner and three previous randomized control trials from Africa showed a 53-60% reduction in the transmission of HIV in heterosexual men[7-9]. Therefore, World Health Organization (WHO) issued a formal policy statement in 2007 recognizing male circumcision as an important intervention for HIV prevention[10]. While clear benefit has been shown for reduction in HIV acquisition in males, the role of male circumcision in male-female transmission remains unclear.

In ecological data, increased rates of male circumcision on a population level are associated with reduced prevalence in women[11]. A systematic review in 2009[12] reviewed a limited pool of epidemiologic evidence related to the impact of male circumcision and transmission of HIV to women. The review included multiple types of study, which were conducted into sub-Saharan Africa, including a single, never-completed clinical trial, two cohort studies of couples involving female partners of HIV-infected men, cross-sectional surveys of couples' serodiscordancy looking for asymmetry in transmission from women to men and vice versa, and several cohort or cross-sectional studies in which the HIV status of women was evaluated in relation to the reported circumcision status of their male partners without knowledge of the men's HIV status. Results were heterogeneous between studies, and the pooled effect estimate included the null. This ambiguity in the previous systematic review's null findings suggests that a re-analysis of the literature which will focus on newly available RCT or cohort studies 7 years later may be of value in clarifying this question. Therefore, this review aimed to assess whether circumcision status of an HIV-infected male changes the risk of HIV transmission to his female sexual partner.

Materials and Methods

We searched the peer-reviewed medical literature in electronic databases including PubMed, EMBASE, and

CENTRAL by restricting our search by study design and language using controlled vocabulary and free text words. We included only randomized clinical trial, cluster randomized trial or cohort study which recruited women, couples, or men asked about their female partners' HIV status. We excluded other observational studies, and studies with participant as HIV infected women and which only assessed the HIV status in male. Search strings came from two concepts "HIV" and "male circumcision". Individual vocabulary for each concept were connected with a Boolean "OR" operator to broaden our search, and the two concepts will be linked by a Boolean "AND". We did not do hand searching of journals or conference proceedings for this review. We imported search results from PubMed, EMBASE, and CENTRAL into Endnote, deduplicated, divided chronologically into 3 sets. One "reviewer pair", reviewed each set of titles and abstracts. We excluded the following types of titles/abstracts as irrelevant: non-human study, study of female genital circumcision, study of men who have sex with men (MSM), cross sectional study, review articles. The reviewer pairs discussed and resolved any discrepancies among themselves before going to full text screening. Studies determined as "maybe-eligible" based on title and abstract screening then proceeded to full text review by new reviewer pairs. We primarily used the Newcastle-Ottawa Scale (NOS) to assess risk of bias for cohort studies[13]. The NOS scale assessed the quality of non-randomized studies using a "star-system" which judged each study on three standpoints: selection of study groups, comparability of groups, and the determination of exposure or outcome. We assessed risk of bias for randomized trials using The Cochrane Collaboration's tool for assessing risk of bias[14]. Two individuals performed independent data extraction for each included 4 articles using Microsoft Excel 2013 and they resolved discrepancies through discussion as a pair and with the larger group when necessary. We anticipated substantial clinical, methodological, statistical heterogeneity among our included studies we assessed the adjusted measures of risk ratio or the incidence rate using a random effect analysis model. Due to methodological and clinical heterogeneity, meta-analysis would not be performed but we would instead conduct qualitative synthesis.

Table -I: Data Extraction from reviewed articles

- Study ID
- Authors
- HIV incidence among women of circumcised HIV+ male partners (Num/Den, CI, p value) (adjusted)
- RR or HR or IRR of HIV incidence in female sexual partner of circumcised HIV+ men compared to uncircumcised HIV+ men (adjusted)
- Sample size
- Type of study: longitudinal(observational), randomize d control trial
- Year of study
- Location of study (city/village, country)
- Age of the baseline study population
- Follow - up period

Results

Search Results:

We identified 5315 articles searching in PubMed, EMBASE and CENTRAL. After deduplication, we excluded 1460 articles and remaining 3855 articles went for screening. Following screening criteria (mentioned in the method section), we excluded 3802 articles and only 53 articles remained for full text evaluation. 48 articles excluded for following reasons (Figure I) and 5 articles were eligible for qualitative and quantitative synthesis. We also searched in clinical trial.gov and conference website but we did not found anything significant to add in this analysis.

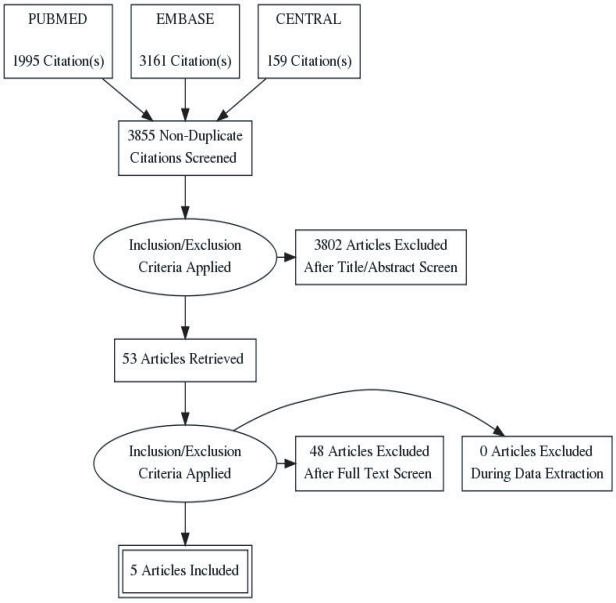

Figure-I: Flow Diagram of Search Strategy

Study and Participants Characteristics

Among 5 studies, one was randomized controlled trial (RCT), 4 cohort studies

RCT: Only one RCT[15] was done to find out the effect of male circumcision on HIV infection of female partner which was done from 2003-2007 in rural Uganda with sample size of 163. Female partners of the trial participants were undergone serological test for HIV infection. More than 96% of the women were over 20 year (15-49 year age). This trial was stopped due to futility issue as female partners in intervention arm reported more HIV infection than control arm (18% vs. 12%). In the subgroup of women, who resumed sex within 5 days

before wound healing, circumcision proved to have harmful effect (HR 3.50 ; 95% CI: 1.14-10.76). Nevertheless in largest group of women (who did not resume sex before wound healing), circumcision was found not associated with female HIV infection (HR: 1.49; 95% CI 0.62-3.57). (Table II and Figure II)

Table-II: Study Characteristics: RCT and Cohort

Study	Setting (year study)	Study of Population	Sample size N	Age range	>1Sexual partner	Male HIV status	Effect Measure (95% CI)
RCT							
Wawer MJ (2009)	Uganda (2003-2007)	Partners of male circumcision patients	163 C=93 U=70	15-49 (96% >= 20y)	11(C) 5 (U)	R	HR= 1.49 (0.62-3.57)
Cohort							
Kapiga SH (1998)	Dar es Salaam Tanzania (1992-1995)	Attendees of clinic	2471	majority over 20	559	N/R	RR=0.29 (0.09-0.97)
Gray RH (2000)	Uganda (1994-1998)	Partners of male circumcision patients	411	15-59	C-309 U-1550	R	IRR=0.41 (0.12-1.38)
Turner AN (2007)	Zimbabwe and Uganda (1999-2002)	Pregnant women visiting antenatal clinic	4417	Mean age 25.2 (SD 4.5)	N/R	N/R	HR=0.78 (0.53-1.14)
Beaten JM (2010)	7 sites in eastern Africa and 7 sites in southern Africa (2004-2007)	General community female	548	25-37	N/R	R	HR=0.53 (0.29-1.11)

C=circumcised; U=uncircumcised; N/R= not reported; R=Reported; RR=relative risk; IRR=incidence rate ratio; HR= hazard ratio

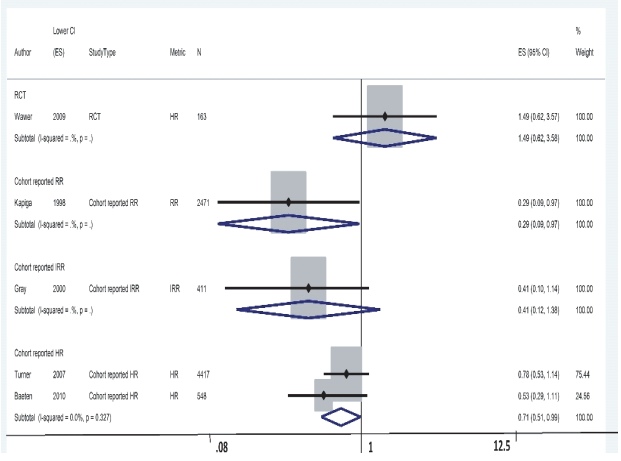

Figure-II: Effect of Male Circumcision on Female HIV Infection

Cohort Studies

All of the cohort studies were conducted in Africa on reproductive age groups women for at least 3 year of follow up. Among4 cohort, one was conducted on pregnant women[16], one on clinic attendee[17], two on general community people[18, 19]. Sample size of cohorts varies from 411 to 4417. Only two of those reported HIV status of male partner. Only one study reported protective effect of circumcision on women (RR: .29; 0.09-0.97) in which the study population were actually attendee of health clinic[17]. In other studies reported a non-significant association of circumcision with female HIV infection. (Table II and Figure II)

Qualitative Synthesis of the Included Studies

There were different kind of study design which made the studies incomparable among each other. The study population includes pregnant women, community women, and health clinic clients. Sample size varies largely from 163 to 4417 and thus effect measure largely varied. Factors responsible for HIV infection is different for this diverse group of people. Two out of five studies did not report male HIV status which made it impossible for us to comment of HIV transmission from male to female. The major strength of the studies were they assessed HIV infection by serological tests.

Study population also consisted of women who had more than 1 sexual partner and had male partner who were polygamous. But they did not reported whether they were using PrEP or condom or combination. Therefore, it was impossible for us to explore circumcision's direct effect on HIV transmission. Ascertainment of exposure in the cohort studies was dependent on women's self-report. There was a possibility of intentionally reporting of false exposure by women when they knew the positive effect of circumcision. Four out of five studies reported statistically non-significant association between male circumcision and HIV infection. The randomized controlled trial, which was terminated early due to futility, suggested an increased risk in association with early resumption of sexual activity shortly after adult male circumcision. One cohort study reported protective effect of circumcision. The studies were relevant in term of outcome determination, comparison and study settings. The effect measure highly varied between studies. Highly variable study population, different reporting of effect measures, lack of enough trial and longitudinal study, adjustment of different confounders in different studies, unreported male HIV status were the main reasons for our failure to conclude a temporal statement for effect of male circumcision on HIV infection in female partner.

Assessment of Bias

RCT: The article on RCT[20] used and reported randomization for intervention assignment and thus took care of confounding. Nothing was mentioned about allocation concealment thus made the study high risk of selection bias. The trial was not blinded as the intervention was a surgical procedure. As outcome was assessed by serological tests in standard laboratory, chance of differential measurement error due to unbinding is low. More than 90% retained in the study, thus chance of attrition bias was lower. There were no co-intervention, outcome were measured at the same time, analysis was done by intention to treat method, baseline character of the both groups were similar and they reported their prefixed outcome in the article. Consequently there were low risk of reporting bias, analysis bias and performance bias, detection bias. There for included RCT had overall low risk for bias.

Cohort

In general, we found high risk of bias in exposure ascertainment for three[17, 21, 22] of 4 cohort studies, selection bias in non-exposed cohort for one study [22,] no outcome determination prior enrollment in one study [22], insufficient follow up time for two study[17, 21] and insufficient follow up time for one study [21].

Female HIV Infection and Male Circumcisions

We found no convincing evidence that male circumcisions has a protective or harmful effect on female partner's HIV status. The included studies in this review had considerable amount of methodological and clinical heterogeneity and therefore a meta-analysis was not performed. Due to limited number of study, subgroup analysis was not done.

Discussion

The study aimed to explore the effect of male circumcision on female partner's HIV infection. The result of our attempt revealed that the studies existing for this topic were too heterogeneous to conduct a meta-analysis. Our findings reported that there is still no convincing evidence that male circumcision prevent HIV transmission in female. Our qualitative synthesis suggested that the studies failed to reliably identify the index partner and his HIV status. Therefore, those studies also unsuccessful to differentiate protection from male circumcision to women. Although they have adjusted for common socio-demographic confounders, adjustment of potential confounder for the circumcision HIV transmission relationship was not done. Result of cohort and RCT was both heterogeneous. Single RCT reported both harmful effect in one group and no effect in other group due to circumcision. Four studies reported no association between male circumcision and HIV transmission. One cohort study[17] where study population was selected from the clinic client, reported male circumcision reduce HIV transmission to female. Only one subpopulation of RCT (resume to sexual activity before wound healing)[15] reported increased HIV transmission in female whose male partner is circumcised . Another limitation of our study was that we could not assess the relationship between our secondary outcome and male circumcision due to data scarcity. The studies which reported our primary outcome did not report any of our secondary outcome. There were separate studies for secondary outcome which was out of our scope according the exclusion criteria fixed in our protocol. Limitation of most the included studies was ascertainment of exposure. Another limitation was adjustment of different type of confounders and loss of follow up or non-response. Previous review conducted on this topic had 10 articles which also included cross sectional studies but we included only RCT and cohort to explore the temporal relationship. Although our review included two more cohort study, this review did not change the interpretation[12]. We confirmed the result of the previous studies with qualitative synthesis. Only a definitive trial can answer this question properly which is not feasible due to availability of other protective measures like condom, PrEP and the nature of the intervention.

In conclusion, this review revealed that male circumcision has no effect on female HIV infection although population level data suggest that male circumcision likely to benefit the women indirectly. Male circumcision was proved to be protective for male to male HIV transmission and largely scaled up in Africa[23]. But the beneficial effect on female is still blurred due to lack of sufficient evidence. During programmatic implication, monitoring of female partners along with their male counterpart also required. The existing prevention programs implement a number of preventive measures to reduce HIV transmission. Due to rapid advancement of pre-exposure prophylaxis, the question of circumcision and HIV infection fortunately is becoming less relevant.

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