

# Male circumcision and human immunodeficiency virus infection: An update on randomized controlled trials and molecular evidences

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Male circumcision is one of the common and oldest surgical modalities performed worldwide for social, cultural, and medical reasons. It is now well documented that 37-39% of men globally are circumcised.<sup>[1]</sup> The frequency of male circumcision was markedly increased in all over the world since three consecutive randomized controlled trials (RCTs) have concluded that male circumcision decreases the risk of acquiring human immunodeficiency virus-1 (HIV-1 or HIV) infection by 50–60% in men.<sup>[2-4]</sup> These trials findings were fully supported by a large number of survey-based studies in United States and Africa.<sup>[5,6]</sup> In agreement with these views, the World Health Organization (WHO) and Joint United Program on HIV/AIDS (UNAIDS) together have issued a formal recommendation on voluntary implementation of male circumcision for HIV prevention.<sup>[7]</sup> In support of these, the American Academy of Pediatrics (AAP) took a similar step in favor of male circumcision for newborns,<sup>[8]</sup> and moreover, this has also been supported by the American College of Obstetricians and Gynecologists.<sup>[6,8]</sup> Male circumcision has now become a valuable component for HIV prevention policy in Sub-Saharan Africa, with almost 15 million circumcisions performed from 2007 to 2016.<sup>[9,10]</sup> Furthermore, UNAIDS has already set a target that 90% of men aged between 15 and 29 years should be circumcised in Africa by 2021 with a total of 27 million more circumcisions on a voluntary basis.<sup>[9,11]</sup> Although the WHO and UNAIDS proposed reaching 80% of male circumcision coverage in HIV widespread countries, but in developed countries, current rates declined far behind the target and circumcision remains continues to be a controversial topic.<sup>[6,12-14]</sup> In spite of these, AAP has recognized the importance of male circumcision and has fully supported the procedure for insurance coverage.<sup>[6,8]</sup> According to the data published so far on RCTs, it is quite clear that male circumcision decreases female-to-male HIV-1 risk but data on circumcised male-to-female HIV-1 transmission are still conflicting.<sup>[15]</sup> One randomized trial

performed in Rakai, Uganda, in 2011 on male-to-female HIV transmission showed that male circumcision does not reduce the HIV infection in female partners, and female partners are more prone when intercourse with HIV-infected circumcised men.<sup>[15]</sup> Grung *et al.* have recently reviewed this aspect closely and they pointed out that the increased risk of HIV in females could be due to early sex after male circumcision.<sup>[9]</sup> In addition, Baeten *et al.* performed a well- designed study on male-to-female HIV-1 transmission on 1096 HIV-1-serodiscordant couples, in which 34% were circumcised men and were HIV-1 infected. They observed that male circumcision decreases transmission in their female partners.<sup>[16]</sup> This was also observed by many other investigators that female partners with circumcised men were found to have a much lower risk of HIV transmission as compared to those females with uncircumcised men.<sup>[17-20]</sup> Thus, there are substantial RCT-based evidence that male circumcision reduces female-to-male or male-to-female HIV transmission.<sup>[5,6,17]</sup> However, the role of male circumcision for the reduction of HIV transmission among homosexual men is still not clear and highly controversial.<sup>[4,5,17]</sup> A study by Buchbinder *et al.* performed in six cities of the United States and found that the uncircumcised men who have sex with men were associated with twice the risk of HIV infection as compared to those with circumcised men.<sup>[21]</sup> Similar observations have also been previously reported by Kreiss and Hopkins.<sup>[22]</sup> However, Grulich *et al.*, in Australia, found no correlation between circumcision and HIV acquisition among homosexual men.<sup>[23]</sup> Similar results have also been reported by Templeton *et al.*<sup>[24]</sup> Furthermore, a meta-analysis by Millett *et al.* also showed no association between circumcision and HIV acquisition in homosexual men.<sup>[25]</sup> These data indicate that male circumcision may work as a safeguard against vaginal insertion but not against anal intercourse,<sup>[6]</sup> and therefore, circumcised men involving sexual intercourse in both forms may have partial protection.

It is now clear that male circumcision reduces the rate of heterosexual HIV-1 transmission but the molecular evidence by which it protects remain poorly understood and controversial. Recently, Prodder and Kaul have somewhat described the biological basis of how it reduces HIV susceptibility.<sup>[26]</sup> They noticed that activation of immune system in foreskin tissues next to subpreputial space promotes HIV in uncircumcised men via epithelial barrier distraction increased maturation of dendritic cells, neutrophils activation/recruitment, and vulnerable CD4 T-cell subsets.<sup>[26]</sup> In addition, they also determined the role of genital microbiome as an inducer of this immune activation.<sup>[26]</sup> Benefits of male circumcision against HIV infection have also been proved anatomically by many investigators on the basis of keratinization of the foreskin.<sup>[17,27-30]</sup> It is now well documented that keratinization in the inner foreskin is less as compared to outer foreskin and this makes uncircumcised men more susceptible to HIV infection.<sup>[27-30]</sup> Moreover, Hussain and Lehner reported Langerhans' cells are significantly more in the mucosal surface of the foreskin,<sup>[31]</sup> and again, this was confirmed by Petterson *et al.* suggesting that circumcision decreases HIV infection by reducing HIV-1 target cells.<sup>[30]</sup> Furthermore, a study on *in vivo* macaque model also noticed that the glans epithelia and inner foreskin are important sites for HIV acquisition in uncircumcised men.<sup>[27]</sup> However, many other reports have shown that keratin thickness is same in the inner and outer foreskin of healthy men,<sup>[32,33]</sup> therefore biological basis on keratin layers alone is not suitable to explain the fact why circumcised men are at lower risk of HIV infection. In support of male circumcision, Fahrbach *et al.* reported a novel aspect that Langerhans cells in the inner foreskin (not in outer) increase their cellular protein expression in the response of external stimuli, suggesting that HIV target cells in the inner foreskin interact with external factors.<sup>[34]</sup> This enhanced response of inner foreskin might explain the underlying biology of how male circumcision reduces the risk of HIV infection. Furthermore, Price *et al.* described another mechanism on the basis of penile microbiota, and they found that circumcision makes significant changes in the overall microbiota and with significant reduction in anaerobic bacterial content.<sup>[35]</sup> These findings indicating that anoxic surroundings of the subpreputial space promote activation of Langerhans cells to present HIV to CD4 cells, and thus, the reduction of anaerobic bacteria after circumcision provides protection against HIV infection.<sup>[35]</sup> In addition, O'Farrell *et al.* observed that circumcised men have significantly lower rates of penile wetness than uncircumcised men, which may also be a factor for reducing the risk of HIV acquisition.<sup>[36]</sup> Another excellent explanation was given by Kigozi *et al.* They calculated the total surface area of the foreskin in HIV-infected men and also in uninfected men and found that mean surface area of the foreskin was significantly more in HIV-infected men as compared to uninfected men.<sup>[37]</sup> Thus, removal of the foreskin by circumcision reduces HIV surgical infection. In short, it is now clear that male circumcision reduces the risk of HIV infection and the pathophysiology behind it seems to be multifactorial, mainly relying on cellular and anatomical

alterations. Evidences for the benefits of male circumcision against the HIV-1 infection are now very supportive and additional research is only likely to confirm what is already known through RCTs and molecular findings.

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