ACTA SCIENTIFIC MICROBIOLOGY (ISSN: 2581-3226)

Volume 2 Issue 2 February 2019

Review Article

How does HIV Gain Entry into Male Genital Tract-Utilizing knowledge from Male Medical Circumcision Trials - A Minireview

Kulvinder Kochar Kaur[1]*, Gautam Allahbadia[2] and Mandeep Singh[3]

[1]*Scientific Director, Dr Kulvinder Kaur Centre for Human Reproduction, Punjab, India*

[2]*Rotunda-A Centre for Human Reproduction, Mumbai, India*

[3]*Consultant Neurologist, Swami Satyanand Hospital, Jalandhar, Punjab, India*

***Corresponding Author:** Kulvinder Kochar Kaur, Scientific Director, Dr Kulvinder Kaur Centre for Human Reproduction, Punjab, India.

Received: November 06, 2018; **Published:** January 03, 2019

Abstract

10years back it was revealed that medical male circumcision (MMC)has been used for preventing HIV, in different parts of the world. This was on the basis of observations that foreskin removal gives up to 60%protection for HIV infection in males. Currently this remains the most useful method short of antiretroviral therapy free prevention method to fight the global epidemic. Why MMC is effective is considered here. It is thought that probably what follows the inflammation of the male genital tract (MGT), probably for protecting against sexually transmitted infections (STIs)-induced pathology, possibly represents a best milieu for immune and microbial changes that is required for getting HIV. The collection of HIV target cells in foreskin tissue along within urethra in response to STI's during and following resolution of infection gives a suggestion that acquisition of HIV1 via sexual contact utilizes the natural immune milieu of the MGT. Hence understanding immunity in the MGT, movement of HIV1 target cells to the urethra and foreskin on coming across microbial signals would give more understanding in how HIV1 gets acquired in MGT which would help in adding more strategies in males to halt the epidemic in all sexual partners being at risk of acquiring infection. Since HIV is more common in females most of global approach has been revolving around finding how this occurs in females, which has left a lot of lacunae in knowledge of this subject and getting more deep insight might help giving a balanced and complete knowledge on viral entry.

Keywords: HIV1,MMC,STI's,MGT,HIV Acquisition; Prevention Strategies; Immune Milieu; Microbial Status

Introduction

Roughly 35 million people who have HIV internationally live in the Sub Saharan Africa (SSA), that roughly sums up over two third of global HIV/AIDS infections. Further it involves adolescent girls and young women disproportionately, with 58% of HIV occurring in SSA involving women [1]. There are multiple factors explaining this, like the presence of sexually transmitted infections (STI's), genital inflammation along with use of exogenous hormone contraceptives [2,3]. Besides that, other sociodemographic factors like the difference in age of the 2 partners, imbalance of gender power along with higher violence against women accounts for this greater incidence in young women [2,3]. One question arises how males get this HIV infection, with male to female transmission being likely to be the source of transmission in women. Men having sex with men (MSM) have 19 times more chances of having HIV as compared to general population [4], with this incidence increasing in various parts of world [5]. Biologically what determines male-male, male to female and female to male sexual networks in greater transmission in high risk groups like adolescents and MSM is not well known. High proportion of MSM in SSA is also reported in recent female sexual partners [6]. Previously it was seen that in early epidemic it was subtype B HIV1 which was found in MSM community as compared to subtype C seen mostly in heterosexual populations, which pointed to 2 different HIV subtypes present in this population [7]. Recently studies in south Africa, Kenya and Senegal show that these observations have changed.

With MSM getting infected with same variants as the heterosexual populations [8-10]. Most reviews focus on female reproduction and how females acquire HIV, but little work has been done on what influences development of HIV in males, possibly those factors give a niche in the male genital tract (MGT) that helps in acquiring HIV.

There is little HIV transmission risk per sex act between males and females, that just does not explain why such high HIV incidence is there that has reached an epidemic proportion both worldwide as well as in SSA. By a metanalysis a risk of developing HIV by heterosexual contact in developed countries is 4 for inser-

tive and 8 for receptive vaginal intercourse that is expressed per 10,000sexual exposures [11]. While in same analysis, a markedly greater risk acquisition for the MSM population, the risk being 138 for receptive and 11 forinsertive anal intercourse per10,000 exposures. This risk acquisition is not easy to determine in view of heterogeneity in published data. A meta-analysis done in eastern and southern Africa reported that both men and women are at a greater risk of getting HIV via heterosexual contact as compared to developed countries data; being 10 and 9/10,000 exposures, respectively [12]. Question raised is why HIV epidemic is so high in SSA. Do cofactors being biological as well as social explain this high heterosexual transmission of HIV. One can't explain this by single factors; like age other sexually transmitted infections (STI), status of circumcision, disease stage usage of antiretroviral drugs, viral load, viral subtype all adding up to how good viral transmission is [13]. Though understanding how HIV gets acquired in women is important, that way one can understand what determines male transmission. Although it is well known that medical male circumcision (MMC) is 56-61% efficacious for HIV prevention in males [13-15], it is important to understand at structural and molecular level how this circumcision helps in protecting against both HIV and STI. This ancient ritual being so helpful, so one needs to exploit the anatomy along with tissue of the uncircumcised penis. Understanding how HIV uses the MGT anatomy and environment to help get access in males is important.

Barrier provided by Foreskin Integrity and Immunity

The foreskin appears to be an important point from where entry of HIV takes place in MGT in view of protection conferred by circumscision. Penile urethra and the testes represent the important parts of MGT which are lined by simple as well as stratified epithelium [16]. Though foreskin is not necessary for penile functioning normally, it is believed to offer some physical and immunological protection, to the sensitive glans penis [17]. This foreskin is a common point of entry of STIs and gets abraded during coitus, that possibly leads to inflammation along with resident HIV target cell exposure making it an important immunological area of MGT [18]. Just like HIV evolved to make use of lymphoid structures for propagating effectively in the body systemically, in the same way HIV uses the structures both in the foreskin along with urethra and the underlying immune cells, to get access into lymphoid structures along with systemic circulation.

Anatomically foreskin is made up of a double layer of stratified epithelium which contain squamous keratinocytes which cover the glans/corona along with the meatus of a flaccid penis [18]. It is thought that once most of foreskin epithelium gets removed via circumcision it=> a dry keratinized epithelium of the glans/corona which is thought to be more resistant to micro abrasions during coitus and limits the chances of HIV to contact target cells which reside in epidermis and dermis, as compared to the moist mucosal epithelium of the glans/corona that is covered by the foreskin in uncircumcised men [19]. The keratin layer gives the 1st line of innate defense against infection of the penile tissues though differences in opinion occur regarding the degree of foreskin keratinization, and thickness of keratin between inner and outer foreskin tissues in various studies published on this subject [20]. A retraction of foreskin occurs in an uncircumscised penis at the time of erection, that exposes the glans penis along with the inner foreskin, that are considered to be greater susceptible to get viral entry as compared to other penile tissues [21]. Explant studies have supplied this information, showing that the inner foreskin shows greater inflammatory cytokine production and HIV target cell activation, as compared to the outer foreskin which lead to the conjuncture that HIV target cells in the inner foreskin have increased interaction with external factors [21,22]. At the time of coitus, the inner foreskin gets exposed to vaginal and/or rectal secretions, being susceptible to micro abrasions, which probably creates extra portals of entry.

It was demonstrated that in the foreskin high density of the HIV target cells, [23,24] along with greater density of CD4+Tcells and langerin expressing Langherham cells (LCs) were present in the inner in comparison to the outer foreskin [24,25]. An inflammatory immune microenvironment'' with in the foreskin was described by Prodger., et al, where they showed that there was an upregulation of HIV coreceptors on CD4+T cells along with raised production of inflammatory cytokines, TNF-α, and IFN-γ by CD8+Tcells [26]. Similarly, Lemos., *et al*. suggested that the protective effects of circumcision might be secondary to removal of inflammed tissue which is not only permeable to HIV but would possess a greater density of HIV target cells [27]. Stratified epithelium seen on surfaces is exposed to environment, which is made up of multiple layers of epithelial cells, that form a physical barrier for external pathogens [28]. Increased numbers of immune cells, like LC's which serve as specialized antigen presenting cells, are specifically present in the stratified squamous epithelium [29]. They have been seen in the upper layers of the epidermis and are proposed as being the 1st line of cells which come into contact with HIV, on infection [30]. The other target cells of HIV like CD4+Tcells, dendritic cells (DC's) [31,32], and macrophages which express C type lectins, that are present in the lower dermis. gp120 subunit of HIV Env binds the C type langerin which h is expressed by circulating LCs after which virus either gets internalized and degraded or transferred to CD4+Tcells, based on the viral load [25,33]. DC's express the C type lectin DC sign, that is also able to bind to gp120, which might help in transfer of HIV -1 from DC's to CD4+T cells [31,32]. Macrophges can selectively capture HIV-1 infected CD4+Tcells that=>infection and efficient transfer of HIV 1 from cell to cell [34]. Such cells are observed in surfaces typically like the meatus (distal end of penile urethra), fossa navicularis (opening), and foreskin [35]. While stratified squamous epithelium spans the exterior of the glans penis and foreskin and transitions into nonkeratinized stratified squamous epithelium in the fossa navicularis [16].

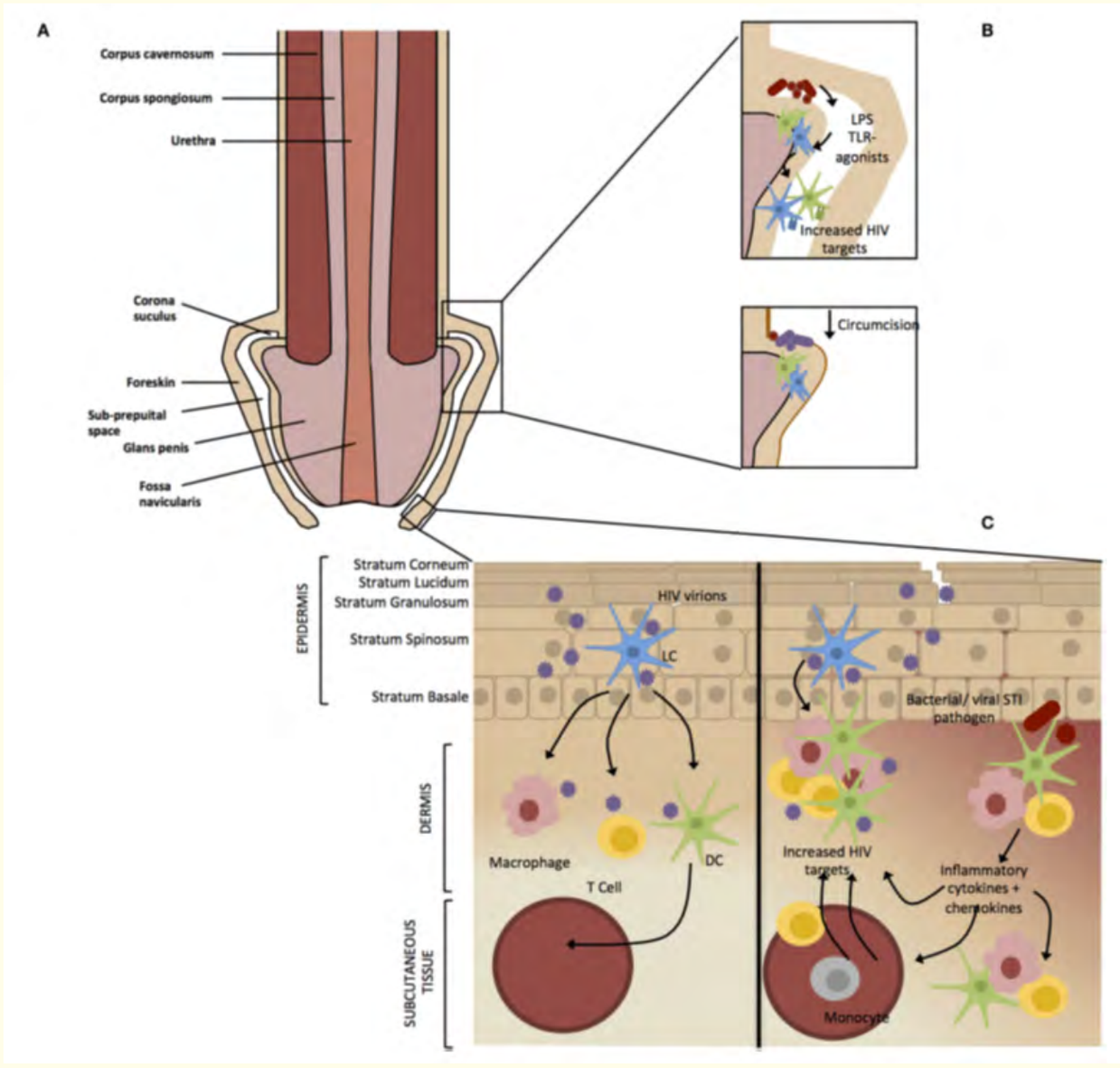

Figure 1: Courtesy ref 88 Factors affecting HIV infection of the male genital tract. (A) The foreskin consists of a double layer of stratified epithelium that covers the glans/corona and meatus of a flaccid penis. (B) Circumcision results in the removal of the majority of the foreskin epithelium leaving a "dry" keratinized surface that is assumed to be resistant to HIV infection. Non-STI genital microbial populations have been shown to modulate genital inflammation through the antigen recognition, which may result in migration or activation of HIV target cells into the foreskin. Circumcision results in a removal of the moist sub-preputial space and decrease in anaerobic bacterial species, which are likely pro-inflammatory. (C) The foreskin is a stratified epithelium consisting of six epidermal layers namely stratum corneum (SC), stratum granulosum (SG), stratum spinosum (SS), and stratum basale (SB). HIV virions crosses the keratinized (light brown) epithelial border through micro abrasions that occur during sexual intercourse or through the formation of viral synapses between HIV-infected cells and epithelial cells [20]. Langerhans' Cells (LCs) reside within the epidermis where they are the first to encounter the virus [21]. Activated LCs migrate into the lower dermal tissues, transferring the virus to resident dermal immune cells such as T cells, macrophages, and epithelial dendritic cells (DCs). Dendritic cells act as professional antigen presenting cells, phagocytosing virions, and migrating to the draining lymph nodes where they present HIV antigens to immature T cells and B cells [22]. Intact virus can be trafficked into the lymph nodes by DCs and transferred to CD4+ T cells [23] where the virus replicates and is disseminated throughout the body [24]. Asymptomatic STIs do not present clinically but inflammation still occurs on a cellular level. The release of pro-inflammatory cytokines by keratinocytes and dermal immune cells in response to an STI would result in recruitment and activation immune cells to the site of infection. This inflammatory environment would result in an accumulation of HIV target cells and therefore increase the efficiency of viral transmission in the case of an HIV infection.

How MMC and other STI's affect HIV Risk

MMC studies showed that strong protection was conferred by circumcision on reducing HIV risk [13-15], although same data was not obtained as convincingly for STI's. In the trial done in Uganda it was shown that MMC carried out in adolescents' boys along with men lead to a decrease in genital ulcerative disease (GUD) [36]. Although both Ugandan and south African trials reported a marked decrease in herpes simplex virus-2(HSV-2) acquisition, the Kenyan trial did not show much decrease in HSV 2 occurring following MMC [36], which gave a suggestion that reduced HIV infection following MMC was independent of both HSV2along with GUD [37]. While it was found by Weiss., *et al*, that MMC markedly decreased the risk of chancroid and syphilis, but only weakly decreased HSV2 infection [38]. It was thought that probably the moist, warm area under the foreskin increases pathogenic growth and that good hygiene of the prenuptial space between the foreskin and glans penis was associated with lesser HIV occurrence. Thus, the dynamic environment in this space influences HIV risk [39,40], with removal of this niche for these particular pathogens protects more commonly diseases which are associated with lesions that occur in foreskin tissue like chancroid as compared to lesion occurring as a result of syphilis and HSV2, both that are present more widely across male gentalia [41]. Further the Kenyan trial showed that no effect on acquisition of neisseria gonorrhea (NG), Chlamydia trachomatis (CT)and Trichomonas vaginalis (TV) was observed thus showing that MMC doesn't protect against non-ulcerative genital disease (NUD) [42]. Although epidemiological studies point to some reduction in risk of cervical neoplasia following circumcision [43,44], other observational studies gave an inconsistent role of circumcision in decreasing HPV transmission to female partners [45,46]. The Ugandan trial showed a reduction in penile HPV carriage [47]. Though controversial [48], asome studies showed greater prevalence of HPV Infection in un circumcised males [49]. Hernandez., et al, further showed circumcision instead of increasing risk of HPV acquiring, decreased clearance of both oncogenic as well as nononcogenic forms of the virus [50]. Thus, more occurrence of HPV In uncircumcised males might be secondary to longer duration of infection instead of increased acquiring [50] which emphasizes on how one needs to consider pathogen specific factors in the epidemiology of STIs in males.

Though inconsistencies are there on efficacy of MMC in decreasing risk of other STI's, evidence is there regarding reduction in GUD. What mechanism is there by which it might or might not impact occurrence of HIV occurrence is not well known. Possibly mucosa disruptions occurring due to ulcerative STIs add to the efficacy of HIV infection since that helps in recruitment along with activation of HIV target cells which are resident and migrate to foreskin tissues [27]. Donovan., *et al.* showed that this inflammatory effect might persist following clearance of infection by finding a greater% age of HIV target cells in the foreskin of men having a history of STIs in contrast to those without history of STIs [51]. One reason why circumcision is protective and coordinating occurrence of HIV and other STIs was given by Sbazo., et al, suggesting that it is decrease in vascularized frenulum, that is at risk of trauma during coitus along with ulcerative lesions [52].

Asymptomatic STIs and HIV risk

STD's increase the risk of acquiring HIV, while preexisting STIs increase the risk of acquiring HIV by 2-3 fold [53], with ulcerartive STIs giving even greater larger risk as compared to non-ulcerative STIs. Thus, a strategy was made to treat STI, to prevent HIV infection, where there is prevalence of both HIV and STIs. An RCT done in Mwanza, Tanzania showed a 38%decrease of HIV, after treating STIs [54]. But these findings not reproduced in next 9 RCTs, with no significant decrease of HIV incidence following therapy for symptomatic STIs [55]. To consider this syndrome based approach In STI might underscore the importance of subclincal inflammation as asymptomatic and nonulcerative and nonulcerative STIs which may add to HIV susceptibility. Irrespective of visible ulcerations, HSV 2has been associated with 3fold increased risk of acquiring HIV [56].

In a case of HSV2 positive following successful treatment with acyclovir, where there was increased expression of mucosal CCR5+CD4+Tcells remaining at the place of herpetic ulcers much long following clearance of the infection [57]. This implied that once immune activation occurs it =>persistence of HIV target cells in the MGT, long after HSV2 resolution. In Ugandan men having asymptomatic HSV2, Prodger., et al, found a greater proportion of HIV target cells CCR5+Tcells in the foreskin of asymptomatic men having HSV2 [58]. Thus both asymptomatic or cleared HSV2 might increase susceptibility of the foreskin to HIV infection. Additionally, besides increased density of HIV target cells, asymptomatic HSV was associated with reduced expression of the epithelial junctional protein claudin in the foreskin, which creates an epithelial barrier that is compromised, and that might be more susceptible to HIV -1 infection [59]. Utilizing genital epithelial monolayers showed that exposure to HIV-1 directly impairs the integrity of mucosal barriers, by disrupting the mucosal barrier via disruption of tight junction markers, namely ZO-1 and occulin which increases HIV exposure/confection with any other STI, with the resultant epithelial cell induced inflammation [60], might be another way by which HIV enters the target cells in the genital submucosa.

Effect of Microbiome of Penis on Integrity of Immune System

This correlation has been well documented in the intestine [61,62], while it is under research in skin [63,64] Circumcision changes the prevalence along with diversity of the microbiota in the penis, which seems to be a possible mechanism by which circumcision protects against HIV [65,66]. It Is believed that Non –STI-genital microbial populations regulate genital mucosal inflammation via antigen recognition and hence increase HIV risk through activation of HIV target cells [67,68]. It was demonstrated by Price., *et al,* that microbes of coronal sulcus, which is the junction between the shaft and glans of penis, mainly are made up of anaerobes along with vaginal taxa before circumcison, while it changes to mainly anaerobes and skin taxa following circumcison [66].

Different microbes were present in another study in coronal sulcus of circumcised and un circumcised males [67]. But on 1st pass urine no difference was found between the microbes, reflecting urethral microbiome is same in men before and following circumcision, which showed that circumcision had no effect on urethral microbes [69]. It is the wet sub preputial space underneath the foreskin which gives an anoxic environment which harbours anaerobic species [66,70]. Mainly anaerobic vaginal bacteria which are associated with bacterial vaginosis (BV) in women raises the inflammation along with HIV susceptibility [71,72] in female genital tract [71,72]. Circumcison is related to a decrease in BV in female partners [73,74], along with decrease in anerobic bacterial species that colonize the coronal sulcus [6]. Since the foreskin covers the urethral opening in most of uncircumcised men, in the sub preputial space proinflammatory microbe community might have a knock –on effect on other probable points of entry of HIV [70]. Thus, it was hypothesized that anaerobes of uncircumcised penis are thus proinflammatory and cause a migration or activation of HIV target cells into the foreskin [66], thus increasing the chances of HIV infection via the urethra and foreskin of uncircumcised men [19].

HIV exploitation of the MGT

Role of subclinical inflammation in raising the chances of infection of the foreskin to HIV infection is not clearin developing countries. There usually a syndrome type approach is kept for managing STI. Commonly asymptomatic STIs like CT and NG are very high in high risk MSM cohorts [75,76], though prevalence of same in general population is not well known. This asymptomatic STIs occurring in men might drive increased proinflammatory cytokines along with chemokines in foreskin tissue and the urethra, hence recruiting activated HIV target cells to the site of infection. Endocervical epithelial cells are thought to be initial niche for Chlamydia infection that is mainly asymptomatic STI [77]. This Chlamydia infection =>an inflammatory cascade =>influx of HIV target cells because of release of proinflammatory cytokines by epithelial cells [93]. It was demonstrated by Buckner., et al, that HIV infection of CD4+CCR5+ cells lines is increased by exposure to supernatant from Chlamydia infected epithelial cells. This proves that Chlamydia infection might facilitate viral infection in the local environment [79].

Hence it is proposed that asymptomatic STI's increase the risk of HIV infection via subclinical inflammation which get modulated by epithelial dysbiosis. The inflammatory events in the MGT following STI infection occur as a natural consequence for protective immunity around the penile tissue. But this subclinical inflammation occurring in the foreskin/urethra of uncircumcised males and urethra of circumcised males acts as a perfect niche for HIV1 to exploit in getting a successful productive infection. Just like the FGT and all mucosal surfaces, innate immune defenses like mucus production, pattern recognition receptors and antimicrobial peptide production are present in MGT [16]. Penile immunity seems to be very active in the FS, urethra and within epithelial tissues [80] and it seems likely that immune production within the MGT is a big survival advantage to the host and is used thus for a survival benefit by HIV1.

Conclusions

Thus it is clear that MMC is an effective method for preventing heterosexual transmission of HIV [81,82], which has been shown to be more effective than any other strategy like treating STI infections, any vaccines or use of any antimicrobial drugs [23]. The complication rate following MMC was low, as seen after the MMC trials being 1. 7 and 7. 6% and were mostly very minor [83,84]. Problem is traditional circumcision which had been done I nonclinical settings ranging from 20-80% in east and south Africa which is associated with serious complication rate [85]. WHO reports. 1millionMMC in south Africa traditional circumcision more common in these areas Based on both cultural and current health services capacity [85]. One needs to work more on this effect of traditional circumcision as it is still very common in these areas on HIV transmission rates along with acceptance of MMC in these communities only being traditional one.

The mechanism by which HIV gets access to the MGT is not clearly understood. Circumcision is an effective strategy to prevent HIV, still 40% of men remain unprotected following circumcision, with condom usage being still regarded he best HIV prevention method, allow accepted globally in a very limited way [86,87]. Why MMC is effective points to that removing the foreskin decreases the natural environment niche for acquisition of HIV1 in the MGT [88]. Still there are lot of lacunae in view of limited access to penile tissue concerning the mode of transmission in males other than foreskin. Further studies have tried to explain on the basis of MGT architecture, where subclinical inflammation along with microbial dysbiosis can be used for getting knowledge to further develop intervention strategies which can prevent acquisition. Additionally, a multidisciplinary approach involving the biology of transmission along with acquisition with the identity of sexual networks between MSM and heterosexual populations is a possible way of understanding this HIV1 epidemic and ways to stop this transmission.

Bibliography

1. Unaids. UNAIDS. The Gap Report 26 Geneva. Joint United Nations Programme on HIV/AIDS (2014).

2. Kelly RJ., *et al*. "Age differences in sexual partners and risk of HIV1 infection in rural Uganda". *Journal of Acquired Immune Deficiency Syndromes* 32 (2003): 446-451.

3. Langen TT. "Gender power in balance on women capacity to negotiate self-protection against HIV/AIDS in Botswana and South Africa". *African Health Sciences* 5 (2005): 188-917.

4. UNAIDS Global AIDS response progress reporting 2014: Construction of Core Indicators for monitoring the 2011 UN Political Declaration on HIV/AIDS Geneva: Joint United Nations Programme on HIV/AIDS (2014).

5. Beyrer C., *et al*. "Global epidemiology of HIV infection in men who have sex with men". *Lancet* 380 (2012): 367-377.

6. Abara WE., *et al*. "HIV epidemic and human rights among men who have sex within Sub Saharan Africa: implications for HIV prevention, care and surveillance". *Global Public Health* 1692 (2015): 1-14.

7. Van Harmelen J., *et al*. "An association between HIV-1subtypes and mode of transmission in Cape Town, South Africa". *AIDS* 11 (1997): 81-87.

8. Middlekoop K., *et al*. "Epidemiology if HIV subtypes among men who have sex with men in Cape Town, South Africa". *Journal of Acquired Immune Deficiency Syndromes* 65 (2014): 473.

9. Ndiaye HD., *et al*. "Surprisingly high prevalence of subtype C and specific HIV1 subtype/CRF distribution in men having sex with men in Senegal". *Journal of Acquired Immune Deficiency Syndromes* 52 (2009): 249-53.

10. Tovana butra S., *et al*. "Evaluation of HIV typa1 strains in men having sex with men and female sex workers in Mombata, Kenya". *AIDS Research and Human Retroviruses* 26 (2010): 123-131.

11. Patel P., *et al*. "Estimating per-act HIV transmission risk". *AIDS* 28 (2014): 1509-1519.

12. Hughes JP., *et al*. "Determinants of per coital act HIV 1 infectivity among African HIV1 serodiscordant couples". *The Journal of Infectious Diseases* 205 (2012): 358-365.

13. Auvert B., *et al*. "Randomized controlled intervention trial of male circumcision for reduction of HIV infection risk: the ANRS 1265 trial". *PLoS Medicine* 2 (2005): e298.

14. Bailey RC., *et al*. "Male circumcision for HIV prevention in young men in Kisumu, Kenya: a randomized trial". *European Eurology* 52 (2007): 605-606.

15. Gray RH., *et al*. "Male circumcision for HIV prevention in men in Rakai, Uganda: a randomized trial". *Lancet* 369 (2007): 657-666.

16. Ngyen PV., *et al*. "Innate and adaptive immune responses in male and female reproductive tracts in homeostasis and following HIV infection". *Cell Molecular Immunology* 11 (2014): 410-427.

17. Taves DR. "The intromission function of the foreskin". *Med Hypothesis* 59 (2002): 180-182.

18. Mclombe SG and Short RV. "Potential HIV1 target cells in the human penis". *AIDS* 20 (2006): 1491-1495.

19. Anderson D., *et al*. "HIV infection and immunity defense of the penis". *American Journal of Reproductive Immunology* 65 (2011): 220-229.

20. Jayathunge PIIM., *et al*. "Male circumcision and HIV transmission: what do we know?" *Open AIDS Journal* 8 (2014): 31-44.

21. Fahrbach KM., *et al*. "Enhanced cellular responses and environmental sampling within inner foreskin explants: implications for the foreskin role in HIV transmission". *Mucosal Immunology* 3 (2010): 410-418.

22. Zhou Z., *et al*. "HIV1 efficient entry in inner foreskin is mediated by elevated CCL5/RANTES that recruits Tcells and fuels conjugate formation with Langerhans cells". *PLoS Pathogen* 7 (2011): e1002100.

23. Padian N., *et al*. "Weighing the gold in the gold standard: challenges in HIV prevention research". *Changes* 24 (2012): 621-635.

24. Hirbod T., *et al*. "Abundant expression of HIV1 target cells and C type lectin receptors in the foreskin tissue of young Kenyan men". *American Journal of Pathology* 176 (2010): 2798-2805.

25. Ganor Y., *et al*. "Within 1h HIV1 uses viral synapses to enter efficiently the inner, but not outer, foreskin mucosa and engages Langerhans Tcell conjugates". *Mucosal Immunology* 3 (2010): 506-522.

26. Prodger JL., *et al*. "Foreskin T cell subsets differ substantially from blood with respect to HIV coreceptor expression, inflammatory profile and memory status". *Mucosal Immunology* 5 (2012): 121-128.

27. Lemos MP., *et al*. "The inner foreskin of healthy men at risk of HIV infection harbours epithelial CD4+CCR5+cells and has features of an inflamed epidermal barrier". *PLoS One* 9 (2014): e108954.

28. Ross HMM and Romell LKG. "Histology, a Text an Atlas, 3rd ed. Baltimore Williams and Wilkins (1995).

29. Merad M., *et al*. "The dendritic cell function ontogeny and function of dendritic cells and their subsets in their steady state and the inflame setting". *Annual Review of Immunology* 31 (2013): 1146.

30. Hladic F and McElrath MJ. "Setting the stage: HIV host invasion". *Natural Review on Immunology* 8 (2008): 447-57.

31. Wu J and Kewalraman VN. "Dendritic cell interactions with HIV: Infection and viral transmission". *Natural Review on Microbiology* 6 (2006): 859-868.

32. Geijtenbeek TB., *et al*. "DC-SIGN, a dendritic cell specific HIV1 binding protein that enhances trans infection of T cells". *Cell* 100 (2000): 587-597.

33. DeWhite I., *et al*. "Langerin is a natural barrier to HIV1 transmission by Langerhans cells". *Nature Medicine* 13 (2007): 367-371.

34. Baxter AF., *et al*. "Macrophage infection via selective capture of HIV1 infected CD4+Tcells". *Cell Host Microbe* 16 (2014): 17-21.

35. Anderson DJ., *et al*. "Human male genital tract –immunity and experimental models". *Mucosal Immunology* 2 (2005): 1647-1659.

36. Tobian AAR., *et al*. "Male circumcision for the prevention of HSV2and HPV infections and syphilis". *The New England Journal of Medicine* 360 (2009): 1298-1309.

37. Mehta SD., *et al*. "Circumcision status and incident herpes simplex virus 2 infection, genital ulcer disease, and HIV infection". *AIDS* 29 (2012): 997-1003.

38. Weiss HA., *et al*. "Male circumcision and risk of syphilis, chancroid and genital herpes: a systematic review and metanalysis". *Sexually Transmitted Infections* 82 (2006): 101-109.

39. O'Farrell N., *et al*. "Association between HIV and sub preputial penile wetness in uncircumcised men in South Africa". *Journal of Acquired Immune Deficiency Syndromes* 43 (2006): 69-77.

40. Nsanze H., *et al*. "Genital ulcers in Kenya: clinical and laboratory study". *The British Journal of Venereal Diseases* 57(1981): 378-381.

41. Mehta SD., *et al*. "Adult male circumcision does not reduce the risk of incident Neisseria gonorrhoeae, Chlamydia trachomatis and trichomons vaginalis: results from a randomized controlled trial". *Kenya Journal of Infectious Diseases* 200 (2009): 370-375.

42. Drain PK., *et al*. "Male circumcision, religion and infectious disease: an ecologic analysis of 118 developing countries". *BMC Infection Disease* 172 (2006).

43. Castellsague X., *et al*. "Male circumcision, penile human papilloma virus infection and cervical cancer in female partners". *The New England Journal of Medicine* 346 (2002): 1105-1112.

44. Kjaer SK., *et al*. "Case control study of risk factors for cervical neoplasia in Denmark I: role of the ''male factor ''in women with one lifetime partner". *International Journal of Cancer* 48 (1991): 38-44.

45. Brinton LA., *et al*. "The male factor in the etiology of cervical cancer among sexually monogamous women". *International Journal of Cancer* 44 (1989): 199-203.

46. Dickson NP., *et al*. "Male circumcision and serologically determined human papilloma virus infection in a birth cohort". *Cancer Epidemiology, Biomarkers and Prevention* 18 (2009): 177-183.

47. Wawer MJ., *et al*. "Effect of circumcision of HIV –negative men on transmission of human papilloma virus to HIV negative women: a randomized trial in Rakai, Uganda". *Lancet* 377 (2011): 209-218.

48. Zhu YP., *et al*. "Relationship between circumcision and human papilloma virus infection: a systematic review and meta-analysis". *Asian Journal of Andrology* 18 (2016): 1-7.

49. Hernandez BY., *et al*. "Circumcision and human papilloma virus infection in men: a site specific comparison". *The Journal of Infectious Diseases* 197 (2008): 787-794.

50. Hernandez BY., *et al*. "Reduced clearance of penile human papilloma virus infection in uncircumcised men". *The Journal of Infectious Diseases* 201 (2010): 1340-1343.

51. Donovan BL., *et al*. "HIV1 target cells in foreskin of African men with varying histories of sexually transmitted infections". *American Journal of Clinical Pathology* 125 (2006): 386-391.

52. Sbazo R and Short RV. "How does male circumcision protect against HIV infection?" *BMJ* 320 (2000): 1592-1594.

53. Sexton J., *et al*. "Meta-analysis and Mata regression in interpreting study variability in the impact of sexually transmitted diseases on susceptibility to HIV infections". *Sexually Transmitted Diseases* 32 (2005): 351-357.

54. Grosskurth H., *et al*. "Impact of improved treatment of sexually transmitted diseases on HIV infections in rural Tanzania: randomized controlled trial". *Lancet* 346.8974 (1995): 530-536.

55. Stillwagon E., *et al*. "Rush to judgement: the STI trials and HIV in sub-Saharan Africa". *Journal of the International AIDS Society* 18 (2015): 19844.

56. Gray RH and Wawer MJ. "Reassessing the hypothesis on STI control for HIV prevention". *Lancet* 371 (2008): 2064-2065.

57. Bomsel M. "Transcytosis of infectious human immunodeficiency virus across a tight human epithelial cell line barrier". *Nature Medicine* 3 (1997): 42-47.

58. Johnson KE., *et al*. "Effects of HIV1 and herpes simplex type2 infection on lymphocyte and dendritic cell density in adult foreskins from Rakai, Uganda". *The Journal of Infectious Diseases* 203 (2011): 602-609.

59. Rohl M., *et al*. "Comparable mRNA expression and inflammatory markers but lower claudin1 mRNA levels in foreskin tissue of HSV2 seropositive versus seronegative asymptomatic Kenyan young men". *BMJ Open* 5 (2015): e006627.

60. Wu L. "Biology of HIV mucosal transmission". *Current Opinion HIV AIDS* 3 (2008): 534-540.

61. Kau AL., *et al*. "Human nutrition, the gut microbiome and the immune system". *Nature* 474 (2011): 327-336.

62. Young YB. "The intestinal microbiota in health and disease". *Current Opinion Gastroenterology* 28 (2012): 63-69.

63. Weyrich LS., *et al*. "The skin microbiome associations between altered microbial communities and disease". *Australia Journal of Dermatology* 56.4 (2015): 268-274.

64. Barnard E., *et al*. "Shaping of cutaneous functions by encounter with commensals". *Journal of Physiology* 594 (2016): 1-17.

65. Liu CM., *et al*. "Male circumcision significantly reduces prevalence and load of genita anaerobic bacteria". *M Bio* 4 (2013): 1-9.

66. Price LB., *et al*. "The effect of circumcision on the penile microbiome". *PLoS One* (2010): e8422.

67. DeJong MA and Geitjenbeek TB. "Human immunodeficiency virus 1 acquisition in genital mucosa: Langerhan cells as key players". *Journal of Internal Medicine* 265 (2009): 18-28.

68. Ogawa Y., *et al*. "Gram positive bacteria enhances HIV1 susceptibility in Langerhan cells but not in dendritic cells via toll like receptor activation". *Blood* 113 (2009): 5157-5161.

69. Nelson DE., *et al*. "Bacterial communities of the coronal sulcus and distal urethra of adolescent males". *PLoS One* 7 (2012): e36298.

70. O'Farrell N., *et al*. "Foreskin length in uncircumcised mn is associated with subpreputial wetness". *International Journal of STD and AIDS* 19 (2008): 821-823.

71. Atashili J., *et al*. "Bacterial vaginosis and HIV acquisition.: a meta-analysis of published studies". *AIDS* 22 (2008): 1493-1501.

72. Myer L., *et al*. "Bacterial vaginosis and susceptibility to HIV infection in South African men: a nested case control study". *The Journal of Infectious Diseases* 192 (2005): 1372-1380.

73. Gray RH., *et al*. "The effect of male circumcision on female partners genitral tract symptoms and vagina infections in a randomized trial in Rakai, Uganda". *American Journal of Obstetrics and Gynecology* 200 (2009): e1-7.

74. Liu CM., *et al*. "Penile microbiota and female partners of Bacterial vaginosis in Rakai, Uganda". *Molecular Biology* 6 (2015): 17-20.

75. Lutz AR. "Screening for asymptomatic extragenital gonococcal Chlamydia in men who have sex with men: significance, recommendations and options for overcoming barriers to testing". *LGBT Health* 2 (2015): 27-34.

76. Rebe K., *et al*. "A cross sectional analysis of gonococcal and chlamydial infections among women who have sex with men in Cape Town, South Africa". *PLoS One* 10 (2015): e0138315.

77. Irwin K. "Observation from the CDC: The silent epidemic of Chlamydia trachomatis: the urgent need for detection and treatment in women the problem: a highly prevalent asymptomatic infection linked". *Journal of Women Health Gender Based Medicine* 9 (2009): 339-343.

78. Ficarra M., *et al*. "A distinct cellular profile is seen in the human endocervix during Chlamydia trachomatis infection". *American Journal of Reproductive Immunology* 60 (2008): 415-425.

79. Buckner LR., *et al*. "Chlamydia trachomatis infection of endocervical epithelial cells enhance early HIV transmission events". *PLoS One* 11 (2016): e0146663.

80. Anderson D., *et al*. "HIV infection of the penis". *American Journal of Reproductive Immunology* 65 (2010): 220-229.

81. World Health Organization. "Joint United Nations Programme on HIV and AIDS. WHO and UNAIDS Announce Recommendations from Expert Consultation on male Circumcision for HIV prevention". World Health Organization (2007).

82. WHO. "WHO Progress Brief-Voluntary Medical Male Circumcision for HIV prevention in Priority countries of East and South Africa. Geneva". World Health Organization. (2014).

83. Weiss HA., *et al*. "Male Circumcision for HIV prevention: from evidence to action?" *AIDS* 22 (2008): 567-574.

84. Muula AS., *et al*. "Prevalence of complications of Male Circumcision in Anglophone Africa: a systematic review". *BMC Urology* 7 (2007): 4.

85. Wolchen A., *et al*. "Traditional Male Circumcision in eastern and south Africa: a systematic review of prevalence and complications". *Bulletin World Health Organ* 88 (2010): 907-914.

86. Bedimo AL., *et al*. "Understanding barriers to condom usage among HIV infected African American women". *Journal of the Association of Nurses in AIDS Care* 9 (1998): 48-58.

87. Ahmed S Lutalo T., *et al*. "HIV incidence and sexually transmitted disease prevalence associated it condom use: a population study in Rakai, Uganda". *AIDS* 15 (2001): 2171-2179.

88. Esra RT., *et al*. "Does HIV Exploit the inflammatory milieu of the male genital tractfor successful infection?". *Frontiers in immunology* 7 (2016): 245.

Volume 2 Issue 2 February 2019