Commentary

BIOMEDICAL Journal of Scientific & Technical Research

ISSN: 2574 -1241

DOI: 10.26717/BJSTR.2026.66.010341

Beyond the Foreskin: Deciphering the Biological Mechanisms of HIV Protection Following Voluntary Medical Male Circumcision

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ARTICLE INFO

Received: July 27, 2026

Published: August 13, 2026

Citation: Silas O Awuor, Rose N Maoga, George O Agal, Abonyo G Ochieng and Mercy A Jacodull. Beyond the Foreskin: Deciphering the Biological Mechanisms of HIV Protection Following Voluntary Medical Male Circumcision. Biomed J Sci & Tech Res 66(3)-2026. BJSTR. MS.ID.010341.

ABSTRACT

Voluntary medical male circumcision (VMMC) remains one of the most effective biomedical interventions for reducing heterosexual HIV acquisition among men. While its protective efficacy has been well established through randomized controlled trials, the biological mechanisms responsible for this protection are multifaceted and extend beyond the physical removal of the foreskin. Emerging evidence demonstrates that VMMC decreases the density of HIV-susceptible immune cells, alters the penile microbiome, reduces local inflammation, strengthens epithelial barrier integrity, and lowers the incidence of sexually transmitted infections that facilitate HIV transmission. Together, these interconnected mechanisms create a less permissive environment for HIV entry and establishment following exposure. Improved understanding of these biological pathways provides valuable insights into HIV pathogenesis and offers opportunities for developing novel non-surgical prevention strategies that mimic the protective effects of circumcision. This commentary summarizes current evidence on the biological mechanisms through which VMMC confers protection against HIV acquisition and discusses their implications for HIV prevention programmes, biomedical innovation, and future research.

Keywords: Voluntary Medical Male Circumcision; HIV Prevention; Penile Microbiome; Mucosal Immunity; Epithelial Barrier; HIV Susceptibility

Commentary

Despite significant advances in HIV prevention and treatment, HIV remains a major global public health challenge, with an estimated 39.9 million people living with HIV and 1.3 million new infections reported in 2023. Sub-Saharan Africa continues to bear the highest burden, particularly among young men in eastern and southern Africa, underscoring the need for effective biomedical prevention strategies [1]. Voluntary medical male circumcision (VMMC) has emerged as one of the most successful interventions in regions with generalized heterosexual HIV epidemics. Since its recommendation by the World Health Organization (WHO) and UNAIDS, more than 35 million procedures have been performed, providing lifelong partial protection following a single intervention and demonstrating high cost-effectiveness compared with prevention strategies requiring sustained adherence [2]. The protective efficacy of VMMC was established through landmark randomized controlled trials in South Africa, Kenya, and Uganda, which consistently demonstrated approximately a 60% reduction in heterosexual HIV acquisition among circumcised men, with long-term follow-up confirming durable protection [3]. While circumcision was initially thought to protect solely through removal of the foreskin, accumulating evidence shows that its benefits arise from multiple interconnected biological mechanisms. Circumcision reduces the density of HIV-susceptible immune cells, reshapes the penile microbiome, decreases immune activation and chronic inflammation, and enhances epithelial barrier integrity, thereby creating a penile environment that is substantially less permissive to HIV infection [4].

Advances in immunology, microbiome science, and molecular epidemiology have transformed understanding of how VMMC modifies the biological pathways involved in HIV transmission. These mechanistic insights not only strengthen the scientific basis for integrating VMMC into comprehensive HIV prevention programmes but also provide opportunities to develop innovative non-surgical interventions that replicate its protective effects. Such research has broader implications for understanding mucosal HIV transmission, guiding vaccine development, and informing next-generation biomedical prevention strategies. This commentary reviews the current evidence on the biological mechanisms underlying VMMC-mediated HIV protection and discusses their implications for HIV prevention and future translational research.

Clinical Evidence Supporting the Protective Effect of Voluntary Medical Male Circumcision

The scientific evidence supporting VMMC is among the strongest for any HIV prevention intervention. Three landmark randomized controlled trials conducted in South Africa, Kenya, and Uganda demonstrated that medical male circumcision reduced heterosexual HIV acquisition by approximately 50–60%, with pooled analyses confirming a protective efficacy of approximately 60% among heterosexual men [3]. The consistency of findings across geographically distinct populations strengthened confidence in the biological plausibility of the intervention and prompted WHO and UNAIDS to recommend VMMC as a core component of combination HIV prevention programmes in countries with high HIV prevalence and low rates of male circumcision [2]. Subsequent implementation studies and mathematical modelling have demonstrated that large-scale VMMC programmes have substantially reduced HIV incidence while proving highly cost-effective by preventing thousands of future HIV infections and reducing long-term treatment costs [3,4]. Importantly, systematic reviews have shown little evidence that VMMC leads to significant sexual risk compensation, reinforcing its value as a safe and sustainable public health intervention when delivered alongside HIV testing, condom promotion, behavioural counselling, ART, and PrEP (14). Nevertheless, VMMC provides partial rather than complete protection and should not be considered a standalone intervention. Instead, its greatest impact is achieved when integrated within comprehensive HIV prevention programmes that address behavioural, biomedical, and structural determinants of HIV transmission [2].

Anatomical Susceptibility of the Inner Foreskin

The inner foreskin is the principal anatomical site facilitating heterosexual HIV acquisition because its thin, lightly keratinized epithelium is more permeable to pathogens and more susceptible to microscopic trauma than the external penile skin. It also contains a high density of activated $CD4^+$ T lymphocytes, macrophages, dendritic cells, and Langerhans cells expressing HIV co-receptors such as CCR5 and CXCR4, which serve as primary targets for viral entry and replication [5]. Voluntary medical male circumcision (VMMC) removes this highly susceptible tissue, reducing the density of HIV target cells, limiting exposure of vulnerable mucosa to infectious genital secretions, and decreasing opportunities for viral entry through epithelial microabrasions, thereby providing an important anatomical barrier against HIV acquisition [5].

Reduction in HIV Target Cell Density and Immune Activation

Beyond reducing the anatomical surface exposed to HIV, voluntary medical male circumcision (VMMC) induces sustained immunological changes that lower HIV susceptibility by decreasing the density of activated $CD4^+CCR5^+$ T lymphocytes, Th17 cells, dendritic cells, macrophages, and other HIV target cells within penile tissues. Circumcision also significantly reduces the production of pro-inflammatory cytokines, including IL-1β, IL-8, TNF-α, and MIP-3α, thereby limiting immune activation and the inflammatory signals that facilitate viral establishment [6]. Importantly, these immunological changes persist long after wound healing, indicating permanent remodeling of the penile mucosal immune environment and contributing to the durable protection against HIV observed in long-term clinical studies [6].

Modulation of the Penile Microbiome

Recognition of the penile microbiome's role in HIV susceptibility has significantly advanced understanding of how voluntary medical male circumcision (VMMC) confers protection. Before circumcision, the moist sub-preputial environment supports anaerobic bacteria that promote chronic inflammation and recruit HIV target cells. Circumcision disrupts this environment by reducing anaerobic bacterial colonization, increasing microbial diversity, and enriching beneficial aerobic commensal organisms, thereby decreasing local immune activation [7]. These microbiome changes reduce inflammatory signaling, preserve epithelial integrity, and create a penile environment that is less permissive to HIV infection. The growing understanding of host–microbiome interactions has also stimulated interest in microbiome-based interventions that could replicate the protective immunological benefits of circumcision without surgery [7].

Reduction of Genital Inflammation

Genital inflammation is a key biological determinant of HIV susceptibility because inflammatory cytokines recruit activated immune cells to the mucosal surface and compromise epithelial barrier integrity, facilitating viral transmission [6]. Voluntary medical male circumcision (VMMC) significantly reduces inflammatory mediators, including IL-8, IL-1β, MIP-3α, and other biomarkers of epithelial disruption, while decreasing activated $CD4^+CCR5^+$ lymphocytes and inflammatory macrophages. By reducing microbial burden, improving genital hygiene, and minimizing inflammation arising from bacterial colonization, sexually transmitted infections, and epithelial injury, circumcision creates a more immunologically quiescent penile environment that is less permissive to HIV acquisition [8].

Enhanced Epithelial Barrier Integrity

Genital epithelium serves as the primary physical barrier against HIV transmission, and disruption of epithelial tight junctions or microscopic abrasions can facilitate viral entry into susceptible immune cells. Evidence indicates that voluntary medical male circumcision (VMMC) enhances epithelial barrier integrity by reducing chronic inflammation, promoting tissue remodeling, and decreasing epithelial permeability, while lower inflammatory cytokine levels preserve intercellular junctions and limit epithelial damage caused by microbial stimulation. Together, these improvements strengthen the penile epithelial barrier and complement the immunological and microbiological effects of circumcision, contributing to its durable protection against HIV acquisition [8].

Reduction in Sexually Transmitted Infections

Voluntary medical male circumcision also decreases the incidence of several sexually transmitted infections (STIs), including genital ulcer disease, high-risk human papillomavirus infection, herpes simplex virus type 2, and syphilis, all of which increase HIV susceptibility by disrupting mucosal barriers and promoting inflammation [8]. Although reductions in STIs explain only part of the protective effect of VMMC, they contribute meaningfully to lowering HIV transmission by reducing genital ulceration, inflammatory infiltrates, and viral shedding. Consequently, the protective benefits of circumcision arise from multiple complementary mechanisms that include anatomical modification, immune regulation, microbiome restructuring, reduced inflammation, strengthened epithelial defenses, and decreased STI burden. These interconnected biological processes collectively create a penile environment that is substantially less conducive to HIV acquisition than that observed before circumcision.

Implications for Global HIV Prevention

Voluntary medical male circumcision (VMMC) is one of the most successful examples of translating biological research into a scalable public health intervention. By providing lifelong partial protection against heterosexual HIV acquisition following a single procedure, VMMC has become a cornerstone of combination HIV prevention programmes in eastern and southern Africa. Large-scale implementation has prevented hundreds of thousands of new HIV infections, reduced long-term healthcare costs, and demonstrated that VMMC is both clinically effective and highly cost-effective in resource-limited settings [2,9]. Despite its proven benefits, VMMC provides only partial protection and should be implemented alongside other HIV prevention strategies, including HIV testing, condom use, PrEP, early antiretroviral therapy, STI management, and behavioural intervention [2,3]. Addressing misconceptions about VMMC through community education is essential to improve uptake and reinforce continued use of comprehensive prevention measures. Furthermore, growing understanding of the roles of the penile microbiome and immune regulation in HIV protection offers promising opportunities to develop innovative non-surgical interventions that could extend the benefits of VMMC to populations where circumcision is unacceptable, inaccessible, or medically contraindicated [9,10].

Conclusion

Voluntary medical male circumcision (VMMC) remains one of the most effective and scientifically validated biomedical interventions for preventing heterosexual HIV acquisition. Its protective effect extends beyond removal of the foreskin and results from multiple complementary biological mechanisms, including reduced HIV target cell density, modulation of the penile microbiome, decreased genital inflammation, enhanced epithelial barrier integrity, and reduced susceptibility to sexually transmitted infections. These mechanistic insights have advanced understanding of mucosal HIV transmission and provide a foundation for developing innovative non-surgical HIV prevention strategies. Continued integration of VMMC into comprehensive combination HIV prevention programmes, alongside ongoing translational research, implementation science, and equitable access to prevention services, will be essential for strengthening global HIV prevention efforts and accelerating progress toward ending the HIV epidemic.

Future Research Directions

Although substantial progress has been made in understanding the biological mechanisms through which voluntary medical male circumcision (VMMC) reduces HIV susceptibility, important knowledge gaps remain. Future research should integrate immunology, microbiome science, genomics, molecular biology, and systems biology to advance next-generation HIV prevention strategies. Priority areas include investigating microbiome-targeted interventions, identifying reliable biomarkers of HIV susceptibility using multi-omics technologies, and applying artificial intelligence and machine learning to improve risk prediction and precision prevention approaches [10]. Further longitudinal studies should examine interactions between VMMC, sexually transmitted infections, genital inflammation, antimicrobial resistance, and co-infections across diverse populations. In addition, development of topical immunomodulators, epithelial barrier enhancers, microbiome-based therapeutics, and mucosal vaccines capable of replicating the biological benefits of circumcision without surgery could substantially expand the HIV prevention toolkit while complementing existing interventions such as PrEP and long-acting antiretroviral therapies.

Declarations

We declare that this is our original work, and no part of this work is under consideration anywhere. We have read and agreed to the published version of the manuscript.

Clinical Trial

Not Applicable.

Consent For Publication

Not Applicable.

Availability Of Data and Material

All the data have been shared in this short commentary.

Competing Interests

The authors declare that there are no competing interests.

Funding

No funding support was received for this work.

Author Contributions

Conceptualization, SAO, GOA and RNO; methodology, All authors; resources, RNO, GOA and SAO; writing—original draft preparation, SAO, GOA and RNO; writing—review and editing, SAO, RNO,AGO, and GOA; Final editing, All authors; visualization, SAO and GOA. All authors have read and agreed to the published version of the manuscript.

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ISSN: 2574-1241

DOI: 10.26717/BJSTR.2026.66.010341

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