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Biological mechanisms


**BACKGROUND:** While microbiome and host regulation contribute independently to many disease states, it is unclear how circumcision in pediatric population influences subsequent changes in penile microbiome.

**OBJECTIVE:** Our study aims to analyze jointly paired taxonomic profiles and assess pathways implicated in inflammation, barrier protection, and energy metabolism.

**DESIGN, SETTING, AND PARTICIPANTS:** We analyzed 11 paired samples, periurethral collection, before and after circumcision, to generate microbiome and mycobiome profiling. Sample preparation of 16S ribosomal RNA and internal transcribed spacer sequencing was adapted from the methods developed by the National Institutes of Health Human Microbiome Project.

**OUTCOME MEASUREMENTS AND STATISTICAL ANALYSIS:** We obtained the predictive functional attributes of the microbial communities between samples using Silva-Tax4Fun and the Greengenes-Phylogenetic Investigation of Communities by Reconstruction of Unobserved States (PICRUSt) approach. The predictive functioning of the microbial communities was determined by linearly combining the normalized taxonomic abundances into the precomputed association matrix of Kyoto Encyclopedia of Genes and Genomes orthology reference profiles.

**RESULTS AND LIMITATIONS:** Several notable microbiome and mycobiome compositional differences were observed between pre- and postcircumcision patients. Pairwise comparisons across taxa revealed a significant decrease (p < 0.05, false discovery rate corrected) of microbiome organisms (Clostridiales, Bacteroidales, and Campylobacterales) and mycobiome
(Saccharomycetales and Pleosporales) following circumcision. A total of 14 pathways were found to differ in abundance between the pre- and postcircumcision groups (p < 0.005, false discovery rate <0.1 and linear discriminant analysis score >3; five enriched and nine depleted). The pathways reduced after circumcision were mostly involved with amino acid and glucose metabolism, while pathways prior to circumcision were enriched in genetic information processing and transcription processes. As expected, enrichment in methyl-accepting chemotaxis protein, an integral membrane protein involved in directed motility of microbes to chemical cues and environment, occurred prior to circumcision, while the filamentous hemagglutinin pathway (a strong immunogenic protein) was depleted after circumcision.

CONCLUSIONS: Our results offer greater insight into the host-microbiota relationship of penile circumcision and may serve to lay the groundwork for future studies focused on drivers of inflammation, infection, and oncogenesis.

PATIENT SUMMARY: Our study showed a significant reduction in bacteria and fungi after circumcision, particularly anaerobic bacteria, which are known to be potential inducers of inflammation and cancer. This is the first study of its kind showing the changes in microbiome after circumcision, and some of the changes that occur in healthy infants after circumcision that may explain the differences in cancer and inflammatory disorders in adulthood.

Combination HIV prevention


INTRODUCTION: Universal HIV testing and treatment aims to identify all people living with HIV and offer them treatment, decreasing the number of individuals with unsuppressed HIV and thus reducing HIV transmission. Longitudinal follow-up of individuals with and without HIV in a cluster-randomized trial of communities allowed for the examination of community- and individual-level socio-demographic and behavioural risk factors, as well as prevalence of detectable virus (PDV) defined as the estimated proportion of the community with unsuppressed viral load.

RESULTS: Overall HIV incidence was 1.49/100 person-years. Communities with less financial wealth and communities with more individuals reporting having sex partners outside of the community or two or more sexual partners had higher HIV incidence. PDV at 2 years of study was 6.8% and was strongly associated with HIV incidence: for every 50% relative reduction in community PDV, there was a 49% (95% confidence interval [CI]: 37%-58%, p < 0.001) relative
decrease in HIV incidence. At the individual level; socio-economic status, AUDIT score, medical male circumcision and certain sexual behaviours were associated with HIV risk.

**CONCLUSIONS:** Using data from the PopART randomized trial, we found several associations of HIV incidence with community-level measures reflecting the sexual behaviour and socio-economic make-up of each community. We also found a strong association between community PDV and HIV incidence supporting the use of PDV as a tool for monitoring progress in controlling the epidemic. Lastly, we found significant individual-level factors of HIV risk that are generally consistent with previous HIV epidemiological research. These results have the potential to identify high-high incidence communities, inform structural-level interventions, and optimize individual-level interventions for HIV prevention.

**CLINICAL TRIAL NUMBER:** ClinicalTrials.gov number, NCT01900977, HPTN 071 [PopArt].

### Cost and costing


Online at: [https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10523817/](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10523817/).

**OBJECTIVE:** To evaluate resource allocation and costs associated with delivery of human immunodeficiency virus (HIV) services in Uganda and the United Republic of Tanzania.

**METHODS:** We used time-driven activity-based costing to determine the resources consumed and costs of providing five HIV services in Uganda and the United Republic of Tanzania: antiretroviral therapy (ART); HIV testing and counselling; prevention of mother-to-child transmission; voluntary male medical circumcision; and pre-exposure prophylaxis.

**FINDINGS:** Country-based teams undertook time-driven activity-based costing with 1119 adults in Uganda and 886 adults in the United Republic of Tanzania. In Uganda, service delivery costs ranged from 8.18 United States dollars (US$) per visit for HIV testing and counselling to US$ 43.43 for ART (for clients in whom HIV was suppressed). In the United Republic of Tanzania, these costs ranged from US$ 3.67 per visit for HIV testing and counselling to US$ 28.00 for voluntary male medical circumcision. In both countries, consumables were the main cost driver, accounting for more than 60% of expenditure. Process maps showed that in both countries, registration, measurement of vital signs, consultation and medication dispensing were the steps that occurred most frequently for ART clients.

**CONCLUSION:** Establishing a rigorous, longitudinal system for tracking investments in HIV services that includes thousands of clients and numerous facilities is achievable in different settings with a high HIV burden. Consistent engagement of implementation partners and standardized training and data collection instruments proved essential for the success of these exercises.
Enhancing uptake


Online at: https://www.thelancet.com/journals/langlo/article/PIIS2214-109X(23)00206-1/fulltext.

**BACKGROUND:** HIV prevention cascades provide a systematic understanding of barriers to prevention. In this study we used mathematical modelling to understand the consequences of these barriers and how the cascade could be strengthened to maximise epidemiological impact, providing potentially important insights for programmes.

**METHODS:** We used an individual-based model of HIV transmission (PopART-IBM), calibrated to data from the Manicaland cohort from eastern Zimbabwe. HIV prevention cascade estimates from this cohort were used as probabilities for indicators in the model representing an individual’s motivation, access, and capacity to effectively use pre-exposure prophylaxis, voluntary male medical circumcision, and condoms. We examined how current barriers affect the number and distribution of HIV infections compared with a no-barrier scenario. Using assumptions about how interventions could strengthen the HIV prevention cascade, we estimated the reduction in HIV infections over a 10-year period through addressing different elements of the cascade.

**FINDINGS:** 21,200 new potentially avertable HIV infections will occur over the next 10 years due to existing HIV prevention cascade barriers, 74.2% of the 28,500 new infections that would occur with existing barriers in a population of approximately 1.2 million adults. Removing these barriers would reduce HIV incidence below the benchmarks for epidemic elimination. Addressing all cascade steps in one priority population is substantially more effective than addressing one step across all populations.

**INTERPRETATION:** Interventions exist in eastern Zimbabwe to reduce HIV towards elimination, but barriers of motivation, access, and effective use prevent their full effect being realised. Interventions need to be multilayered and address all steps along the HIV prevention cascade. Models incorporating the HIV prevention cascade can help to identify the main barriers to greater effectiveness.

**FUNDING:** National Institutes of Mental Health, Bill & Melinda Gates Foundation, and Medical Research Council Centre for Global Infectious Disease Analysis funding from the UK Medical Research Council and UK Foreign, Commonwealth & Development Office (FCDO).

Epidemiological studies


Online at: https://www.thelancet.com/journals/langlo/article/PIIS2214-109X(23)00206-1/fulltext.
INTRODUCTION: Significant regional variations in the HIV epidemic hurt effective common interventions in sub-Saharan Africa. It is crucial to analyze HIV positivity distributions within clusters and assess the homogeneity of countries. We aim at identifying clusters of countries based on socio-behavioural predictors of HIV for screening.

METHOD: We used an agglomerative hierarchical, unsupervised machine learning, approach for clustering to analyse data for 146,733 male and 155,622 female respondents from 13 sub-Saharan African countries with 20 and 26 features, respectively, using Population-based HIV Impact Assessment (PHIA) data from the survey years 2015-2019. We employed agglomerative hierarchical clustering and optimal silhouette index criterion to identify clusters of countries based on the similarity of socio-behavioural characteristics. We analyse the distribution of HIV positivity with socio-behavioural predictors of HIV within each cluster.

RESULTS: Two principal components were obtained, with the first describing 62.3% and 70.1% and the second explaining 18.3% and 20.6% variance of the total socio-behavioural variation in females and males, respectively. Two clusters per sex were identified, and the most predictor features in both sexes were: relationship with family head, enrolled in school, circumcision status for males, delayed pregnancy, work for payment in last 12 months, Urban area indicator, known HIV status and delayed pregnancy. The HIV positivity distribution with these variables was significant within each cluster.

CONCLUSIONS/FINDINGS: The findings provide a potential use of unsupervised machine learning approaches for substantially identifying clustered countries based on the underlying socio-behavioural characteristics.


BACKGROUND: To address knowledge gaps, this study examined social determinants, such as education attainment and HIV prevention, among sexually active men (SAM), with a focus on voluntary medical male circumcision (VMMC).

METHODS: Two nationally representative surveys, the Eswatini Demographic and Health Survey 2006 and the Eswatini HIV Incidence Measurement Survey 2016, were used to estimate whether or not VMMC at the individual and community levels contributes to HIV disparities to any meaningful extent. Multilevel logistic regression models further explored the educational gradient in HIV infection for 2006-2007 and 2016 with regard to VMMC among SAM, while adjusting for household poverty, sexual practices and individual characteristics.

RESULTS: Among SAM with tertiary education, HIV prevalence declined from 25.0% in 2006-2007 to 10.5% in 2016. A 51% decrease in HIV prevalence was found to be associated with an increase in VMMC (adjusted odds ratio 0.49; 95% CI 0.40 to 0.60). Compared with SAM with tertiary education, those who had a lower level of education were more likely to have HIV infection and this education gradient effect had become particularly profound in 2016.
CONCLUSIONS: VMMC began to be promoted in 2008 in Eswatini and results suggest its effect, along with the education attainment effect, significantly resulted in a meaningful reduction in HIV prevalence among SAM by 2016.

Impact and coverage


Voluntary medical male circumcision (VMMC) has primarily been promoted for HIV prevention. Evidence also supports that male circumcision offers protection against other sexually transmitted infections. This analysis assessed the effect of circumcision on syphilis, hepatitis B virus (HBV) infection and HIV. Data from the 2015 to 2019 Population-based HIV Impact Assessments (PHIAs) surveys from Rwanda, Tanzania, Uganda, Zambia, and Zimbabwe were used for the analysis. The PHIA surveys are cross-sectional, nationally representative household surveys that include biomarking testing for HIV, syphilis and HBV infection. This is a secondary data analysis using publicly available PHIA data. Univariate and multivariable logistic regression models were created using pooled PHIA data across the five countries to assess the effect of male circumcision on HIV, active and ever syphilis, and HBV infection among sexually active males aged 15-59 years. Circumcised men had lower odds of syphilis infection, ever or active infection, and HIV, compared to uncircumcised men, after adjusting for covariates (active syphilis infection = 0.67 adjusted odds ratio (aOR), 95% confidence interval (CI), 0.52-0.87, ever having had a syphilis infection = 0.85 aOR, 95% CI, 0.73-0.98, and HIV = 0.53 aOR, 95% CI, 0.47-0.61). No difference between circumcised and uncircumcised men was identified for HBV infection (P = 0.75). Circumcised men have a reduced likelihood for syphilis and HIV compared to uncircumcised men. However, we found no statistically significant difference between circumcised and uncircumcised men for HBV infection.

Infant male circumcision


INTRODUCTION: Traditional male circumcision (TMC) inculcates masculine-dominance norms in young men. Early infant male circumcision (EIMC) and medical male circumcision (MMC) can potentially minimise these adverse gender norms. We explored the perceptions about EIMC and MMC among communities practising TMC in Kenya.

METHOD: We conducted focus group discussions with men and women and councils of elders, and key informant interviews with traditional circumcisers. Data were analysed using NVivo 10.

RESULTS: Most participants described MC as a rite of passage into adulthood, with the preferred age for MC to occur at 10 to 15 years old. Interestingly, awareness of the advantages of EIMC,
especially among younger men and women, was high. Participants acknowledged that TMC reinforces hegemonic masculinity that undermines gender equality. Except among traditional circumcisers and some members of councils of elders, MMC and female providers were largely deemed acceptable.

CONCLUSION: EIMC and MMC are slowly gaining acceptance, providing important tools to challenge adverse gender norms associated with TMC.


Male circumcision is a protective HIV prevention strategy. However, uncircumcised Zambian men are reluctant to undergo voluntary medical male circumcision (VMMC). Tailored interventions are necessary to stimulate the uptake of early infant male circumcision (EIMC) and VMMC in Zambia. This feasibility study presents the formative process of utilising the PRECEDE framework in the development of a family-centred EIMC/VMMC intervention, Like Father Like Son, and its application in an existing VMMC intervention, Spear & Shield. We found that fear of the pain associated with EIMC procedures, foreskin disposal, beliefs in children's autonomy and rights, and men's dominance in health decision-making were factors affecting EIMC uptake. Perceived benefits for infants included improved hygiene, protection from HIV infection, and faster recovery. Reinforcing factors included female partners and fathers' MC status. The availability and access to EIMC services and information, skill and experience of health workers, and engagement and belief in traditional circumcision practices were factors enabling EIMC uptake. These individual, interpersonal, and structural factors positively and negatively influencing EIMC uptake in the Zambian clinic context were integrated into the intervention for expecting parents. Feedback from community advisory boards suggested the process was effective in developing a culturally tailored and acceptable EIMC/VMMC promotion intervention.


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Online at: [https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0289819](https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0289819).

Voluntary Medical Male Circumcision (VMMC) is an effective strategy for HIV prevention in areas with high prevalence of, and risk for, HIV. More than 361,000 male neonates are born each year in Zambia, many of whom could be eligible for Early-Infant Medical Circumcision (EIMC). Building on successful implementation strategies utilized in our Spear & Shield program, this pilot study, "Like Father, Like Son" (LFLS), evaluated the feasibility and acceptability of offering combined EIMC and VMMC services and couple-level behavioral interventions. A total of N = 702 pregnant women and their male partners (n = 351 couples) were recruited and enrolled. Couples were assessed twice pre-birth, 2 weeks post birth, and 6 months post birth. Expectant mothers were an average of 15.05 weeks pregnant (SD = 8.83). Thirty-nine pregnancies did not result in a live birth (11%), 14 couples withdrew from the study or were lost to follow-up prior to delivery (4), and 148 babies were born female (42%), leaving 150 couples with a male infant in the analytic sample (43%). The LFLS study achieved significantly higher EIMC rates (35%) in comparison with previously observed EIMC study rates in Zambia (11%), and significantly higher than hypothetical comparison rates up to 30%. Relative to baseline rates, odds of VMMC among couples' older sons increased by 31% at post-intervention and by 90% at two-weeks following birth. Overall, this pilot study found the LFLS intervention to be feasible, acceptable, and effective in doubling the rate of EIMC in comparison with a previous longitudinal study in Zambia. Future research should consider a family-centric approach to promotion of male circumcision for infants and adolescents. LFLS may be effective in promoting father-son "bonding" by MC status; a bond that may be a bridge to increase both EIMC and VMMC uptake in newborns and couples' older sons and is a novel leverage point for promotion of this HIV prevention strategy.

**Men and boys**


Adolescent girls and young women's exceptionalism with HIV interventions has left adolescent boys and young men (ABYM) trailing behind, thus becoming a marginalized and underserved population. The scoping review aimed to provide an overview of interventions that have targeted sexual risk behaviors in ABYM in Sub-Saharan Africa (SSA) over the previous 21 years with critical insights on 'what works' in preventing the sexual transmission of HIV. A scoping
review guided by Arksey and O'Malley's (in Int J Soc Res Methodol 8(1):19-32, 16) framework and the 2015 Johanna Briggs Institute's guidelines was conducted. A search of literature published between 2000 and 2020 was reviewed and twenty nine interventions from nine Sub Saharan African countries that met the eligibility criteria were reviewed. The review provides evidence on the successes and the limitations of sexual risk behavior interventions for ABYM in SSA. There is clear and consistent evidence that interventions reduce sexual risk behaviors in adolescent boys and young men. Their efficiency seems to grow with the length and intensity of the intervention. Positive effects were generally observed in condom use and on measures of HIV knowledge, attitudes and sexual behaviors as well as uptake of HIV tests and voluntary male circumcision. This review shows that sexual-risk interventions engaging men and boys in SSA are promising and warrant further rigorous development in terms of conceptualization, design and evaluation.


Voluntary medical male circumcision (VMMC) is an HIV prevention intervention that has predominantly targeted adolescent and young men, aged 10-24 years. In 2020, the age eligibility for VMMC shifted from 10 to 15 years of age. This report describes the VMMC client age distribution from 2018 to 2021, at the site, national, and regional levels, among 15 countries in southern and eastern Africa. Overall, in 2018 and 2019, the highest proportion of VMMCs were performed among 10-14-year-olds (45.6% and 41.2%, respectively). In 2020 and 2021, the 15-19-year age group accounted for the highest proportion (37.2% and 50.4%, respectively) of VMMCs performed across all age groups. Similarly, in 2021 at the site level, 68.1% of VMMC sites conducted the majority of circumcisions among men aged 15-24 years. This analysis highlights that adolescent boys and young men are the primary recipients of VMMC receiving an important lifetime reduction in HIV risk.

Safety and quality


AIM: Medical male circumcision (MMC) standards are critical in promoting clients' safety and quality care. The aim is to report on factors that influence non-compliance with standards for MMC in the Lesotho context.

DESIGN: A qualitative, explorative, descriptive research design was used.

METHOD: Four focus group interviews were held with 19 purposively selected registered nurses providing routine MMC for one year or more.
**RESULTS:** Three themes emerged namely: knowledge of quality standards, barriers to compliance, and perceived enabling working environment. Findings highlight barriers such as infrastructure, the high targets that are set for programmes, and societal and cultural issues. Fatigue and burnout were prevalent among MMC providers due to workload. These providers stated carelessness in their work was brought on by overconfidence in their skills, leading to poor compliance with quality standards.

**PUBLIC CONTRIBUTION:** Implementing public health interventions in a clinical setting requires careful planning to respond to epidemics.


**BACKGROUND:** Voluntary medical male circumcision (MC) is a biomedical HIV prevention method that requires post-operative follow-up for healing confirmation. Recent research found that a two-way texting (2wT) app providing SMS-based telehealth for MC patients was safe and reduced provider workload. We evaluated 2wT usability among MC clients in South Africa assigned the 2wT intervention within a larger randomized controlled trial (RCT) of 2wT safety and workload.

**METHODS:** This quantitative usability study is within an RCT where 547 men used 2wT to interact with an MC provider via SMS. The sub-study involved the first 100 men assigned to 2wT who completed a usability survey 14 days after surgery. Acceptability was assessed through 2wT response rates of the 547 men. Regression models analyzed associations between age, wage, location, potential adverse events (AEs), and 2wT responses.

**RESULTS:** Men assigned to 2wT found it safe, comfortable, and convenient, reporting time and cost savings. High response rates (88%) to daily messages indicated acceptability. Age, wage, and location didn't affect text responses or potential AEs.

**CONCLUSION:** 2wT for post-MC follow-up was highly usable and acceptable, suggesting its viability as an alternative to in-person visits. It enhanced confidence in wound self-management. This SMS-based telehealth can enhance MC care quality and be adapted to similar contexts for independent healing support, particularly for men.


**BACKGROUND:** Surgical voluntary medical male circumcision (VMMC) is a safe procedure; however, maintaining quality standards at scale, particularly during scale-up, is a challenge making ongoing quality management (QM) efforts essential. This study describes program quality measured by rates of adverse events (AEs) over four years of VMMC implementation in
Namibia, compares AE rates over time, and discusses QM processes that contextualize AE trends and illustrate improvements in quality as the program matured. The International Training and Education Center for Health (I-TECH) assisted the Namibian Ministry of Health and Social Services (MoHSS) in expanding VMMC in three regions among boys and men over 10 years of age between January 2015 and September 2019.

METHODS: A comprehensive package of QM strategies was implemented by multi-disciplinary onsite teams with support from national and international technical advisors. Retrospective routine MoHSS data from the VMMC register, client forms, and monthly AE reports were collected during implementation in the three regions to assess the impact of QM interventions on AEs and to calculate the proportion of clients who experienced AEs over time. The proportion of clients who experienced an AE over time was compared using a Cochran-Armitage test for trend.

RESULTS: Between January 2015 and September 2019, 40,336 clients underwent VMMC and 593 (1.5%) clients experienced a post-operative AE in the three supported regions. The AE rate was highest in the first quarter of clinical service delivery in each region (January-March 2015 in Oshana and Zambezi, October-December 2017 in Kharas) but declined over the implementation period as the program matured. This observed trend between program maturity and declining AE rates over time was significant (p < 0.001) when compared using a Cochran-Armitage test for trend.

CONCLUSIONS: As the I-TECH-supported VMMC program matured, QM measures were introduced and routinized, and clinical quality improved over time with the rate of AEs decreasing significantly over the implementation period. Applying systematic and continuous QM processes and approaches across the continuum of VMMC services and considering local context can contribute to increased clinical safety. QM measures that are established in more mature program sites can be quickly adopted to respond to quality issues in program expansion sites.