HIV RISK FACTORS

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Human Behavior and HIV

- Human behavior plays a key role in most of the disease conditions in life.
- **Socialization**: A life long process through which individuals in society develop an awareness of social norms and values, and achieve a distinct sense of self.
- **Norms**: Rules and expectations of conduct, which either prescribes a given type of behavior or forbids it.

Human Behavior and HIV

- **Values**: Culturally defined standards held by human individuals or groups about what are desirable, proper, beautiful, good or bad that serve as broad guidelines for social life.
- **The individualistic interpretation of disease**: Places emphasis on the individual as responsible for his or her health status.
- Health compromising behavior by individuals is the main factor causing ill health.

Relative Risk

High risk:
- Sharing needles
- Unprotected sex
- Breast feeding

Lower risk:
- Protected sex
- Any opportunity for exchange of body fluids
- Occupational exposure

No risk:
- Casual contact

Behaviors Likely to Increase Risk to HIV

- Certain behaviors can increase your HIV risk. These are some of the most common risk factors:
  - Having unprotected vaginal, anal, or oral sex with someone who is infected with HIV or whose HIV status you don't know.
  - Having many sexual partners.
  - Having sex with a sex worker or an IV drug user.
  - Sharing needles, syringes, or equipment used to prepare or inject drugs with someone who is HIV infected.
  - Using needles for piercing or tattooing that are not sterile.

Other Possible HIV/AIDS Risk Factors

- Other factors may also increase your HIV risk. For example, having sex under the influence of alcohol or drugs may lead to other risky behaviors, such as having unprotected sex.
- Having another sexually transmitted disease (STD), such as herpes, chlamydia, syphilis, or gonorrhea. STDs may cause changes in tissue that make HIV transmission more likely.

Other Possible HIV/AIDS Risk Factors

- Having sex after drinking alcohol or taking drugs.
- Having a mother who was infected with HIV before you were born.
- Having had a blood transfusion or received blood products before 1985. Since that time, however, all blood is tested for HIV.
- Having fewer copies of a gene that helps to fight HIV.
  - Although not yet available, a screening test might one day be able to identify those who are more likely to get HIV and develop AIDS.

Risk Factors for Sexual HIV Transmission

- Transmission of HIV is facilitated in the presence of other infectious diseases, especially when they are associated with ulcerative lesions of the genital mucosa.
- The higher the viral load in the genital tract, the more easily HIV is transmitted.
- **Sexual contact** between male and female accounts for >90% of HIV transmissions in Kenya.

Risk Factors for Sexual HIV Transmission

- Although there are challenges in quantifying risk by sex act, studies consistently report that anal intercourse is a higher risk act than vaginal intercourse, which in turn is a higher risk act than oral intercourse.
- There is also an increased risk associated with receptive intercourse (both vaginal and anal) compared with insertive intercourse.

Risk Factors for Sexual HIV Transmission

- The risk estimates for the sexual transmission of HIV, per sex act, range widely, from
  - 0.5% to 3.38% (with mid-range estimates of 1.4% to 1.69%) for receptive anal intercourse;
  - 0.06% to 0.16% for insertive anal intercourse;
  - 0.08% to 0.19% for receptive vaginal intercourse (i.e., male-to-female); and
  - approximately 0.05% to 0.1% for insertive vaginal intercourse (i.e., female-to-male).

Risk Factors for Sexual HIV Transmission

- The risk of transmission from unprotected oral intercourse (whether penile-oral or vaginal-oral) is markedly lower than for anal or vaginal intercourse, and findings suggest a low but non-zero transmission probability.
- The risk of transmission to the receptive partner increases with ejaculation and the presence of oral ulcers and sexually transmitted infections (STIs) in the oropharynx.

Risk Factors for Mother-to-Child Transmission of HIV

- A major risk factor in transmission of HIV and a barrier to prevention of VT is lack of awareness of HIV status among pregnant women.
- In the absence of any preventive intervention, for example, highly active antiretroviral treatment (HAART), mother-to-child transmission (also known as “vertical” transmission) ranges from about 15% to 45% depending on whether breastfeeding alternatives are available.

Risk Factors for Mother-to-Child Transmission of HIV

- As with other modes of transmission, maternal plasma viral load has been consistently associated with the risk of vertical transmission.
- Since HAART, (used to suppress viral replication), was introduced in 1997, the rate of mother-to-child transmission has dropped dramatically globally.

Risk Factors for Mother-to-Child Transmission of HIV

- Beyond viral load, there are several factors associated with an increased risk of vertical transmission.
- Concurrent STIs and co-infection with either hepatitis C or active tuberculosis increase the risk of vertical transmission.

Risk Factors for Mother-to-Child Transmission of HIV

- Mother-to-child HIV transmission can also occur through breastfeeding. The probability of transmission of HIV through breastfeeding is in the range of 9% to 16%.
- Co-factors that are associated with risk of transmission from breastfeeding include duration and pattern of breastfeeding, maternal breast health, and high plasma or breast milk viral load.

Risk Factors for Mother-to-Child Transmission of HIV

- While mode of delivery was associated with vertical transmission, since the introduction of HAART, studies indicate that there are probably no additional benefits to elective caesarean section for women with low viral loads.
- Obstetric events, including prolonged rupture of membranes and intrapartum use of fetal scalp electrodes or fetal scalp pH sampling, have been found to increase the risk of perinatal transmission of HIV.

Occupational Risk Factors

- Many factors can increase the risk of HIV infection due to occupational exposure in developing countries:
  - Less stringent safety regulations or standards
  - Unfamiliar practice conditions and equipment
  - Limited availability of personal protective equipment or safety-engineered devices
  - Increased prevalence of injection therapy and unsafe infection practices in many countries

Occupational Risk Factors

- Challenging practice conditions that might result in barriers to Standard Precaution adherence (such as natural disasters or conflict zones)
- Performing unfamiliar medical procedures
- High prevalence of HIV infection (diagnosed and undiagnosed)
- Limited access to HIV treatment, resulting in high viral titers in source patients
- Limited resources for postexposure evaluation and treatment

MEASURES TO REDUCE RISKS OF HIV

Measures to Reduce HIV Risks

- Because HIV is transmitted through infected blood, semen, or vaginal secretions, or through a mother's milk during breastfeeding, these are the most important steps you can take to lower your HIV risk and the risk to others:
- Use a latex condom or square of latex or plastic wrap ("dental dam") each *and every* time you have anal, vaginal, or oral sex. (If you have a latex allergy, use polyethylene condoms with oil-based lubricants.)

Measures to Reduce HIV Risks

- Learn more about how to practice safer sex.
- Learn about the HIV drug Truvada. It has been approved for use in those at high risk as a way to prevent HIV infection. Truvada should be used in conjunction with safe sex practices.
- Don't share needles, syringes, or equipment used to prepare injection drugs or to inject them. HIV can stay in syringes for a month or longer. Seek treatment for drug use, but in the meantime, be sure to use a clean needle each time you inject.

Measures to Reduce HIV Risks

- See a qualified professional who uses sterile equipment if you plan to get a tattoo or have your body pierced.
- Don't share toothbrushes or razors.
- Talk to a doctor about getting tested for HIV if you are pregnant or planning to become pregnant. If you're HIV-positive, seek counseling and treatment, which can prevent HIV from being passed to a fetus or infant in most cases.
- Do not breastfeed if you have a newborn and are HIV-positive.

HIV TRANSMISSION

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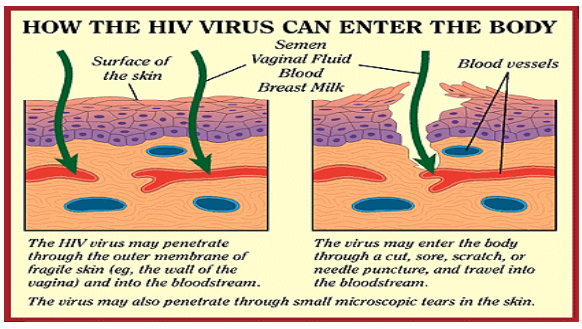
Transmission



Fluids that can Transmit HIV

Fluids that DO transmit HIV:

- Blood
- Semen
- Vaginal Fluid
- Breast Milk

(**in order of the highest concentration of HIV**)

Fluids that DO NOT transmit HIV:

- Saliva
- Tears
- Mucus
- Urine
- Sweat
- Feces

HIV Transmission

HIV is not transmitted by:

- Coughing, sneezing
- Insect bites
- Touching, hugging
- Water, food
- Kissing
- Public baths
- Handshakes
- Work or school contact
- Using telephones
- Sharing cups, glasses, plates, or other utensils

Major Modes of Transmission of HIV in Adults

- Sexual contact
  - Commercial sex
  - Casual sex
  - Marital sex
  - Men who have sex with men (MSM)
- Injecting drug use
- Blood transfusions
- Medical injections and/or Occupational exposure

Sexual HIV Transmission

- Although there are challenges in quantifying risk by sex act, studies consistently report that anal intercourse is a higher risk act than vaginal intercourse, which in turn is a higher risk act than oral intercourse
- The strongest predictor of HIV sexual transmission is **plasma viral load**.
- As plasma viral load increases, the risk of transmission also increases.

Sexual HIV Transmission

- Much of what is known about viral load and HIV transmission is derived from studies of heterosexual populations. As such, little is known about how viral load affects the risk of transmission through anal intercourse.
- The presence of a concomitant STI has also been found to affect HIV transmission. STIs increase susceptibility to HIV by a factor of 2 to 4 and increase transmissibility 2 to 3 times.

Sexual HIV Transmission

- Typical genital coinfections (STIs) in African countries are chlamydia, gonorrhea, *Treponema pallidum, and Herpes simplex virus type 2*.
- Less frequent agents as *Haemophilus ducreyi, Klebsiella granulomatosis,* and HTLV-1.
- HTLV-1 is a well-known retrovirus that is transmitted commonly in Africa, and which can accelerate the deterioration of the immune function in the HIV-infected.

Sexual HIV Transmission

- Male circumcision decreases the risk of female-to-male sexual transmission of HIV by 50% to 60%.
- However, there is little epidemiological evidence to suggest that circumcision reduces the risk of transmission to female partners of circumcised men or is effective in the prevention of HIV among men who have sex with men (MSM).

HIV Transmission among Drug Users

- For people who inject drugs, risk of transmission per injection from a contaminated needle has been estimated to be between 0.7% and 0.8%.
- However, studies of contact with improperly discarded needles outside of the healthcare setting suggest that such exposures represent a low risk for HIV transmission, likely due to the low viability of the virus outside the body.

HIV Transmission among Drug Users

- Sharing ancillary injecting equipment (eg. filters or cookers) during drug injection has been shown to increase the risk of transmission, even in the absence of sharing needles and syringes.
- Other factors that increase risk of HIV transmission for people who inject drugs include:
  - Injecting in unsafe locations
  - Type of drug used
  - Frequency of drug injection

HIV Transmission among Drug Users

- People using non-injection drugs are also at risk of HIV infection.
- Drug use can alter sexual behaviours by increasing risk taking.
- In addition, several drugs have been reported to be independent risk factors for HIV transmission.

HIV Transmission by Blood

- Transmission of HIV and other blood-borne viruses can occur during transfusion of blood components (ie, whole blood, packed red cells, fresh-frozen plasma, cryoprecipitate, and platelets) derived from the blood of an infected individual.
- Depending on the production process used, blood products derived from pooled plasma can also transmit HIV and other viruses, but recombinant clotting factors cannot.

HIV Transmission by Blood

- The risk of HIV transfusion through infected blood products exceeds that of any other risk exposure.
- Ninety percent of recipients transfused with HIV antibody-positive blood are found to be HIV infected at follow-up.
- The 90% probability of sero-conversion is independent of the age or sex of the recipient, the reason for transfusion, and the type of component transfused (excluding washed red blood cells, which transmit HIV at a lower rate).

HIV Transmission by Blood

- HIV disease due to transfusion progresses in the recipient at rates comparable to those in individuals infected for similar duration but by other routes.
- It is likely that host factors, particularly the recipient's age and immune status, and perhaps other as-yet-undefined cofactors influence the progression to AIDS.

HIV Transmission by Occupational Exposure

- The risk of occupational exposure to HIV is most closely related to the activities and duties of the health care worker.
- Additionally, the geographic location and practice setting can also affect the risk of exposure and the quality of postexposure care.
- Accidental infected needle prick to a health care worker; results in 0.03% transmission.

HIV Transmission by Occupational Exposure

- HIV may be transmitted occupationally to health care workers who are:
  - Exposed to blood and other potentially infectious bodily fluids via percutaneous injury or
  - Splash exposures to mucous membranes or nonintact skin.
  - Unfamiliar practice environments can put the health care worker at increased risk of exposure.

HIV Transmission by Occupational Exposure

- In addition to blood, cerebrospinal fluid, synovial fluid, pericardial fluid, pleural fluid, peritoneal fluid, amniotic fluid, semen, and vaginal secretions are considered potentially infectious.
- Saliva, urine, sputum, nasal secretions, tears, feces, vomitus, and sweat are not considered infectious for HIV unless they are visibly bloody.

HIV Transmission by Occupational Exposure

- Typically, exposures occur as a result of percutaneous exposure to contaminated sharps, including needles, lancets, scalpels, and broken glass (from capillary or test tubes).
- Skin exposures to potentially infectious bodily fluids are only considered to be at risk for HIV infection if there is evidence of compromised skin integrity (for example, dermatitis, abrasion, or open wound).

HIV TRANSMISSION IN CHILDREN

HIV Transmission in Children

- A basic difference between **pediatric** and **adult** HIV infection is the **main route of transmission** which is mother to child.
- Transmission of HIV occurs via sexual contact, other exposures to live-virus-containing fluids and tissues including vertical transmission (VT) from mother to child.

Vertical Transmission

- VT can occur **before** (intrauterine), **during** (intrapartum), or **after delivery** (mostly through breast-feeding).
- Breast-feeding is responsible for 30-50% of VT in developing countries
- Breast-feeding is the cause of 90% of pediatric HIV globally and is predominantly a disease of resource-poor regions.

Breast Feeding and HIV

- Breast feeding is an efficient mode of transmission of HIV and can be responsible for up to 50% of cases of VT in some regions; between 320,000 and 800,000 infections per year globally.
- Although transmission can occur at any point during breast feeding, the first 6 weeks of life entail the greatest risk, comprising about 67% of transmissions.

Breast Feeding and HIV

- The greater cellular composition of colostrum and early milk has been suggested as a mechanism for high transmission.
- The frequency of breast-milk transmission is also increased if the mother's $CD4^+$ count is less than 200 cells/mL.

Breast Feeding and HIV

- The World Health Organization (WHO) recommends that women be counseled about the risk of HIV transmission through breast feeding.
- When replacement feeding is affordable, feasible, acceptable, sustainable, and safe, avoidance of all breast feeding by HIV-infected mothers is recommended.

Breast Feeding and HIV

- When replacement feeding is not possible, exclusive breast feeding is recommended and breast feeding should be discontinued as soon as possible.
- In some regions and cultures, premastication of solid foods by an adult prior to feeding of an infant occurs. If the adult is HIV-infected, this practice can result in infection of the child

Priority Populations and Programs

Route	Population	Intervention
Sex work	SW and clients	Out-reach, condoms, STI Treatment
Casual sex	Youth, military, truckers, etc.	Out-reach, condoms, STI
Low risk	Married couples	Promote testing
IDU	IDU	Risk elimination, harm reduction
MSM	MSM	Out-reach, condoms, STI Treatment
Injection	Patients	Sterile needles
Blood	Transfusion recipients	Screening
Mother-to-child	Pregnant women	PMTCT

Male circumcision to reduce sexual transmission of HIV

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Purpose of review

Three large trials among African heterosexual men in the last decade have confirmed that male circumcision reduces HIV acquisition. This review summarizes recent data regarding circumcision performed primarily to reduce HIV in high-prevalence settings.

Recent findings

Male circumcision more than halved the acquisition of HIV in the trials, and was associated with few adverse events and high levels of satisfaction. An additional trial found no direct reduction in HIV risk for female partners of circumcised men. Evidence for an HIV-protective effect of circumcision in men who have sex with men is weak and inconclusive. Acquisition of HSV-2 and high-risk human papillomavirus are both reduced in circumcised heterosexual men, whereas acquisition of common male urethral pathogens are not. Concerns exist that behavioural disinhibition could offset benefits of this intervention, and it remains to be seen whether the low rate of adverse events and adoption of safer sexual practices observed in the trials will be maintained in circumcision programmes outside trial settings.

Summary

The evidence that circumcision reduces HIV in African heterosexual men is clear. The impedance of political, cultural and logistic factors on expansion of much-needed African circumcision services requires urgent attention.

Keywords

circumcision, HIV, male, sexually transmitted diseases

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Introduction

Observational evidence supporting a reduction in HIV risk among circumcised men began mounting soon after HIV/AIDS was first recognized. In the past 5 years, a trio of African circumcision trials have accounted for 35 of over 660 articles listed in PubMed regarding circumcision and HIV. Most importantly, these trials have provided much-needed randomized data that circumcision more than halves the risk of HIV acquisition in heterosexual African men [1••–3••].

Subsequently, a number of global health agencies including WHO/UNAIDS have recommended male circumcision to be an integral component of HIV prevention efforts in hyper-endemic heterosexual HIV epidemics when male circumcision prevalence is low [4]. However, the roll-out of male circumcision in such countries has been variable, hampered by cultural concerns, religious beliefs, insufficient funding, inadequate health infrastructure and human resources, lack of political will and concerns regarding cost–effectiveness [5•–7•].

The article will summarize the clinical trial data published to date, and discuss recent developments on the impact of male circumcision (from here referred to simply as 'circumcision') on susceptibility to HIV and other sexually transmissible infections (STIs), global HIV epidemiology and sexual behaviour.

Biological plausibility that circumcision reduces the risk of HIV

A number of biological factors modified by circumcision may influence penile susceptibility to HIV. These include degree of tissue keratinization, density and superficiality of HIV target cells, alteration of the penile microenvironment, direct effects on HIV transmission-cofactor STIs, intercourse-related trauma, and possibly, retention of infectious secretions below the foreskin.

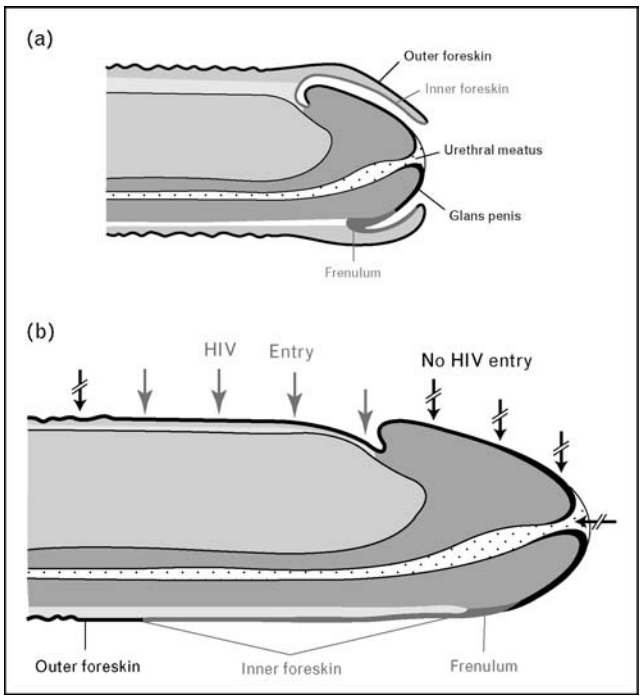
An important factor hypothesized to increase HIV susceptibility in uncircumcised men is a thinner keratin layer of the inner aspect of the foreskin compared with the outer foreskin or glans [8,9]. However, recently published studies have reported no significant difference in keratin thickness [10•], or even a thicker keratin layer of the inner, compared with outer, foreskin [11]. Such observations seem counter-intuitive and at odds with the macroscopic appearance of penile tissue. Indeed, the former study [10•] used foreskins from donors being circumcised for unknown medical indications, thus

underlying foreskin pathology could itself have influenced keratin thickness.

During intercourse the foreskin is usually retracted, exposing a large surface area of high-density superficial Langerhans' and other HIV target cells to HIV-infected tissues and secretions (Fig. 1). Strengthening the biological plausibility of this hypothesis are findings from the Rakai trials that men with larger foreskin surface areas are at increased risk of HIV acquisition [12•].

The first molecular analysis of penile bacterial diversity was recently published and provided further insight into possible biological mechanisms contributing to reduced HIV susceptibility of circumcised men. In a dozen HIV-negative Ugandan men, circumcision altered microbiota at the penile corona [13••]. A significant decrease in putative anaerobic bacteria was observed, possibly due to removal of subpreputial anoxic microenvironments by circumcision. Such anaerobic bacteria may mediate genital mucosal inflammation or coinfections in uncircumcised men. Thus a reduction in these anaerobic bacteria after circumcision could act alongside removal of the inner foreskin mucosa to reduce the number of activated Langerhans' cells and thus lower the risk of HIV acquisition [13••]. Should the presence or absence of specific penile bacteria be associated with HIV acquisition in future trials of men who acquire HIV, an antimicrobial approach to modify the penile microenvironment could provide a nonsurgical avenue for HIV risk reduction.

Figure 1 Flaccid and erect uncircumcised penis



(a) Flaccid uncircumcised penis. (b) Erect uncircumcised penis with the foreskin retracted showing likely sites of HIV-1 entry. Reproduced with permission from [8].

Both genital ulcer disease (GUD) and HSV-2 appear to be independent cofactors facilitating HIV transmission [14]. Circumcision reduced the risk of HSV-2 in addition to symptomatic GUD irrespective of HSV-2 status in the Rakai trials [15•]. The proportion of reduced HIV acquisition in circumcised men statistically attributable to reductions in symptomatic GUD and incident HSV-2 was estimated to be only 11.2 and 8.6%, respectively [15•]. Although other STIs are also believed to increase HIV-acquisition risk [16], the circumcision trials have found no protective effect of circumcision on syphilis, gonorrhoea or chlamydia [17••,18••,19•].

Lessons from the African adult male circumcision trials

Circumcision provided a 50–60% reduction in HIV-acquisition risk in the three African trials involving over 1000 participants [1••–3••]. In Kenya, efficacy was further increased at 42 months, confirming the longer-term benefits of circumcision for HIV prevention [20].

In addition to the protective effect of circumcision on HIV acquisition, circumcised male participants appear to be at reduced risk of HSV-2 [18••,21•], high-risk prevalent human papillomavirus (HPV) [18••,22•], but not syphilis [18••]. The lack of a protective effect of circumcision on incident syphilis is at odds with the majority of observational data [23]. In contrast, the trials confirmed the balance of observational evidence that circumcision has little, if any, impact on male urethral gonorrhoea, chlamydia or trichomoniasis [17••,19•].

Male circumcision was well tolerated under the controlled condition of clinical trials with few participants experiencing adverse events [1••,24,25]. However, most circumcisions in Africa are currently performed by traditional practitioners in informal settings in which the rate of adverse events are over twice that of circumcision performed by clinicians in more formal healthcare settings [26]. Adverse events were more common in trial participants who resumed sexual activity before circumcision wound healing, among HIV-infected participants and in procedures performed by less experienced surgeons [1••,24,27]. Healing was somewhat slower among HIV-infected, compared with HIV-uninfected participants [24]. Postcircumcision pain was reported by fewer than 15% of participants [28], and was mostly mild and short-lived [2••]. Sexual dysfunction was not associated with adult circumcision [29,30]. In fact, circumcised Kenyan trial participants actually reported increased

penile sensitivity and enhanced ease of reaching orgasm [29]. Similar positive sexual experience outcomes were reported by most female partners. Over 97% reported their sexual satisfaction was unchanged or improved following their male partners' circumcision in Rakai [31]. Resumption of normal (nonsexual) activities after circumcision was rapid and over 90% of participants were satisfied with the outcome [1••,25,30].

Although early resumption of sexual intercourse (<42 days from circumcision) was reported by almost one-quarter of Orange Farm participants, under 6% of those enrolled in Kenya and Uganda reported early sex [32•]. No increased HIV risk was observed as a result of delayed healing or early sex in a combined analysis of the trials [32•], although power was limited by a low number of HIV seroconversions in the 6-month postcircumcision period.

Behavioural disinhibition

An integral component of all three randomized circumcision trials [1••–3••] was ongoing risk-reduction counselling, which undoubtedly reduced sexual risk behaviours among all study participants. Only the South African study showed consistent patterns of risk compensation following circumcision [1••,3••,33]. Circumcised participants reported a significantly higher mean number of sexual partners during both year 1 and year 2 of follow-up [1••] and a number of other sexual risk behaviours were nonsignificantly more common. Despite this, the substantial protective effect of circumcision remained among participants in the Orange Farm trial [1••] and was remarkably consistent with results of the two other trials [2••,3••].

Mathematical models suggest there would be a substantial decline in circumcision efficacy for HIV prevention if risk behaviours increase across an entire population [5•]. Men circumcised as neonates could be at low risk of behavioural compensation as they are unlikely to recall, or be conscious of, a change in their own HIV risk. Nonetheless, knowledge that a man's circumcision status affects his susceptibility to HIV could change social norms leading to community-wide risk compensation [7•].

Of concern is whether the intensive behavioural interventions implemented in the circumcision trials will accompany the broader African roll-out of circumcision. Participants in the trials were informed that the evidence for circumcision preventing HIV was unknown [1••] or inconclusive [33]. Now that this evidence is irrefutable [34], current programmes are promoting circumcision as a definitive and effective prevention strategy. It is unclear how behaviour may change in response to a one-off partially effective intervention. In addition, the lack of observed increase in risk behaviour during the short follow-up of the trials may not translate to the long-term risk reduction necessary to maintain the protective effect of circumcision. Promoting a combination circumcision/safer sex-prevention package to ensure individuals understand that circumcision does not completely remove the risk of HIV acquisition will be challenging.

Male circumcision for prevention of HIV acquisition by female partners

There is clearly an indirect population-level benefit of male circumcision for female HIV acquisition. Reducing HIV prevalence among men via circumcision will diminish the risk of onward HIV transmission to female sexual partners [5•,35••]. An indirect HIV-protective effect may also be mediated by the effect of circumcision on reducing female genital infections; important cofactors facilitating HIV acquisition in women [36•,37••]. The African trials found women with circumcised male partners to be at lower risk of *Trichomonas vaginalis*, bacterial vaginosis and possibly GUD [36•,37••]. A direct HIV-protective effect of male circumcision for female partners has been suggested by some, but not all, observational studies [35••].

Male circumcision had no impact on HIV acquisition among female partners in a recently reported Ugandan trial. Seventeen (18%) females in the intervention arm compared with 8 (12%) in the control arm acquired HIV during 24 months of follow-up [adjusted hazard ratio (AHR) 1.59, 95% confidence interval (CI) 0.62–3.57] [37••]. Unfortunately, few serodiscordant couples enrolled and early termination of the study resulted in limited power. Early postcircumcision resumption of sexual intercourse among HIV-infected men may have resulted in increased HIV transmission to some female partners in the trial. However, as the increased transmission risk is short-lived during healing, mathematical models suggest even high levels of early postcircumcision sex are unlikely to have an adverse population-level effect on female HIV acquisition [5•].

Two prospective observational studies of monogamous HIV-serodiscordant partners have found borderline significant protective effects of male circumcision on female HIV acquisition [38•,39]. A possible reduction in female HIV acquisition from circumcised immunocompetent HIV-1-infected African males over 18 months of follow-up was recently reported in the largest ($n = 1000$ couples) of these studies based on data from the Partners in Prevention HSV suppression trial (hazard ratio 0.62, 95% CI 0.35–1.10) [38•].

Both these prospective studies were included in a recent systematic review and meta-analysis analysing the effect

of circumcision on African female HIV acquisition [35••]. The random-effects meta-analysis, which included the Ugandan trial data and six longitudinal analyses, suggested little direct effect of male circumcision on female HIV acquisition [summary relative risk (RR) 0.80, 95% CI 0.53–1.36], although between-study heterogeneity ($P = 0.05$) urges caution when interpreting this figure.

The logistics of a further circumcision trial to definitively answer the question of male-to-female HIV transmission appear almost insurmountable. Around 10 000 serodiscordant heterosexual couples would need to be enrolled and followed for at least 2 years [35••]. Thus high-quality prospective observational research will be relied upon for the foreseeable future.

Male circumcision and HIV among men who have sex with men

Male circumcision appears to have little impact on HIV acquisition among men who have sex with men (MSM), although all evidence to date has been observational [40]. A meta-analysis involving over 50 000 MSM participants studied prior to February 2008 reported no overall effect of circumcision on the odds of HIV infection [odds ratio (OR) 0.95, 95% CI 0.81–1.11] [41••].

Biological plausibility suggests that any direct protective effect male circumcision may afford MSM would be limited to those practising the insertive role in anal intercourse. However, the results of such studies assessing this have provided conflicting results. The meta-analysis authors analysed three studies among MSM who primarily engaged in insertive anal sex and no association was observed between male circumcision and HIV (OR 0.71, 95% CI 0.23–2.22) [41••]. This analysis included the first published prospective data which found circumcised insertive MSM to be at significantly lower risk of HIV, despite limited power due to the relative inefficiency of HIV transmission to insertive partners (hazard ratio 0.11, 95% CI 0.01–0.92) [42•]. Likewise, the first study of predominantly insertive MSM in a resource-poor setting was recently published and found a substantial reduced odds of HIV in South African MSM, among whom over 75% were exclusively the insertive partner (OR 0.22, 95% CI 0.15–0.32) [43•].

There are even fewer data on the impact of male circumcision on STI acquisition among MSM [40]. The only longitudinal study to assess the association with a broad range of STIs was recently published, and found circumcised MSM to be at significantly reduced risk of syphilis (AHR 0.36, 95% CI 0.15–0.89), but none of the other STIs examined [44•].

As MSM continue to bear a disproportionate burden of HIV and STIs [45,46] additional prevention strategies are clearly required. However, current evidence suggests that a circumcision intervention would be of limited HIV/STI-prevention benefit to this population [40].

Generalizability of African trial findings to resource-rich settings

It remains unclear whether trial findings in African settings can be generalized to heterosexuals in resource-rich settings. Substantial disparities often exist between such areas in terms of heterosexual HIV and STI prevalence, at-risk populations, principal mode of HIV transmission, genital hygiene, and access to condoms and safer sex education. Despite such differences, it is likely circumcision would have a protective, although attenuated, effect on HIV incidence and prevalence in some resource-rich countries.

A number of cost–effectiveness analyses have recently been published using local data to ascertain the potential utility of circumcision on HIV epidemics in non-African settings. Authors from the US Centers for Disease Control and Prevention estimated that the risk of HIV would be reduced in all heterosexual US males by 17% by neonatal circumcision [47•]. The greatest impact was estimated to occur among black (21% reduction) and Hispanic (12% reduction) males. These US populations are disproportionately affected by HIV and have lower circumcision rates than white US males, but poor access to neonatal circumcision services. Among MSM, a recent mathematical transmission model estimated that adult circumcision could be cost effective in resource-rich settings [48•]. Nonetheless, plausible levels of behavioural disinhibition could easily offset the benefits of an MSM circumcision intervention, and the initial financial investment required may be prohibitive [48•].

Conclusion

Circumcision appears acceptable to adult men, their female partners and parents as an STI/HIV prevention intervention in high-prevalence African settings, even among traditionally noncircumcising populations [49]. Resources should be focused on HIV-uninfected men to maximize the prevention impact of mass circumcision programs. However, systematic refusal to circumcise HIV-positive men should be avoided as it may stigmatize all uncircumcised men in these populations [5•]. In the long term, circumcising men prior to sexual debut has the greatest potential population-level benefit, as the partially protective effects are cumulative over a man's sexual lifetime [7•]. Circumcising newborns may be optimal as neonatal circumcision is better tolerated, easier and more cost effective than circumcision at older ages [7•,50], despite the greater time delay between circumcision and prevented infections [51•]. Unfortunately, political,

cultural and logistic challenges continue to impede the successful implementation of circumcision programmes in many sub-Saharan African countries [6•].

Proponents and opponents of circumcision will continue to debate its benefits, ethics and acceptability, often with unyielding conviction in their beliefs. Health benefits for circumcised males in addition to HIV risk reduction include reduced risk of infant UTIs, penile carcinoma and dermatoses, and some, but not all, STIs [17••,18••,19•,*22*•,47•]. There is little if any evidence of significant HIV protection for female partners of circumcised men and circumcised MSM overall.

There is an urgent need for rapid and comprehensive expansion of circumcision programs in sub-Saharan Africa. In such high HIV-prevalence settings with limited healthcare and HIV/STI-prevention resources, the benefits of male circumcision are clear. For resource-rich countries with low heterosexual HIV prevalence and accessible medical care, HPV vaccination, condoms and health education, the arguments in favour of routine circumcision are less compelling.

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References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 354–355).

1 Auvert B, Taljaard D, Lagarde E, *et al.* Randomised controlled intervention trial •• of male circumcision for reduction of HIV infection risk: the ANRS 1265 trial. PLoS Med 2005; 2:e298.
See Bailey [2••] below.

2 Bailey RC, Moses S, Parker CB, *et al.* Male circumcision for HIV prevention in •• young men in Kisumu, Kenya: a randomised controlled trial. Lancet 2007; 369:643–656.
This randomized trial of male circumcision was published in the same edition of *The Lancet* as Gray *et al.* [3••] and both trials confirmed the landmark findings of Auvert *et al.* [1••] from 2 years previously that circumcision reduced the risk of HIV acquisition among heterosexual African men by 50–60%.

3 Gray RH, Kigozi G, Serwadda D, *et al.* Male circumcision for HIV prevention in •• men in Rakai, Uganda: a randomised trial. Lancet 2007; 369:657–666.
See Bailey [2••] above.

4 WHO/UNAIDS Technical Consultation. Male circumcision and HIV prevention: research implications for policy and programming. http://www.who.int/hiv/mediacentre/MCrecommendations_en.pdf; March 2007. [Accessed 28 January 2010]

5 UNAIDS/WHO/SACEMA Expert Group on Modelling the Impact and Cost of • Male Circumcision for HIV Prevention. Male circumcision for HIV prevention in high HIV prevalence settings: what can mathematical modelling contribute to informed decision making? PLoS Med 2009; 6:e1000109.
Reports the outcome of three expert group meetings convened in the last 5 years to assess the potential population-level effects of male circumcision in HIV incidence predicted by a number of mathematical models. These models suggest large benefits for heterosexual men in high-HIV, low-circumcision prevalence settings over a 10-year time horizon.

6 de Bruyn G, Martinson NA, Gray GE. Male circumcision for HIV prevention: • developments from sub-Saharan Africa. Expert Rev Anti Infect Ther 2010; 8:23–31.
Guy de Bruyn and colleagues present an excellent and comprehensive review on the impact of male circumcision on HIV and other STIs in Africa. Of special interest is their presentation and analysis of the recent experience, operational challenges and progress of circumcision scale-up in selected sub-Saharan countries.

7 Kalichman SC. Neonatal circumcision for HIV prevention: cost, culture, and • behavioral considerations. PLoS Med 2010; 7:e1000219.
This brief but insightful perspective was published alongside a circumcision cost–effectiveness analysis from Rwanda (Binagwaho *et al.* [51•] below), and underscores the importance of considering cultural and behavioural factors in the scale-up of circumcision interventions in southern Africa.

8 McCoombe SG, Short RV. Potential HIV-1 target cells in the human penis. AIDS 2006; 20:1491–1495.

9 Patterson BK, Landay A, Siegel JN, *et al.* Susceptibility to human immunodeficiency virus-1 infection of human foreskin and cervical tissue grown in explant culture. Am J Pathol 2002; 161:867–873.

10 Dinh MH, McRaven MD, Kelley Z, *et al.* Keratinization of the adult male foreskin • and implications for male circumcision. AIDS 2010; 24:899–906.
This study provides conflicting data to those of previous studies, and reports the thickness of internal and external penile keratin layers to be no different among 16 donor specimens, with great interdonor and intradonor heterogeneity in penile keratin thickness.

11 Qin Q, Zheng XY, Wang YY, *et al.* Langerhans' cell density and degree of keratinization in foreskins of Chinese preschool boys and adults. Int Urol Nephrol 2009; 41:747–753.

12 Kigozi G, Wawer M, Ssettuba A, *et al.* Foreskin surface area and HIV • acquisition in Rakai, Uganda (size matters). AIDS 2009; 23:2209–2213.
An amusing title for a study that found men with larger foreskin surface areas to be at highest risk of HIV acquisition. This finding supports biological hypotheses that the foreskin is especially susceptible to HIV.

13 Price LB, Liu CM, Johnson KE, *et al.* The effects of circumcision on the penis •• microbiome. PLoS One 2010; 5:e8422.
The first molecular data of circumcision-related changes in the penile microenvironment that provide an additional biological hypothesis as to why circumcised men are at reduced risk of HIV.

14 Tobian AA, Quinn TC. Herpes simplex virus type 2 and syphilis infections with HIV: an evolving synergy in transmission and prevention. Curr Opin HIV AIDS 2009; 4:294–299.

15 Gray RH, Serwadda D, Tobian AA, *et al.* Effects of genital ulcer disease and • herpes simplex virus type 2 on the efficacy of male circumcision for HIV prevention: analyses from the Rakai trials. PLoS Med 2009; 6:e1000187.
This study presents data regarding the effect of circumcision on GUD and HSV-2, and the consequent indirect HIV-protective effects achieved by circumcision.

16 Fleming DT, Wasserheit JN. From epidemiological synergy to public health policy and practice: the contribution of other sexually transmitted diseases to sexual transmission of HIV infection. Sex Transm Infect 1999; 75:3–17.

17 Mehta SD, Moses S, Agot K, *et al.* Adult male circumcision does not reduce •• the risk of incident *Neisseria gonorrhoeae*, *Chlamydia trachomatis* or *Trichomonas vaginalis* infection: results from a randomized, controlled trial in Kenya. J Infect Dis 2009; 200:370–378.
This paper describes the first longitudinal data on urethral STIs from the African randomized heterosexual trials. The findings support observational data and trial data from Orange Farm that circumcision has little impact on common male urethral pathogens.

18 Tobian AA, Serwadda D, Quinn TC, *et al.* Male circumcision for the prevention •• of HSV-2 and HPV infections and syphilis. N Engl J Med 2009; 360:1298–1309.
This important study described the first randomized circumcision data that male circumcision prevents HSV-2 acquisition in addition to lowering the prevalence of high-risk HPV infection in circumcised heterosexual African men. However, in contrast to most observational data, circumcision had no effect on syphilis acquisition, a finding that merits further investigation.

19 Sobngwi-Tambekou J, Taljaard D, Nieuwoudt M, *et al.* Male circumcision and • *Neisseria gonorrhoeae*, *Chlamydia trachomatis,* and *Trichomonas vaginalis*: observations in the aftermath of a randomised controlled trial for HIV prevention. Sex Transm Infect 2009; 85:116–120.
This cross-sectional analysis from the final follow-up visit of the Orange Farm circumcision trial found no association of circumcision with prevalent urethral *Chlamydia* or gonorrhoea, but circumcised participants had a borderline lower prevalence of urethral trichomoniasis. The authors propose this finding may account for the lower prevalence of vaginal trichomoniasis in female partners of circumcised men.

20 Bailey RC, Moses S, Parker CB, *et al.* The protective effect of male circumcision is sustained for at least 42 months: results from the Kisumu, Kenya trial [abstract #THAC0501]. XVII International AIDS Conference; 3–8 August 2008; Mexico City, Mexico.