

## Male circumcision and HIV infection: 10 years and counting

Daniel T Halperin, Robert C Bailey

A decade has passed since publication of Cameron and colleagues' prospective study<sup>1</sup> that showed a greater than eight-fold increased risk of HIV-1 infection for uncircumcised men. Today, many observers of the AIDS pandemic are puzzled by the glaring discrepancies in HIV seroprevalence between different countries and regions, despite the presence of what seem to be similar risk factors. For example, the November, 1998 UNAIDS/WHO Report on the AIDS Epidemic concludes, "It is not fully understood why HIV infection rates take off in some countries while remaining stable in neighbouring countries over many years."

We argue that since Cameron and colleagues' landmark study, the epidemiological and biological evidence that links lack of circumcision with HIV transmission has become compelling and that lack of male circumcision is one of the main causes of many regional discrepancies in rates of HIV infection. Furthermore, as increasing numbers of men in some traditionally non-circumcising communities seek safe affordable circumcisions to avoid AIDS and other sexually transmitted diseases (STDs), it is time for the international health community to add male-circumcision services to the current limited armamentarium of AIDS prevention measures in countries with a high prevalence of heterosexually transmitted HIV and STDs.

### Epidemiological findings

In their study of the risk factors for HIV infection among 422 men who visited commercial sex workers in Nairobi, Kenya, Cameron and colleagues found that men who were not circumcised had a 8.2-fold increased risk of seroconversion, compared with circumcised men.<sup>1</sup> Subsequently, six more prospective studies from four countries investigated the relative risk of heterosexual HIV-1 infection in uncircumcised men. Four studies reported significant relative risks that ranged from 2.3 to 4.5 after multivariate analyses, and in the other two prospective studies multivariate risk ratios were 3.0 or greater, but were not significant.<sup>2</sup> Of 38 cross-sectional studies, 27 from eight countries found a significant association between lack of male circumcision and HIV infection, five found a trend towards an association, five found no association, and one reported an increased risk of infection in men who had been circumcised.<sup>2,3</sup> In 1994, Moses and colleagues<sup>3</sup> established that, on the basis of

the information available at the time, the association between lack of male circumcision and HIV infection met all but three of Hill's criteria for making causal inferences; an additional 17 studies from eight countries have since been published. That circumcision is partially protective has been documented even in settings in which circumcised men have higher risk profiles for HIV transmission (eg, more sexual partners, alcohol use, and some STDs).<sup>4,5</sup>

More recently, while epidemiologists have been investigating the protective effect of male circumcision against HIV infection, a wider public discussion has ensued with regard to why, 20 years into the pandemic, some countries continue to retain fairly low HIV seroprevalence, whereas in other places, sometimes even neighbouring regions, rates of infection are many times higher (table). For example, rates of HIV-1 infection continue to be much lower in the Philippines (0.06% of the adult population), in Bangladesh (0.03%), and in Indonesia (0.05%) than in Thailand (2.2%), India (0.8%), and Cambodia (2.4%). Such dramatic discrepancies, sometimes on the order of ten-fold to 50-fold, have been attributed to differences in surveillance systems or the implication is made that governments, non-governmental organisations, and international agencies have mounted more effective prevention programmes in countries that have low HIV seroprevalence. Yet the pandemic has been raging for too long and surveillance and prevention efforts have been too pervasive for such a widespread, consistent pattern to be so easily explained.

### Biological mechanisms

For over a decade researchers have suggested that the foreskin provides a vulnerable portal of entry to HIV and other pathogens.<sup>6</sup> The highly vascularised prepuce has been discovered to contain a higher density of Langerhans cells—primary target cells for sexual transmission of HIV—than cervical, vaginal, or rectal mucosa.<sup>7</sup> Other scientists and clinicians have noted that the foreskin is more susceptible to traumatic epithelial disruptions during intercourse, which allows additional vulnerability to HIV.<sup>1</sup> An intact foreskin also exposes a man to greater risk of ulcerative STDs, such as chancroid, syphilis, and herpes, that are known cofactors for HIV infection.<sup>2</sup>

Although the increased risk of HIV transmission in uncircumcised men is independent of genital-ulcer diseases,<sup>1,6</sup> a cycle of amplification occurs in which these diseases enhance transmission of HIV—HIV infection increases the frequency of genital-ulcer disease, and lack of male circumcision augments the transmission of both genital-ulcer diseases and HIV. This amplification was highlighted by Cameron and colleagues,<sup>1</sup> who found that all but one of the 24 seroconversions occurred in men

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<20% circumcised	Seroprevalence*	>80% circumcised	Seroprevalence*
<b>Sub-Saharan Africa</b>			
Zimbabwe	25.84	Kenya	11.64†
Botswana	25.10	Congo (Brazzaville)	7.64
Namibia	19.94	Cameroon	4.89
Zambia	19.07	Nigeria	4.12
Swaziland	18.50	Gabon	4.25
Malawi	14.92	Liberia	3.65
Mozambique	14.17	Sierra Leone	3.17
Rwanda	12.75	Ghana	2.38
		Gambia	2.24
		Guinea	2.09
		Benin	2.06
<b>South and southeast Asia</b>			
Cambodia	2.40	Pakistan	0.09
Thailand	2.23	Philippines	0.06
Myanmar	1.79	Indonesia	0.05
India	0.82	Bangladesh	0.03
Nepal	0.24		

Countries within each geographical region have similar risk factors for heterosexual HIV infection (eg, multiple sexual partners, widespread STDs, low condom use). Countries excluded from table because: (1) estimated proportion of men circumcised >20%, <80%; (2) similar risk factors for heterosexual HIV epidemic not present; (3) insufficient information.

\*June 1998 UNAIDS/WHO % estimates. †Excluding the predominately non-circumcising region around Kisumu, western Kenya, where HIV-1 seroprevalence is 34.9%, national seroprevalence would be about 8%.

#### HIV-1 seroprevalence in sub-Saharan African and south/southeast Asian countries by estimated proportion of men circumcised

who had a genital-ulcer disease, were uncircumcised, or had both risk factors.<sup>1</sup> Since the probability of female-to-male transmission of HIV-1 is otherwise very low, as rare as one per 9000 acts of unprotected vaginal intercourse in the absence of facilitating risk factors,<sup>8</sup> a widespread heterosexual AIDS epidemic is unlikely. However, when a large proportion of men are uncircumcised and STDs are common, conditions are ideal for an explosive epidemic of HIV infection.<sup>9</sup>

Male circumcision, were it to be adopted by a substantial proportion of men within customarily non-circumcising societies, could have a huge impact on the HIV pandemic in developing countries. If the relative risk of HIV-1 infection for uncircumcised men is 2.5 (near the low end of the risks found in the prospective studies) in a country where 20% of men are not circumcised, which is roughly the situation in countries such as Nigeria and Indonesia, the proportion of heterosexual HIV-1 infections in men attributable to lack of circumcision is 23%.<sup>10,11</sup> On the other hand, if 80% of men are not circumcised, as is roughly the case in Zambia and Thailand, an estimated 55% of HIV-1 infections in men are attributable to lack of circumcision. In populous regions such as South Asia where a large population of men are uncircumcised, the number of infections attributable to lack of male circumcision could soon reach into the millions.

#### Public-health response

In the face of such compelling evidence, we would expect the international health community to at least consider some form of action. However, the association between lack of male circumcision and HIV transmission has met with fierce resistance,<sup>12</sup> cautious scepticism,<sup>13</sup> or, more typically, utter silence, which is evidenced by a dearth of public-health information on the issue. For example, the Johns Hopkins Media/Materials Clearinghouse has been unable to identify among its comprehensive collection of over 30 000 health communication materials a single pamphlet, poster, or flyer that mentions lack of male circumcision in relation to HIV/AIDS.

Circumcision is a surgical procedure that outside of the USA, Canada, Australia, and South Korea is restricted mainly to specific cultural and religious groups. Perhaps because circumcision is usually imbedded in a complex web of deeply held cultural values and religious beliefs, many health professionals have been hesitant to integrate it with other HIV and STD prevention strategies. Yet these same health professionals have seldom hesitated to promote use of condoms or attempt other sweeping changes in sexual behaviour—practices that may be equally charged with deeply rooted cultural and religious meanings. Although promotion of changes in sexual behaviour and condom use remain two of the three cornerstones of HIV prevention in most developing countries (STD treatment now constitutes the third), male circumcision remains largely unexplored, at least by the international public-health community.

#### Response on the ground

In east and southern Africa, increasing numbers of people are becoming aware of the differences in prevalence of AIDS and STDs between circumcised and uncircumcised men, and they are taking action. Male circumcision is increasingly recommended by traditional healers.<sup>14</sup> Private clinics that specialise in male circumcision, many of which are run by people with minimum or no medical training, are sprouting up in Tanzania, western Kenya, Rwanda, and Uganda,<sup>2,9</sup> and many advertise their services as a way to alleviate chronic STD infection and AIDS. Young men and adolescents in east and southern Africa are increasingly electing circumcision—both the medically safe procedure and more precarious non-clinical methods—in regions where traditionally they have avoided the practice. In a recent Ugandan study, 23% of non-Muslim men not belonging to any traditionally circumcising ethnic group reported that they were circumcised.<sup>5</sup> In western Kenya, 60% of uncircumcised men stated that they would prefer to be circumcised;<sup>15</sup> similarly, researchers in Tanzania concluded that “ethnic group or religious denomination are no longer the sole determination of male circumcision”.<sup>16</sup> As the leader of a South African traditional healers’ organisation has reflected, “When tradition and the health of our people are in conflict, it is tradition we must sacrifice.”<sup>14</sup>

#### Time for action

By avoiding this issue altogether, medical professionals and public-health authorities may inadvertently be harming the very individuals whom they are trying to help. As increasing numbers of men and boys turn to circumcision as perceived protection from AIDS, many will be exposed to harm by untrained practitioners who use unsafe methods. Yet, contrary to some popular misconceptions, safe and inexpensive male circumcision is routinely performed in developing countries in clinical settings. The procedure is normally performed on an outpatient basis with local anaesthesia, and most men return to light work activities the next day.

The hour has passed for the international health community to recognise the compelling evidence that show a significant association between lack of male circumcision and HIV infection. It is time to take the following actions: to provide communities with accurate, balanced information so that individuals can make informed choices; to provide the training and resources

needed to offer safe, voluntary male circumcision in which pain is kept to a minimum; and to begin investigations of the feasibility of acceptable male-circumcision interventions in communities with high HIV and STD seroprevalence where circumcision has traditionally not been practiced. To our knowledge, these actions have so far been adopted only in western Kenya on a trial basis.<sup>15</sup>

Finally, an important caution is in order. Offering male-circumcision services as a way to prevent HIV transmission will be counterproductive if men opt for the procedure believing it will fully protect them from AIDS. As the results of Kelly and colleagues' study<sup>17</sup> suggest, although male circumcision before age 20 has a protective effect, when the procedure is preformed on adults it may not reduce the risk of HIV transmission. One explanation for this finding, in addition to the possibility of infection before circumcision, is adoption of circumcision by those individuals who are already at increased risk of infection. Male-circumcision interventions must not be perceived by individuals or communities as a substitute for other HIV and STD prevention strategies. Rather, information about and services for male circumcision should be integrated with existing AIDS prevention and reproductive health programmes in places with a high prevalence of HIV infection.

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## Male circumcision and HIV infection

Sir—Daniel T Halperin and Robert C Bailey (Nov 20, p 1813),<sup>1</sup> urge widespread prophylactic circumcision in the parts of Africa that have not yet embraced it. Their viewpoint, however, leaves unasked questions, such as why does Europe, where the men are largely uncircumcised, enjoy one of the lowest HIV rates in the world, while North America, where men are usually circumcised, suffers one of the highest.<sup>2</sup>

Until such questions are answered *The Lancet* should refrain from promoting the controversial public-policy outlined in this viewpoint. The popular press, famously unable to distinguish between sensational editorials and solid research, has already dangerously distorted this review. For example, the Nov 18, 1999, press release by the University of California at San Francisco (Halperin's institution) bears the alarmist headline "Male circumcision could prevent millions of HIV infections" (<http://www.ucsf.edu/pressure/1999/11/111901.html>). Not until the fifth paragraph of the release does one learn that Halperin and Bailey were examining African and Asian studies, the results of which have not held true in Europe and North America.

Halperin compounds the error of his press release in an interview he granted the Californian newspaper *The Bay Area Reporter* on Nov 24, 1999, (<http://www.ebar.com/barnnews.htm#article2>). In that interview, Halperin says, "If I were a top [insertive partner in anal intercourse], and I didn't like to use condoms, I would consider getting circumcised", thus explicitly contradicting his own caveat in *The Lancet*: "male circumcision interventions must not be perceived by individuals or communities as a substitute for other HIV and STD prevention strategies."

Halperin and Bailey rightly warn that a public misunderstanding of their position might have disastrous effects on HIV containment. They claim their first priority is "to provide communities with accurate, balanced information so that individuals can make informed choices." Their publicity efforts so far, however, inspire little confidence that their information would be balanced or accurate.

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1 Halperin DT, Bailey RC. Male circumcision

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2 World Health Organization. Global Programme on AIDS: The Current Global Situation of the HIV/AIDS Pandemic Quarterly Report. 3 July, 1995.

Sir—Daniel T Halperin and Robert C Bailey<sup>1</sup> call on the international health community to promote male circumcision as a means of curbing the AIDS pandemic. They acknowledge that five cross-sectional studies found no association between male circumcision and HIV infection, and one reported an increased risk of infection in men who had been circumcised.

The logical weaknesses in the appeal for mass prophylactic circumcision have been exposed by Canadian ethicist Eike-Henner Kluge.<sup>2</sup> Should circumcision be promoted because there is some evidence that this operation might reduce the risk of HIV infection, even though there is also evidence to the contrary? If the answer is "yes", then the same approach should be adopted in similar situations. Whenever there is some evidence that surgery may reduce the risk of developing particular disease, but there is also evidence the surgery may have no prophylactic effect whatsoever, or even increase the risk of developing that particular disease, then the surgery should still be done on every person in whom the disease could develop.

Clearly, a great many body parts would be candidates for such surgery. What would the total cost come to, and what would be the overall impact on public health.

The authors compare male circumcision to other preventative measures such as use of condoms and promotion of safe sex. Unlike circumcision, however, the latter two strategies are safe, certain to be effective, and do not involve amputation of healthy erogenous tissue.

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2 Kluge EH. Male circumcision in Canada. *Can Med Assoc J* 1994; 150: 1542.

Sir—Daniel Halperin and Robert Bailey<sup>1</sup> cite cross-sectional and prospective studies indicating an association between lack of male circumcision and heterosexual HIV transmission in developing countries, that have a high frequency of sexually transmitted infections, and where

men often have multiple sexual partners. In the investigators' analysis of attributable risk, they use an odds ratio of 2.5 (the low end of the odds ratio found in five significant prospective studies).<sup>2</sup> A recent meta-analysis of male circumcision and HIV transmission recorded similar results.<sup>3</sup>

How many HIV infections have been prevented by male circumcision in developing countries with all the classic risk factors for a widespread heterosexual AIDS epidemic? Most of west Africa has high levels of sexually transmitted infections, sex work, polygamy, or other forms of multiple sexual partnering, and generally low levels of condom use, but there is also widespread practice of male circumcision.<sup>4</sup> Parts of south and southeast Asia also have, if generally to a lesser extent, many of these characteristics. HIV-1 frequency in west Africa clusters between 1% and 5% of those aged 15-49. In comparison, the predominately non-circumcising east and southern African nations have rates approaching 25%, and among the eight nations Halperin and Bailey cite, the average is around 20%. (In the Ivory Coast, the one west African country where substantial numbers of men are uncircumcised, frequency is 10%.)

Let us assume that male circumcision accounts for about half the disparity in heterosexual HIV rates between low frequency circumcising, and high frequency non-circumcising countries, and that some unidentified factors account for the other half of these large and continuing regional differences. With available census figures and the June, 1998, WHO/UNAIDS HIV seroprevalence data, it can be estimated that if male circumcision had not been a widespread practice, HIV frequency would have reached at least 10% in the 11 West African countries in Halperin and Bailey's study. This estimate suggests that about 6 million additional adults would now be infected in the region. In addition, vertical transmission would have occurred in many children.

A similarly conservative estimate of the impact in the four south and southeast Asian countries with a high male circumcision rate would be the following. In the absence of male circumcision, HIV frequency in Pakistan and Bangladesh might now be half that found in India (—ie, about 0.4%), and in Indonesia and the Philippines it might be around 1%, still under half the frequency in Thailand and Cambodia, where absence of male

circumcision is postulated as a factor driving spread.<sup>5</sup> Under these assumptions, an additional 2 million adults would now be infected in these four Asian countries.

Hence, it is possible that 8 000 000 or more adult HIV infections have been prevented by male circumcision in 15 African and Asian countries. Even though these estimates may be inaccurate, there is no doubt that if the relation between absence of male circumcision and increased risk of HIV is valid then the numbers of HIV infections prevented are large.

We suggest that male circumcision services should be more widely available. Clearly, as Halperin and Bailey conclude, absence of male circumcision should not be considered in isolation from other AIDS prevention strategies. For example, several anecdotal reports by medical anthropologists and other observers from various countries suggest that some uncircumcised men have greater difficulty or discomfort in the use of condoms.

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#### Authors' reply

Sir—While Justin A Pittas-Giroux is incorrect in his assertion that North America has “one of the highest” HIV rates in the world (many of the Asian and all of the African countries cited in our article have much higher HIV rates than the 0.76% rate in the US),<sup>1</sup> he is correct to point out that there are higher HIV rates in North America than in most European countries. It is important to recognise that in North America and Europe most HIV infections occur through receptive anal sex and injecting drug use, not through heterosexual transmission,<sup>2</sup> the focus of our article. Lack of male circumcision is expected to contribute most to female-to-male HIV transmission, which is responsible for a very small

proportion of infections in Europe and North America.

Remarkably, there is consistent evidence that female-to-male HIV transmission, compared with male-to-female transmission, is much higher in Europe than in the USA, just as expected given the greater prevalence of uncircumcised men on that continent. Data from the European Multicenter Partners Study and comparable research from the USA suggest that the ratio of female-to-male transmission (compared with male to female transmission) is about 10 fold higher in Europe.<sup>3</sup> Although other factors may also be at work, lack of male circumcision is a logical co-factor accounting for such large differences in infectivity.

The one study cited by Dennis C Harrison in which an association between male circumcision and HIV infection was reported, examined HIV infection in Rwandan women, who were asked the circumcision status of their male partners, which was not clinically verified.<sup>4</sup> As noted by the investigators, few of the male partners were circumcised, and might have come from a population with higher-risk sexual behaviours. In view of the more than 35 epidemiological studies showing an increased risk of HIV infection for men who are not circumcised—now including seven prospective studies<sup>5</sup>—we stand by our assertion that it is time for the international health community to take notice and consider ways to introduce male circumcision information and services in regions where they are not now available. Malcolm Potts' letter with rough estimates of the millions of HIV infections avoided by male circumcision in countries where infections are transmitted primarily heterosexually, reinforces the large impact this additional HIV prevention strategy could have.

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- 1 UNAIDS/WHO. Report on the Global HIV/AIDS Epidemic, June 1998.
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transmission of HIV-1 among sexual partners. San Francisco: Seventh Conference on Retroviruses and Opportunistic Infections, Jan 30, 2000 (abstr 193).

Sir—Daniel T Halperin and Robert C Bailey report:<sup>1</sup> “In east and southern Africa . . . male circumcision is increasingly recommended by traditional healers. Private clinics that specialise in male circumcision, many of which are run by people with minimum or no medical training, are sprouting up in (various parts of Africa).” I am the researcher cited by Halperin and Bailey who discovered that some indigenous healers from South Africa that practice circumcision were promoting and recommending male circumcision in the early 1990s. The healers claimed that they only recommended hospitals as appropriate places to carry out circumcisions. I have seen more recent evidence of such “response on the ground”, as Halperin and Bailey refer to it. A few weeks ago, I stumbled upon a US-supported private health organisation in Indonesia. In one of its brochures it was suggested that male circumcision is protective against HIV/AIDS infection, and that if men are not circumcised, they at least ought to carefully wash their genital area after coitus.

Most venereologists would applaud the practice of post-coital hygiene, since this is thought to help prevent foreskin infections. But would reading this brochure make, say, a Balinese man decide to be circumcised? And what if he went to an untrained, unskilled, self-appointed circumciser who caused sepsis?

As health professionals, we need to be prepared to advise on the issue of male circumcision and risk of HIV-1. At the very least, we may need to develop a harm reduction response to what people in some parts of the world are apparently electing to do themselves. We may, for example, need to develop a response that advises men who have decided to be circumcised as an adult to have the operation done in a safe clinical setting under local anaesthesia. We also need to advise (as Halperin and Bailey emphasise) that you can still become infected with HIV-1 even if your chances of such infection might be decreased.

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