Correspondence

Major Potential Confounder Not Addressed

Jennifer Vines

This is the first of 12 Correspondence pieces in this issue that are in response to an important PLoS Medicine *Research Article: Auvert B, Taljaard D, Lagarde E, Sobngwi-Tambekou J, Sitta R, et al. (2005) Randomized, controlled intervention trial of male circumcision for reduction of HIV infection risk: The ANRS 1265 trial. PLoS Med 2(11): e298. Readers wishing to add their own views may do so using our E-letters facility, where the debate continues.*

In the article by Auvert et al. regarding incidence rates of HIV infection in circumcised versus uncircumcised men, the finding of 60% fewer infections among the former group is compelling [1]. I must echo the comments submitted by others and question these findings in light of the fact that the authors did not control for other sources of HIV transmission, such as exposure through blood transfusions or infected needles. While the literature supports sexual (primarily heterosexual) activity as the main route of HIV transmission in South Africa, the behavioral factor of "attending a clinic for a health problem related to the genitals," initially reported by approximately 10% of both the intervention and the control group, corresponds to a significantly elevated HIV incidence rate. It is plausible that these men presented with urogenital complaints that resulted in antibiotic or other therapeutic treatments administered with unsterile needles. This could represent a significant confounder since the uncircumcised men, if indeed more prone to sexually transmitted infections (STI), were more likely to present for STI care and become infected through the health-care setting rather than through unprotected sexual intercourse. Controlling for this route of infection could result in a smaller difference between HIV infection rates in the circumcised versus uncircumcised groups, indicating that circumcision may not be as effective at decreasing HIV transmission as the article suggests. ■

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The Protective Effect of Male Circumcision as a Faith Lift for the Troubled Paradigm of HIV Epidemiology in Sub-Saharan Africa

John J. Potterat, Devon D. Brewer, Stephen Q. Muth, Stuart Brody

Auvert and colleagues present preliminary evidence for the protective effect of male circumcision on HIV acquisition [1]. Their report also reveals several problems with the widely held assumption that penile–vaginal sex accounts for the overwhelming majority of HIV transmission in sub-Saharan Africa.

We are baffled that the factor most strongly associated with incident HIV infection—attendance at "a clinic for a health problem related to the genitals" (rate ratio, 5.7)—is neither highlighted nor specifically discussed. Given evidence for increased risk of acquiring HIV from treatment for sexually transmitted diseases (STDs) in sub-Saharan Africa (relative to untreated STDs) [2], such a context for HIV acquisition should have been more assiduously explored, especially regarding nosocomial transmission.

Regrettably, the authors did not control for blood exposures (e.g., other types of medical or dental care, including care from "street doctors" and village injectionists, injections with syringes kept at home, ritualistic procedures, and injection drug use). Nor did they assess anal intercourse, the variable most strongly associated with sexual transmission of HIV. Anal intercourse is not uncommon in sub-Saharan Africa [3]. The authors also did not ask participants to specify the sex of their nonspousal partners, despite much evidence for bisexual behavior on the part of many "heterosexual" men in sub-Saharan Africa [3].

Furthermore, the authors did not report the relationship between level of condom use and HIV incidence. The need for more detailed investigation of sexual exposures is underlined by the negligible associations between such traditional measures of sexual risk—any type of unprotected sex, the number of sexual exposures ("contacts"), and the number of nonspousal partners—and HIV incidence [1]. Indeed, these results replicate the frequent lack of association between sexual behavior variables and HIV incidence or epidemic trajectories in sub-Saharan Africa [4]. (The authors should also report HIV incidence in persons reporting no sexual activity during specified study intervals.) Of concern as well is the high per coital act–HIV transmission probability implied by the data presented. A high transmission probability would suggest that the HIV prevalence in their participants should be greater than the 4%–5% observed at baseline.

Until all modes of HIV transmission—by sex and by puncturing—are comprehensively investigated [5,6], the most effective means of preventing HIV transmission will remain shrouded. In light of the anomalies and lacunae in Auvert and colleagues' study, the protective effect of male circumcision they observed amounts to a faith lift for the empirically beleaguered paradigm of heterosexual HIV transmission in sub-Saharan Africa [7]. ■

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Estimated Protection Too Conservative

James D. Shelton

The randomized study by Auvert et al. [1] on male circumcision to prevent HIV infection is clearly a landmark study, which supports compelling observational evidence of strong protection [2]. However, I believe the highlighted 60% degree of protection from the "intent-to-treat" analysis is probably too conservative. Deep in the article, we learn that the "per protocol" analysis, which addressed the 10.3% of men allocated to the noncircumcision group who nevertheless decided to be circumcised outside of the study, found a relative risk of 0.24%—or a protective effect of 76%.

Some might argue that the intent-to-treat analysis is more scientific, and reduces the impact of some selection or behavioral bias in those who opted for circumcision notwithstanding their allocation to the control arm. For example, it could be that men allocated to the noncircumcision group who were predisposed to less risky behavior but wanted to be extra safe might have chosen to be circumcised. In the opposite direction, those who were indulging most in risky behavior might have chosen to be circumcised to reduce their risk.

In my view, however, if we are interested in the true biologic effect, it is not very scientific to bias in favor of the analysis with a 10% contamination of that biological effect. In this study, we are fortunate enough to have quite richly reported behavioral data. More analysis of the per protocol analysis should have been presented, including the behavior of the crossovers. It is reasonably likely that any difference in the behavior of the crossovers would have little impact since, in the intent-to-treat analysis, adjustment for the increase in riskier behavior in the treatment group had little effect on the overall result.

The paper should have had prominent presentation of both analyses. In either case, the protection is quite substantial. But from an epidemiologic and personal perspective, what amounts to a failure rate of 40% versus 24% could be quite important. ■

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On Evidence in Support of Male Circumcision in HIV Prevention: What Next?

Adamson Sinjani Muula

The study by Auvert et al. [1] will certainly go into the history of HIV prevention as a landmark. The study is important because the results are the first blinded randomized study demonstrating that HIV can be prevented by male circumcision (MC). Double-blinded studies are considered to be the gold standard in research but because of the nature of this intervention, double blinding was impossible—i.e., it was impossible for the men to be circumcised without them knowing that they had been circumcised.

The study suggests that MC could join the interventions for HIV/AIDS already available—i.e., highly active antiretroviral therapy (HAART), short-course antiretroviral therapies and caesarean section in preventing mother-to-child transmission, postexposure prophylaxis, condoms, abstinence, and treatment of sexually transmitted infections (STIs). Like many other health interventions, MC (if its effectiveness is further demonstrated in subsequent randomized studies and then adopted within national policies) will be indicated and

suitable for some people, but not for others, for a variety of reasons. It would therefore be unfortunate if we were to start promoting MC at the expense of other intervention measures. The authors did not suggest that we should do so, but there is always the danger that some people will seek to boost efforts on one intervention whilst neglecting others.

The other challenge is that medical practice is conservative—i.e., it is unlikely that any country will immediately include MC in its policy for the prevention of HIV. The reasons include the following: these findings may not be corroborated in forthcoming studies and the potential harms still need to be considered in order to assess the cost–benefit ratio. Even in South Africa where the study was carried out, it will be a while before MC is incorporated into the national HIV prevention policy. Interestingly, however, the institutional review board stopped the study prematurely—as is always deemed ethical—suggesting implicitly perhaps their endorsement of MC and that it ought to be standard practice.

The authors indicate that "to wish to be circumcised" was one of the inclusion criteria. It is not clear to me what "wishing" meant—i.e., was it that they found MC acceptable or that they wanted to be circumcised but, for some reason, had not had the opportunity? If the interpretation is the latter, it would be important later to identify the barriers to MC that may operate in countries in southern Africa. Knowledge of these barriers will inform the policy debates.

While the policy debates rage, the scientific community has an enormous responsibility—i.e., ensuring that well-conducted studies are carried out in other settings to either confirm or dispute the findings. Results from other settings will be awaited with eagerness.

Researchers in the HIV field face the dilemma of not subjecting their study subjects to undue harm through stigmatization and discrimination. In several southern African countries, providing HIV test results to clients of health services and research participants is at the discretion of the client. The fact that there is no requirement for people who test positive to inform others who may benefit from the disclosure is, in my opinion, an important omission in the prevention of HIV in the region. It may be useful to include, at the time of obtaining informed consent, the statement, "Should you test HIV positive, we will encourage you to inform your sexual partners about the test results."

While it has been demonstrated that MC can be effective, it has yet to be determined why this might be the case. The authors have suggested that perhaps the keratinization that may ensue, more rapid drying of the glans penis after sexual intercourse, and prevention of STIs may be reasons. These are plausible explanations, but it will require separate studies to elucidate the mechanism(s).

The authors suggest that if women were aware of the effectiveness of MC, this would in turn lead them to encourage males to be circumcised. While I agree that all stakeholders ought to be mobilized in promoting an effective HIV intervention, or any public health intervention, the "role" of women, sadly, is minimal in decision making in most parts of the southern African region. But this does not mean that attempts should not be made to involve women. ■

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Two Groups Not on All Fours

Hugh Young

A prime requirement in any controlled study is that as far as possible, all conditions apart from the one being tested should be the same.

In the Auvert study, the men from the intervention group were instructed, in effect, as follows: "When you are circumcised you will be asked to have no sexual contact in the six weeks after surgery. To have sexual contact before the skin of your penis is completely healed could lead to infection if your partner is infected with a sexually transmitted disease. It could also be painful and lead to bleeding. If you desire to have sexual contact in the six weeks after surgery, despite our recommendation, it is absolutely essential that you use a condom" (Text S3 in [1]).

So the men in the intervention group were given very different instructions about sexual behaviour than those in the control group—in precisely the field where their risk of HIV infection was most affected. This could have differentially affected their sexual behaviour, and perhaps how they reported it. The time they spent waiting for and recovering from their surgery could also have exposed them to more safe-sex information and influence than the control group.

The control group was given no medical intervention at all. The study would have come closer to reaching equivalence between the two groups if a placebo surgery had been performed on the penis, such as opening and suturing an annular incision on the shaft, but leaving the foreskin, the supposed portal of HIV infection. The control group would then have needed identical instructions to those given to the intervention group; then, the two groups would have had much more equivalent risk. ■

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Rubbery Figures?

Michael Glass

I have been following reports of the Auvert et al. study [1] and have found four different figures for seroconversions.

An abstract from the 3rd International AIDS Conference (Rio de Janeiro, 24–27 July 2005) reported 15 seroconversions in the circumcised group and 45 seroconversions in the uncircumcised group [2]. On 29 July 2005, the Science and Development Network reported 18 seroconversions in the circumcised group and 51 in the uncircumcised group [3]. A paper in the *New Scientist*, published on 6 August 2005, reported 15 seroconversions in the circumcised group but 51 in the uncircumcised group [4]. Finally, on 23 October 2005, a paper in *PLoS Medicine* reported that there were 20 seroconversions in the circumcised group and 49 in the uncircumcised group [1]. It seems strange that the figures should have so much variance.

If we just look at the official figures—15 to 45 at the International AIDS Conference and 20 to 49 in *PLoS Medicine*—between 1 August 2005 and 23 October 2005, it appears that there have been four seroconversions among the uncircumcised and five seroconversions among the circumcised. In less than three months, a 3:1 difference has shrunk to a 2.45:1 difference.

Why are the numbers of seroconversions so much at variance in reports published by reputable journals? ■

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Rush to Judgment

Richard Winkel

How have Auvert et al. [1] controlled for the nonrandomization implicit in using a pool of men who want to be circumcised? Such self-selection increases the likelihood of recruiting men who are experiencing sexual difficulties—such as tight foreskins, a common but easily treatable problem leading to foreskin tearing—which would certainly skew the statistics.

I also find it fascinating that the male prepuce has gone straight from being an inconsequential "flap of skin" to being a complex immunological organ, just in time to be infected by a virus that targets immune cells. Is this an indication of accelerated evolution, perhaps driven by medicine's century-long obsession with the purported pathologies of male genitals, or perhaps just a demonstration of medicine's capacity to deceive the public?

It's equally fascinating that the obvious concern about the impact of male circumcision on male-to-female HIV transmission seems to be of no interest to researchers. There are good reasons to expect [2,3]—and empirical evidence for (see "Heterosexual Transmission, Europe versus the United States" at http://www.circumstitions.com/HIV.html#hetero)—the thesis that male genital mutilation causes a significant increase in the rate of male-to-female HIV transmission. The net effect of circumcision in a given population may be evident in the vastly different rates of HIV infection in the United States and Europe, where routine medical genital surgery on normal, healthy, nonconsenting children is unknown. Although the collateral damage of male circumcision to women might be prevented by routine female genital mutilation, as shown in this impolitic study [4], one would hope common sense and decency might preemptively stop a new medical crusade against normal human anatomy. ■

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Male Circumcision Increases Risk for Females

Jonathan Sykes

Auvert et al. argue that male circumcision provides a protective effect for males [1]. On the other hand, Chao et al. identified circumcision of the male partner as a risk factor for females [2]. Auvert et al. do not provide information on the overall effect of male circumcision on HIV transmission and infection [1]. Male circumcision may in fact worsen the epidemic. It is imperative, therefore, that further studies be conducted to determine the overall effect before implementing mass circumcision campaigns to control HIV infection. ■

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The Money Issue

Mpho Selemogo

Auvert et al. must be commended for showing some appreciation of the ethical issues raised by their research trial [1]. The Research Article itself and the accompanying ethical review by Cleaton-Jones [2], however, curiously seem to take the money issue lightly. The *PLoS Medicine* Editorial is quite right in identifying the R300 payment to participants as an issue [3].

Rather than just identifying what R300 means in terms of the euro, we need an idea of the sum's effect on the average person enrolled in the study in order to best review issues of autonomy, which are often so problematic in such research. What was its impact on the recruitment process? Was the average income for the participants so low that declining to participate in the study and turning down the money was not an economically feasible option? The absence of such critical socioeconomic data leaves us wondering if this money was meant as a force for recruitment or indeed as a compensation for participation, as the authors assert. ■

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Male Circumcision and HIV in Africa

Taiwo Lawoyin, O. A. Kehinde

We wish to congratulate Auvert et al. [1] on their work and wish them more success in their endeavors. Quite a number of studies have shown that circumcised males in heterosexual unions do have lower HIV rates [2–4]. It would be good to know to what extent circumcision affects the HIV rates in sub-Saharan African countries presently bearing the brunt of the disease.

Though ecological studies should be interpreted with caution, it would also be interesting to find out how this information helps us to better understand why some African countries with similar behavior have a much lower HIV rate than others [4–6]. West African countries, for example, have significantly higher circumcision rates than countries in the eastern and southern parts of Africa. HIV rates also appear to be generally lower in West Africa [7].

Also it would be interesting to find out if more African males who are not circumcised are ready to have this procedure done as a form of added protection, as there seem to be pockets of resistance to the procedure [8,9]. ■

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Authors' Reply

Jennifer Vines raises the question of other potential sources of HIV [1]. During our follow-up, 569 participants received blood transfusions, were hospitalized, or received injections. We observed 15 infections among those who had such a nosocomial risk factor during the period when HIV infection occurred. We observed 50 infections among those without such a risk factor. In a multivariate analysis of risk factors of HIV infection during the follow-up, the presence of a nosocomial risk factor was not significantly associated with HIV infection (rate ratio [RR] = 1.7; $p = 0.092$). Among those with a nosocomial risk factor, the protective effect of the intervention (intention-to-treat analysis) is about 58%. Among those without a nosocomial risk factor, the protective effect of the intervention is about 62%. In a multivariate analysis, when taking into account the nosocomial risk factors, the association between group of randomization and HIV infection was unchanged (protection of 60% versus 60%). The fact that patients with a nosocomial risk factor were not significantly more at risk of HIV infection, and were protected by male circumcision in a similar way to those without a nosocomial risk factor, strongly supports the view that the majority of HIV infections observed in our study were due to sexual transmission.

John Potterat and colleagues make a number of points to which we must respond [2]. The association between clinic attendance for a health problem related to genitals and HIV infection is most likely due to genital herpes, which is common in South Africa and strongly associated with HIV. We believe that those who became HIV positive also became infected with HSV-2 just before, at the same time, or just after the acute primary HIV infection. Primary genital herpes infection concomitant with HIV infection can lead to clinic attendance because of herpes genital lesions, and can explain the observed association.

In this population of young men, as shown in Table 4 of our Research Article [3], we did not observe any significant association between reported sexual behaviour characteristics and HIV infection when controlling for other factors, including the randomisation group. However, in univariate analysis, there is an association between HIV infection and number of sexual contacts (RR = 2.0; $p = 0.035$) and risk of infection (RR = 1.7; $p = 0.045$). This last variable includes lack of condom use. We believe that because of the small number of infections, and the importance of male circumcision on the transmission of HIV, the factors associated with sexual behaviour do not appear in the multivariate analysis. In addition, we think that the HIV status of female partners of these young men is a key factor. In Table 4, it is clear that HIV infection increases with the age of the participants, which is a proxy for the risk of having a partner who is infected with HIV for two reasons: (1) because the age of female partners increase with age of their male partners and (2) because, in young women, HIV status is strongly associated with age.

We did ask the sex of all reported sexual partners. We found that 0.07% of these reported partners were men. Three participants reported sexual partnerships with men. None became infected during the follow-up.

At recruitment, HIV prevalence was 0.7% (two out of 278) among those who reported never having any sexual contact, and 4.8% (144 out of 2,994) among those who reported having sexual contact ($p < 0.001$).

HIV incidence was about two out of 100 per year in the control group during the follow-up. Knowing that HIV incidence increases with age, and assuming that the incidence is negligible before 17, we can estimate the HIV incidence between the age of 17 (median age of first sexual experience) and the age of 21 (age at recruitment) by about half the incidence of the control group during the follow-up, leading to an estimated HIV incidence of one out of 100 per year. It means that the HIV prevalence of the participants between this four-year period (17–21) goes up from 0% to 4%. We observed about 4.5% at recruitment, which is consistent with this analysis.

We agree with the comment by James Shelton [4]. When looking at the crossovers, we found that they were protected by male circumcision. This implies that the difference between the intention-to-treat analysis and the per-protocol analysis is at least partly caused by the dilution effect of crossovers. Therefore, we believe, as does Shelton, that the 60% degree of protection obtained from the intent-to-treat analysis is probably too conservative.

We also agree with the points made by Adamson S. Muula and would like to note that, for many researchers, the results of this trial are not surprising and are consistent with many other studies published since 1986 [5].

With reference to the comment by Hugh Young [6], we reported analyses in our paper to account for this six-week period and for differences of behaviour between the two arms of the trial. These analyses show that the six-week period of abstinence cannot explain the outcome of the trial, and that participants in the intervention group were slightly more sexually active. Therefore, we strongly believe that the difference in rate of infection can be attributed to male circumcision. We think the study design suggested by Young would be unlikely to obtain ethical approval and would be unacceptable to participants.

Michael Glass has read a number of reports of our study. During the trial, we collected about 12,000 blood samples, performed about 12,000 clinical examinations, and collected about 48,000 questionnaires. We were careful to enter all these data with a double-entry procedure and even a triple-entry procedure for the laboratory data. This, of course, took considerable time. Nevertheless, we wanted to make available to the international community some preliminary information as soon as possible. We decided to release the results of the trial in a preliminary form at the International AIDS Society Conference in Rio de Janeiro. It is often the case that the results presented in a conference do not correspond exactly with those presented in the abstract, and that the final published results can be slightly different from those given in the oral presentation. We knew that this might be a problem, and we were careful to indicate to the *PLoS*

Medicine editors that the results would be finalized only after the conference.

In addition, there is not just one numerical value but two: the result given by the per-protocol analysis and the result given by the intention-to-treat analysis, each having a wide confidence interval.

The magnitude of the effect in a trial of this nature cannot, in any case, predict precisely what to expect in an actual intervention program for four reasons. Firstly, the trial was conducted in a specific population (young men of the age range 18–24); it was not representative of the whole population. Secondly, the participants received intense counselling periodically throughout the follow-up period. Thirdly, they were informed that the result of the trial was unpredictable. Finally, the duration of the follow-up period was short. This is why operational research should be conducted to test if male circumcision, in association with existing and validated prevention methods, can be used in a community intervention.

Richard Winkel has also raised a number of concerns [7]. Our participants were recruited among the general population of the area. This neither implies that they are representative of this population nor that they are very different. HIV prevalence among those who were recruited is similar to what was expected, and clinical examination rarely revealed a tight foreskin. We do agree that the results obtained in this trial have to be confirmed by other trials, but also, as mentioned above, by conducting operational research.

Winkel seems to believe that the foreskin has only recently been linked to the transmission of infectious diseases. Hutchinson in 1854 noticed an association between male circumcision and a lower rate of syphilis. The first paper on the association between male circumcision and HIV infection was published in 1986. In addition, it is possible that male circumcision was practiced by the Egyptians, for health reasons, at least 3,000 years ago. Contrary to what Winkel has written, researchers are working on the effect of male circumcision on male-to-female transmission, despite technical difficulties. The ongoing trial in Uganda should yield new knowledge on this issue.

The aim is not to conduct a "new medical crusade against normal human anatomy" [7]. It is to reduce the mortality due to AIDS by reducing the spread of HIV, especially in the worst-infected countries.

In response to Jonathan Sykes [8], we would like to point out that several well-conducted meta-analyses and systematic reviews have shown that male circumcision is associated with lower rates of HIV infection among males. These studies have been quoted in our paper reporting our trial. It is rarely argued that male circumcision might worsen the epidemic, even if the safety of male circumcision is a real problem. The main remaining scientific problems are (1) to have the result of the South African study confirmed by the other ongoing trials and (2) to demonstrate that safe male circumcision is protective at population level by conducting applied research studies.

We can assure Mpho Selemogo [9] that we did consider the issue he raises very seriously when designing the trial. The guidelines of the HREC (the ethics committee of the University of the Witwatersrand) are quite clear that participation should be voluntary and that there should be no evidence of inducement. The minimum basic salary in South Africa is roughly R1,500 per month, which translates to about R70 per day. The R300 that we gave participants was distributed in increments across five visits. For the inclusion visit, participants received R30. For the three-month visit, they received R40; for the 12-month visit, R80; and for the final visit, R150. On average, participants received R75 per visit. The primary reasoning for an incremental compensation was because of the duration of the trial, and also to balance requirements of cohort retention. However, the increments were within the ethical bounds set by the HREC. In addition, we thought that it would eliminate the risk of recruiting people wishing to participate for immediate financial gain. We asked all participants why they wanted to be part of the study. A very small percentage (0.3%) indicated that they were participating for financial reward. The majority participated for the safe and free circumcision and to improve their health, 37.7% and 40%, respectively.

The honoraria paid during this trial compare very favourably to those paid to participants in other trials in the region. (For a drug trial, the current compensation, as stipulated by the Medicines Control Council, is R150 per visit.)

Finally, we do agree with Taiwo Lawoyin [10]. More research is needed to fill the gaps in this area. Nevertheless, we hope that these gaps will not be used as arguments to delay the use of male circumcision in slowing the spread of HIV in those countries of sub-Saharan Africa that have high rates of HIV infection and low rates of male circumcision, and where acceptability studies have already revealed a potential for this prevention method. Male circumcision should always be used in combination with other validated prevention methods. ■

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Male Circumcision and HIV Control in Africa

Michel Garenne

In a recent article, Auvert and colleagues present the results of their randomized controlled trial on male circumcision to prevent HIV transmission [1]. They conclude that male circumcision reduced the risk of HIV infection by some 60% (95% confidence interval, 32%–76%). The trial was certainly well conducted, and it nicely confirmed observational studies, which came to the same conclusion [2]. However, a number of their concluding statements deserve a comment.

Auvert and colleagues claim a "degree of protection equivalent to a vaccine of high efficacy" [1]. This is obviously overstated. A vaccine of high efficacy is expected to offer long-term protection of 95% or above. Smallpox was eradicated with such a highly efficient vaccine. If control of tetanus, measles, and poliomyelitis has been largely achieved in the world, it has been a result of high-efficacy vaccines. Furthermore, the analogy with vaccines appears misleading. A 96%-efficient measles vaccine means that 96% of vaccinated persons exposed to measles are indeed protected against infection. Protection lasts for many years, and revaccination permits dealing with loss of immunity over time. What Auvert and colleagues show is different: they show a 60% reduction in disease incidence over an 18-month period among circumcised men compared with uncircumcised men with similar exposure. To our knowledge, this does not mean that those men are really "protected" against HIV, especially in the case of repeated exposure. It simply means "reduced risk," or reduced probability of contamination.

A closer analogy of the "reduced risk" offered by male circumcision is that offered by contraception. Modern and efficacious methods such as hormonal contraceptives (pill, injectables, implants) or intra-uterine devices (IUDs) do offer high protection, usually 99% or above for women who are exposed repeatedly (every month) to risk of pregnancy. Highly efficacious methods do protect these women against unwanted pregnancy. On the contrary, a less efficacious method such as rhythm method (periodic abstinence) reduces fecundity by some 50%, but offers little protection against unwanted pregnancy. Even though women using consistent rhythm methods will have a lower number of pregnancies over their lifetime than women who use no contraceptive methods at all, they will be unlikely to achieve their desired family size, as could women using highly effective methods.

Similarly, for persons who are highly exposed to risk of HIV infection, as are the young men of South Africa, a 60% reduction in annual risk will ultimately protect only a smaller proportion. Basic probability calculations show that in discordant couples exposed for 30 years, some 74% will contract the HIV virus if circumcised, compared with 97% if uncircumcised (with incidence of 11% per year)—a small reduction indeed if compared with a highly efficacious vaccine (comparable figures would be 4% versus 97% for children vaccinated against measles who are exposed between 1 and 15 years of age).

One could argue that the population effect could exceed the individual risk for a variety of reasons ranging from herd immunity to prevention of other sexually transmitted diseases (STIs). If all men are circumcised, then prevalence among women will be lower, and men will have lower risk of being exposed and infected. However, several natural experiments do not confirm this argument. For instance, Tanzania has some 110 ethnic groups, some groups using universal male circumcision, others not circumcising. After controlling for urbanization, there was no difference in male HIV prevalence between the two groups: in urban areas, HIV seroprevalence was 9.5% in circumcised groups and 9.7% in uncircumcised groups, and conversely, 4.6% and 5.2%, respectively, in rural areas—none of the differences being significant [3]. In South Africa, the KwaZulu-Natal province, where few are circumcised, has a higher HIV seroprevalence than other provinces, reaching 37% among antenatal clinic attendants in 2003. But, in the Eastern Cape, where circumcision is the rule, the dynamics of the epidemic are almost the same, simply lagging a few years behind, increasing from 4.5% in 1994 to 27% in 2003. Finally, it was argued that the large epidemic in Abidjan, Côte d'Ivoire, and surrounding areas in the late 1980s was largely due to the lack of male circumcision of the local ethnic groups. This, however, did not impede the rapid increase in HIV infection among migrant workers from Burkina Faso and Mali living in Abidjan, who were circumcised.

For highly exposed men, such as men living in southern Africa, the choice is either using condoms consistently, with extremely low risk of becoming infected, or being circumcised, with relatively high risk of becoming infected. This is quite similar to women's choice to either use a highly efficacious contraceptive method or use a folk method. Some women make the second choice for religious reasons, with the obvious consequences. Is there a rationale for promoting the idea of circumcision when better choices are available? Regular condom use was found to be protective at the individual level and also effective for stopping HIV epidemics, as in Thailand [4,5].

Concluding that "male circumcision should be regarded as an important public health intervention for preventing the spread of HIV" [1] appears overstated. Even though large-scale male circumcision could avert a number of HIV infections, theoretical calculations and empirical evidence show that it is unlikely to have a major public health impact, apart from the fact that achieving universal male circumcision is likely to be more difficult than universal vaccination coverage or universal contraceptive use. ■

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PfHRP2 Measures Schizogony, Not Mechanical Blockage

Ian Clark

As noted in Dondorp et al. [1], histidine-rich protein 2 (PfHRP2) is released at schizont rupture as part of the regular 48-hour developmental cycle of the erythrocytic form of the parasite. Since this release of PfHRP2 into the circulation occurs while the parasitized red cell is adhering to vascular endothelium, it can act as an indirect marker for this sequestration. Therefore, as might be expected for a parasite that sequesters for a fixed part of its repeated 48-hour cycle of development, both the total biomass and sequestered biomass were calculated to be associated with severity of disease.

The authors use these data to further the case for the traditional concept that disease symptoms in falciparum malaria—including coma, high lactate, and renal failure—arise because erythrocytes containing mature forms of the parasites sequester within the microvasculature of the vital organs. We may safely infer from the authors' previous publications their acceptance of the conventional wisdom that this sequestration mechanically obstructs vessels, leading to tissue hypoxia through poor oxygen transport.

Parasites are inside sequestering red cells when they burst and release PfHRP2, but it may be bursting, not sequestration, which matters most in disease pathogenesis. PfHRP2 is a marker for the degree of schizogony not, as implied, of vascular blockage caused by sequestration. Clinical tolerance to falciparum malaria, common in endemic areas in age groups with high parasite densities, demonstrates this well. Those who champion mechanical vascular obstruction must accept this as a state in which appreciable sequestration occurs only in harmless locations, such as larger veins and nonvital organs. It is not known where red cells containing mature parasites lodge in these individuals, and if they stop using these locations during serious illness. If they do not stop, PfHRP2 released from schizonts adhering in harmless locations would add to the total concentration in the circulation, but would not be a marker for obstruction.

Other molecules released at schizogony include the trigger(s) that generate the inflammatory cytokines, which have formed the basis of a mainstream argument for the pathophysiology of malarial disease for the past 25 years (see [2,3,4] for recent reviews). An undiscussed reason for PfHRP2 release correlating with serious illness might be its value as a surrogate for these cytokine-triggering molecules liberated from bursting red cells postschizogony. An awareness of these concepts has allowed molecules of host origin, such as increased plasma levels of the soluble form of one of the receptors for tumor necrosis factor, to be considered alongside PfHRP2 as a marker for the parasite biomass [5].

If the cultural gap between the mechanical and the cytokine approach to malarial disease could be spanned, useful knowledge on roles of inflammatory cytokines in sepsis, such as details of how cytokine-induced mitochondrial dysfunction causes a functional hypoxia [6,7], could more readily be applied to understanding malarial disease. ■

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Authors' Reply: Response to Ian Clark

We are grateful for Ian Clark's suggestions [1] in response to our research article [2]. Much remains to be learned about the pathogenesis of cerebral malaria. It is certainly hard to disprove that triggering local immune responses contributes in some way to the pathophysiology of cerebral malaria. Local overproduction of NO, HMGB1, cytokines, or other mediators yet to be discovered could impair neurotransmission. But their roles remain hypothetical, and thus far, none of the proposed hypotheses have passed the stage of showing a correlation between the severity of disease and the proposed mediator. A role in murine malaria pathogenesis cannot be translated directly to human pathophysiology since the basic pathophysiological phenomena are essentially different in these animals. Although the concept of impairment of microcirculation in severe malaria by sequestered parasitized erythrocytes causing local tissue dysoxia, acidosis, and metabolic dysfunction is a simple one, there is considerable evidence that it is correct. Lactate/pyruvate ratios are, in contrast with sepsis, clearly increased in severe malaria, which is compatible with anaerobic glycolysis as a source of lactate production [3]. Of the human malarias, only *Plasmodium falciparum* sequesters in vital organs, and this is also the species responsible for the vast majority of malaria-related deaths. Autopsy studies of fatal malaria cases show convincing correlations between extent of sequestration in the brain and coma as a presenting symptom [4]. Direct visualisation of the microcirculation in patients with severe malaria shows blockage of capillaries, which become patent after the patient's recovery. Strong support for the central role of parasite sequestration in the pathophysiology of lethal malaria comes from the largest trial ever conducted on severe malaria, which showed that artesunate reduces mortality by 34% compared with quinine [5]. Both artesunate and quinine are very active against sequestered parasites, preventing their development to schizonts, but unlike quinine, artesunate is also active against the younger forms of the parasite, preventing their maturation and sequestration in the microcirculation of vital organs. The greatest mortality benefit in this trial compared with quinine was in patients with high parasitaemias, indicating that prevention of sequestration (rather than prevention of schizont rupture) saved lives. ■

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