epidemiology in sub-Saharan Africa. PLoS Med 3: e64. DOI: 10.1371/journal.pmed.0030064
3. 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: e298. DOI: 10.1371/journal.pmed.0020298
4. Shelton JD (2006) Estimated protection too conservative. PLoS Med 3: e65. DOI: 10.1371/journal.pmed.0030065
5. Muula AS (2006) On evidence in support of male circumcision in HIV prevention: What next? PLoS Med 3(1): e66. DOI: 10.1371/journal.pmed.0030066
6. Young H (2006) Two groups not on all fours. PLoS Med 3: e75. DOI: 10.1371/journal.pmed.0030075
7. Winkel R (2006) Rush to judgment. PLoS Med 3: e71. DOI: 10.1371/journal.pmed.0030071
8. Sykes J (2006) Male circumcision increases risk for females. PLoS Med 3: e72. DOI: 10.1371/journal.pmed.0030072
9. Selemogo M (2006) The money issue. PLoS Med 3: e73. DOI: 10.1371/journal.pmed.0030073
10. Lawoyin T, Kehinde OA (2006) Male circumcision and HIV in Africa. PLoS Med 3: e74. DOI: 10.1371/journal.pmed.0030074

Citation: Auvert B, Taljaard D, Lagarde E, Sobngwi-Tambekou J, Sitta R, et al. (2006) Authors' reply. PLoS Med 3(1): e67.

Competing Interests: The authors have declared that no competing interests exist.

DOI: 10.1371/journal.pmed.0030067

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. ■

Michel Garenne
Institut Pasteur
Paris, France
E-mail: mgarenne@pasteur.fr

References

1. 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: e298. DOI: 10.1371/journal.pmed.0020298
2. Weiss HA, Quigley MA, Hayes RJ (2000) Male circumcision and risk of HIV infection in sub-Saharan Africa: A systematic review and meta-analysis. AIDS 14: 2361–2370.
3. Tanzania Commission for AIDS, National Bureau of Statistics, ORC Macro (2005) Tanzania HIV/AIDS indicator survey 2003-04. Calverton (Maryland): Tanzania Commission for AIDS, National Bureau of Statistics, ORC Macro. Available: http://www.measuredhs.com/pubs/pdf/FR162/00FrontMatter.pdf. Accessed 15 December 2005.
4. De Vicenzi I (1994) A longitudinal study of human immunodeficiency virus transmission by heterosexual partners. N Engl J Med 331: 341–346.
5. Zenilman JM (2005) Behavioral interventions: Rationale, measurement, and effectiveness. Infect Dis Clin North Am 19: 541–562.

Citation: Garenne M (2006) Male circumcision and HIV control in Africa. PLoS Med 3(1): e78.

Competing Interests: The author has declared that no competing interests exist.

DOI: 10.1371/journal.pmed.0030078

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. ■

Ian Clark
Australian National University
Canberra, Australian Capital Territory, Australia
E-mail: ian.clark@anu.edu.au

References

1. Dondorp AM, Desakorn V, Pongtavornpinyo W, Sahassananda D, Silamut K, et al. (2005) Estimation of the total parasite biomass in acute falciparum malaria from plasma PfHRP2. PLoS Med 2: e204. DOI: 10.1371/journal.pmed.0020204
2. Clark IA, Cowden WB (2003) The pathophysiology of falciparum malaria. Pharmacol Ther 99: 221–260.
3. Maitland K, Marsh K (2004) Pathophysiology of severe malaria in children. Acta Trop 90: 131–140.
4. Boutlis CS, Riley EM, Anstey NM, de Souza JB (2005) GPI in malaria pathogenesis and immunity: Potential for therapeutic inhibition and vaccination. Curr Topics Microbiol Immunol 197: 145–185.
5. Ochola LB, Marsh K, Lowe B, Gal S, Pluschke G, Smith T (2005) Estimation of the sequestered parasite load in severe malaria patients using both host and parasite markers. Parasitology 131: 449–458.
6. Singer M, De Santis V, Vitale D, Jeffcoate W (2004) Multiorgan failure is an adaptive, endocrine-mediated, metabolic response to overwhelming systemic inflammation. Lancet 364: 545–548.
7. Callahan LA, Supinski GS (2005) Sepsis induces diaphragm electron transport chain dysfunction and protein depletion. Am J Resp Crit Care Med 172: 861–868.

Citation: Clark I (2006) PfHRP2 measures schizogony, not mechanical blockage. PLoS Med 3(1): e68.

Competing Interests: The author has declared that no competing interests exist.

DOI: 10.1371/journal.pmed.0030068