Male Circumcision for the Prevention of Acquisition and Transmission of Sexually Transmitted Infections

The Case for Neonatal Circumcision

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The American Academy of Pediatrics (AAP) male circumcision policy states that while there are potential medical benefits of newborn male circumcision, the data are insufficient to recommend routine neonatal circumcision. Since 2005, however, 3 randomized trials have evaluated male circumcision for prevention of sexually transmitted infections. The trials found that circumcision decreases human immunodeficiency virus acquisition by 53% to 60%, herpes simplex virus type 2 acquisition by 28% to 34%, and human papillomavirus prevalence by 32% to 35% in men. Among female partners of circumcised men, bacterial vaginosis was reduced by 40%, and *Trichomonas vaginalis* infection was reduced by 48%. Genital ulcer disease was also reduced among males and their female partners. These findings are also supported by observational studies conducted in the United States. The AAP policy has a major impact on neonatal circumcision in the United States. This review evaluates the recent data that support revision of the AAP policy to fully reflect the evidence of long-term health benefits of male circumcision.
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The American Academy of Pediatrics (AAP) male circumcision policy[1] states:

> [E]xisting scientific evidence demonstrates potential medical benefits of newborn male circumcision; however, these data are not sufficient to recommend routine neonatal circumcision. All studies that have examined the association between UTI [urinary tract infection] and circumcision status show an increased risk of UTI in uncircumcised males, with the greatest risk in infants younger than 1 year of age. Evidence regarding the relationship of circumcision to STD [sexually transmitted diseases] in general is complex and conflicting.

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Although the policy was initiated in 1999 and reaffirmed in 2005,[1,2] it has been publicly questioned.[3-5] However, the American College of Obstetricians and Gynecologists and the American Medical Association have accepted the policy.[6,7]

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During the past 4 years, substantial new data have been published on the health benefits of circumcision. While the historical evidence strongly suggests that male circumcision reduces urinary tract infections and penile inflammatory disorders in infants, we reviewed the more recent evidence with regard to effects on sexually transmitted infections (STIs) in adulthood.

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NEONATAL MALE CIRCUMCISION RATES

Estimates of the rate of male circumcision in the United States vary between studies. A 2004 Nationwide Inpatient Sample estimated that only 55.9% of boys born in US hospitals are circumcised.[8] However, this rate does not include newborn circumcisions that are noncoded hospital diagnoses or boys who are circumcised at a later date in nonhospital settings.[9] The population-based prevalence is likely closer to 79%, as reported by the National Health and Nutrition Examination

Table. Male Circumcision and HIV and STI Acquisition in Men and Transmission to Female Partners

STI	Ratio (95% Confidence Interval) by Study Location[a]		
	Uganda	South Africa	Kenya
Male protection benefit			
HIV	0.43 (0.24-0.75)[b]	0.40 (0.24-0.68)[b]	0.47 (0.28-0.78)[b]
High-risk HPV	0.65 (0.46-0.90)[c]	0.68 (0.52-0.89)[c]	
HSV-2	0.72 (0.56-0.92)[d]	0.66 (0.32-1.12)[b]	
Syphilis	1.10 (0.75-1.65)[d]		
Neisseria gonorrhoeae		0.87 (0.60-1.26)[c]	0.95 (0.68-1.34)[b]
Chlamydia trachomatis		0.56 (0.32-1.00)[e]	0.87 (0.65-1.16)[b]
Trichomonas vaginalis		0.53 (0.28-1.02)[e]	0.77 (0.44-1.36)[b]
GUD	0.53 (0.43-0.64)[c]		
Female protection benefit			
HIV	1.49 (0.62-3.57)[d]		
Bacterial vaginosis	0.60 (0.38-0.94)[c]		
Trichomonas vaginalis	0.52 (0.05-0.98)[c]		
GUD	0.78 (0.63-0.97)[c]		

Abbreviations: GUD, genital ulcer disease; HIV, human immunodeficiency virus; HPV, human papillomavirus; HSV-2, herpes simplex virus type 2; STI, sexually transmitted infection.

[a] The data shown are from publications of the 3 randomized controlled trials that presented the efficacy of male circumcision using different statistical methods. All ratios are adjusted (except for South African HSV-2 and Kenyan bacterial STIs) and represent an intention-to-treat analysis.

[b] The ratio expressed is an incidence rate ratio.

[c] The ratio expressed is a prevalence rate ratio.

[d] The ratio expressed is a hazard ratio.

[e] The ratio expressed is an odds ratio.

Surveys.[10] Rates of circumcision in the United States vary by ethnicity, ranging from 88% in white males, 73% in African American males, and 42% in Mexican American males.[10] Circumcision is also highest among boys born to families of higher socioeconomic status, those with private insurance, and boys born in the Northeast or Midwest.[11]

HUMAN IMMUNODEFICIENCY VIRUS PREVENTION

Observational studies suggested that male circumcision reduces heterosexual human immunodeficiency virus (HIV) acquisition in men,[12] a finding supported by 3 large randomized controlled trials of more than 10 000 men conducted in South Africa, Kenya, and Uganda. The trials enrolled HIV-negative men and randomized them to circumcision upon enrollment or after 21 to 24 months. All 3 trials demonstrated that male circumcision significantly decreased male heterosexual HIV acquisition by 50% to 60%,[13-15] despite differences in age eligibility criteria, urban vs rural settings, and surgical procedure (**Table**). The South African trial, which enrolled 3128 men aged 18 to 24 years in a periurban township, found an intent-to-treat efficacy of 60% (95% confidence interval [CI], 32%-76%).[15] The Kenyan trial enrolled 2784 men aged 18 to 24 years in an urban setting and found an intent-to-treat efficacy of 53% (95% CI, 22%-72%).[14] The Ugandan trial enrolled 4996 males aged 15 to 49 years in a rural setting and found an intent-to-treat efficacy of 57% (95% CI, 25%-76%)[13]; furthermore, the protective effect of circumcision increased with longer time from surgery. All 3 randomized trials were consistent with previous ecological and observational studies in Africa, Europe, and the United States.[16] Owing to this new evidence, the World Health Organization in conjunction with the Joint United Nations Program on HIV/AIDS recommended that male circumcision be provided as an important intervention to reduce heterosexually acquired HIV in men.[17]

There are concerns that the results of the 3 African randomized controlled trials of heterosexually acquired HIV in men may not be applicable within the United States, where more than 1 million individuals are living with HIV/AIDS.[18] In part, this concern arises from different routes of HIV transmission in the United States, including through intravenous drug users and men who have sex with men (MSM), which constitute a substantial proportion of HIV infections in the United States. While African Americans represent only 13% of the total population, they account for 48% of all HIV infections.[18] Rates of HIV in inner cities such as Washington, DC, approach levels seen in Africa, with 3% to 5% of the total adult population living with HIV, with 6.5% of African American males in Washington, DC, living with the virus.[19] Heterosexual exposure is becoming the leading mode of HIV transmission, with 38% of incident cases among youth (ages 13-24 years) in Washington, DC.[19] Additionally, in a retrospective study of 394 Baltimore, Maryland, STI clinic patients with known heterosexual HIV exposure, HIV infection was 22% among uncircumcised men compared with 10% in circumcised men (adjusted prevalence rate [PR], 0.49; 95% CI, 0.26-0.93).[20] Thus, the results of the African trials appear to be relevant to heterosexuals at high risk of HIV infection in the United States.

Some have speculated that the findings of the adult male circumcision trials may not be applicable to neonatal circumcision. However, the large majority of the observational data are from individuals who were cir-

cumcised as infants. The remarkable consistency between the observational studies and the randomized controlled trials demonstrates that this concern is unfounded and further establishes the long-term protective effect of male circumcision.

Male circumcision and HIV protection among MSM have not been studied as well as heterosexual transmission. Several observational studies in MSM suggest that male circumcision is associated with decreased HIV infection,[21,22] while others found no protective effect.[23] In a meta-analysis of 53 567 MSM, the odds of being infected with HIV were not significantly lower among circumcised compared with uncircumcised men (odds ratio [OR], 0.95; 95% CI, 0.81-1.11).[24] However, a significant protective effect was found in MSM studies conducted prior to the availability of highly active antiretroviral treatment (OR, 0.47; 95% CI, 0.32-0.69).[24] The protective effect of circumcision among MSM is complicated by both insertive and receptive sexual practice, and it is possible that circumcision only protects against insertive intercourse. This is supported by the Soweto Men's Study of men who participate in exclusive insertive anal intercourse, which found that uncircumcised men have a higher risk of HIV infection than circumcised men (adjusted OR, 4.5; 95% CI, 3.1-6.7).[25] Thus, studies that do not differentiate between these practices may be confounded. It is noteworthy, however, that in a recent HIV vaccine trial, circumcised MSM had a significantly lower risk (relative risk, 0.26) of HIV acquisition compared with uncircumcised MSM participants.[26] Thus, further research is required to determine whether male circumcision can definitively reduce HIV acquisition among MSM.

HERPES SIMPLEX VIRUS TYPE 2 PREVENTION

Several observational studies have suggested that male circumcision significantly decreases herpes simplex virus type 2 (HSV-2) infection,[27,28] while others showed no association.[29-31] A meta-analysis estimated a relative risk of 0.88 (95% CI, 0.77-1.01) for HSV-2 infection associated with circumcision.[32] Many of the observational studies, however, had limited statistical power, were vulnerable to confounding by sexual practices correlated with a high risk of acquisition, and evaluated the status of circumcision solely on the basis of self-report. Thus, the potential efficacy of male circumcision for the prevention of sexually transmitted HSV-2 infections can only be determined by randomized trials.

To evaluate the efficacy of male circumcision for prevention of HSV-2 incidence, 3393 HIV and HSV-2 antibody–negative men (1684 in the intervention arm and 1709 in the control arm) from the Rakai, Uganda, male circumcision trial were evaluated. The cumulative probability of HSV-2 seroconversion during 2 years was 7.8% in the circumcised group and 10.3% in the control group (adjusted hazard ratio, 0.72; 95% CI, 0.56-0.92) (Table).[33] The HSV-2 incidence was lower in the intervention group than in the control group among almost all subgroups. The randomized controlled trial of circumcision in South Africa also evaluated HSV-2 acquisition among 2974 HIV-negative and HIV-positive men. The HSV-2 incidence was 3.54 in 100 person-years in uncircumcised men and 2.33 in 100 person-years in circumcised men, with an unadjusted incidence rate ratio of 0.66 (95% CI, 0.32-1.12).[34] Thus, 2 independent randomized trials found that male circumcision decreased HSV-2 acquisition by 28% to 34%.

BACTERIAL STI PREVENTION

The evidence that male circumcision may prevent bacterial STIs is equivocal. Two observational studies reported that male circumcision was associated with decreased syphilis infection,[35,36] while others showed no association.[31,37] A meta-analysis estimated a decreased risk of syphilis associated with circumcision, with a relative risk of 0.67 (95% CI, 0.54-0.83).[32] In a secondary end point analysis of the randomized trial conducted in Rakai, no significant difference was observed in syphilis acquisition by study arm (adjusted hazard ratio, 1.10; 95% CI, 0.75-1.65) (Table).[33] However, this analysis had limited power. The randomized trial in South Africa found that the prevalence of *Neisseria gonorrhoeae* was similar between the circumcised and uncircumcised men (adjusted PR, 0.87; 95% CI, 0.60-1.26).[38] However, in the South African trial, both *Trichomonas vaginalis* (adjusted OR, 0.53; 95% CI, 0.28-1.02) and *Chlamydia trachomatis* (adjusted OR, 0.56; 95% CI, 0.32-1.00) infections were decreased among circumcised men, which was of borderline statistical significance.[39] The randomized trial in Kenya did not find a significant difference between circumcised and uncircumcised men for *N gonorrhoeae* (incidence rate ratio, 0.95; 95% CI, 0.68-1.38), *C trachomatis* (incidence rate ratio, 0.87; 95% CI, 0.65-1.16), or *T vaginalis* (incidence rate ratio, 0.77; 95% CI, 0.44-1.36) infections.[40]

HUMAN PAPILLOMAVIRUS PREVENTION

Many observational studies have suggested that male circumcision decreases both penile cancer and human papillomavirus (HPV) carriage,[41-44] but some studies found no protective effect.[45,46] In an evaluation of multiple anogenital sites of 463 men in the United States, male circumcision was protective against HPV infection of the urethra, glans penis, and penile shaft, with an adjusted OR of 0.53 (95% CI, 0.28-0.99).[47] Among men in Tucson, Arizona, it was also recently shown that circumcised men were 6 times more likely to clear oncogenic HPV infection compared with uncircumcised men.[48]

To determine the effects of circumcision on HPV prevalence in the randomized controlled trial in Rakai,[33] 307 men in the intervention arm and 302 in the control arm were evaluated for HPV prevalence at baseline and year 2. While enrollment prevalence of high-risk HPV was comparable in both study arms, the point prevalence of any high-risk HPV infection at the 2-year visit was lower in the intervention arm (18.0%) than in the control arm (27.9%), with an adjusted PR of 0.65 (95% CI, 0.46-0.90) (Table). In the randomized trial conducted in South Africa, 637 men in the intervention arm and 627 men in the control arm were evaluated for

high-risk HPV at 21 months postenrollment.[38] The prevalence of high-risk HPV was lower in the intervention arm (14.8%) than in the control arm (22.3%), with an adjusted PR of 0.68 (95% CI, 0.52-0.89). These findings, in conjunction with the observational studies, indicate that circumcision should now be accepted as an efficacious intervention for reducing penile HPV infection by 32% to 35% in men.

HPV PREVENTION IN FEMALE PARTNERS

Some[42,49] but not all[50] observational studies have shown that female partners of circumcised men have a significantly reduced risk of cervical cancer. While it is likely that male circumcision decreases HPV infection in female partners and consequently may reduce cervical cancer, the definitive effects will not be determined until the female partners of the men in the Ugandan circumcision trial are evaluated for HPV.

BACTERIAL VAGINOSIS AND TRICHOMONIASIS PREVENTION IN FEMALE PARTNERS

Male circumcision may have benefits for a male's female partner owing to reduced prevalence of male HIV and other STIs. One observational study suggested that female partners of circumcised men have decreased bacterial vaginosis and *T vaginalis* infections,[51] though other studies observed no association between bacterial vaginosis and male circumcision status.[52,53] Among 1638 female partners of men in the randomized trial of male circumcision in Rakai, the female partners of circumcised men had decreased genital ulcer disease (adjusted PR, 0.78; 95% CI, 0.63-0.97), trichomonas infection (adjusted PR, 0.52; 95% CI, 0.05-0.98), and bacterial vaginosis (adjusted PR, 0.60; 95% CI, 0.38-0.94) compared with the partners of uncircumcised men (Table).[54] Severe bacterial vaginosis was markedly reduced among the female partners of circumcised men (adjusted PR, 0.39; 95% CI, 0.24-0.64). This is consistent with recent findings that circumcised men in the Rakai trial have a significant reduction in penile proinflammatory anaerobic bacteria.[55] Therefore, male circumcision is likely to benefit female partners.

While the randomized trials have not evaluated the role of circumcision to reduce *C trachomatis* infection, 1 observational study found that female partners of circumcised men have a significantly reduced rate of seropositivity to *C trachomatis* compared with uncircumcised men (adjusted OR, 0.20; 95% CI, 0.06-0.63).[56]

HIV TRANSMISSION IN FEMALE PARTNERS

Observational studies have suggested that male circumcision decreased HIV transmission to female partners.[57,58] Male circumcision prior to puberty was associated with reduced female HIV acquisition in initially HIV-negative female partners in a discordant relationship with an HIV-infected man (relative risk, 0.49; 95% CI, 0.26-0.82). However, postpubertal circumcision did not significantly affect female HIV risk (relative risk, 0.70; 95% CI, 0.25-1.55).[58] The nonstatistically significant postpubertal circumcision data may be due to confounding, since it involved a subgroup analysis of a small number of individuals in a cohort study.[59] The randomized trial in Rakai assessed discordant couples of HIV-positive men and HIV-negative women and found no effect of male circumcision on male-to-female HIV transmission during 2 years of observation (adjusted hazard ratio, 1.49; 95% CI, 0.62-3.57; $P=.37$).[60] In a subanalysis, HIV transmission was significantly increased among couples who resumed sex prior to complete healing of the circumcision wound ($P=.04$).[60] The apparent contradiction between the observational studies and the randomized trial may be due to the men in the observational studies having been circumcised in childhood, whereas men in the trial were circumcised as adults. Thus, incomplete wound healing in HIV-infected men enrolled in the trial may have offset potential longer-term effects of circumcision on male-to-female HIV transmission. Therefore, neonatal male circumcision likely decreases HIV transmission, but the potential effects of adult male circumcision on female HIV acquisition remains unclear.

BIOLOGIC PLAUSIBILITY OF MALE CIRCUMCISION FOR REDUCTION OF VIRAL STIs

The biological mechanisms whereby circumcision could reduce viral STIs may be due to anatomic and/or cellular factors. The foreskin is retracted over the shaft during intercourse and this exposes the preputial mucosa to vaginal and cervical fluids.[61] It has been hypothesized that viral infections may enter the mucosa through microtears in the preputial mucosa. The moist subpreputial cavity may also provide a favorable environment for viral survival. The inner mucosa of the foreskin is lightly keratinized compared with the epithelium of the shaft, coronal sulcus, and glans, which may facilitate mucosal access of HIV, HSV-2, or HPV. The mucosa of the foreskin also contains a high density of dendritic (Langerhans) cells, macrophages, and $CD4^+$ T cells, which are all targets of HIV[62]; HIV is able to penetrate the foreskin, infecting Langerhans cells.[63,64] Thus, there is biological plausibility to the findings that circumcision reduces male HIV acquisition.

RISKS OF MALE CIRCUMCISION

While the rates of neonatal circumcision complications vary widely between studies, the generally accepted rate is between 0.2% and 0.6% of operations.[1,65,66] The most common complications are bleeding and local infection.[65,66] The bleeding, which is usually a slight oozing, is most often controlled with pressure, and the infection is treated with wound care or antibiotics.[67] While other complications such as phimosis and concealed penis, adhesions, fistula, meatitis, meatal stenosis, and injury to the glans may occur,[68] they are extremely rare.[1,65-67]

Among adults, there have been anecdotal reports of circumcision causing sexual dysfunction or decreased satisfaction. However, there were no reported differences in sexual satisfaction in the randomized study arms in either the Ugandan or Kenyan male circumcision trials

or among men before and after they were circumcised.[69,70] In addition, it has been hypothesized that behavioral disinhibition may counteract any protective effects of male circumcision. However, there was no consistent or substantial evidence of change in sexual behavior after circumcision in the Kenyan or Ugandan randomized controlled trials.[13,14] Thus, there are risks to neonatal circumcision, but serious long-term complications are extremely rare.

ETHICAL CONSIDERATIONS FOR NEONATAL CIRCUMCISION

Some commentators consider neonatal circumcision to be ethically questionable because it causes bodily mutilation and is conducted without consent of the infant.[71] However, others argue that there are long-term benefits for the child that justify the procedure and that parents have the right to consent for their minor child. Even before publication of the male circumcision trials, 2 ethicists weighed the evidence and concluded that "nontherapeutic circumcision of infant boys is a suitable matter for parental discretion."[72] If, as has been argued, circumcision should be delayed until the child can assent or consent to the procedure, it would place the individual at higher risk, since complications of adolescent or adult circumcision are higher than neonatal circumcision.[1,65,66,73] Parents make many medical decisions on behalf of their minor children. For example, immunization entails risk but confers long-term benefit, and the AAP endorses vaccines for infection prevention as long as the parents are informed of potential risks and benefits and consent to the procedure.

The rare short-term risks of neonatal circumcision need to be weighed against the potential benefits accrued in infancy and childhood (eg, reduction of urinary tract infections), the longer-term benefits that may accrue in adolescence and adulthood (eg, reduced risks of HIV, HSV-2, and HPV), as well as possible benefits to female sexual partners of circumcised men (eg, reduced bacterial vaginosis and trichomonas). This is a complex assessment and it is understandable that some physicians have been hesitant to recommend neonatal circumcision owing to concerns over possible immediate complications of the procedure balanced against the more remote potential benefit of disease prevention. However, the evidence for long-term benefits of circumcision has increased substantially in recent years, and the preponderance of this evidence suggests that there are significant reductions in risk for men at high risk of HIV or STI exposure. We believe that the AAP needs to bear in mind these longer-term effects of the procedure so as to appropriately inform parents on the medical risks and benefits for their children.

Current AAP policy also affects insurance coverage. Medicaid does not cover the cost of male circumcision in 16 states, and neonatal circumcision rates are 24% lower in states without coverage compared with states with Medicaid coverage.[8] The lack of Medicaid coverage differentially affects disadvantaged minorities, who as adults have the highest risk of HIV and STIs. These socioeconomically disadvantaged groups could benefit most if Medicaid covered the costs of neonatal circumcision. Thus, the AAP's policy has important implications for the health of disadvantaged minorities.

CONCLUSIONS

The World Health Organization/Joint United Nations Program on HIV/AIDS has concluded that "the research evidence that male circumcision is efficacious in reducing sexual transmission of HIV from women to men is compelling . . . and has been proven beyond reasonable doubt."[17] In 2007, the American Urological Association revised their policy to state that "circumcision should be presented as an option for health benefits."[74] However, the AAP, American College of Obstetricians and Gynecologists, and American Medical Association are likely to have the greatest influence on parental decisions and insurance coverage for neonatal circumcision in the United States. With the mounting evidence that male circumcision decreases viral STIs, genital ulcer disease, and penile inflammatory disorders in men, and bacterial vaginosis, *T vaginalis* infection, and genital ulcer disease in their female partners, it is time for the AAP policy to fully reflect these current data.

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REFERENCES

1. Circumcision policy statement: American Academy of Pediatrics Task Force on Circumcision. *Pediatrics.* 1999;103(3):686-693.
2. AAP publications retired and reaffirmed. *Pediatrics.* 2005;116(3):767.
3. Dickerman JD; American Academy of Pediatrics. Circumcision in the time of HIV: when is there enough evidence to revise the American Academy of Pediatrics' policy on circumcision? *Pediatrics.* 2007;119(5):1006-1007.
4. Flynn P, Havens P, Brady M, et al. Male circumcision for prevention of HIV and other sexually transmitted diseases. *Pediatrics.* 2007;119(4):821-822.
5. Schoen EJ, Wiswell TE, Moses S. New policy on circumcision: cause for concern. *Pediatrics.* 2000;105(3, pt 1):620-623.
6. American College of Obstetricians and Gynecologists Committee on Obstetric Practice. Circumcision: number 260, October 2001. *Obstet Gynecol.* 2001; 98(4):707-708.
7. Council on Scientific Affairs. *Report 10: Neonatal Circumcision.* Chicago, IL: American Medical Association; 1999.
8. Leibowitz AA, Desmond K, Belin T. Determinants and policy implications of male circumcision in the United States. *Am J Public Health.* 2009;99(1):138-145.
9. Schoen EJ. Ignoring evidence of circumcision benefits. *Pediatrics.* 2006;118(1): 385-387.
10. Xu F, Markowitz LE, Sternberg MR, Aral SO. Prevalence of circumcision and herpes simplex virus type 2 infection in men in the United States: the National Health

and Nutrition Examination Survey (NHANES), 1999-2004. *Sex Transm Dis*. 2007; 34(7):479-484.
11. Nelson CP, Dunn R, Wan J, Wei JT. The increasing incidence of newborn circumcision: data from the nationwide inpatient sample. *J Urol*. 2005;173(3): 978-981.
12. Weiss HA, Quigley MA, Hayes RJ. Male circumcision and risk of HIV infection in sub-Saharan Africa: a systematic review and meta-analysis. *AIDS*. 2000;14 (15):2361-2370.
13. Gray RH, Kigozi G, Serwadda D, et al. Male circumcision for HIV prevention in men in Rakai, Uganda: a randomised trial. *Lancet*. 2007;369(9562):657-666.
14. 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(9562):643-656.
15. Auvert B, Taljaard D, Lagarde E, Sobngwi-Tambekou J, Sitta R, Puren A. Randomized, controlled intervention trial of male circumcision for reduction of HIV infection risk: the ANRS 1265 Trial. *PLoS Med*. 2005;2(11):e298.
16. Weiss HA, Halperin D, Bailey RC, Hayes RJ, Schmid G, Hankins CA. Male circumcision for HIV prevention: from evidence to action? *AIDS*. 2008;22(5): 567-574.
17. Joint United Nations Programme on HIV/AIDS. New data on male circumcision and HIV prevention: policy and programme implications. Montreux, Switzerland: Joint United Nations Programme on HIV/AIDS; 2007.
18. HIV/AIDS Surveillance Report, 2007. Atlanta, GA: US Department of Health and Human Services, Centers for Disease Control and Prevention; 2009:19.
19. Government of the District of Columbia Department of Health. District of Columbia HIV/AIDS Epidemiology Update 2008. http://www.doh.dc.gov/hiv. June 1, 2009.
20. Warner L, Ghanem KG, Newman DR, Macaluso M, Sullivan PS, Erbelding EJ. Male circumcision and risk of HIV infection among heterosexual African American men attending Baltimore sexually transmitted disease clinics. *J Infect Dis*. 2009;199(1):59-65.
21. Buchbinder SP, Vittinghoff E, Heagerty PJ, et al. Sexual risk, nitrite inhalant use, and lack of circumcision associated with HIV seroconversion in men who have sex with men in the United States. *J Acquir Immune Defic Syndr*. 2005;39(1): 82-89.
22. Kreiss JK, Hopkins SG. The association between circumcision status and human immunodeficiency virus infection among homosexual men. *J Infect Dis*. 1993; 168(6):1404-1408.
23. Millett GA, Ding H, Lauby J, et al. Circumcision status and HIV infection among black and Latino men who have sex with men in 3 US cities. *J Acquir Immune Defic Syndr*. 2007;46(5):643-650.
24. Millett GA, Flores SA, Marks G, Reed JB, Herbst JH. Circumcision status and risk of HIV and sexually transmitted infections among men who have sex with men: a meta-analysis. *JAMA*. 2008;300(14):1674-1684.
25. Lane T, Raymond HF, Dladla S, et al. Lower risk of HIV infection among circumcised MSM: results from the Soweto Men's Study [abstract MOPDC105]. Presented at: The 5th International AIDS Society Conference; Cape Town, South Africa; July 19-22, 2009.
26. Buchbinder SP, Mehrotra DV, Duerr A, et al; Step Study Protocol Team. Efficacy assessment of a cell-mediated immunity HIV-1 vaccine (the Step Study): a double-blind, randomised, placebo-controlled, test-of-concept trial. *Lancet*. 2008;372 (9653):1881-1893.
27. Auvert B, Buve A, Lagarde E, et al; Study Group on the Heterogeneity of HIV Epidemics in African Cities. Male circumcision and HIV infection in four cities in sub-Saharan Africa. *AIDS*. 2001;15(suppl 4):S31-S40.
28. Weiss HA, Buve A, Robinson NJ, et al; Study Group on Heterogeneity of HIV Epidemics in African Cities. The epidemiology of HSV-2 infection and its association with HIV infection in four urban African populations. *AIDS*. 2001;15(suppl 4):S97-S108.
29. Lavreys L, Rakwar JP, Thompson ML, et al. Effect of circumcision on incidence of human immunodeficiency virus type 1 and other sexually transmitted diseases: a prospective cohort study of trucking company employees in Kenya. *J Infect Dis*. 1999;180(2):330-336.
30. Reynolds SJ, Shepherd ME, Risbud AR, et al. Male circumcision and risk of HIV-1 and other sexually transmitted infections in India. *Lancet*. 2004;363(9414): 1039-1040.
31. Gray R, Azire J, Serwadda D, et al. Male circumcision and the risk of sexually transmitted infections and HIV in Rakai, Uganda. *AIDS*. 2004;18(18):2428-2430.
32. Weiss HA, Thomas SL, Munabi SK, Hayes RJ. Male circumcision and risk of syphilis, chancroid, and genital herpes: a systematic review and meta-analysis. *Sex Transm Infect*. 2006;82(2):101-110.
33. 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(13):1298-1309.
34. Sobngwi-Tambekou J, Taljaard D, Lissouba P, et al. Effect of HSV-2 serostatus on acquisition of HIV by young men: results of a longitudinal study in Orange Farm, South Africa. *J Infect Dis*. 2009;199(7):958-964.
35. Bwayo J, Plummer F, Omari M, et al. Human immunodeficiency virus infection in long-distance truck drivers in east Africa. *Arch Intern Med*. 1994;154(12): 1391-1396.
36. Cook LS, Koutsky LA, Holmes KK. Circumcision and sexually transmitted diseases. *Am J Public Health*. 1994;84(2):197-201.
37. Urassa M, Todd J, Boerma JT, Hayes R, Isingo R. Male circumcision and susceptibility to HIV infection among men in Tanzania. *AIDS*. 1997;11(3):73-80.
38. Auvert B, Sobngwi-Tambekou J, Cutler E, et al. Effect of male circumcision on the prevalence of high-risk human papillomavirus in young men: results of a randomized controlled trial conducted in orange farm, South Africa. *J Infect Dis*. 2009;199(1):14-19.
39. Sobngwi-Tambekou J, Taljaard D, Nieuwoudt M, Lissouba P, Puren A, Auvert B. Male circumcision and *Neisseria gonorrhoeae*, *Chlamydia trachomatis* and *Trichomonas vaginalis*: observations after a randomised controlled trial for HIV prevention. *Sex Transm Infect*. 2009;85(2):116-120.
40. 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(3):370-378.
41. Schoen EJ, Oehrli M, Colby C, Machin G. The highly protective effect of newborn circumcision against invasive penile cancer. *Pediatrics*. 2000;105(3):E36.
42. Castellsagué X, Bosch FX, Munoz N, et al; International Agency for Research on Cancer Multicenter Cervical Cancer Study Group. Male circumcision, penile human papillomavirus infection, and cervical cancer in female partners. *N Engl J Med*. 2002; 346(15):1105-1112.
43. Baldwin SB, Wallace DR, Papenfuss MR, et al. Human papillomavirus infection in men attending a sexually transmitted disease clinic. *J Infect Dis*. 2003;187 (7):1064-1070.
44. Lajous M, Mueller N, Cruz-Valdez A, et al. Determinants of prevalence, acquisition, and persistence of human papillomavirus in healthy Mexican military men. *Cancer Epidemiol Biomarkers Prev*. 2005;14(7):1710-1716.
45. Weaver BA, Feng Q, Holmes KK, et al. Evaluation of genital sites and sampling techniques for detection of human papillomavirus DNA in men. *J Infect Dis*. 2004; 189(4):677-685.
46. Shin HR, Franceschi S, Vaccarella S, et al. Prevalence and determinants of genital infection with papillomavirus, in female and male university students in Busan, South Korea. *J Infect Dis*. 2004;190(3):468-476.
47. Nielson CM, Schiaffino MK, Dunne EF, Salemi JL, Giuliano AR. Associations between Male anogenital human papillomavirus infection and circumcision by anatomic site sampled and lifetime number of female sex partners. *J Infect Dis*. 2009; 199(1):7-13.
48. Lu B, Wu Y, Nielson CM, et al. Factors associated with acquisition and clearance of human papillomavirus infection in a cohort of US men: a prospective study. *J Infect Dis*. 2009;199(3):362-371.
49. Drain PK, Halperin DT, Hughes JP, Klausner JD, Bailey RC. Male circumcision, religion, and infectious diseases: an ecologic analysis of 118 developing countries. *BMC Infect Dis*. 2006;6:172.
50. Brinton LA, Reeves WC, Brenes MM, et al. The male factor in the etiology of cervical cancer among sexually monogamous women. *Int J Cancer*. 1989;44(2): 199-203.
51. Gray RH, Wawer M, Thoma M, et al. Male circumcision and the risks of female HIV and sexually transmitted infections acquisition in Rakai, Uganda [abstract 128]. Presented at: The 13th Conference on Retroviruses and Opportunistic Infections; Denver, CO; February 5-8, 2006.
52. Schwebke JR, Desmond R. Risk factors for bacterial vaginosis in women at high risk for sexually transmitted diseases. *Sex Transm Dis*. 2005;32(11): 654-658.
53. Zenilman JM, Fresia A, Berger B, McCormack WM. Bacterial vaginosis is not associated with circumcision status of the current male partner. *Sex Transm Infect*. 1999;75(5):347-348.
54. Gray R, Kigozi G, Serwadda D, et al. The effects of male circumcision on female partners' genital tract symptoms and vaginal infections in a randomized trial in Rakai, Uganda. *Am J Obstet Gynecol*. 2009;200(1):42.e1-42.e7.
55. Price L, Johnson KE, Rattray R, et al. Circumcision is associated with significant changes in the penis bacterial microbiota [abstract 1062]. Presented at: The 16th Conference on Retroviruses and Opportunistic Infections; Montreal, QC; February 8-11, 2009.
56. Castellsagué X, Peeling RW, Franceschi S, et al; IARC Multicenter Cervical Cancer Study Group. Chlamydia trachomatis infection in female partners of circumcised and uncircumcised adult men. *Am J Epidemiol*. 2005;162(9):907-916.
57. Baeten JM, Donnell D, Inambao M, et al. Male circumcision and male-to-female HIV-1 transmission risk: a multinational prospective [abstract LBPEC06]. Pre-

sented at: The Fifth International AIDS Society Conference; Cape Town, South Africa; July 19-22, 2009.
58. Gray RH, Kiwanuka N, Quinn TC, et al; Rakai Project Team. Male circumcision and HIV acquisition and transmission: cohort studies in Rakai, Uganda. *AIDS*. 2000;14(15):2371-2381.
59. Halperin DT, Weiss HA, Hayes R, et al. Response to Ronald Gray, Male circumcision and HIV acquisition and transmission: cohort studies in Rakai, Uganda (2000, 14:2371-2381). *AIDS*. 2002;16(5):809-812.
60. Wawer MJ, Makumbi F, Kigozi G, et al. Circumcision in HIV-infected men and its effect on HIV transmission to female partners in Rakai, Uganda: a randomised controlled trial. *Lancet*. 2009;374(9685):229-237.
61. Szabo R, Short RV. How does male circumcision protect against HIV infection? *BMJ*. 2000;320(7249):1592-1594.
62. McCoombe SG, Short RV. Potential HIV-1 target cells in the human penis. *AIDS*. 2006;20(11):1491-1495.
63. Dinh M, Barry S, Anderson M, et al. HIV-1 interactions and infection in adult male foreskin explant cultures [abstract 502]. Presented at: The 16th Conference on Retroviruses and Opportunistic Infections; Montreal, QC; February 8-11, 2009.
64. Fischetti L, Barry SM, Hope TJ, Shattock RJ. HIV-1 infection of human penile explant tissue and protection by candidate microbicides. *AIDS*. 2009;23(3):319-328.
65. Christakis DA, Harvey E, Zerr DM, Feudtner C, Wright JA, Connell FA. A trade-off analysis of routine newborn circumcision. *Pediatrics*. 2000;105(1, pt 3):246-249.
66. Wiswell TE, Geschke DW. Risks from circumcision during the first month of life compared with those for uncircumcised boys. *Pediatrics*. 1989;83(6):1011-1015.
67. Alanis MC, Lucidi RS. Neonatal circumcision: a review of the world's oldest and most controversial operation. *Obstet Gynecol Surv*. 2004;59(5):379-395.
68. Hutcheson JC. Male neonatal circumcision: indications, controversies and complications. *Urol Clin North Am*. 2004;31(3):461-467, viii.
69. Kigozi G, Watya S, Polis CB, et al. The effect of male circumcision on sexual satisfaction and function, results from a randomized trial of male circumcision for human immunodeficiency virus prevention, Rakai, Uganda. *BJU Int*. 2008;101(1):65-70.
70. Krieger JN, Mehta SD, Bailey RC, et al. Adult male circumcision: effects on sexual function and sexual satisfaction in Kisumu, Kenya. *J Sex Med*. 2008;5(11):2610-2622.
71. Hinchley G. Is infant male circumcision an abuse of the rights of the child? yes. *BMJ*. 2007;335(7631):1180.
72. Benatar M, Benatar D. Between prophylaxis and child abuse: the ethics of neonatal male circumcision. *Am J Bioeth*. 2003;3(2):35-48.
73. Kigozi G, Gray RH, Wawer MJ, et al. The safety of adult male circumcision in HIV-infected and uninfected men in Rakai, Uganda. *PLoS Med*. 2008;5(6):e116.
74. American Urological Association. Circumcision. http://www.auanet.org/content/guidelines-and-quality-care/policy-statements/c/circumcision.cfm. June 1, 2009.

Babies are always more trouble than you thought—and more wonderful.
—Charles Osgood