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Can Routine Neonatal Circumcision Help Prevent Human Immunodeficiency Virus Transmission in the United States?

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Abstract

Primary prevention of human immunodeficiency virus (HIV) continues to pose an important challenge in the United States. Recent clinical trials conducted in Kenya, South Africa, and Uganda have demonstrated considerable benefit of male circumcision in reducing HIV seroincidence in males. These results have ignited debate over the appropriateness of implementing routine provision of neonatal circumcision in the United States for HIV prevention. This paper discusses major contextual differences between the United States and the three African countries where the clinical trials were conducted, and cautions that the applicability of the scientific data from Africa to this country must be carefully considered before rational policy recommendations regarding routine neonatal circumcision can be made as a strategy to prevent the spread of HIV in the U.S.

Keywords

human immunodeficiency virus; neonatal circumcision; prevention

Introduction

Primary prevention of human immunodeficiency virus (HIV) continues to pose an important challenge in the United States. An estimated 1.0–1.2 million Americans were living with HIV (Glynn & Rhodes, 2005) and 40,000 new infections occurred each year (Centers for Disease Control and Prevention, 2006a). Despite recent advances in HIV/AIDS treatment, including highly active antiretroviral therapy (HAART), HIV remains an incurable condition (Hamers & Downs, 2004). In 2006, 14,627 Americans died with AIDS (Centers for Disease Control and Prevention, 2008).

Recent clinical trials conducted in Kenya, South Africa, and Uganda have demonstrated considerable benefit of male circumcision in reducing HIV seroincidence in males (51–60% reduction in the relative risk) (Auvert et al. 2005; Bailey et al., 2007; Gray et al., 2007). These results have ignited debate over the appropriateness of implementing routine provision of neonatal circumcision in the United States for HIV prevention (McNeil, 2007).

Evidence on Male Circumcision as a Preventive Strategy and Implications for the U.S

Until these recent clinical trials, there have been no randomized studies assessing male circumcision as a preventive strategy for heterosexual acquisition of HIV in men (Siegfried et al., 2003). A systematic review assessing the role of male circumcision in preventing heterosexual acquisition of HIV in men using evidence from 37 observational studies published in or before 2004 reported that many studies failed to control for confounding factors such as genital ulcer disease, co-occurring sexually transmitted infections (STI), unsafe medical

practices, viral load, religion, culture, socioeconomic status, condom use, migration status, age, and study location (Siegfried et al., 2005). Because the vast majority of these 37 studies were conducted in Africa and Asia, we have a limited understanding of the effects of male circumcision on HIV prevention in the U.S.

Further, though several studies have been conducted, the cost-effectiveness of routine neonatal circumcision has not yet been established for the U.S. setting. Research by Lawler et al. (Lawler, Bisonni, & Holtgrave, 1991) and Ganiates et al. (Ganiats, Humphrey, Taras, & Kaplan, 1991) in the early 1990s found minimal differences in lifetime cost and utility between circumcised and uncircumcised newborns (without considering the spread of STI). By incorporating data on additional medical sequelae as they became available, particularly the transmission of HIV and STI, Van Howe (Van Howe, 2004) conducted the most recent cost-effectiveness analysis in the U.S. setting. The study demonstrated that over the lifetime, neonatal circumcision is associated with \$828 incremental costs and a 0.0153 reduction in quality adjusted life years (QALYs) for each neonate. Poor quality data was identified as the “greatest handicap in the development” of these cost-effectiveness analyses (Van Howe, 2004). Notably, this analysis preceded the recent clinical trials conducted in Kenya, South Africa, and Uganda.

These clinical trials have methodological advantages over most previous studies, and hence provide better quality data. Beyond using the randomized controlled study design, the clinical trial in Kenya adjusted for baseline variables that were slightly imbalanced between the two study groups (despite randomization) (Bailey et al., 2007) and the Ugandan trial adjusted for postulated potential confounders identified in previous studies, including baseline age, marital status and sexual risk behaviors (Gray et al., 2007). Still, caution should be taken in adopting these data in any rigorous evaluations of a policy for routine provision of neonatal circumcision to prevent HIV in the United States due to major contextual differences between the United States and Africa.

Major Contextual Differences between the United States and Africa

Several factors differ between these two distinct regions, such as age at circumcision, dominant mode of HIV transmission, biological factors, HIV transmission dynamics, and health care system factors.

Adult versus Neonatal Circumcision

In the United States, the majority of adult men are already circumcised (Xu et al. 2007); male circumcision is generally practiced at birth. National Hospital Discharge Survey data indicate that the overall rate of neonatal circumcision has remained near 65% since data collection began in 1979, and that 56% newborn males born in U.S. hospitals were circumcised in 2003 (Child Trends DataBank, 2004). In contrast, the minimum age of enrollees in the recent clinical trials in Kenya, South Africa, and Uganda was 15 years. This major difference in age at circumcision precludes direct comparison of the effectiveness of circumcision between the two geographic regions. Assessment of the effectiveness of a prevention intervention initiated at birth entails parameters beyond age at circumcision. In particular, 39.3% of 9th grade male students in the U.S. have had sexual intercourse and 8.8% of male students have their first sexual intercourse before age 13 (Centers for Disease Control and Prevention, 2006b). Because in the U.S. circumcision is generally performed at birth, sexual exposures during young adolescent age must be considered when evaluating the effects of circumcision on HIV prevention in the U.S.

Dominant Modes of HIV Transmission

In the United States, the most common mode of transmission for HIV infection was penile-anal sexual contact, accounting for about 49% of all reported HIV or AIDS cases diagnosed in 2006 (Centers for Disease Control and Prevention, 2008). This is followed by high-risk heterosexual contact and use of non-sterile drug injecting equipment, accounting for 33% and 13% of the reported HIV/AIDS cases diagnosed in 2006, respectively (Centers for Disease Control and Prevention, 2008). These patterns differ from the population in which the three randomized trials in Kenya, South Africa, and Uganda were conducted where heterosexual transmission of the HIV was the predominant mode (Kahn, Marseille, & Auvert, 2006; Chen et al. 2007). Because the African clinical trials focused on the risk of heterosexual HIV transmission from females to males, the potential impact of male circumcision on reducing HIV infection associated with other modes of transmission, such as male-to-male and injection drug use transmission, remains largely unknown (National Institute of Allergy and Infectious Diseases, 2006). A recent systematic review identified only two studies of male circumcision in relation to the risk of male-to-male HIV transmission (Fankem, Wiysonge, & Hankins, 2007). The authors of the review cautioned against any conclusions regarding the biological effect of male circumcision on HIV transmission in the male-to-male population due to the potential for unmeasured confounding factors in these two observational studies.

In addition, 27% of American adults and adolescents living with HIV/AIDS in 2006 were women (Centers for Disease Control and Prevention, 2008). Of them, 73% were infected during high-risk heterosexual contact (Centers for Disease Control and Prevention, 2008). Moreover, 92% of HIV/AIDS cases in children (<13 years) were attributable to vertical transmission from mother (Centers for Disease Control and Prevention, 2008). The Kenyan, South African and Ugandan trials primarily examined HIV acquisition among circumcised versus non-circumcised males; hence the impact of circumcision on reduction in male-to-female transmission is unknown to date (National Institute of Allergy and Infectious Diseases, 2006; Auvert et al. 2005). In order to fully assess the benefit of any HIV prevention strategy, it is essential to consider the effect among both men *and* women.

Biological Factors and Transmission Dynamics

HIV acquisition and transmission are associated with several biologic factors including seroprevalence, viral load, co-occurring STI, stage of disease, duration of infectiousness, genetic haplotype, viral subtype, and levels of mucosal immune response (Aral & Holmes, 1999; Quinn, 2006), several of which differ significantly between the U.S. and Africa. For instance, the prevalence of HIV infection among adults and adolescents in the U.S. was estimated at 0.14% at the end of 2005 in the 37 areas with confidential name-based HIV infection reporting (Centers for Disease Control and Prevention, 2006a). In contrast, HIV prevalence in the countries in which the circumcision trials were conducted range from an estimated 6.2–7% in Uganda and Kenya to nearly 25% in South Africa (Joint United Nations Programme on HIV/AIDS (UNAIDS), 2006). Applying the number needed to treat (NNT) concept (Laupacis et al. 1988), the markedly different prevalence of HIV infection in the U.S. raises considerable questions about the number of procedures necessary to prevent a single case of HIV transmission compared to Africa. The number of males needed to be circumcised to prevent one new HIV infection could be substantial in the U.S. This raises the potentially controversial issue of recommending widespread prevention when only a small targeted group might benefit. Moreover, this makes the cost-effectiveness of male circumcision less promising in the U.S. than in African countries.

The transmission dynamics of HIV are also influenced by the phase of the epidemic, population prevalence, transmission probability, and specific characteristics of transmission networks (e.g., sexual mixing, partner concurrency). The presence of co-occurring STI, such as

gonorrhea, chlamydia, herpes simplex virus or syphilis, also increases the risk of HIV transmission during unprotected sexual contact between an infected and uninfected partner (Cameron et al., 1989). Between- and within-country differences in patterns of sexual behavior, including age at sexual initiation, current and lifetime number of sex partners, frequency and consistency of sexual activity, mode of recruitment of sex partners, and duration of sexual partnerships (Aral & Holmes, 1999) have important implications for HIV prevention strategies. For example, studies show that the higher likelihood of having more than one long-term sexual partner at a time among Ugandan men than men in Thailand and the U.S. has contributed to the more generalized spread of HIV in Uganda (Morris 2002). Five percent of the study participants in the Kenyan circumcision trial had Chlamydia trachomatis (Bailey et al. 2007), while in the U.S., the rate of chlamydial infection was 348 per 100,000 population in 2006 (Centers for Diseases Control and Prevention, 2007). Moreover, 34% of the participants in the Ugandan trial had two or more sexual partners in the past 12 months (Gray et al. 2007) and 42% of the participants in the Kenyan circumcision trial had at least two partners in the previous 6 months (Bailey et al. 2007). This compares to 19.5% of American males ages 15 to 44 who had two or more sexual partner in the last 12 months (U.S. Census Bureau, 2008). Regional differences in these factors must be considered.

Health Care System

Fundamental differences between health care systems in the United States and Africa could influence the rates of HIV transmission, as well as the cost-effectiveness of HIV prevention interventions. There is better public health infrastructure and access to clinical, laboratory, and pharmacy in the U.S., which could lead to early detection and treatment of HIV infected patients and patients with other STIs. Moreover, utilization rates of advanced medical technologies are higher among patients in the U.S., particularly with regard to HAART therapy. Seventy percent of HIV-infected Americans receive antiretroviral therapy (UNAIDS, 2007), while in sub-Saharan Africa, it is estimated that less than one quarter (23%) of those in need of antiretroviral treatment are receiving it (UNAIDS, 2006). Use of HAART could substantially lower viral load and shorten the level and duration of infectiousness.

In addition, infection control in the health care setting varies across countries. The transmission probability for contaminated medical injections and contaminated blood products has been estimated at 0.45% and 92.5%, respectively (Baggaley et al. 2006). Thus, differences between countries in the exposure to blood-borne pathogens in the health care setting also affect the probability of infection among susceptible individuals (Hu et al. 1991). It was estimated that 6% of HIV infections in Africa was due to blood transfusions and 1.6% was due to contaminated medical injections and other health care procedures (Gisselquist et al. 2003, Chin et al. 1990). More recent data suggest that unsafe health care exposures in sub-Saharan Africa might have played an even larger role in the spread of HIV (Deuchert & Brody 2006; Gisselquist et al. 2003). By contrast, the risk of transfusion-transmitted HIV infection is extremely low in the U.S. (1 in 677,000 units) (Glynn et al. 2000; Kleinman et al. 1997).

Finally, as an incurable condition, HIV/AIDS requires costly lifelong treatment (Hamers & Downs, 2004). Differences in the cost of medical care between countries could significantly influence the cost-effectiveness of an HIV prevention intervention. The per capita health expenditure in the U.S. was \$6,096 in 2004 compared to \$748, \$135, and \$86 in South Africa, Uganda, and Kenya, respectively (United Nations Development Programme, 2007). An intervention found to be cost-effective in one country may not prove to be cost-effective in another due to such wide differences in cost of care. Caution needs to be taken when translating HIV prevention strategies across countries.

Future Directions and Emphasis for Research

Encouraging data from the recent clinical trials in Kenya, South Africa, and Uganda has raised the question regarding the implications for HIV prevention in the U.S. However, acceptability of routine neonatal circumcision in the U.S. is an issue at the intersection of medicine, public health, religion, culture, ethics, law, and human rights. Before neonatal circumcision can be recommended as a strategy to prevent the spread of HIV in the U.S., the applicability of the clinical trial data from Kenya, South Africa, and Uganda to this country must be carefully considered.

Assessment of the impact of male circumcision in the U.S. must consider exposures occurring during adolescence (because in the U.S. circumcision is generally performed at birth), differences in factors influencing HIV transmission dynamics, including the heterogeneity in HIV prevalence, as well as differences in other biological and behavioral factors that impact transmission. In addition, despite the widely recognized burden of HIV/AIDS-related diseases, resources available to combat the epidemic are limited (Marseille et al., 2002). Comprehensive cost-effectiveness analysis considering the various elements of HIV transmission in the context of the United States will be instrumental in elucidating the potential cost, benefit, and risks of HIV prevention strategies.

Clearly, more research addressing the following questions would greatly inform the discussion regarding the utility of routine neonatal circumcision in HIV prevention in the U.S.: What is the effect on HIV transmission when circumcision is performed at birth? What is the effect on HIV prevention specifically in the context of the U.S. epidemic (particularly seroprevalence and predominant mode of transmission)? What is the magnitude of the impact of circumcision on reduction in male-to-female transmission? Whether it is cost-effectiveness to perform routine neonatal circumcision in preventing HIV transmission in the U.S. setting? These important questions *must* be answered before rational policy recommendations regarding neonatal circumcision can be made.

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