Male Circumcision and Risk for HIV-1 Seroconversion in sub-Saharan Africa

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11 April 2003

A Master's paper submitted to the faculty of the University of North Carolina at Chapel Hill in partial fulfillment of the requirements for the degree of Master of Public Health in the School of Public Health, Public Health Leadership Program.

INTRODUCTION

The modern era has seen its share of infectious diseases. Epidemics of smallpox, polio, measles, whooping cough and tuberculosis mark the early history of public health in the United States and the World. The formation of public health institutions has led to the partial or complete eradication of many of these serious diseases. However, in the new millennium, public health finds itself waging a battle against what could be perceived as history's most virulent infection—Human Immunodeficiency Virus (HIV-1). Two types of HIV have been identified; HIV Type 1 (HIV-1) and HIV Type 2 (HIV-2). HIV-1 is the more virulent and is the predominant type found in the sub-Saharan region.

Over the past several decades, HIV-1 has infected some 65 million individuals worldwide and claimed more than 25 million lives [1]. As of December 2002, there were more than 42 million people worldwide living with HIV/AIDS and during the same year, more than 3 million died from an AIDS-related illness. In 2002, more than 5 million people were newly infected with HIV-1, representing a net increase in prevalence of approximately 2 million (Table 1).

The affects of HIV are far reaching—not only impacting patients and their families, but also taxing world economies due to the associated costs. Scientific, medical, and public health communities find themselves challenged daily to discover more about the disease, develop more treatment options, and implement effective interventions to control its spread.

Nowhere has the devastation of HIV/AIDS been more ravaging than in underdeveloped or third world nations where poverty, lack of information, lack of access to healthcare, and volatile sociopolitical conditions fuel the spread of the epidemic [2]. According to the most recent data from UNAIDS/WHO, some 29.4 million individuals in sub-Saharan Africa live with HIV-1 infection. In 2002 alone, approximately 3.5 million new infections occurred in the region (or, 70% of all new infections *in the World)* while their northern counterparts (North Africa and

the Middle East) demonstrated a much lower prevalence rate of 550,000 and an incidence of just 83,000 (Table 2). In addition to the sociopolitical and economic conditions that may facilitate the spread of HIV-1, there are widely accepted behavioral practices and habits that are known to increase the risk of acquiring the infection. Intravenous (IV) drug use, having multiple sex partners (particularly without the use of prophylactics), and men having sex with men (MSM) are the most commonly accepted modes of HIV-1 transmission. In Europe and North America, the most common modes of HIV-1 transmission are IV drug use and MSM relationships (Table 2). In contrast, heterosexual contact is the major mode of HIV-1 transmission in sub-Saharan Africa (including the countries of Zimbabwe, Zambia, Ivory Coast, Benin, Ghana, Cameroon, Namibia, Central African Republic, Democratic Republic of Congo, Nigeria, South Africa, Kenya, Tanzania, Uganda, Malawi, Rwanda, and Botswana, Figure 1.). In fact, it is estimated that over 90% of HIV-1 infections in African males were acquired via vaginal intercourse [3]. This is hardly surprising since it is widely accepted that the cervical environment is very susceptible to HIV-1 infection [4]. Additionally, in some countries in sub-Saharan Africa, young females are disproportionately affected and represent approximately twice the number of HIV-1 cases as young men [2]. Therefore, controlling the spread of HIV-1 to males should be primary public health objective in sub-Saharan Africa, and any conditions that predispose males to HIV-1 infection during heterosexual intercourse require further investigation.

In an attempt to explain the disparity between the HIV-1 rates observed in different countries and regions of sub-Sahara, epidemiologist have spent decades examining various behavioral and cultural practices. The behavioral risk factors identified were found to be similar across many ethnic groups and regions, and did not fully explain the difference observed in HIV-1 rates [5-8]. This finding taken with the results of other epidemiological studies suggested

another previously undefined cultural practice may be present, and lead researchers to hypothesize that the geographical differences in HIV-1 prevalence may be related to the practice of male circumcision.

The suggestion of an association between male circumcision and risk of infection is not a new hypothesis. Hutchison, more than 150 years ago, noted a difference in the incidence rate of syphilis (a sexually transmitted infection, STI) among non-Jewish vs. Jewish males [9]. In the 1980s, Nairobi physician Francis Plummer observed that uncircumcised men were more likely to have genital ulcers [10, 11]. However, it was not until Fink's work in 1987 that circumcision status was specifically associated with HIV-1 infection. Fink hypothesized that lack of circumcision increased the risk of acquiring HIV-1. Since then, numerous epidemiological studies have been conducted to examine this hypothesis and most support Fink's findings [13, 14].

This paper will examine some of the biological, ecological and epidemiological evidence that supports the existence of a relationship between circumcision status and susceptibility to HIV-1 infection in sub-Saharan Africa.

BIOLOGICAL EVIDENCE

The penis of an uncircumcised male physically differs from a circumcised penis. The foreskin is a flap of skin and mucosa (similar to tissue in the mouth or vagina) that folds over the glans (head). The foreskin adheres closely to the glans until approximately age 8 when it loosens and becomes retractable. During circumcision, the foreskin is pulled back and a section is cut away, exposing the glans. After circumcision, the glans and remaining foreskin, which are partially composed of mucosa, begin to thicken and toughen (or *keratinize*), becoming more like

the exposed skin (stratified squamous epithelium) found on the body [4, 10]. This type of keratinized tissue is rather resilient to minor trauma because of its thickness. In contrast, during intercourse, the foreskin of the uncircumcised penis pulls backward, exposing mucosal tissue. Mucosal tissue is easily damaged, and can become inflamed, irritated, and/or torn (or cause *microlesions*) during sexual intercourse. Mucosal damage results in lymphocytes, including macrophages, dendritic cells and Langerhans cells, moving into the damaged area. Scientists have discovered that HIV-1 binds to specific receptors on these lymphocytes and may cause primary HIV-1 infection [4, 10, 12, 13]. Given that the mucosal tissue on the uncircumcised penis contains high densities of HIV-1 target cells (including lymphocytes, Langerhans cells, and macrophages) and has a large surface of mucosal tissue vulnerable to microlesions, many in the scientific community believe that these factors may increase the risk of HIV-1 infection.

Little immunologic work has been done characterizing the cellular differences between the circumcised and uncircumcised penis. Most of the research on HIV-1 infection pathways has been conducted on cervical tissue (which is similar to foreskin mucosa) and is being used as a springboard to describe male genitalia susceptibilities. The basis for the hypothesis of non-circumcision is akin to the infectious process seen in the environment of cervical tissue—a known HIV-1 infection site.

During the infection process, the HIV-11 targets several major cells found in human mucosa: CD4+ T cells (lymphocytes), macrophages, and Langerhans cells (LCs). During primary infection HIV-1 attaches itself to CD4+ T cells on the cell surface. Following the binding of the HIV-1 to a co-receptor (usually CCR5 in primary infection and CXCR4 during the later stages of infection), the virus penetrates the CD4+ T cell and replicates. The virus is

then released from the host cell (CD4+ T cell) and can infect other lymphocytes, macrophages, and LCs.

In cervical mucosa, susceptibility to HIV-1 infection is associated with the number of HIV-1 target cells and expression of HIV-1 co-receptors [4, 13]. A sexual transmission model involving simian immunodeficiency virus (SIV) in the genital tract mucosa of female rhesus macaques showed that the SIV targets the LCs of the vaginal mucosa, fuses with adjacent CD4 + lymphocytes, migrates to deeper tissue, and SIV is detectable in the lymphatic system within 2 days [13]. A study of male macaques showed the infection process to be similar to that of females when the foreskin or penile urethra is exposed to SIV. The LCs become infected. These animal studies support a comparative study which demonstrated antigen presenting LCs in human foreskin as a primary target for HIV-1 infection [14].

A recent immunologic study by Patterson (2002) looked at the biological mechanisms responsible for possible increased HIV-1 susceptibility in human foreskin. Patterson assessed the number of major HIV-1 target cells in the human foreskin, the expression of the HIV-1 co-receptor in human foreskin, and the susceptibility of human foreskin to HIV-1 infection. He concluded that the surface of the uncircumcised penis is in fact more susceptible to HIV-1 infection than the circumcised penis [4].

The study was conducted ex vivo using 8 pediatric and 6 adult foreskins with (n=3) and without (n=11) prior history of STIs. The 14 foreskin specimens were collected from males ranging in age from 10 months to 65 years who had undergone elective or corrective procedures. Cervical biopsies of 6 HIV-1 seronegative women without history of STIs were used as controls. The 14 foreskin samples were stained for HIV-1 target cells with CD4+ T cells, macrophages, and LC antibodies and then analyzed using quantitative immunohistochemistry. Findings

showed quantities of 0.4 to 3.1% CD4+ T cells, 1.9 to 15.6% LCs, and 0.1 to 2.7% macrophages. CD4+ T cells were primarily found in the submucosa and the majority of LCs were found in the epithelium. The proportion of all 3 types of HIV-1 target cells increased with the age of the patients. Patterson found that foreskin mucosa contained higher mean proportions of CD4+ T cells (22.4%), macrophages (2.4%), and LCs (11.5%) in adults than in children (4.9%, 0.3%, and 6.2% respectively) or in cervical mucosa (6.2%, 1.4%, and 1.5%, respectively). The mean proportions of each cell type were greater for adults than children, with statistically significant differences for CD4+ T cells and macrophages but not for LCs. Males with a history of infection had the highest proportions of CD4+ T cells and LCs.

In a subset of adult samples that included the external foreskin surface there were statistically significant fewer CD4+ T cells and LCs compared with the inner mucosal surface. The percentage of macrophages was similar in external foreskin surface and inner mucosal surface. Patterson also noted that the extent of keratinization of the epithelium was much greater in the external foreskin surface than the inner mucosal surface.

Patterson also found that compared to the ectocervix (an HIV-1 susceptible mucosal tissue with similar types of HIV-1 target cells), there are statistically significantly more quantities of CD1a+ (a particular type of LC) in adult foreskin (9.7%) and in pediatric foreskin (6.1%) compared with ectocervical tissue (1.1%,). The foreskin may therefore be more susceptible to HIV-1 infection than the cervix because of an increased percentage of LCs.

HIV-1 co-receptor expression was analyzed using 6 adult foreskin and 6 cervical specimens. The majority of cells expressed CCR5; all 6 adult male foreskin and 5/6 cervical samples. Cells expressing the highest levels of CCR5 were found in the submucosa (of LCs) and were statistically significantly increased compared with the number of cells expressing CCR5 in

the cervix. With this evidence, Patterson demonstrated that there was a high level of HIV-1 co-receptor expression in the human foreskin, a necessary mechanism for HIV-1 infection.

After the cellular structure and biological mechanisms were confirmed, Patterson investigated the infectivity of target cells by HIV-1. After exposure to HIV-1, foreskin and ectocervical biopsies were quantified for HIV-1pol DNA copies per 1,000 cells. Mean HIV-1 DNA in adult male foreskin tissue was nine times that of cervical tissue samples without known previous exposure to STIs. Inner mucosal foreskin (previously found to have higher percentage of target cells and HIV-1 co-receptor expression) was more susceptible to HIV-1 infection than cervical tissue. Qualitative assessments using immunochemistry revealed the HIV-1 infection to be primarily in CD4+ T cells and LCs at the base of the epithelial layer. In addition, when measuring the level of HIV-1 DNA in the external foreskin, it appeared that keratinization and the presence of fewer HIV-1 target cells offered protection against HIV-1 infiltration from the outer surfaces of infected foreskin tissues in vitro. The HIV-1 DNA levels were below the limits of detection.

This study presents compelling evidence that the inner surface of the foreskin has higher densities of HIV-1 target cells and higher levels of HIV-1 co-receptor expression than cervical tissue-- suggesting the inner foreskin to be more susceptible to HIV-1 than cervical tissue. While the researchers demonstrated a difference in inner and external foreskin infectivity (external foreskin was not infected), no studies were done using circumcised penile tissue. This represents a limitation of the study. However, to evaluate the potential infectivity of the penile shaft, biopsies of outer foreskin were used for comparison. The researchers assumed that the composition of the stratified squamous epithelium of the keratinized external foreskin was similar to the surface of the penile shaft. From their findings, it was inferred that the penile

shaft is less susceptible to HIV-1 infection given its lower number of HIV-1 target cells and keratinized surface, and, in the absence of microlesions, trauma, or genital ulcerative disease (GUD), is not the likely site of HIV-1 infection. The epithelium of the glans has been implicated as the pathway for HIV-1 infection in uncircumcised males because is it presumably less keratinized (since protected by the foreskin) [4]. However, in a study of Australian cadavers, epithelial tissue of the glans was found to be equally keratinized in circumcised and uncircumcised males. The glans does not therefore seem the likely pathway of HIV-1 infection, though it is possible that post-mortem changes are responsible for the similarities in keratinization. Patterson suggest a more likely transmission route is through the urethral mucosa or through disruptions in the penile shaft epithelia caused by trauma or GUD [4].

Immunologic data suggests the physical composition of the uncircumcised penis renders it more susceptible to HIV-1 infection. The conditions of the previously described study were very well controlled with the ability to select for STI exposure, age, and sexual history. However, in reality, these and other potential confounders exist that can make the distinction between circumcision status and HIV-1 susceptibility less perfect. In the section to follow, ecological evidence of HIV-1 trends will be examined to determine if there are geographic associations between HIV-1 seroprevalence and circumcision practices.

Ecological Evidence

In sub-Saharan Africa, circumcision is limited to certain ethnicities and religious sects; primarily Muslims, Christians, and some ethnic groups practice. In their ecological study, Moses et al. demonstrated a geographic relationship between HIV-1 seroprevalence and male circumcision practices at a societal level [15].

Using several ethnogeographic databases and a Yale University database, Moses identified the male circumcision practices for over 700 African societies. A US Census Bureau database (which collates information from all available sources) was used as a source of HIV-1 seroprevalence data as were data from scientific literature and abstracts, scientific conferences, and government publications. Criteria were applied to compiled data to standardize and extract potential confounders. The geographic analysis was limited to studies during 1986 or later with a sample size of at least 100 persons. To control for confounding factors, Moses et al. excluded studies involving "high risk" activity such as studies of prostitutes, barmaids/men, long distance truck drivers, hospitalized patients, patients with HIV-1 associated disease, and prisoners. Study participants must have been $\geq$ 15 years of age and considered members of the general worker population, antenatal clinic attendees, and/or blood donors. Data on HIV-1 and HIV-2 were combined and where studies yielded conflicting seroprevalence information, an average was taken. To avoid over-reporting in areas where studies were conducted in the same population but at different times, the researchers used the most recent data.

The resultant database contained male circumcision and HIV-1 seroprevalence data from 140 geographically distinct locations in 41 different countries. A map was constructed demonstrating the usual male circumcision practice of these countries. The researchers were unable to determine male circumcision practices in a few societies, however, none of these locations were those for which they had HIV-1 seroprevalence data so the analysis was unaffected. The vast majority of non-circumcision societies are located in sub-Saharan Africa beginning in southern Sudan and covering most of Uganda, parts of western Kenya and western Tanzania, Rwanda, Burundi, Zambia, Malawi, Zimbabwe and parts of Botswana, Namibia, Mozambique and South Africa. There were large pockets of non-circumcising societies in West

Africa, namely eastern/central Ivory Coast and parts of western/central Ghana. Seroprevalence data was then superimposed over the circumcision practices map (Figure 2). Moses et al., found that in regions of Africa where circumcision was widely practiced, there was lower HIV-1 prevalence (mean HIV-1 seropositivity of 1.41%). In contrast, societies that did not practice circumcision presented with higher HIV-1 seroprevalence (mean=7.37%, ratio =5.2:1). Variations were noted within and between countries with regard to circumcision practices. The researchers also observed that there were locations in parts of Angola, the Republic of Congo, and Guinea-Bissau (traditionally circumcising societies) with relatively high HIV-1 seroprevalence rates. However, of the 68 datapoints (31 nations) with seroprevalence of <1%, all but 2 fell within nations that practice circumcision. Of 17 datapoints (7 nations) with HIV-1 seroprevalence of >10%, all but 1 were in areas were circumcision was not practiced.

Though compelling, Moses' work is not without limitations including the inability to determine if HIV-1 seropositive persons were lifelong natives or if they migrated there, age at circumcision, if sexual behaviors differed within and between regions, if circumcision practices persisted or had changed over time, and if other religious or other cultural practices such as hygiene affected the analysis. Other studies have been conducted suggesting that [at least some of] these behaviors do not in and of themselves explain the increased HIV-1 seroprevalence in sub-Saharan Africa, therefore the associations demonstrated between HIV-1 seroprevalence and circumcision may be important [5-7]. Consistent with Moses' 1990 study, current trends in Africa and Asia show that countries where 20% or less of men are circumcised have *higher* HIV-1 rates than countries where more than 80% of the men are circumcised [3].

EPIDEMIOLOGICAL STUDIES

As of 1994, World Health Organization reported that some 551 AIDS-related research studies had been conducted in 33 African countries [16]. Much data has been produced and studies are continually being published identifying links between HIV-1 surgence and lack of male circumcision in sub-Saharan Africa. Key studies in Kenya, Uganda, Tanzania and other countries have contributed to the body of knowledge, and meta-analyses of available HIV-1 transmission data have been performed. Among the research are studies assessing the risk for HIV-1 acquisition by age of male circumcision, employment type (e.g., trucking employees, sex workers), STI co-infection, religious affiliation, sexual practices, cultural practices and other suspected risk factors. In Moses et al.'s 1994 literature review of 30 epidemiological studies of non-circumcision and HIV-1 risk, 18 cross-sectional studies from 6 countries reported a statistically significant association, 4 studies from 4 countries showed a trend towards association, while 4 studies from 2 countries found no association between circumcision and HIV-1 susceptibility. Two prospective cohort studies reported significant association as did 2 ecological studies [17]. Moses' review demonstrated that in studies where there was a significant association, the odds ratios (OR) between non-circumcision and risk for HIV-1 seroconversion ranged from 1.5 to 8.4.

In contrast, Van Howe's 1999 meta-analysis of 33 studies found that circumcision slightly increased the risk of HIV-1 acquisition (OR 0.94, 95% CI 0.89 – 0.99) [18]. However, Van Howe's work is criticized for using methodology contrary to standard statistical theory including non-systematic approaches to literature search, use of unadjusted risk ratios, and for failure to employ weighted averages such that large studies did not convey undue influence over smaller ones [13, 19-21]. When O'Farrell (2000) reanalyzed the same 33 studies using the

appropriate statistical techniques, non-circumcision was strongly associated with HIV-1 infection odds of 1.43 (fixed effects model) or 1.67 (random effects model) [21]. Particularly in high-risk groups where genital ulcers and other STIs heighten vulnerability to HIV-1 infection, circumcision seems to offer a protective effect. While much research is still needed in the area, the vastness of the epidemiological research currently available exceeds the abilities of this discussion and as such, Weiss et al's meta-analysis (which is widely cited in research and discussions on the topic of male circumcision and HIV-1 risk in sub-Saharan Africa) will be used as a limited representation of all the epidemiological studies.

Weiss et. al's meta-analysis (2000) demonstrated similar results to Moses' 1994 analysis [20]. In Weiss's meta-analysis, data was compiled using a systematic approach that began with a search of Medline, Pre-Medline, HeatlhStar and Popline databases for all published studies up to April 1999 of risk factors for HIV-1 infection among men in sub-Saharan African that included circumcision as a potential risk factor. Key words and search conditions yielded more than 400 articles. Studies of HIV-1-2 risk were further eliminated, as were studies with insufficient details to calculate a crude risk ratio (RR). Studies that appeared in more than one publication or were a subset of another study were not included as to avoid over reporting and duplication of data. Twenty-seven eligible papers related to female-male transmission of HIV-1 and circumcision remained. Significant effort was taken to ensure the appropriateness of data and studies of all designs (e.g., cohort, case-control, and cross-sectional) were included in the meta- analysis. Studies were further stratified into population-based studies, studies of men at high risk for HIV-1 (such as truckers, STI clinic attendees, patrons of sex workers, those with GUD) and other populations (e.g., factory workers and volunteers). The studies included in the meta-analysis are listed in Table 3. Odd ratios (OR) were used as estimates of relative risk.

Twenty-one of the 27 studies included in the analysis demonstrated that circumcised men were at lower risk of HIV-1 infection than their uncircumcised counterparts. The association was statistically significant in 14 of these studies. Six (of 21) studies suggested a positive association where male circumcision increased HIV-1 risk, however, it should be noted that 4/6 studies were conducted in Mwanza, Tanzania and the association was not statistically significant. This inconsistency with the overall data may represent the presence of confounders not identified or addressed in the original research, and additional studies in this country would be beneficial. With a highly significant pooled risk ratio for all 27 studies of 0.52, (95% CI 0.40 – 0.68), Weiss concluded that circumcision accrues a protective affect against HIV-1 acquisition in males. It should be noted, however, that there was a statistically significant heterogeneity between studies which may be a potential limitation for the meta-analysis.

In studies (15/27) where adjustments were made for confounders, the risk ratio strengthened the association where the crude RR was 0.54 (CI 0.39-0.74) and adjusted RR was 0.45 (CI 0.34-0.58). Confounders that were adjusted included age and at least one other factor such as sociodemographics (e.g., marital status, area of residence, ethnic group), sexual behavior (e.g., number of sexual partners ever, last year, last 4 months, and relations with sex workers), condom use, and presence of STIs.

Results from the stratified studies were also supportive of the general results. Crude risk ratios of the 12 studies classified as population-based studies showed little association between circumcision and HIV-1 seroprevalence (crude RR=0.93, CI 0.71-1.21). However, when results for the 6 population studies that adjusted for confounders were analyzed, the adjusted RR revealed a significant reduction of HIV-1 risk among circumcised males (adjusted RR= 0.56, CI 0.44 – 0.70). These 6 population studies were not shown to be significantly heterogeneous.

Results from the high HIV-1 risk strata (STI clinic attendees, long distance truck drivers, patients with tuberculosis, and hospital patients) showed significant association between HIV-1 risk and non-circumcision, with a crude RR of 0.27 (CI 0.22 – 0.33). These results were largely unchanged after adjusting for confounders (7 studies) with an adjusted RR of 0.29, CI 0.20 – 0.41 but there was a statistically significant between-study heterogeneity.

To avoid the statistical analysis limitations of Van Howe's meta-analysis, Weiss reanalyzed the data after extracting results from the largest study (6821 men representing 25% of the total meta-analysis population). The results showed this large study did not influence the meta-analysis with crude RR of 0.52, (CI 0.40 – 0.68) and adjusted RR of 0.42 (CI (0.32 – 0.55)—results very similar to the overall findings of O'Farrell's meta-analysis (crude OR 0.60, CI 0.45 – 0.80).

By adjusting for confounders, Weiss et al. have avoided a potential limitation in their research. After the adjustments were made in the population-based studies, causal associations were strengthened whereas adjustments in high-risk populations (where the crude RR already demonstrated a strong association) left the risk ratio relatively unchanged. This suggests that even when behaviors were present that should have increased HIV-1 risk, circumcision seemed to protect men from contracting HIV-1 infection. Another potential confounder in the meta-analysis is the effect of religion. There is limited data about the relationship between religion, circumcision, and HIV-1 seroprevalence, however, a study of Muslim men in Rwanda showed circumcision to have a protective effect (crude RR = 0.18, CI 0.02-1.20). While the association between circumcision and HIV-1 seroprevalence was weaker among Christians (crude RR 0.79, CI 0.5-1.23), it is noted that unlike Muslims, most Christians are circumcised post-puberty [22]. According to research conducted in Uganda, risk for HIV-1 increased with age of circumcision

(adjusted OR = 0.39 with prepubertal circumcision, 0.46 for men circumcised at ages 13-20, and 0.78 among men circumcised after age 20) [23]. Results from a similar study in Tanzania are contrary to those of Uganda where pre-pubertal circumcision seemed to increase risk for HIV-1 (adjusted RR = 1.50) and decreased risk after puberty (adjusted RR = 0.37) [24]. It is unclear why these results differ from other studies. The impacts of religion and age of circumcision on HIV-1 transmission therefore warrant further study in their own right to determine if there are concurrent behavioral patterns that decrease HIV-1 risk such as societal expectations, alcohol and drug use, post-coital bathing, fewer sexual partners, and or circumcision method (e.g., traditional or by medical professionals).

Another limitation of the data included in the meta-analysis is the reliance on subjects to report circumcision status. A study into the reliability of circumcision self-report conducted in Tanzania found a margin of error, where roughly 30% of men who thought themselves to be circumcised were found not to be upon physical examination [25]. This suggests circumcision may have been over-reported in studies where status was not physically confirmed including studies referenced in the meta-analysis. Future research into the associations between circumcision and HIV-1 would be strengthened by clinical confirmation of circumcision status. Finally, it might be suggested that works included in this meta-analyses do not capture all the available data, as search criteria and eligibility requirements were imposed and bias may have been introduced. Further, it is possible that only studies whose results showed statistical significance were published. Though human error could have resulted in the exclusion of some eligible studies, it should be noted the authors took a systematic approach to article selection as to enhance continuity in scope and research methodology. Bias is therefore unlikely since a wide range of behavioral and biological risk factors were examined. Two eligible studies published

after the meta-analysis are mentioned in the author's discussion and both demonstrate with statistical significance that lack of circumcision increases susceptibility to HIV-1 in sub-Saharan Africa [11, 26]. Lavreys' prospective cohort study of trucking company employees in Kenya was not included in the meta-analysis but this study supports an association between non-circumcision and increased risk of HIV-1 infection (HRR = 4.0, 95% CI 1.9 – 8.3) and GUD with an HRR = 2.5, (95% CI 1.1-5.3) [11]. After controlling for potential confounders such as sexual behavior and presence of STIs, the observed protective effect remained [11]. Overall, the Weiss meta-analysis seems to be a thoughtfully executed analysis of HIV-1 risk among uncircumcised men and has become a widely cited reference in subsequent publications of the subject.

DISCUSSION

While it is true much work remains to be done on the subject of male circumcision status and risk for HIV-1 acquisition in sub-Saharan Africa, it is abundantly clear that observed associations cannot be discounted. The evidence to date overwhelmingly suggests circumcision provides protection against HIV-1 in this population. Biologically, the uncircumcised penis is more susceptible to HIV-1 infection due to higher densities of HIV-1 target cells and HIV-1 expressing co-receptors than cervical tissue or tissue similar to that of a circumcised penis. Langerhans cells are present in adult foreskin mucosa in much greater densities than in children and female cervical tissue and therefore seem to render the mucosa more vulnerable to HIV-1 infection. Additionally, it would appear that the less keratinized surface of the foreskin inner mucosa is more vulnerable to microtears, inflammation, and genital ulcerative diseases which HIV-1increases susceptibility to HIV-1 infection. A great limitation of the Patterson study was

failure to compare infectivity of tissue from a circumcised penis to uncircumcised foreskin. External foreskin was substituted for circumcised penile tissue. Additional studies exploring the differences in keratinization of circumcised vs. uncircumcised penises as well as pathways of infection are underway and will provide additional insight to this critical piece of the immunological puzzle.

Ecological evidence suggests the distribution of HIV-1 seroprevalence coincides with the geographical spread of traditionally non-circumcising societies. It should noted the distribution of circumcision practices also run along religious boundaries where traditionally circumcising areas are also areas with strong Muslim presence or where they make up a significant majority (Figure 3). Many identify religion as a strong potential confounder, as it is difficult to distinguish the effects of religious practices on HIV-1 susceptibility and if circumcision and religion are independent variables of risk. The affects of religion on HIV-1 acquisition bear grounds for further study, however, it is important to keep Moses' ecological data in perspective as documentation of the geographical distribution of the disease relative to circumcision practices. Because the results from these studies were published many years ago, the field would benefit from updated ecological studies to assess current seroprevalence data relative to circumcision geography, including assessment of whether those who have seroconverted are native to their current location.

In a meta-analysis of 27 studies, 21 showed that circumcision reduced susceptibility to HIV-1 infection where circumcised men were at half the risk for acquiring HIV-1 as uncircumcised men. After adjusting for confounders, the protective effect became stronger. As Bailey offers, "such an increase in protective effect after adjustment for behavioral factors makes it unlikely that the effect could be explained by residual confounding alone, and suggests that the

effect of circumcision is a true biological one." Though there is risk for heterogeneity in meta-analyses, meta-analyses are useful tools that can be used to demonstrate consistency (or inconsistency) in research findings. Weiss's meta-analysis seems a well-executed attempt of consolidating the observational data surrounding risk factors for HIV-1 infection among men in sub-Saharan Africa where lack of circumcision is a potential risk factor. While room for error exists when human judgement is relied upon to identify eligible research, the authors took a systematic approach to identifying appropriate data for analysis and were careful to avoid the blunders of Van Howe's meta-analysis. As a result, the meta-analysis has been cited in numerous articles on the subject and currently represents one of the most critical and widely referenced synopses of the association between male circumcision status and HIV-1 risk.

Those who criticize circumcision as a preventative measure against HIV-1 commonly cite confounding factors such as religious practices, sexual behavior patterns, and penile hygiene as reason to dismiss or at least question the reported associations. However, research shows these potential confounders alone do not result in increased risk for HIV-1 infection among men. Thus, behavior alone does not confound the observation that non-circumcision increases risk for HIV-1 acquisition.

Conclusion

The ecological, biological, and epidemiological evidence overwhelmingly suggest that a relationship between male circumcision and HIV-1 seroprevalence exists in sub-Saharan Africa. To progress the issue, additional studies are needed to determine if potential confounding factors lend to an overestimation of the protective effects of circumcision. As work continues in the area, it is conceivable that circumcision will emerge as a tool to prevent the spread of HIV-1 in

sub-Saharan Africa. Evidence suggests that many Africans have already begun to open up to the idea of circumcision as a preventative tool against HIV-1, even though it may conflict with their traditional practices and beliefs. In a place where limited resources, poor socio-political conditions, sexually transmitted infections, and lack of education will continue to fuel the spread of HIV-1, circumcision may be a viable intervention.

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TABLE 1

GLOBAL SUMMARY OF THE HIV/AIDS EPIDEMIC

DECEMBER 2002

SOURCE: UNAIDS/WHO REPORT DECEMBER 2002

Number of people living with HIV/AIDS Total		**42 million**
	Adults	38.6 million
	Women	*19.2 million*
	Children under 15 years	3.2 million
People newly infected with HIV in 2002 Total		**5 million**
	Adults	4.2 million
	Women	*2 million*
	Children under 15 years	800 000
AIDS deaths in 2002	**Total**	**3.1 million**
	Adults	2.5 million
	Women	*1.2 million*
	Children under 15 years	610 000

TABLE 2

REGIONAL HIV/AIDS STATISTICS AND FEATURES, END OF 2002

SOURCE: UNAIDS/WHO REPORT DECEMBER 2002

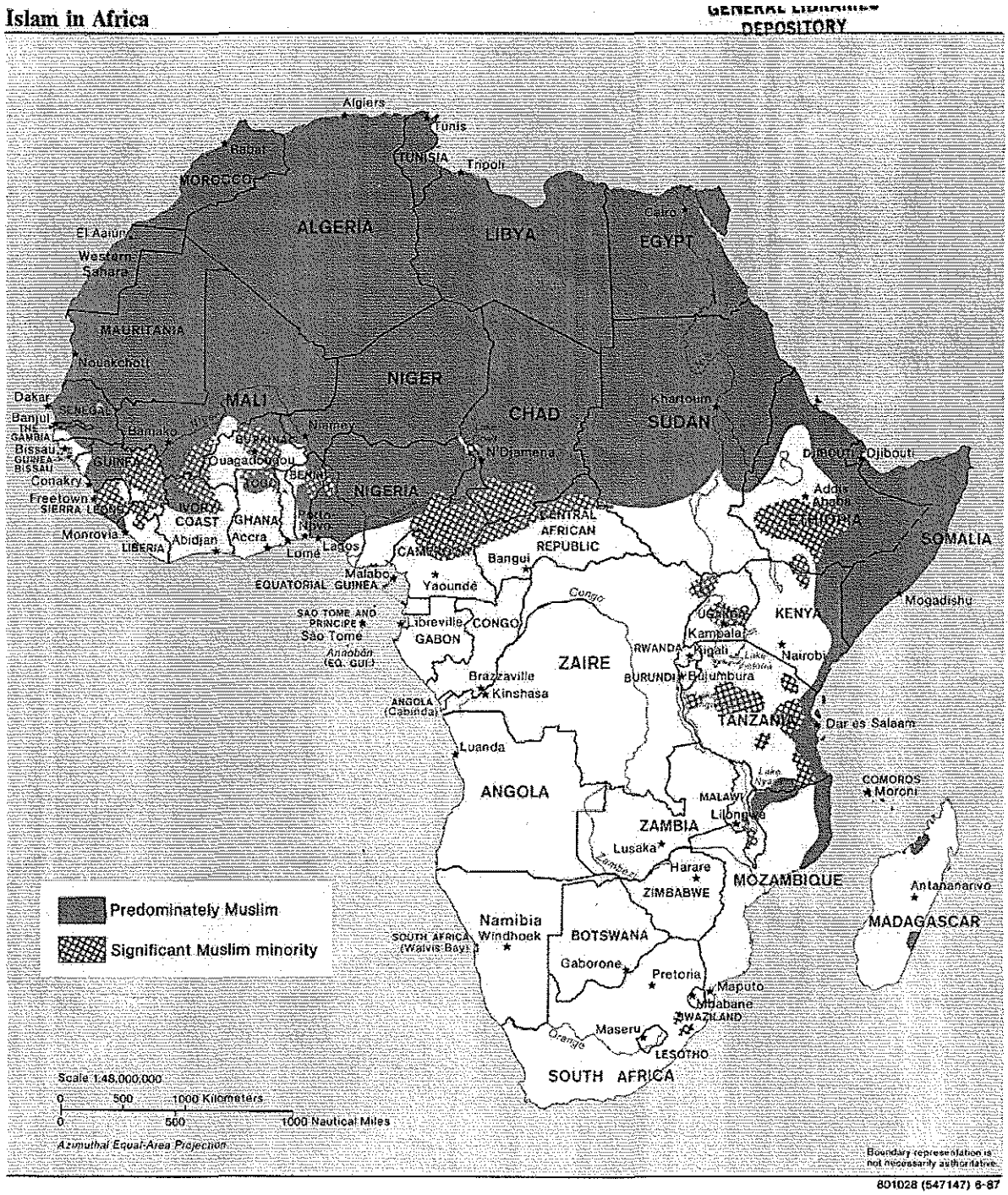
Region	Epidemic started	Adults and children living with HIV/AIDS	Adults and children newly infected with HIV	Adult prevalence rate (*)	% of HIV-positive adults who are women	Main mode(s) of transmission (#) living for adults with HIV/AIDS
Sub-Saharan Africa	late '70s early '80s	29.4 million	3.5 million	8.8%	58%	Hetero
North Africa & Middle East	late '80s	550 000	83 000	0.3%	55%	Hetero, IDU
South & South-East Asia	late '80s	6.0 million	700 000	0.6%	36%	Hetero, IDU
East Asia & Pacific	late '80s	1.2 million	270 000	0.1%	24%	IDU, hetero, MSM
Latin America	late '70s early '80s	1.5 million	150 000	0.6%	30%	MSM, IDU, hetero
Caribbean	late '70s early '80s	440 000	60 000	2.4%	50%	Hetero, MSM
Eastern Europe & Central Asia	early '90s	1.2 million	250 000	0.6%	27%	IDU
Western Europe	late '70s early '80s	570 000	30 000	0.3%	25%	MSM, IDU
North America	late '70s early '80s	980 000	45 000	0.6%	20%	MSM, IDU, hetero
Australia & New Zealand	late '70s early '80s	15 000	500	0.1%	7%	MSM
TOTAL		**42 million**	**5 million**	**1.2%**	**50%**	

* The proportion of adults (15 to 49 years of age) living with HIV/AIDS in 2002, using 2002 population numbers.

Hetero (heterosexual transmission), IDU (transmission through injecting drug use), MSM (sexual transmission among men who have sex with men).

FIGURE 3

ISLAM IN AFRICA, 1987



Source: United States Central Intelligence Agency database—1987

FIGURE 1

MAP OF POLITICAL BOUNDARIES

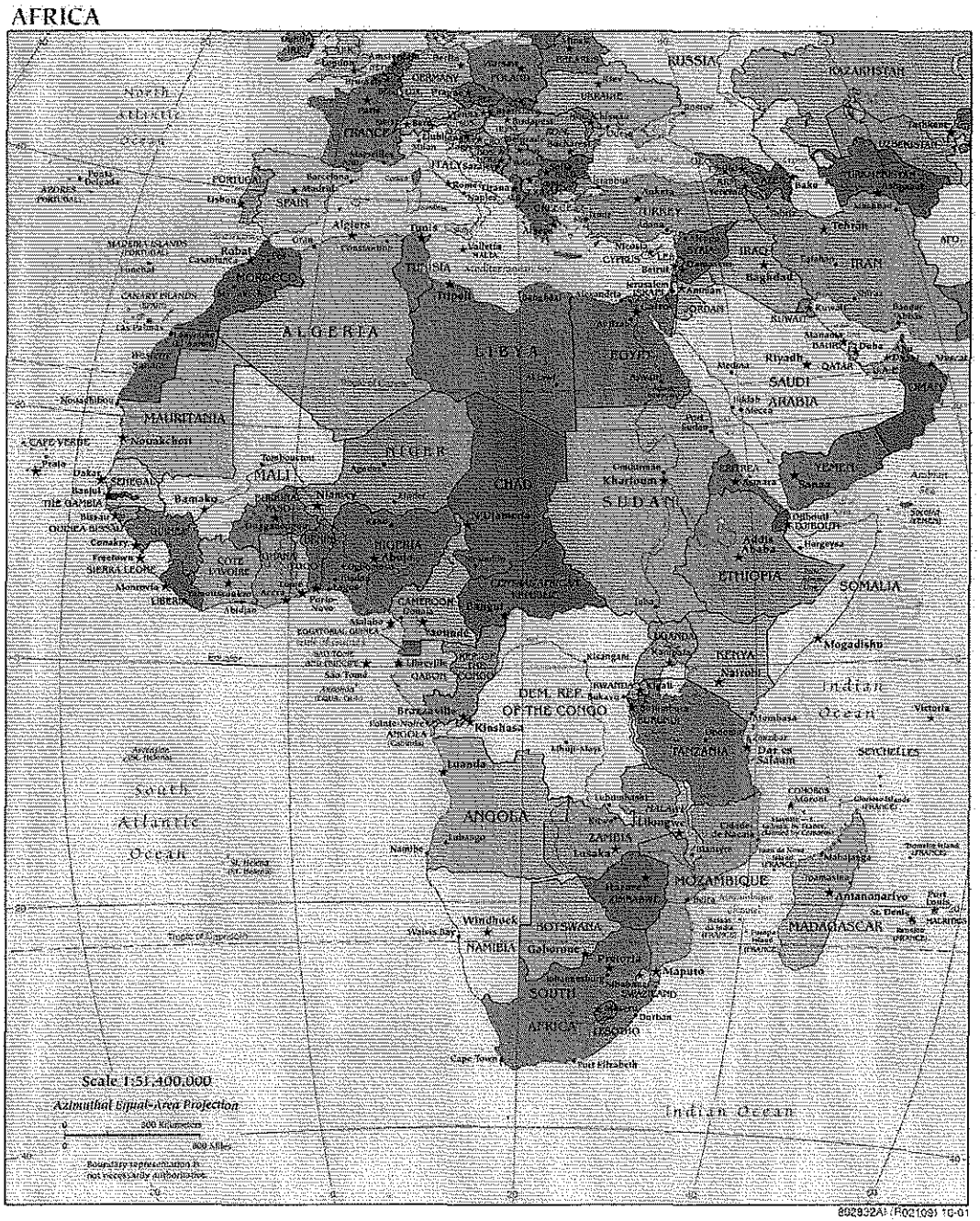
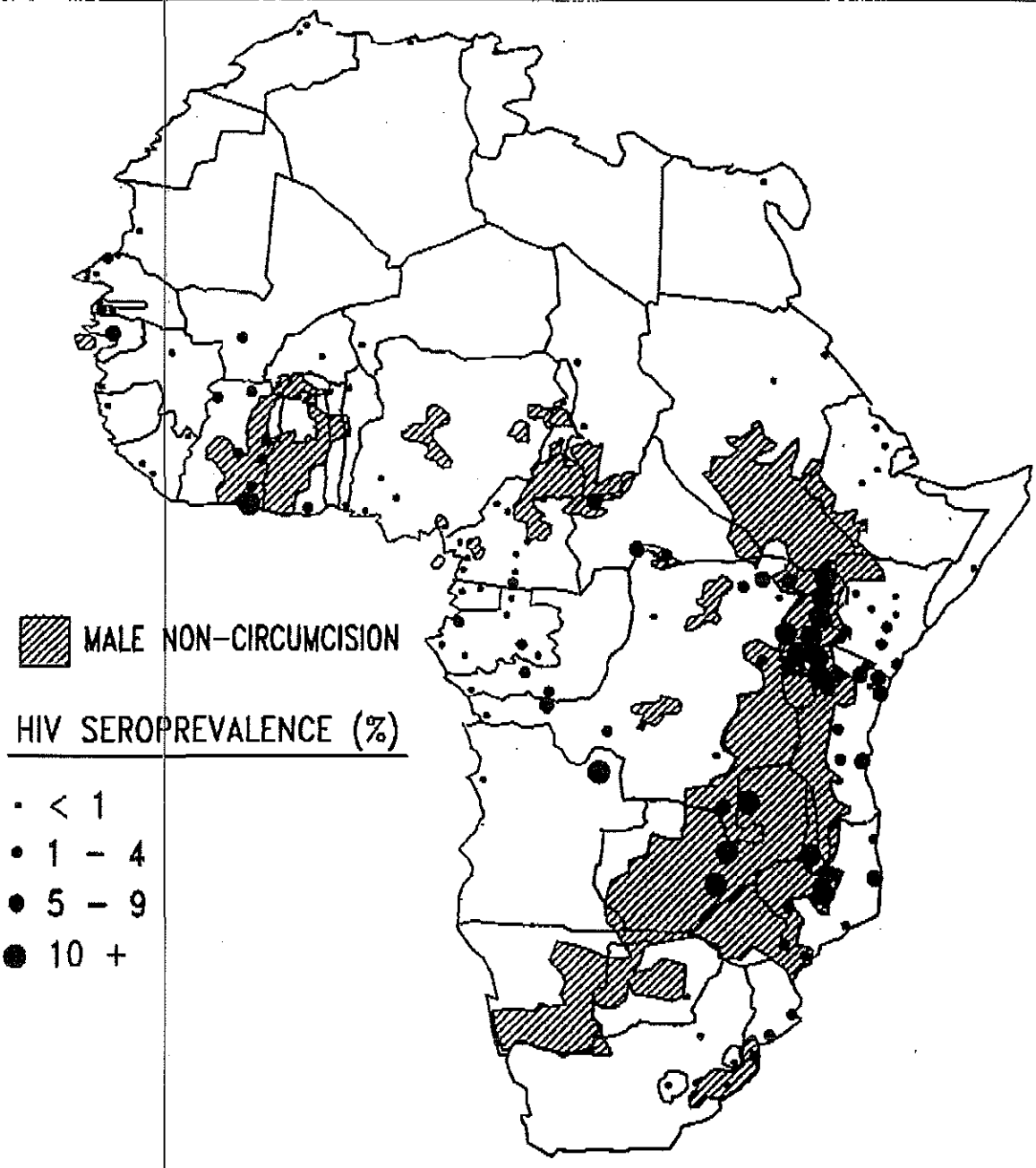


FIGURE 2

HIV SEROPREVALENCE AND MALE CIRCUMCISION IN AFRICA



Map of Africa showing political boundaries and usual male circumcision practice, with point estimates of general adult population HIV seroprevalence superimposed.