

## **Transmission probability of HIV and Herpes Simplex Virus**

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### **Burden of Herpes Simplex Virus infection**

Herpes Simplex Virus type 2 (HSV-2) is a sexually transmitted infection and the most common cause of genital herpes in developing countries (1). Because of its spread and its morbidity, ability to cause sickness in the population, HSV-2 infection is of major health concern. HSV-2 infections are lifelong, but many individuals have no or mild symptoms. Therefore the majority of genital herpes infections are transmitted from individuals unaware that they have the infection or who are asymptomatic – do not have any symptoms - when transmission occurs (2). When symptomatic, very painful genital lesions can occur.

In 2003, the estimated total number of people aged 15 to 49 living with HSV-2 worldwide (prevalence) was 536 million. 123.7 million (23%) resided in sub-Saharan Africa, among whom 63% were women (1). HSV-2 prevalence in the adult general population of sub-Saharan Africa ranges from 30% to 80% among women and from 10% to 50% among men (3). These rates are substantially higher than those in developed countries and in other developing regions (1). Within sub-Saharan Africa, prevalence is higher in eastern, middle and southern Africa, and lower in western Africa (1). As in the developed world, HSV-2 prevalence is higher in women than in men and increases with age (3).

Few epidemiological studies have estimated the incidence, number of people newly infected, of HSV-2 infection in the developing world. A review estimated the number of new HSV-2 infections among 15 to 49 year olds worldwide in 2003 at 23.6 million, 26% of which having occurred in sub-Saharan Africa (1).

### **HIV and HSV-2 infection**

Genital herpes is associated with a two- to three-fold increased risk of HIV acquisition and an up to five-fold increased risk of HIV transmission per sexual act, and may account for 40% to 60% of new HIV infections in populations where HSV-2 has a high prevalence (1). Hence, it has been argued that HSV-2 could have a major role in fuelling the spread of HIV and that significant numbers of HIV

infections could potentially be averted if HSV-2 could either be prevented or suppressed. However, two recent trials reported that HSV-2 suppressive therapy currently available did not reduce HIV acquisition (4, 5).

HIV, in turn, increases the risk of HSV-2 transmission (6). Outbreaks of HSV-2 are generally more severe, extensive, persistent, and invasive for those with more advanced HIV disease (7). In fact, persistent HSV-2 infection was one of the original opportunistic infections that resulted in the identification of AIDS (8).

However, few data are available on the interaction of HIV and HSV-2 infections.

### **Two studies, consistent results**

Using data from a randomized controlled trial on male circumcision conducted in Orange Farm, South Africa (9), two studies (10, 11) analysed the interactions of HIV and HSV-2 infections and their transmission probabilities (chances). The clinical trial took place between February 2002 and July 2004, recruited 3274 uncircumcised 18 to 24 year-old men which were randomized into two groups and followed-up for 21 months. In the intervention group, male circumcision was offered immediately after randomization whereas in the control group it was offered after the end of the follow-up period. At the start of the study, participants were tested for HSV-2 and HIV. During each follow-up visit (after 3, 12 and 21 months), circumcision status was assessed by a nurse via genital examination and blood samples were obtained and tested for HIV and HSV-2. Information about sexual behaviour was collected, including number of partners over time, number of sexual contacts with each partner, reported condom use with each partner and age of each partner.

The first study (10) was conducted to assess the role of HSV-2 status on HIV acquisition by young men and its potential influence on the protective effect of male circumcision on HIV acquisition. The protective effect of male circumcision on HSV-2 acquisition was also analyzed. Longitudinal data of the male circumcision trial were processed by

statistical analysis, controlling for (taking into account the effect of) background characteristics and sexual behaviour. Results showed a strong association (relationship) between HSV-2 status and HIV incidence. When compared to participants who stayed HSV-2 negative during follow-up, HIV incidence was three times higher among participants who were HSV-2 positive at recruitment and seven times higher among participants who became HSV-2 positive during follow-up. Thus, the proportion of all HIV incident cases due to HSV-2 infection in the population (population attributable fraction) was estimated at 27.8%. HSV-2 status did not alter the protective effect of male circumcision on HIV acquisition since the protective effect of male circumcision on HIV acquisition was the same among HSV-2 positive and HSV-2 negative men. Male circumcision reduced the HSV-2 female-to-male transmission.

The second study (11) was aimed at estimating the female-to-male transmission probabilities (FtoMTPs) of HSV-2 and HIV, and at assessing the effect of each virus and of male circumcision on these FtoMTPs. FtoMTP was defined as the probability for a man to become infected following an act of sexual intercourse or a partnership with an infected female partner. This analysis was conducted using a specific mathematical modelling applied to the data of the male circumcision trial. This model took simultaneously into account sexual behaviour, condom use, circumcision status, the effect of circumcision on HIV and HSV-2 acquisition, the effect of HIV status on HSV-2 acquisition and the effect of HSV-2 status on HIV acquisition. The HIV and HSV-2 statuses of each female partner of the male trial participants was estimated using data from a cross-sectional study conducted in the same township. The per-sex-act FtoMTPs of HIV and HSV-2, for an uncircumcised and non-condom user man, in the absence of the other virus in both partners, were 0.0047 and 0.0067, respectively. A recent meta-analysis found a very similar HIV-1 transmission probability, estimating the pooled (combined) per-sex-act HIV FtoMTP in the general population of low-income countries at 0.0038 (12). Analyses of the effect of each virus on the FtoMTPs suggested that HSV-2 infection enhanced HIV acquisition and conversely, that HIV infection could enhance HSV-2 acquisition. Indeed, HSV-2 in either partner increased the HIV per-sex-act FtoMTP three-fold. Conversely, HIV in either partner increased the HSV-2 per-sex-act FtoMTP by a factor of 2.5. In addition, male circumcision significantly reduced the per-sex-act FtoMTPs of HIV and of HSV-2.

So, using the same dataset, these two different study approaches, statistical analyses and transmission mathematical modelling, provided consistent results. They both demonstrated that

HSV-2 infection was an important risk factor of HIV acquisition, with a three-fold increase of HIV incidence and HIV per-sex-act FtoMTP among HSV-2 positive men compared to HSV-2 negative men. These findings are consistent with the two- to four-fold increased risk of HIV acquisition associated with prevalent HSV-2 as previously reported (6, 13, 14). Moreover, the statistical analyses showed that HSV-2 status did not alter the protective effect of male circumcision on HIV acquisition and provided the first empirical estimate of the population fraction of HIV incident cases attributable to HSV-2 at over 25%. Whereas previous research has yielded inconclusive results, this is the first study to demonstrate the protective effect of male circumcision on HSV-2 acquisition. In both the statistical analysis and the mathematical model, circumcised men had a lower risk of HSV-2 acquisition and a lower HSV-2 per-sex-act FtoMTP. Furthermore, these results were confirmed by analyses conducted on data from the male circumcision trial conducted in Rakai (Uganda) (15) where the probability of acquiring HSV-2 infection during the 24-month follow-up period was lower among the circumcised group. The mathematical model confirmed the protective effect of male circumcision on HIV transmission (HIV per-sex-act FtoMTPs were significantly lower among circumcised men) and the increased risk of HSV-2 transmission for HIV-positive men (HSV-2 per-sex-act FtoMTPs were significantly higher among HIV infected men).

Data from the other two male circumcision trials conducted in Uganda (16) and in Kenya (17) are to be analyzed to assess HSV-2 transmission probabilities, in order to confirm the present findings. Furthermore, modelling studies are needed to better understand the interactions between HIV, HSV-2, male circumcision and sexual behaviour, including condom use. Not only in the short term, as studied by randomized controlled trials, but also in the long term.

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