10 Ghys PD, Fransen K, Diallo MO, *et al.* The associations between cervico-vaginal HIV shedding, sexually transmitted diseases and immunosuppression in female sex workers in Abidjan, Cote d'Ivoire. *AIDS* 1997;11:F85–93.
11 Mostad SB, Overbaugh J, DeVange DM, *et al.* Hormonal contraception, vitamin A deficiency, and other risk factors for shedding of HIV-1 infected cells from the cervic and vagina. *Lancet* 1997;**350**:922–7.
12 Laga M, Alary M, Nzila N, *et al.* Condom promotion, sexually-transmitted diseases treatment, and declining incidence of HIV-1 infection in female Zairian sex workers. *Lancet* 1994;**344**:246–8.
13 Ghys P, Laga M. On the impact of different STD control strategies on HIV transmission in sex workers from Abidjan, Ivory Coast. Xth Int Conf on AIDS and STD in Africa, Abidjan, Ivory Coast, 1997, abstract B205.
14 Grosskurth H, Mosha F, Todd J, *et al.* Impact of improved treatment of sexually transmitted diseases on HIV infection in rural Tanzania: randomised controlled trial. *Lancet* 1995;**346**:530–6.
15 Mayaud P, Mosha F, Todd J, *et al.* Improved treatment services significantly reduce the prevalence of sexually transmitted diseases in rural Tanzania: results of a randomised controlled trial. *AIDS* 1997;11: 1873–80.
16 Robinson NJ, Mulder DW, Auvert B, *et al.* Proportion of HIV infections attributable to other sexually transmitted diseases in a rural Ugandan population: simulation model estimates. *Int J Epidemiol* 1997;**26**:180–9.
17 Hitchcock P, Fransen L. Preventing HIV infection: lessons from Mwanza and Rakai (commentary). *Lancet* 1999;**353**:513–15.
18 Trichonova L, Borisenko K, Ward H, *et al.* Epidemic of syphilis in the Russian Federation: trends, origins, and priorities for control. *Lancet* 1997;**350**: 210–13.
19 World Bank. *World development report 1993. Investing in health.* New York: Oxford University Press, 1993.

Genital ulcer disease in Africa: many pieces are still missing from the puzzle

In the wake of the HIV/AIDS epidemic so called classic STDs are at last receiving the attention they deserve as important public health problems. This has resulted in increased research efforts in this area. For instance, since the late 1980s several population based cohort studies have been set up in Uganda and Tanzania. Though the primary objective of these studies is to better understand the mechanisms of HIV epidemics and/or to assess the effectiveness of different interventions to prevent HIV spread, they also provide invaluable information on the epidemiology of other sexually transmitted infections. The study presented by Kamali *et al* in this issue of *Sexually Transmitted Infections* (p 98) was conducted within a prospective cohort study in Uganda. It is one of the rare studies so far that provide estimates of the prevalence and incidence of sexually transmitted infections in a general population. These estimates were obtained from serological investigations.

The prevalence and incidence of infection with *Treponema pallidum* were assessed with well established serological tests—that is, RPR and TPHA. Infection with *Haemophilus ducreyi* was ascertained with an experimental test, which has a fair sensitivity and specificity for recent, culture proved *H ducreyi* genital ulcer.[1] However, the rate at which seropositive subjects sero-revert and at which stage is unknown. The prevalence of *H ducreyi* infection may thus be an underestimate of the proportion of subjects in this population who have ever been infected with this pathogen. The incidence data are more interesting. In both men and women the incidence of *H ducreyi* infection was higher than the incidence of syphilis, but the difference was larger in men than in women.

Most published studies on the aetiology of genital ulcer disease (GUD) in Africa date from the 1980s, before polymerase chain reaction (PCR) techniques were available for the diagnosis of syphilis, chancroid, and herpes simplex infection. Diagnosis was based on culture of *H ducreyi* and of herpes simplex virus, and syphilis serology with or without dark field microscopy. The aetiology of GUD remained undetermined in 15% to 35% of cases. The majority of these studies, which were conducted in the Gambia, Kenya, Rwanda, Swaziland, and South Africa, found that *H ducreyi* was the most frequent aetiology of GUD.[2–8] Syphilis ranked second with the exception of the study from Rwanda, where it was the first cause of GUD in women.[6] Also, more recent studies from Lesotho and Abidjan, Ivory Coast, where PCR was employed for the diagnosis, found that *H ducreyi* was the most frequent aetiology of GUD.[9 10] The latter study was conducted among female sex workers, 25% of whom tested positive on RPR and on TPHA. Nevertheless *T pallidum* was not detected in any of the 235 ulcerations examined. To our knowledge there is only one instance where syphilis was found to be the leading aetiology of GUD in both men and women—that is, in a study from Durban, South Africa from the early 1990s.[11 12] There are still many unanswered questions about the epidemiology of syphilis and of chancroid in Africa (and elsewhere). For instance, we do not have clear explanations for the differences in the prevalence of positive syphilis serology in different parts of Africa. Chancroid seems to be prevalent everywhere on the continent, but recently there has been anecdotal evidence from Nairobi, Kenya, that its importance may be diminishing (F Plummer, personal communication). This too needs to be further explored.

The most striking finding of the study by Kamali *et al* is the high prevalence and incidence of HSV-2 infection, several times higher than the prevalence and incidence of *H ducreyi* infection and of syphilis. More than 75% of women aged 25 years or more and about half of the men aged 35 years or more, are infected with HSV-2. Similar high rates have been found in Mwanza Region, Tanzania.[13] Much lower prevalence rates have been found in industrialised countries. In a population based study in the United States, conducted between 1976 and 1980, the overall prevalence of HSV-2 infection was 16.4% among all adults, but 41% among Afro-Americans.[14] Studies among pregnant women in several European countries found prevalence rates ranging from 9.7% to 27.9%.[15] Pregnant women attending the antenatal clinic of a west London hospital had an overall prevalence of HSV-2 of 10.4%, but among African women who were born in Africa, prevalence was over 30%.[16] Apart from the morbidity associated with HSV-2 infection, the high prevalence and incidence found in Uganda and Tanzania raise important questions regarding the role of this infection in the spread of HIV. There are several issues to be considered.

Several follow up studies, among homosexual men and among Thai conscripts, have examined the role of HSV-2 infection as a risk factor for the acquisition of HIV infection.[17–21] HSV-2 infection was found to be associated with a higher risk of HIV seroconversion in all studies except the one by Kingsley *et al.*[18] The association remained after adjusting for sexual behaviour, strongly suggesting a biological interaction between HSV-2 infection and HIV infection. It is now well established that

genital ulcerations enhance the infectiousness of HIV infected subjects and the susceptibility of HIV uninfected subjects. The first question then is how many subjects with HSV-2 infection ever become symptomatic with genital lesions. Studies in industrialised countries found that 10% to 30% of HSV-2 infected subjects, examined outside an STD clinic setting, ever had genital symptoms.[22-24] In Mwanza, Tanzania, positive HSV-2 serology was found to be associated with a recent history of genital ulceration.[13] However, in populations such as the one of Mwanza Region, estimating the proportion of HSV-2 infections that were symptomatic would be very difficult, considering the high prevalence and incidence of other pathogens that also cause GUD. Indirect evidence for the aetiological role of HSV-2 infection in GUD can be obtained from studies among patients presenting to health services. While in the United States and in Western Europe most genital ulcerations nowadays are due to herpes simplex virus, the majority of the above mentioned African studies found that only 5% to 20% of GUD were due to herpes simplex virus.[2-9 11 12] Studies among patients with genital ulcerations have limitations as they can only provide information about the relative importance of one pathogen compared with other pathogens. On the other hand, it is conceivable that in HIV uninfected Africans HSV-2 infection remains more often asymptomatic than in populations in industrialised countries. Infection with HSV-1 has been found to be protective against symptomatic HSV-2 infection[23 25] and studies that have assessed the prevalence of HSV-1 in African populations found prevalence rates above 85%, which is higher than is generally found in industrialised countries.[9 15 16] Even so, where HIV-1 is highly prevalent, as is the case in many parts of sub-Saharan Africa, more genital ulcerations due to HSV-2 are to be expected, because of the association between HIV and HSV-2 and because HIV infection is a risk factor for (severe) HSV-2 genital lesions. In the Lesotho study HSV-2 was more frequently found in genital lesions in HIV infected patients than in HIV uninfected patients, but HIV seropositive patients were also more often HSV-2 seropositive than HIV uninfected patients.[9] However, among STD patients in Kigali no association was found between HIV infection and HSV-2 as aetiology of GUD.[6] Among HIV infected sex workers in Abidjan, there was no association between CD4+ count and the proportion of ulcerations in which herpes simplex virus was detected.[26] It is not clear why no association was found, even though it is well documented that advanced HIV disease is associated with severe genital HSV-2 ulcerations. One possible explanation is that HIV patients with severe lesions are not found in STD clinics, but attend other health services—for example, specialised AIDS clinics.

The second question is what role asymptomatic or subclinical reactivation of HSV-2 infection plays in the transmission and the natural history of HIV infection? It has been suggested that in HIV infected patients reactivation of HSV infection enhances the replication of HIV, which may result in an increase in HIV viral load, enhanced infectiousness, and faster progression to AIDS.[27]

There is also evidence that HIV infection enhances the transmission of HSV-2. As mentioned above HIV infection is a risk factor for HSV-2 genital lesions, which enhance the transmission of both HIV and HSV-2. Moreover, it has been shown that HIV infection enhances the shedding of HSV-2 regardless of symptoms.[28]

In conclusion, there is evidence to suggest that HIV and HSV-2 interact with each other so that the spread of both infections is enhanced. So far we lack hard epidemiological data to substantiate this hypothesis, especially in sub-Saharan Africa. Recent developments in HSV type specific serological tests and DNA amplification techniques for the detection of herpes simplex virus should allow us to conduct more and better research on this infection. *T pallidum* and *H ducreyi* still seem to be more important causes of genital ulcerations in sub-Saharan Africa than herpes simplex. But this may change if the incidence of HSV-2 infection increases with increasing prevalence rates of HIV infection and if the curable (bacterial) sexually transmitted infections come under control.

I wish to thank N J Robinson for his useful comments on an earlier draft.

ANNE BUVÉ

STD/HIV Research and Intervention Unit, Institute of Tropical Medicine, Nationalestraat 155, B-2000 Antwerp, Belgium

1 Museyi K, Van Dyck E, Vervoort T, *et al.* Use of an enzyme immunoassay to detect serum IgG antibodies to Haemophilus ducreyi. *J Infect Dis* 1988;**57**:1039–43.
2 Mabey DCW, Wall RA, Bello CSS. Aetiology of genital ulceration in the Gambia. *Genitourin Med* 1987;**63**:312–15.
3 Nsanze H, Fast MV, D'Costa LJ, *et al.* Genital ulcers in Kenya. Clinical and laboratory study. *Br J Vener Dis* 1981;**57**:378–81.
4 Fast MV, D'Costa LJ, Nsanze H, *et al.* The clinical diagnosis of genital ulcer disease in men in the tropics. *Sex Transm Dis* 1984;**11**:72–6.
5 Plummer FA, D'Costa LJ, Nsanze H, *et al.* Clinical and microbiologic studies of genital ulcers in Kenyan women. *Sex Transm Dis* 1985;**12**:193–7.
6 Bogaerts J, Ricart CA, Van Dyck E, *et al.* The aetiology of genital ulceration in Rwanda. *Sex Transm Dis* 1989;**16**:123–6.
7 Meheus A, Van Dyck E, Ursi JP, *et al.* Aetiology of genital ulcerations in Swaziland. *Sex Transm Dis* 1983;**10**:33–5.
8 Duncan MO, Bilgeri YR, Fehler HG, *et al.* The diagnosis of sexually acquired genital ulcerations in black patients in Johannesburg. *Southern African Journal of Sexually Transmitted Diseases* 1981;**1**:20–3.
9 Morse SA, Trees DL, Htun Y, *et al.* Comparison of clinical diagnosis and standard laboratory and molecular methods for the diagnosis of genital ulcer disease in Lesotho: association with human immunodeficiency virus infection. *J Infect Dis* 1997;**175**:583–9.
10 Van Dyck E, Koblavi SA, Ghys PD, *et al.* Diagnosis of genital ulcers in female sex workers by multiplex PCR and in vitro antibiotic susceptibility of H ducreyi strains in Abidjan, Côte d'Ivoire. International Congress of Sexually Transmitted Diseases, Seville, 19–22 October 1997, abstract no P362.
11 O'Farrell N, Hoosen AA, Coetzee KD, *et al.* Genital ulcer disease in women in Durban, South Africa. *Genitourin Med* 1991;**67**:322–6.
12 O'Farrell N, Hoosen AA, Coetzee KD, *et al.* Genital ulcer disease in men in Durban, South Africa. *Genitourin Med* 1991;**67**:327–30.
13 Obasi A, Mosha F, Quigley M, *et al.* Antibody to HSV-2 as a marker of sexual risk behaviour in rural Tanzania. *J Infect Dis* 1999; (in press).
14 Johnson RE, Nahmias AJ, Magder LS, *et al.* A seroepidemiologic survey of the prevalence of herpes simplex virus type 2 infection in the United States. *N Engl J Med* 1989;**321**:7–12.
15 Nahmias AJ, Lee FK, Beckman-Nahmias S. Sero-epidemiological and -sociological patterns of herpes simplex virus infection in the world. *Scand J Infect Dis* 1990;(suppl) **69**:9–36.
16 Ades AE, Peckham CS, Dale GE, *et al.* Prevalence of antibodies to herpes simplex virus types 1 and 2 in pregnant women, and estimated rates of infection. *J Epidemiol Community Health* 1989;**43**:53–60.
17 Holmberg SD, Stewart JA, Gerber AR, *et al.* Prior herpes simplex virus type 2 infection as a risk factor for HIV infection. *JAMA* 1988;**259**:1048–50.
18 Kingsley LA, Armstrong J, Rahman A, *et al.* No association between herpes simplex virus type-2 seropositivity or anogenital lesions and HIV seroconversion among homosexual men. *J Acquir Immune Defic Syndr* 1990;**3**:773–9.
19 Keet IPM, Lee FK, van Griensven GJP, *et al.* Herpes simplex virus type 2 and other genital ulcerative infections as a risk factor for HIV-1 acquisition. *Genitourin Med* 1990;**66**:330–3.
20 Nelson KE, Eiumtrakul S, Celentano D, *et al.* The association of herpes simplex virus type 2 (HSV-2), Haemophilus ducreyi, and syphilis with HIV infection in young men in Northern Thailand. *J Acquir Immune Defic Syndr* 1997;**16**:293–300.
21 Nopkesorn T, Mock PA, Mastro TD, *et al.* HIV-1 subtype E incidence and sexually transmitted diseases in a cohort of military conscripts in Northern Thailand. *J Acquir Immune Defic Syndr* 1998;**18**:372–9.
22 Cowan FM, Johnson AM, Ashley R, *et al.* Relationship between antibodies to herpes simplex virus (HSV) and symptoms of HSV infection. *J Infect Dis* 1996;**174**:470–5.
23 Koutsky LA, Ashley RL, Holmes KK, *et al.* The frequency of unrecognized type 2 herpes simplex virus infection among women. *Sex Transm Dis* 1990; **17**:90–4.
24 Siegel D, Golden E, Washington E, *et al.* Prevalence and correlates of herpes simplex infections. The population-based AIDS in multiethnic neighborhoods study. *JAMA* 1992;**268**:1702–8.
25 Breinig MK, Kingsley LA, Armstrong JA, *et al.* Epidemiology of genital herpes in Pittsburgh: serologic, sexual, and racial correlates of apparent and inapparent herpes simplex infections. *J Infect Dis* 1990;**162**:299–305.
26 Ghys PD, Diallo MO, Ettiègne-Traoré V, *et al.* Genital ulcers associated with human immunodeficiency virus-related immunosuppression in female sex workers in Abidjan, Ivory Coast. *J Infect Dis* 1995;**172**:1371–4.
27 Heng MCY, Heng SY, Allen SG. Co-infection and synergy of human immunodeficiency virus-1 and herpes simplex virus-1. *Lancet* 1994;**343**: 255–8.
28 Augenbraun MH, Feldman J, Chirgwin K, *et al.* Increased genital shedding of herpes simplex virus type 2 in HIV-seropositive women. *Ann Intern Med* 1995;**123**:845–7.