

HIV-STD INTERACTIONS

J.P. Coulaud

A - Links Between HIV and other STDS

Both HIV and the traditional STDs share a common mode of transmission through sexual contact, and the same behavioural risk factors. It makes sense that there might be some connection between HIV infection and other STDs. In 1984, health authorities in Kinshasa, Zaire, reported first that 50% of AIDS cases had a past history of STD compared to 14% of controls. A past history of STDs was reported in 35% (Tanzania) and 70% (Rwanda) of HIV/AIDS infected persons (1-2).

On the other hand, the proportion of HIV seropositive among STD clinic attenders compared to the overall population was 9.2% vs. 4.4% in Tanzania, 29% vs. 9% in Zambia, 18.5% vs. 4.3% in Burundi and 30% vs. 1.4% in rural Rwanda, respectively (2). The association between STDs, and HIV seemed stronger with increasing episodes of STD infection (3). The first studies have been performed in prostitutes and pregnant women, the latter being a marker of the young sexually active "general population".

Three mechanisms are mentioned in the literature which explain in what manner STDs and HIV may interact with one another. The first is termed "epidemiological synergy" (4). Under this mechanism, co-infection with HIV prolongs or increases infectiousness of the person with the STD. The STD further facilitates HIV transmission, at the community level. The two infections, mutually reinforce one another. This mechanism may be applicable to chancroid, genital herpes and syphilis. The second mechanism acts in a unidirectional way in which the STD may promote HIV transmission but HIV infection does not cause an increase in the prevalence of the STD. Gonorrhoea, chlamydia and trichomoniasis may behave in this fashion.

The third mechanism acts also in a unidirectional way representing the traditional opportunistic infection pattern. HIV infection may alter the natural history of the STDs. Genital warts and hepatitis B or C may be implicated here.

There are biological explanations for these three mechanisms. Under the theory of "epidemiological synergy", there is increased presence of lymphocytes and macrophages when one is infected with some STDs. These cells are targets of HIV infection. In the HIV/negative individual with genital ulceration, there are more target cells which may be infected. In the HIV-seropositive person with genital ulceration, the ulcerations are further exacerbated by HIV infection and their pathogens are passed on to the partner. HIV has been isolated from the surface of genital ulcers and from cervical and vaginal secretions (5,6). Especially for women, the presence of genital ulcers increases the risk of HIV infection. For men, the lack of circumcision, concomitant with genital ulcers is a cofactor in HIV acquisition. In addition, for women, disruption of the epithelial cells in the genital tract is common. Early sexual activity is more conducive to this epithelium breakage due to immaturity of the genital tract cells and to cervical ectopy which is usual in young adolescent. This has profound implications for Africa since the cultural pattern is one of relationships between older men, with many different sexual partners, and young women (7) or even now, very young girls. In the presence of genital ulcer disease,(GUD) bleeding is easily induced during sexual intercourse. A portal of entry for the HIV virus is then present, making infection easier.

It is reasonable to think that the immune systems of poor people with multiple sex partners are in a continually activated state, making these individuals more susceptible to many diseases including

HIV/STD. Repeated reactivation of T lymphocytes may weaken the body's immune response towards HIV acquisition and/or progression of HIV.

There are very few studies that look directly at circumcision and STDs. A study in the US at a public health STD clinic found the prevalence of current syphilis was higher in uncircumcised men than in circumcised (OR = 4.0 95% CI = 1.9, 8.4), as was the prevalence of gonorrhoea (OR = 1.6, 95% CI = 1.2, 2.2) (9). A study of genital ulcers in Kenya reported a higher prevalence among the ethnic group which is traditionally uncircumcised (10). A case-control study from the same population (men presenting with an STD) confirmed that chancroid and other genital ulcer disease develop more commonly in uncircumcised men (11).

A review of epidemiological studies (8), identified 30 relevant studies concerning circumcision and HIV transmission. A cycle appears to be emerging in which genital ulcer disease enhances HIV transmission, HIV infection increases genital ulcer disease frequency, and the lack of male circumcision augments the transmission of both (12). But the interpretation of most of these results is limited by the poor assessment of sexual behaviour and other potential confounders.

B - Sexually transmitted diseases enhance the risk of HIV transmission

1. The first studies

Many of them have been done in sub-Saharan Africa.

a) Role of genital ulcers diseases

Chancroid

The available data support a significant association between the genital ulcer diseases (GUD), and HIV infection. Chancroid, in particular, has been found to be a true risk factor for HIV transmission and acquisition rather than simply being a marker for high-risk behaviour. Among several cross-sectional and case-control studies, three studies showed an association between a past history of GUD and HIV infection: a study of truck drivers in Nairobi, Kenya (13) one among men attending an STD clinic in Nairobi (14), and one from a random sample of people from Mwanza, Tanzania (15). In a population-based survey and a case-control study from the same population group in Masaka, Uganda, a recent history of genital ulcer was found to be a significant risk factor for HIV infection in adults (16).

Several other studies report an association between the presence of GUD and concurrent HIV infection: in Kampala among male and female STD clinic patients, and among male STD clinic patients in Durban, South Africa (17). A cross-sectional study of male STD clinic attenders in Zimbabwe showed that male-to-female transmission of HIV is facilitated by the presence of genital ulcers in infected men (18). Another cross-sectional study in Abidjan among male STD clinic attenders showed prior and current genital ulcers to be associated with HIV (19). Chancroid was the primary cause of ulcers in the study of male STD clinic patients in Nairobi (11) where a history of GUD and current GUD was associated with HIV infection. In two prospective studies in Nairobi, men presenting to an STD clinic with GUD were nearly 5 times as likely to seroconvert and female prostitutes with GUD had a threefold increase in the risk of HIV seroconversion (20-21).

Syphilis

A majority of cross-sectional studies have found significant associations between HIV infection and T. palladium antibodies. HIV infection was associated with TPHA positive reaction in studies of

pregnant women in Kinshasa, (Zaire)(22), Yaoundé (Cameroon)(23), and Malawi (24); and among STD clinic patients in Zimbabwe(27) and in Cameroon (26). In a random selection of population in Mwanza, (Tanzania)(15), the presence of syphilis was associated with HIV infection. After adjustment for risk variables linked to sexual behaviour, a study of gynaecological inpatients in Dar es Salaam found syphilis infection associated with a more than two times higher risk of HIV infection (27). Thirty-three percent of HIV-seropositive pregnant women were RPR positive compared to 9.5% of HIV-seronegative pregnant women ($p < 0.05$) in study in Soweto, (South Africa)(28). In a case-control study of women attending family planning clinics in Nairobi, RPR positivity was associated with a three/fold increase in HIV infection (29).

But a few cross-sectional studies found no significant associations between syphilitic antibodies and HIV infection including a study of Zambian prisoners (30), prostitutes in Tanzania (31), outpatients in south-western Uganda (32), or in STD patients in Tanzania (33).

Genital herpes

Herpes simplex 2 virus (HSV) is the other major cause of genital ulceration found in Africa. However, it may only cause 5-15% of ulcerations in the region (34) In other countries, studies reviewed suggest that herpes may be an independent risk factor for HIV infection. A case-control study of patients attending STD clinics in the US (35) found HSV infections associated with an increase risk of HIV (OR=2.0, 95% CI = 1.2-3.2). A cross-sectional study of prostitutes in Kinshasa, Zaire, reported HSV as the identifiable cause of 12% of GUD, and that HSV was more common among HIV positive women (96% vs. 76%) (36). A study conducted in Zimbabwe found that a past history of herpes in the man was a factor for HIV serologic concordance between married couples (2).

b) Role of non ulcerative STDs

Gonorrhoea

Many of the first studies did not find significant differences between HIV seropositive and seronegative individuals and current gonococcal infection (3). In Zaire, cross-sectional studies of pregnant women showed no difference in current gonococcal infection and HIV seropositivity (37-38-39). Two other studies of high-risk women in Kinshasa, concluded that there was no significant association between current gonococcal infection between HIV-positive and HIV negative women (40-41). Cross-sectional studies of prostitutes in Tanzania (31), male blood donors in Zimbabwe (42), and pregnant women in Kigali, Rwanda (43) found no association between gonococcal infection and HIV seropositivity. Also, a prospective study of pregnant women in Nairobi, Kenya, found no difference in the incidence of gonococcal infection between HIV-positive and HIV-negative women (44).

However, a study in Mwanza (Tanzania) found genital discharge as a risk factor for HIV infection (15). A cross-sectional study in Uganda, focusing on a history of gonorrhoea, found a greater risk of HIV infection with increasing number of gonorrhoea episodes (45). A prospective study of HIV-negative prostitutes in Kinshasa found incident gonorrhoea was associated with an increased risk of HIV seroconversion (46). In Malawi, a cross-sectional study of pregnant women found HIV infection significantly associated with gonorrhoea (47) and a prospective study of pregnant women found incidence of gonorrhoea significantly higher among HIV-seropositive women (48). A cross-sectional study of women attending family planning clinics in Nairobi found that both a history of gonorrhoea and a positive gonorrhoea culture were associated with a twofold increase in HIV infection (29).

Chlamydia

Overall, evidence demonstrating a link between chlamydia and HIV infection is scanty. Cross-sectional or case-control studies of pregnant women in Kinshasa (22-38), or female prostitutes in Kinshasa (36), or prostitutes in northern Tanzania (31), and STD clinic patients in Nairobi (49), found no association between chlamydia and HIV serostatus.

A prospective study of high-risk women in Kinshasa, however, showed incident chlamydial infection associated with an increased risk of HIV seroconversion in women (46). Two other studies found significant differences between HIV positive and negative individuals and presence of chlamydial infection (28-50). This might be attributable to an accompanying inflammatory response associated with chlamydia infection, which attracts lymphocytes.

Trichomoniasis

Research linking trichomoniasis with HIV is limited. A few studies have documented an association between trichomoniasis and HIV infection. A prospective study of pregnant women in Malawi found trichomoniasis as a risk factor for seroconversion (51). A cross-sectional study of pregnant women in Kinshasa, Zaire, reported an association between trichomoniasis and HIV (22). After adjusting for sexual behaviour, a cross-sectional study of gynaecological inpatients in Dar es Salaam found trichomonas vaginalis infection associated with nearly three times higher risk of HIV infection (52). A prospective study of prostitutes in Kinshasa found incident trichomoniasis associated with an increased risk of HIV seroconversion in women (46). However, two cross-sectional studies in Kinshasa, one of prostitutes and one of pregnant women revealed no significant associations between trichomonas infection and HIV serostatus (36-38).

c) On the whole, *ulcerating and non ulcerating STDs* enhance the risk of HIV transmission with a mean OR of 3 to 7. As STDs are usually considered as at least 10 fold more frequent in developing countries than in Western industrialized countries, the risk of sexual transmission is in average 50 fold higher in Africa than in Europe. We may add also a 10 fold higher risk due to multiple simultaneous partnership and it becomes obvious that the risk may be easily 500 fold higher for a young African than for a young European of same sex and age.

In an other hand, ulcerative STD such as chancroid (OR = 5) may appear the most dangerous but in an epidemiological point of view their attributable risk is lower than for gonococcal and chlamydial infections (OR between 3 and 4) which are extremely common whilst chancroid cases remain scanty.

At last most of these reports were cross-sectional or case control studies, and therefore failed to document the temporal sequence of STD and HIV infection. Consequently, the interpretation of these studies include: 1) STDs are cofactors that increase an individual's susceptibility to, or transmissibility of HIV; 2) STDs are more easily identified in HIV-infected individuals; or 3) STDs are surrogate markers of high risk behaviour that puts the individual at risk of HIV infection (53). Longitudinal cohort studies that follow HIV-uninfected individuals prospectively to determine the incidence of HIV and STDs have the advantage of documenting whether or not an STD preceded the HIV-infection. But these longitudinal studies, with the exception of discordant couple studies cannot accurately measure sexual behaviour, however, and give little information on the sexual partner(s) of study participants.

2. The recent studies

Data from recent reports, provide further evidence of the enhancing effect of STDs on HIV transmission, by examining the impact of the treatment of STDs on HIV shedding and incident HIV infection in a community-based trial.

Several studies from Africa, Europe and the USA have documented an increased prevalence of HIV shedding in the genital tracts of individuals with either STDs or endogenous infection. At an STD clinic in Mombasa, Kenya, investigators tested 189 endocervical specimens and 87 lateral vaginal-wall specimens from HIV-1-infected women for HIV-1 infected cells, using an HIV- 1 DNA polymerase chain reaction (PCR) assay (54). The detection of endocervical HIV- 1 DNA was independently associated with *Neisseria gonorrhoeae* (odds ratio 4.5) but not with *Chlamydia trachomatis*.

In a preliminary report from Abidjan, Cote d'Ivoire (55) investigators found that HIV-1, measured by PCR on the supernatant of cervico-vaginal lavage specimens of 381 HIV-1-infected female sex workers, was more frequent in those with visible ulcers (47% versus 21%), in those with *N. gonorrhoeae* (30% versus 20%), and in those with *C. trachomatis* (40% versus 23%). After treatment for STDs, the persistence of HIV-1 in the cervico-vaginal lavage was less frequent in those sex workers who were cured than in those who were not cured, although the decrease in frequency was not significant. Specifically, HIV-1 was detected in one out of three women with healed ulcers compared with eight out of 10 with persistent ulcers, and in seven out of 21 women with gonococcal infection compared with six out of eight who had persistent gonococcal infection.

The impact of the treatment of urethritis in men on HIV-1 shedding in urethral secretions and seminal plasma has been reported in four studies. These studies show that urethritis increases HIV shedding in men, and that providing effective antibiotic treatment results in a rapid reduction of seminal HIV in a study from Nairobi, Kenya, (56). HIV DNA was detected in 44% of 48 men with gonococcal urethritis and 19% of 26 men without urethritis. After successful treatment of the 48 men who had gonococcal urethritis, urethral HIV-DNA detection decreased to 21%. In a report on one HIV-1 infected man with chlamydial urethritis a 50-fold post-treatment reduction in HIV-1 RNA was noted in seminal plasma (57).

In an other report on the effect of treating four men with gonococcal and non-gonococcal urethritis, copies of HIV-1 DNA decreased from two-to four-fold 10 days after effective treatment (58). In Malawi, semen collected before treatment and 2 weeks after treatment from 78 men with urethritis, and at enrolment and 2 weeks later from 45 men without urethritis (controls), was tested to measure the concentration of HIV-1 RNA. At enrolment, men with urethritis had a significantly higher median HIV-1 concentration compared with the controls; 125000 copies/ml versus 17000 copies/ml, respectively. There was a significant decline in HIV-1 shedding after treatment in the men with urethritis. At 2 weeks post-enrolment, the median HIV concentration was not statistically different between treated patients and controls, 37000 copies/ml versus 23000 copies/ml, respectively (59).

These reports show the increase of shedding of HIV in the presence of STDs, and the dramatic effects of STD treatment. In contrast, there is little data on the potential mechanisms by which STDs might increase an HIV-seronegative individual's susceptibility to HIV infection. A study of 20 women with non-ulcerative STDs and 22 women with no infection reported a localized increase in endocervical CD4 lymphocytes in the women with STDs compared with the women without STDs.

In an other study in US, it has been shown that local CD4+ cells increase obviously during chlamydia trachomatis cervicitis and come back to baseline one week after therapy discontinuation (60).

On the other hand, prospective studies from Asia, Africa and the Caribbean continue to report a strong association between HIV seroconversion and STDs. In a discordant partner study from Haiti (61), incident HIV infection was more common in sexually active partners who did not use condoms, in female partners of HIV-infected men, and in the presence of STD syndromes. Interestingly, seroconversion was more common when the STD was present in the seronegative partner. In the HIV-seronegative partner, new HIV infection was more likely to occur in persons with genital ulcerations (relative risk 6.89) positive syphilis serology (relative risk 2.9) and with a vaginal or urethral discharge (relative risk 2.6).

A cohort of 891 HIV-1-seronegative high-risk patients attending an STD clinic in India, who were followed every 3 months was evaluated for HIV infection and behavioural risk factors. The stronger risk factors for HIV seroconversion in this cohort were genital ulcerations (relative risk 4.3) and cervicitis or urethritis (relative risk 3.0)(62). Similar results, underlining the risk of urethritis, were observed in a prospective two years studies of Thai military recruits.

All these data obviously showed the potential major benefit of an intervention strategy of STDs prevention and treatment.

The first longitudinal study has been done in Zairian prostitutes (Kinshasa) (46). During the two years follow up with surveillance and counselling and condoms providing, rates of STDs and HIV seroconversion gradually declined similarly in women who regularly were using preservatives.

More recently the Thai 100% condom project obtained the same result in Thai prostitutes of Bangkok brothels and their customers (63). Two randomised community-based trial have been completed.

The Mwanza trial gave the major results. In Mwanza, after randomising six paired communities on the basis of baseline HIV prevalence, improved STD control of symptomatic patients presenting to health facilities was implemented at the intervention sites. Investigators demonstrated an overall 42% reduction in HIV incidence over the 2 years of the study, from 1.9% in the control communities to 1.2% in the intervention community (risk ratio 0.58; $p = 0.007$). HIV incidence was lower in each of the six intervention communities compared with controls, and was reduced in both sexes and in all age groups (64). There was no difference in the reported sexual behaviour or condom use between the intervention and the control communities. The Rakai district study in Uganda (65) is a community-based randomised clinical trial on the impact of intensive STD control on STD and HIV transmission. Intervention and control communities have been tested for STDs every 6 months using DNA amplification technology and serology. In the intervention communities all adults between the ages of 15 and 59 years are treated with antibiotics, covering all major bacterial and protozoal STDs. The study hopes to identify which STDs are most strongly associated with HIV transmission. The preliminary results of this trial have documented a high prevalence of asymptomatic STDs, and a significant reduction in STD prevalence 6-9 months after the first community treatment. The fact that many STDs are asymptomatic favours preventive intervention since half of STDs infection are not identified and therefore are not treated.

The final results confirm the decrease of a STD transmission after intervention but HIV 1 transmission remains stable in this area; probably because when prevalence is high in the general population, the part of STD attributable risk is limited.

D - HIV and the immune deficiency may effect STDs natural history

Since the beginning HIV epidemics, clinical and biological abnormalities have been described in STDs occurring in HIV infected persons. Length of symptoms may be increase and treatment failures are relatively common. Some of these STDs may appear as authentic opportunistic infections

1. Chancroid

In a case-control study of men in Nairobi (66-67) presenting with chancroid, the HIV-positive group had more ulcers per patient and treatment failure at day 7 was more common in the HIV/positive group.

According some authors, treatment failures at day seven with conventional drugs such as cotrimoxazole or Erythromycin may be a marker of HIV seropositivity and they recommend HIV testing of the patients.

2. Syphilis

The prevalence of syphilis and serological response to standard therapy did not differ in HIV/positive and HIV-negative prostitutes in Kinshasa (68). In a case control study in New-York (69), HIV-positive patients with primary syphilis were less likely to be considered as "serologically cured" than patients with primary syphilis who were HIV negative. Many others studies gave discordant results. In summary, if we consider all the reports devoted to syphilis-HIV co-infection, the natural history of syphilis may be totally normal with typical clinical pattern of both primary and secondary syphilis (but some giant ulcers and increase of cases of severe secondary syphilis with neurological involvement may occur), with typical pattern and progression of serology (but more patients may remain seropositive than usually), with the same rate of successful treatment (but the failure rate may be higher). On a practical point of view, there is no need to increase the doses of Benzathine Penicillin. Ceftriaxone does not seem more effective than Penicillin G during secondary syphilis. In an other hand, diagnosis of syphilis may be difficult in patients with severe immune deficiency due to lack of significant positive serology (disappearance of specific antibodies related to immunodeficiency).

3. Genital herpes

The possible impact of HIV on Herpes simplex includes increase of shedding, larger lesions, longer duration, higher recurrence rate of genital lesions and an increased incidence of acyclovir resistance (70). In this case, Foscavir by intravenous route may be needed. In developing countries where Acyclovir is often lacking, genital and perineal lesions, especially in women, may become extremely painful with large and deep ulcerations which may be super-infected and be a cause of death.

4. Gonorrhoea and Chlamydia Infections

There are no data which indicate that HIV infection alters the clinical presentation of gonorrhoea or chlamydia (4). However, there are some indications that previously acquired HIV infection may promote development of gonococcal complications, such as pelvic inflammatory disease (PID) and increase in penicillin resistant strains of gonorrhoea (4). In Nairobi (71), a prospective study of prostitutes found that HIV-positive women were three times as likely to acquire cervical gonorrhoea

and about three times as likely to acquire gonococcal PID than were HIV-negative women. One study suggests (72) that HIV infection may alter the clinical course and response to therapy of PID. Two other recent studies, one from the US and one from Abidjan,(73-74) Côte d'Ivoire, suggest that HIV prevalence is high in women with PID, that the illness is more severe at presentation in HIV-positive women but the response to therapy is similar, (similar length of hospitalisation and similar rate of sequelae).

More recent studies confirm the common occurrence of PID in HIV seropositive women, probably due to sex practices and behaviour. There are currently no published data which document any changes in the natural history of chlamydial infection or trichomonas infection as a result of HIV infection. Success rate after treatment are similar in both seropositive and seronegative women.

5. Human Papilloma virus (HPV infection)

Genital warts are very common in HIV seropositive men and women with florid extensive lesions and recurrences difficult to treat (75-76-77). In homosexual and bisexual men, anal lesions may be the cause of anal carcinoma and systematic examination must be counselled to receptive partners.

HPV infection is better known in women. Many studies in US but also in West Europe have underlined the risks in HIV seropositive women.

- HIV shedding is more frequent
- Oncogenous subtypes (mainly HPV 16 and HPV 18) are more frequently found. Pap smears abnormalities concern more than 50% of infected women
- Dysplasia and especially grade 2 and 3 lesions are more common, more persistent and more recurrent.
- Local treatments (laser...) fail more frequently than in seronegative women.

Occurrence and severity of HPV lesions are correlated with the CD4+ cell decrease and may be considered as an authentic opportunistic infection. CDC guidelines recommend Pap smear at first visit and colposcopy in case of inflammation or presence of koilocytes. If the first smear is normal, surveillance has to be done yearly. If the first smear is inflammatory, surveillance has to be done each six months.

Since 1993, the invasive cervix carcinoma is an AIDS defining event. But this event is less common than it was initially thought and only 2% in US and France of women AIDS new cases correspond to that event. With the lengthening of survival related to antiretroviral therapy, the risk of cervix carcinoma occurrence may increase in the next decade.

BIBLIOGRAPHY

1. Mhalu F.S. Inter-relationships between HIV infection and other sexually transmitted diseases. *East African Medical Journal*; 67:512-517 (1990).
2. Pepin J., Plummer F.A., Brunham R.C., et al. The interaction of HIV infection and other sexually transmitted diseases: an opportunity for intervention. *AIDS*; 3:3-9 (1989).
3. Piot P., Laga M. Genital ulcers, other sexually transmitted diseases, and the sexual transmission of HIV. *British Medical Journal*; 298:623-624 (1989).
4. Wasserheit J.N. Epidemiological synergy: interrelationships between human immunodeficiency virus infection and other sexually transmitted diseases. *Sexually Transmitted Diseases*; 19:61-77 (1992).
5. Kreiss, J.K., Coombs R., et al. Isolation of human immunodeficiency virus from genital ulcers in Nairobi prostitutes. *Journal of Infectious Diseases*; 160:380-384 (1989).

6. Clemetson, D.B.A., Moss G.B., et al. Detection of HIV DNA in cervical and vaginal secretions. *Journal of the American Medical Association*; 269:2860-2864 (1993).
7. Duncan M.E., Tibaux G., Pelzer A., et al. First coitus before menarche and risk of sexually transmitted disease. *The Lancet*; 335:338-340 (1990).
8. Moses, S, Plummer F.A., et al. Is there an association between lack of male circumcision and risk for HIV infection? A review of the epidemiological evidence. VIIIth International Conference on AIDS in Africa. Abstract n° M.P.C.084 (1993).
9. Cook, L., Koutsky L.A., et al. Circumcision and sexually transmitted diseases. *American Journal of Public Health*; 84:197-201 (1994).
10. Nsanze H, Fast M.V., et al. Genital ulcers in Kenya. *British Journal of Venereal Disease*; 57:378-381 (1981).
11. Simonsen J.N., Cameron D.W., et al. Human immunodeficiency virus infection among men with sexually transmitted diseases: experience from a center in Africa. *The new England Journal of Medicine*; 319:274-278 (1988).
12. Jessamine, P.G., Plummer F.A., et al. Human immunodeficiency virus, genital ulcers and the male foreskin: Synergism in HIV-I transmission. *Scandinavian Journal of Infectious Diseases*; 69:181-186 (1990).
13. Bwayo J.J., Omari A.M., Mutere A.N., et al. Long distance truck-drivers: prevalence of sexually transmitted diseases (STDs). *East African Medical Journal*; 68:425-429 (1991).
14. Greenblatt R.M., Lukehart S.A., Plummer F.A., et al. Genital ulceration as a risk factor for human immunodeficiency virus infection. *AIDS*; 2:47-50 (1988).
15. Borgdorff M.W., Barongo L.R., et al. HIV infection in Mwanza region Tanzania: prevalence and risk factors. VI International Conference on AIDS in Africa. Abstract n° M.A.265 (1991).
16. Nunn A.J., Kengeya-Kayondo J.F., et al. Risk factors for HIV-I infection in adults in a rural Ugandan community: a population study. *AIDS*; 8:81-86 (1994).
17. Nkya W.M., Gillespie S.H., et al. Sexually transmitted diseases in prostitutes in Moshi and Arusha, Northern Tanzania. *International Journal of STD & AIDS*; 2:432-435 (1991).
18. Hudson C.P., Hennis A.J.M., et al. Risk factors for the spread of AIDS in rural Africa: evidence from a comparative seroepidemiological survey of AIDS, hepatitis B and syphilis in southwestern Uganda. *AIDS*; 2:255-260 (1988).
19. Salebe O., Riedner G., et al. HIV Infection among STD patients and correlated conditions in Mbeya, Tanzania. vm International Conference on AIDS. Abstract n° PoC4715 (1992).
20. Catterall R.D. STD - third African regional conference. *British Journal of Venereal Disease*; 59:337-339 (1983).
21. Hook E.W., Cannon R.O., et al. Herpes simplex virus infection as a risk factor for human immunodeficiency virus infection in heterosexuals. *The Journal of Infectious Diseases*; 165:251-255 (1992).
22. Nzila N., Laga M., et al. HIV and other sexually transmitted diseases among female prostitutes in Kinshasa. *AIDS*; 5:715-721(1991).
23. Mokwa K., Batter V., et al. Prevalence of sexually transmitted diseases (STD) in childbearing women in Kinshasa, Zaire, associated with HIV infection. VII International Conference on AIDS. Abstract n° W.C.3251(1991).
24. Luyeye M., Gerniers M., et al. Prevalence des facteurs de risque pour les MST chez les femmes enceintes dans les soins de santé primaires à Kinshasa. V International Conference on AIDS in Africa. Poster T.P.C.8 (1990).
25. Lebughe I., Nzila N., Edidi B. HIV and STD prevalence and risk factors among pregnant women aKending primary health care centers in Kinshasa, Zaire.IX International Conference on AIDS. Abstract n° PO-B11-1536 (1993).
26. Nzila N., Laga M., et al. HIV and other sexually transmitted diseases among female prostitutes in Kinshasa. *AIDS*; 5:715-721(1991).

27. Bazola M., Manoka T., et al. The impact of HIV infection on the incidence of STD in high-risk women. VII International Conference on AIDS. Abstract n° W.C.104 (1991).
28. Bassett M.T., Latif A.S., et al. Sexual behavior and risk factors for HIV infection in a group of male factory workers who donated blood in Harare, Zimbabwe. *Journal of Acquired Deficiency Syndromes*; 5:556-559 (1992).
29. Mosha F., Grosskurth H., et al. The impact of STD intervention of HIV infection: a cohort study of 12,000 people, intermediate results. IX International Conference on AIDS. Abstract n° PO-C35-3383 (1993).
30. Temmerman M., Ali F.M., et al. Rapid increase of both HIV-1 infection and syphilis among pregnant women in Nairobi, Kenya. *AIDS*; 6:1181-1185 (1992).
31. Berkley S.F., Widy-Wirski R., et al. Risk Factors associated with HIV infection in Uganda. *The journal of infectious diseases*; 160:22-30 (1989).
32. Laga M., Manoka A., et al. Non-ulcerative sexually transmitted diseases as risk factors for HIV-1 transmission in women: results from a cohort study. *AIDS*; 7:95-102 (1993).
33. Dallabetta, G.A., Miotti P.G., et al. High socioeconomic status is a risk factor for human immunodeficiency virus type 1 (HIV-1) infection but not for sexually transmitted diseases in women in Malawi: implications for HIV-1 control. *The journal of Infectious Diseases*; 167:36-42 (1993).
34. Miotti P., Liomba G., et al. Rate of new sexually transmitted diseases (STD) is higher in HIV-1 infected than uninfected women in Malawi. VII International Conference on AIDS in Africa. Abstract n° T.P. 069 (1992).
35. Waigwa S.R.N., Maitha G., et al. HIV- 1 prevalence in patients with *C. trachomatis* infections in Nairobi. VIII International Conference on AIDS, Abstract n° PoB3515 (1992).
36. Kell P.D., Barton S.E., et al. Sexually transmitted diseases in HIV-1 seropositive women at presentation. *International Journal of STD & AIDS*; 2:204-206 (1991).
37. Miotti P., Canner J., et al. Rate of new HIV-1 infection in a cohort of women of child-bearing age in Malawi. IXth International Conference on AIDS, Berlin. Abstract n° POC03-2613 (1993).
38. Ocheng D., Msauka A., et al. Prevalence of sexually transmitted diseases (STDs) in females at 7 truck stops in Tanzania. Vmth International Conference on AIDS in Africa, Marrakech. Poster Th. P.C.070 (1993).
39. Mertens TE., Hayes RJ., Smith PG.: Epidemiologic method to study the interaction between HIV infection and other sexually transmitted diseases. *AIDS*; 4:57-65 (1990).
40. Mostad S., Welch M., Chohan B., Reilly M., Overbaugh J., Madaliya K., Martin H., Nyange P., Ndinya-Achola JO., Kreiss J.: Cervical and vaginal HIV-1 DNA Shedding in female STD clinic attenders. XIth International Conference on AIDS. Vancouver, July 7-12. Abstract We.C. 333 (1996).
41. Ghys PD., Fransen K., Diallo MO., Ettigne-Traor V., Maurice C., Hoyi Adonsou YM., Kalish M., Brown T., Steketee R., Coulibaly I-M., et al: The associations between cervico-vaginal HIV-1 shedding and sexually transmitted diseases, immunosuppression, and serum HIV-1 viral load in female sex workers in Abidjan, Cte d'Ivoire XIth International Conference on AIDS. Vancouver, Canada, July 7-12. Abstract WeC.332 (1996).
42. Moss GB., Overbaugh J., Welch M., Reilly M., Bwayo J., Plummer FA., NdinyaAchola JO., Malisa MA., Kreiss JK., Human Immunodeficiency virus DNA in urethral secretions in men: association with gonococcal urethritis and CD4 cell depletion *J Infect Dis*; 172:1469-1474 (1995).
43. 43 . Eron JJ., Gilliam B ., Fiscus S ., Dyer J., Cohen M. HIV- 1 shedding and Chlamydial urethritis (letter) *JAMA*; 275-86 (1996).
44. Atkins MC., Carlin EM., Emery VC., Griffiths PD., Boag F.: Fluctuations of HIV load in semen of HIV positive patients with newly acquired sexually transmitted disease. *BMJ*; 313-341-342 (1996).

45. Hoffman I., Maida M., Royce R., Costello Daly C., Kazembe P., Ver nazza P., Dyer J., Zimba D., Nkata E., Cachenje E., et al; Effects of urethritis therapy on the concentration of HIV in seminal plasma. XIth Intemational Conference on AIDS. Vancouver, July 7-12. Abstract Mo.C.903 (1996).
46. Dallabetta G., Diomi MC. Treating sexually transmitted diseases to control HIV transmission. *Current opinion in Infectious Diseases*; 10:22-25 (1997).
47. Deschamps M-M., Pape JW., Hafner A., Johnson WD. Heterosexual transmission of HIV in Haiti. *Ann Inter Med*; 125:324-330 (1996).
48. Mehendale SM., Rodrigues JJ., Brookmeyer RS., Gangakhedkar RR., Divekar AD., Gokhale MR., Risbud AR., Paranjape RS., Shepherd MR., Rompalo AE., et al: Incidence and predictors of human immuno-deficiency virus type 1 seroconversion in patients attending sexually transmitted disease clinics in India. *J. Infect. Dis*; 172: 1486-1491(1995).
49. Rojanapithayakorn W., Hanenberg R. The 100% Condom rogram in Thailand. *AIDS*, 10, 1-7 (1996).
50. Grosskurth H., Mosha F., Todd J., Senkoro K., Newell J., Klokke A., Changulucha J., West B., Mayaud P., Bavyole A., et al: A community trial of the impact of improved sexually transmitted disease treatment on the HIV epidemic in rural T~n7ania: 2. Baseline survey results *AIDS*; 9:927-934 (1995).
51. Wawer MJ., Gray RH., Quinn TC.: AIDS intervention in Uganda. *Science*; 270:564-565 (1995).
52. Tyndall M., Malisa., et al. The effect of HIV infection on the clinical features and response to treatment of genital ulcer disease due to chancroid. VIIth Intemational Conference on AIDS. Florence. Abstract n° M.B.2296 (1991).
53. Tyndall M., M. Malisa., et al. Ceftriaxone no longer predictably cures chancroid in Kenya. *Journal of Infectious Diseases*; 167:469-471(1993).
54. Kivuvu M., Malele B., et al. Syphilis among HIV+ and HIV- prostitutes in Kinshasa; prevalence and serologic response to treatment. V International Conference on AIDS in Africa. Poster T.P. C.7 (1990).
55. Telzak E.E., Greenberg M.S.Z., et al. Syphilis treatment response in HIV-infected individuals. *AIDS*; 5:591-595 (1991).
56. Laga M., Nzila N., et al. The interrelationship of sexually transmitted diseases and HIV infection: implicatiuons for the control of both epidemics in Africa. *AIDS*; 5 (suppl 1); S55-63 (1991).
57. 57. Wambugu P., Plummer F.A., et al. Are sexually transmitted diseases (STD) opportunistic infections in HIV-I infected women ? VII International Conference on AIDS, Abstract n° M.C.3061(1991).
58. 58. Hoegsberg B., Abulafia O., et al. Sexually transmitted diseases and human immunodeficiency virus infection among women with pelvic inflammatory disease. *American Journal of Obstetrics and Gynecology*; 163:1135-1139 (1990).
59. 59. Irvin K., Rice R., et al. The clinical presentation and course of pelvic inflammatory disease in HIV+ and HIV-women: preliminary results of a multicenter study. IXth International Conference on AIDS, Berlin. Abstract n° WS-B07-1(1993).
60. 60. Kamenga M., Tourc C.K., et al. HIV infection in women with PID in Abidjan. Cote d'Ivoire. IXth International Conference on AIDS, Berlin. Abstract n° WS-B07-2 (1993).
61. 61. Maiman, M., Fruchter R.G., et al. Recurrent cervical intraepithelial neoplasia in human immunodeficiency virus-seropositive women. *Obstetrics & Gynecology*; 82:170-174. (1993).
62. 62. Mandelbatt, J.S., Fahs M., et al. Association between HIV infection and cervical neoplasia: implications for clinical care of women at risk for both conditions. *AIDS*; 6:173-178

- 63.63. Feingold, A.R., Vermund S.H., et al. Cervical cytological abnormalities and Papillomavirus in women infected with human immunodeficiency virus. *Journal of Acquired Immune Deficiency Syndllomes*; 3:896-903 (1990).