1110-5704
African Journal of Urology

Vol. 9, No. 3, 2003
111-116

GLOBAL HEALTH CONCERNS

RECENT DEVELOPMENTS IN SEXUALLY TRANSMITTED INFECTIONS RESEARCH FOR THE PREVENTION OF HIV TRANSMISSION AND ACQUISITION

F.J. NDOWA AND S. DLUDLU
Department of Reproductive Health and Research, World Health Organization, Geneva, Switzerland

INTRODUCTION

Sexually transmitted infections (STIs) are a major global cause of acute illness, infertility, long term disability and premature death, with severe medical and psychological consequences for millions of men, women and infants. The World Health Organization (WHO) estimated that 340 million new cases of curable STIs, namely, syphilis, gonorrhoea, chlamydia and trichomoniasis occurred globally in men and women aged 15-49 years in 1999.[1]

Research has provided strong evidence that both ulcerative and non-ulcerative STIs promote HIV transmission by augmenting both HIV infectiousness and susceptibility through a variety of biological mechanisms. The evidence for this has been gathered from biological, cohort and community intervention studies.[2] Some STIs have also been shown to be less responsive to standard therapy in the presence of HIV immune-suppression. This bi-directional interaction of STIs and HIV is an important element in the control of STIs in their own right as well as for the prevention of HIV. As a consequence of this observation, dynamic public health programs should include treatment of STIs as one of the key elements in the fight against HIV.

THE RESEARCH AND EVIDENCE MWANZA, RAKAI AND MASAKA

The results of the Mwanza trial in Tanzania in 1995, which demonstrated a 38% decrease in HIV incidence in areas where STI services had been strengthened, offered convincing evidence that STI control represented a cost-effective mechanism for preventing HIV transmission. The design of the study in Mwanza was a community-based, randomized, controlled, unblinded cohort. The intervention was the syndromic treatment of symptomatic STI patients through improved clinic-based services, which were continuously available for 24 months. Training and supervision were also key components of this trial.[3]

Between 1994 and 1998 another community-based randomized trial was completed in the Rakai district in Uganda. The study design was a randomized, controlled, community-based, open cohort offering periodic, directly observed home-based mass treatment every 10 months. The intervention community was offered STI treatment and the control arm received anthelminthics and iron-folate. Treatment was administered irrespective of symptoms or laboratory testing and both arms received identical health education, condom and serological counselling services. After three rounds of treatment the trial was concluded without showing effect on HIV-1 incidence.[4]

Although the results from Rakai appeared to be contradictory to the Mwanza experience, there are some important observations to show that these two important trials were complementary but not comparable to each other. The two trials tested different interventions and used different methods for effect evaluation, in different epidemiological environments. The stages of the HIV epidemic were different, the role played by incurable and/or persistent infections, such as genital herpes and bacterial vaginosis, was important and the importance of symptomatic and asymptomatic STIs need to be taken into account.[5]

A third community-based, randomized, controlled trial was conducted between 1994 and 2000 in the Masaka district, south-western

Uganda. This mammoth trial allocated 18 rural communities to receive 3 different types of interventions: behavioural interventions alone in one arm of the trial, behavioural and enhanced STI treatment in the second arm and routine government health services with additional community development activities in the control arm. The results of this study showed an increase in condom use, substantial reduction in incidence of active syphilis and prevalence of gonorrhoea but no measurable reduction in the incidence of HIV.[6]

The most probable explanation for the findings in Masaka was the stage of the HIV epidemic. This setting was one in which the reduction of HIV transmission was already occurring and, therefore, the interventions were probably not of sufficient intensity to have a measurable impact on HIV. There were noted behavioural changes towards safer sex in the whole study population unrelated to the trial interventions, in response to a number of factors. Some of these are the fact that the HIV epidemic itself was exerting influence on the behavioural attitudes of the people of Uganda, information for behaviour change was being disseminated from government sources and some non-governmental sources had been very influential in some parts of the country.

Finally, another important community intervention trial was the Mema kwa Vijana (meaning "Good Things for Young People" in Swahili) project conducted from 1999 to 2002 in the Mwanza district of Tanzania. This was an innovative package to measure the impact of adolescent sexual and reproductive health intervention on HIV, other STIs and unintended pregnancies. The intervention had four major components:

* In-school sexual and reproductive health education through teacher-led, peer assisted program
* Youth-friendly reproductive health services through education of health care providers
* Community-based condom promotion and distribution, for and by youth
* Community activities to create a supportive environment for the interventions to take place.

The outcome of this intervention showed that knowledge and attitudes were statistically significantly better in the intervention than the comparison communities. Reported behaviour change, such as use of condoms and fewer lifetime partners since the start of the follow-up period, was better among adolescent boys in the intervention group compared to the controls. Biological outcomes, in terms of HIV incidence, HSV-2 prevalence and unintended pregnancies showed minor differences which did not reach statistical significance.[7] Some of the lessons learnt from this latest community intervention trial are that it is feasible to provide sex and skills education in an African rural, school setting and that it does not necessarily lead to increased promiscuity, as some critics to the idea have propounded. Furthermore, it should be noted that, in the short term, change in knowledge and skills does not affect risk-taking, especially when the entire community is not included in the intervention since sexual networks, especially for young girls, may go beyond their school peers.

If sufficient data is available, modelling can be used to delve further into results of studies without conducting additional ones. An interesting exercise was the simulation model of the effects of single round mass treatment, syndromic management, a combination of the two and no intervention, based on parameters from the Mwanza and Rakai scenarios, using the STDSIM model. The results of this simulation were that a single-round mass treatment would steeply reduce STI incidence resulting in STI prevalences of 50-80% lower than without the intervention. However, without further intervention, prevalences would increase over time and approach levels observed in the absence of the intervention within 5 to 10 years. The effect of mass treatment on HIV would be a reduction of incidence by up to 50% for the first 6 months after the intervention. The incidence would rise over time thereafter if there are no additional interventions. If a single-round of mass treatment were combined with improved STI treatment services, then the effect on HIV incidence would be a steep reduction within the first year and a continued decrease thereafter. The reduction in cumulative HIV incidence over 2 years (57%) would be much larger than the impact of either mass treatment or symptomatic STI treatment in isolation.[8]

In other words information and data from these studies, when entered into a simulation model, seem to indicate that a single mass treatment strategy can give rise to a reduction

in HIV incidence in the short term, but combined with improved STI treatment the effect would be particularly effective, both in the short and long term, under the right epidemiological conditions.

RESEARCH ON SPECIFIC STI PATHOGENS

Genital ulcer diseases

Genital ulcer diseases have been reported to be associated with HIV transmission since the beginning of the HIV epidemic. Syphilis, chancroid (caused by Haemophilus ducreyi) and genital herpes caused by herpes simplex virus type 2 (HSV-2) have been implicated.[9,10]

HSV-2

In recent years, HSV-2 has been shown to be increasingly the major cause of genital ulcer disease (GUD) in developing countries. In South Africa HSV-2 was shown to be playing an increasingly important role in genital ulcerative diseases among men with genital ulcers from a mining community.[11,12] Similar data has been reported from Botswana where in 2002 the aetiology of GUD was HSV-2 in 60% of cases and chancroid in 1% compared to 24% and 26% respectively in 1993. Syphilis serology in women attending antenatal care was 2% in 2002 compared to 18% in 1993.[13] In China, in a total of 227 male and female patients enrolled, syphilis alone was diagnosed in 35% of cases, genital herpes alone in 19% and both infections were present in 28 patients (12%) and no case of chancroid was identified.[14]

Interactions between HSV-2 and HIV have been illustrated to increase transmission and acquisition of either infection. In a prospective study in rural Tanzania, the results suggested that HSV-2 played such an important role in the transmission of HIV that it was recommended that HSV-2 infections should be part of the focus for programs to adequately control HIV transmission.[15] HIV-infected women have also been shown to shed HSV-2 from the genitalia more commonly than women not infected with HIV and most of this shedding is asymptomatic.[16,17] This suggests increased HSV-2 transmission in dually infected individuals. Another study demonstrated frequent recovery of HIV-1 from genital herpes simplex virus lesions in HIV-1-infected men, suggesting that the efficiency of transmission of sexually transmitted HIV was enhanced by genital herpes infection.[18]

NON-ULCERATIVE DISEASES

Gonorrhoea and Chlamydia

Non-ulcerative STIs also seem to facilitate HIV infection. A study in Nairobi, Kenya found gonorrhoea, bacterial vaginosis and genital warts independently associated with HIV.[19] Another study looked at rectal gonorrhoea as an independent risk factor for HIV infection in a cohort of homosexual men in Canada and found that it was associated with HIV seroconversion after adjustment for a number of HIV risk factors. Although the authors could not rule out that rectal gonorrhoea may not have been directly associated with HIV infection but rather with other residual lifestyle factors not fully adjusted for in their analysis, the relationship with gonococcal involvement of a specific anatomic site gave support to a biological association between gonorrhoea and HIV infection, rather than to alternative non-biological explanations. They postulated that gonorrhoea results in inflamed rectal mucosa, compromising its integrity and, thereby, predisposing an individual to subsequent HIV infection.[20] In Thailand a history of gonorrhoea or chlamydia in female partners of HIV-seropositive male blood donors was associated with increased risk of infection in heterosexual women.[21] Another study conducted in men in Malawi investigated the hypothesis that STIs increased the likelihood of transmission of HIV-1 RNA through increased concentration of the virus in semen. The study found that HIV-1 seropositive men with urethritis had HIV-1 RNA concentrations in seminal plasma eight times higher than those in seropositive men without urethritis, despite similar CD4 counts and blood plasma viral RNA. Gonorrhoea was associated with the greatest concentration of HIV-1 in semen. After the urethritis patients received antimicrobial treatment directed against STI, the concentration of HIV-RNA in semen decreased significantly at two weeks to reach similar levels to those of men without urethritis. In the control group neither the blood plasma viral RNA concentration nor the seminal plasma HIV-RNA concentrations changed during the 2-week period.[22] This is further suggestion that gonococcal urethritis increases the infectiousness of men with HIV1.

In an attempt to quantify the relationship between non-ulcerative STIs and HIV trans-

mission, a simulation study, also using data from Uganda (from 1980-1990), found that in a low STI prevalence scenario non-ulcerative STIs increased two-fold the likelihood of HIV transmission and in a high prevalence setting the increase was ten-fold.[23] Chlamydia alone was found to increase the shedding of HIV from the genitalia and also increased susceptibility in HIV negative individuals.[24]

Trichomonas Vaginalis

The infections which cause vaginitis have traditionally not been considered as seriously as those that cause cervical infections until the advent of HIV. Of the non-ulcerative STIs, Trichomonas vaginalis infection has become important in the transmission of HIV and has been shown to increase the transmission of HIV by about two-fold.[25,26] It is suggested that the presence of this organism creates an abnormal vaginal milieu which increases HIV acquisition.[27]

Bacterial Vaginosis

Bacterial vaginosis (BV), not a true sexually transmitted infection, has been associated with antenatal sero-conversion of HIV. In a cross-sectional study of women attending their first antenatal care visit in Malawi HIV-seronegative women were enrolled and followed during pregnancy and after delivery. BV was significantly associated with antenatal and postnatal HIV seroconversion. In this study the attributable risk of BV alone was 23% for antenatal HIV seroconversions and 14% for postnatal seroconversions.[28] In a prospective cohort study of sex workers in Mombasa, Kenya, BV was found to be associated with increased risk of HIV-1 acquisition.[25]

CONCLUSION

Despite seemingly conflicting or inconclusive results from large community intervention trials, there is ample strong evidence that both ulcerative and non-ulcerative STIs promote HIV transmission by augmenting HIV infectiousness and HIV susceptibility through a variety of mechanisms. At a population level the community level intervention trial results seem to indicate that the timing and duration of the interventions are important. One would speculate also that the Mema Kwa Vijana intervention needs to be expanded and applied for a longer duration (a decade, at least) before biological impact can be expected to emerge to a significant degree.

The available data leave no doubt that other STIs facilitate HIV transmission and, therefore, early STI treatment is still one of the key interventions of a comprehensive HIV prevention package. At a country policy level the task should be to explore mechanisms that make the implementation of the STI component more effective in order to exert as maximal an impact as possible on HIV incidence. Improving access to quality STI clinical services should be a priority and, additionally, targeting such services to populations in the early phase of the HIV epidemic (adolescents in any stage of the HIV epidemic will be a prime candidate for this) will have the most effect. Such services should be provided in a horizontal manner allowing, and actively involving, the private sector in the process, as well as all the other health disciplines such as Paediatrics, Obstetrics, Gynaecology, Urology, Family Planning services, among other sexual health services. Along with the provision of high quality, continuous STI treatment, other innovative approaches should also be explored. For example, targeted mass treatment among high frequency transmitters, (e.g. sex workers in many settings) repeated at relatively short intervals (periodic presumptive treatment strategies) may be considered. Another strategy involves focusing STI screening and treatment in both private and public health services which serve individuals who are HIV infected or at higher risk for HIV acquisition. Such services include counselling and voluntary testing centres, services providing mother-to-child HIV prevention services and TB services in high HIV prevalence settings. Additional resources, both financial and human, need to be identified and put in place for such strategies to be implemented or explored.

Although more research is needed to have a better understanding of the impact of treating some STIs on HIV, much knowledge and information has been gathered over the past two decades to enable policy makers to act now at all levels of the health system.

It must be emphasized, however, that for both HIV and the other STIs prevention from getting infected in the first place remains paramount. Even in countries with the highest HIV prevalence, the majority of the population

remains uninfected. Greater effort should be put into strategies for primary prevention, especially involving children and adolescents.

REFERENCES

1. Global prevalence and incidence of selected curable sexually transmitted infections. Overview and estimates 2001. *World Health Organization, Geneva*

2. Fleming DT and Wasserheit JN. From epidemiological synergy to public health policy and practice: the contribution of other sexually transmitted diseases to sexual transmission of HIV infection. *Sex Transm Infect* 1999, 75:3-17.

3. Grosskurth H, Mosha F, Todd J *et al.* Impact of improved treatment of sexually transmitted diseases on HIV infection in rural Tanzania: randomized controlled trial. *Lancet* 1995, 346:530-536.

4. Wawer MJ, Gray RH, Sewankambo NK *et al.* A randomized community trial of intensive sexually transmitted disease control for AIDS prevention, Rakai, Uganda. *AIDS* 1998, 12:1211-1225.

5. Grosskurth H, Gray R, Hayes R *et al.* Control of sexually transmitted diseases for HIV-1 prevention: understanding the implications of the Mwanza and Rakai trials. *Lancet* 2000, 355:1981-1987.

6. Kamali A, Quigley M, Nakiyingi J *et al.* Syndromic management of sexually transmitted infections and behaviour change interventions on transmission of HIV-1 in rural Uganda: a community randomised trial. *Lancet* 2003, 361:645-652.

7. Hayes R, Obasi A, Ross DA, Changalucha J, Gavyole A. Mema kwa Vijana. A randomized controlled trial of an adolescent sexual and reproductive health intervention programme in rural Mwanza, Tanzania. In: *Fifteenth Biennial Congress of the International Society for Sexually Transmitted Diseases Research (ISSTDR),* Ottawa, Canada, July 27-30, 2003, Abstracts 0695, 0697, 0698, 0699, 0700.

8. Korenromp EL, Van Vliet C, Grosskurth H *et al.* Model-based evaluation of single-round mass treatment of sexually transmitted diseases for HIV control in a rural African population. *AIDS* 2000, 14:573-593.

9. Cameron DW, Simonsen JN, D'Costa LJ *et al.* Female to male transmission of human immunodeficiency virus type 1: risk factors for seroconversion in men. *Lancet* 1989, 2:403-407.

10. Plummer FA, Simonsen JN, Cameron DW *et al.* Cofactors in male-female sexual transmission of human immunodeficiency virus type 1. *J Infect Dis* 1991, 163:233-239.

11. O'Farrell N. Increasing prevalence of genital herpes in developing countries: implications for heterosexual HIV transmission and STI control programmes. *Sex Transm Infect* 1999, 75:377-384.

12. Lai W, Chen CY, Morse SA *et al.* Increasing relative prevalence of HSV-2 infection among men with genital ulcers from a mining community in South Africa. *Sex Transm Infect* 2003, 79:202-207.

13. Rahman M, Paz-Bailey G, Regoeng M *et al.* Changing patterns of STD in Botswana 1993-2002: approaches to GUD management. In: *Fifteenth Biennial Congress of the International Society for Sexually Transmitted Diseases Research (ISSTDR),* Ottawa, Canada, July 27-30, 2003, abstract 0334.

14. Wang QQ, Mabey D, Peeling RW *et al.* Validation of syndromic algorithm for the management of genital ulcer diseases in China. *Int J STD AIDS* 2002, 13:469-474.

15. del Mar Pujades Rodriguez M, Obasi A *et al.* Herpes simplex virus type 2 infection increases HIV incidence: a prospective study in rural Tanzania. *AIDS* 2002, 16:451-462.

16. Augenbraun M, Feldman J, Chirgwin K *et al.* Increased genital shedding of herpes simplex virus type 2 in HIV-seropositive women. *Ann Intern Med* 1995, 123:845-847.

17. Mbopi-Keou FX, Gresenguet G, Mayaud P *et al.* Interactions between herpes simplex virus type 2 and human immunodeficiency virus type 1 infection in African women: opportunities for intervention. *J Infect Dis* 2000, 182:1090-1096.

18. Schacker T, Ryncarz AJ, Goddard J *et al.* Frequent recovery of HIV-1 from genital herpex simplex virus lesions in HIV-1 infected men. *JAMA* 1998, 280:61-66.

19. Fonck K, Kidula N, Kirui P *et al.* Pattern of sexually transmitted diseases and risk factors among women attending an STD referral clinic in Nairobi, Kenya. *Sex Transm Dis* 2000, 27:417-423.

20. Craib KJ, Meddings DR, Strathdee SA *et al.* Rectal gonorrhoea as an independent risk factor for HIV infection in a cohort of homosexual men. *Genitourin Med* 1995, 71:150-154.

21. Nagachinta T, Duerr A, Suriyanon V *et al.* Risk factors for HIV-1 transmission from HIV-seropositive male blood donors to their regular female partners in northern Thailand. *AIDS* 1997, 11:1765-1772.

22. Cohen MS, Hoffman IF, Royce RA *et al.* Reduction of concentration of HIV-1 in semen after treatment of urethritis: implications for prevention of sexual transmission of HIV-1. *Lancet* 1997, 349:1868-1873.

23. Dodd R. Quantifying the STD-HIV connection. *AIDS Anal Afr* 1994, 4:16.

24. Mabey D. Interactions between HIV infection and other sexually transmitted diseases. *Trop Med Int Health* 2000, 5:A32-36.

25. Laga M, Manoka A, Kivuvu M *et al.* Non-ulcerative sexually transmitted diseases as risk factors for HIV-1 transmission in women: results from a cohort study. *AIDS* 1993, 7:95-102.

26. Ghys PD, Diallo MO, Ettiegne-Traore V *et al.* Genital ulcers associated with human immunodeficiency virus-related immuno-suppression in female sex workers in Abidjan, Ivory Coast. *J Infect Dis* 1995, 172:1371-1374.

27. Moodley P, Connolly C, Sturm AW. Interrelationships among human immunodeficiency virus type 1 infection, bacterial vaginosis, trichomoniasis and the presence of yeasts. *J Infect Dis* 2002, 185:69-73.

28. Taha TE, Hoover DR, Dallabetta GA *et al.* Bacterial vaginosis and disturbances of vaginal flora: association with increased acquisition of HIV. *AIDS* 1998, 12:1699-1706.

All correspondence to be sent to:

Dr. Francis J. Ndowa
Department of Reproductive Health and Research
World Health Organization
Avenue Appia 20
CH – 1211 Geneva 27

ndowaf@who.int