Sexually Transmitted Infections

Editorials

From Mwanza and Rakai to Beijing and Moscow? STD control and HIV prevention

Trying to persuade the readers of this journal of the public health importance of STDs would be like taking coals to Newcastle. Worldwide, most people would agree that the control of STDs should be given high priority. For developing countries, however, there is less agreement on how best this goal could be achieved, and to what extent STD control can contribute to the prevention of HIV infection. Many STD experts and policy makers are confused, particularly as a consequence of the Ugandan mass treatment trial. This trial, conducted in the Rakai district of Uganda, found some effect of STD mass treatment on the prevalence of STDs, but none on HIV incidence.[1]

The review by Flemming and Wasserheit[2], recently published in this journal, is an extremely enlightening contribution that should help to provide clarity and to show the way forward for both policy decisions and STD research. The review gives a carefully collated summary of what is presently known about the STD-HIV cofactor effect and the impact of STD treatment on HIV transmission, both at individual and population level.

Strong statistical associations between STDs and HIV infection have been documented repeatedly in cross sectional and case-control studies, almost from the onset of the AIDS pandemic.[3] However, the interpretation of these observations was difficult, because they were potentially explicable through confounding factors such as risky sexual behaviour which are difficult to measure and because the time sequence of events was not known in most cases.[4]

The longitudinal studies of the late 1980s and early 1990s confirmed that indeed STDs often preceded HIV seroconversion, and allowed correction for some confounding variables, although residual confounding could not be ruled out.[5 6]

The evidence was not conclusive but seemed to be sufficiently strong to recommend STD control as a means for HIV prevention in addition to other strategies, and syndromic case management was identified as the preferred approach for all areas and countries that lack a dense net of high quality diagnostic services.[7 8]

More recently, the enhancing role of STDs on the transmission of HIV infection was demonstrated through a series of biological studies which showed that in HIV positive individuals, the shedding of HIV in semen or cervicovaginal secretions was increased in the presence of a variety of STDs,[9–11] and that HIV shedding decreased substantially after STD treatment.

Evidence for the STD-HIV cofactor hypothesis became overwhelming when intervention studies demonstrated that effective STD treatment not only reduced STD prevalence but had a major impact on HIV incidence in sex workers from Kinshasa and Abidjan,[12 13] or in the general rural population from Mwanza Region, Tanzania, as shown in the context of a community based randomised controlled trial.[14 15] It is understandable that the results of the Rakai study, again a community based randomised controlled trial, came initially as a great surprise.

Flemming and Wasserheit[2] discuss some of the possible explanations for the difference in the results of the Rakai trial and the other intervention studies, notably the Mwanza study. The list is long, and includes differences in the stage of the HIV epidemic (mature epidemic in Rakai versus an earlier stage in Mwanza), differences in the accessibility to STD services for patients with reinfection (lack of such services in Rakai, but continuous availability in Mwanza), and differences in the prevalences of treatable STDs (probably higher proportion of ulcers due to genital herpes in Rakai than in Mwanza). Random error may also play a role (possible underestimation of impact in Rakai and overestimation in Mwanza).

The proportion of HIV infections attributable to the enhancing effect of STDs seems likely to decrease with the progression of the HIV epidemic. This hypothesis is supported by the results of epidemiological modelling,[16] and seems to be consistent with the results of the Rakai study.

The list of STDs for which a cofactor effect on HIV transmission has been demonstrated is long, and at the minimum comprises genital ulcers, gonorrhoea, chlamydia infection, and trichomoniasis. But we still know very little about the size of the cofactor effects of different STDs per sexual act. It seems that in Rakai only a small fraction of HIV incident cases were attributable to STDs. However, studies like those from Mwanza or Rakai can in general only attempt to estimate the fractions which are due to an increased *susceptibility* to HIV infection related to STDs in initially HIV negative individuals, because usually little is known about the presence of STDs in the HIV positive partners. Shedding studies suggest that the increase in *infectiousness* in HIV positive STD patients may be substantial and it is possible that this is of great importance

in mature epidemics, but unfortunately the relative importance of these effects is extremely difficult to measure.

There seems to be a growing consensus that the results of the Rakai trial are complementary rather than contradictory to those of other intervention studies.[2 17] Of course, everybody would have welcomed a result from Rakai showing a substantial impact of mass treatment on HIV incidence, but the lessons we are learning from Rakai may be extremely helpful for the policy decisions urgently needed in countries such as India, China, Brazil, or in those of the former Soviet Union.

What are these implications? Obviously, repeated rounds of STD mass treatment did not have an impact on HIV incidence when performed in the context of a late epidemic (where HIV is widely distributed in the general population) and in a situation with a limited rate of treatable STDs. Providing effective STD services is, however, of paramount importance for all countries that have medium or high STD prevalences at least in parts of their populations, and that are still in the earlier stages of their HIV epidemics. The list of countries fulfilling these criteria is long; and not at all restricted to developing countries. For example, at present the Russian Federation and many of the newly independent states of the former Soviet Union are experiencing a frightening STD epidemic, with an annual incidence of syphilis that has increased more than 60-fold in Russia between 1988 and 1996.[18]

If funds are limited, such countries should focus initially on comparatively easily identifiable high risk populations such as sex workers, truck drivers, and migrant labourers who often comprise large populations of men separated from their families.

But even in countries with mature HIV epidemics, there is always an extremely vulnerable HIV negative subgroup of the general population—young people who have just entered their sexually active life. If we want to rescue the next generation from the HIV disaster in Africa and elsewhere, we must concentrate on risk reduction *and* effective STD case management in adolescents and young people. This implies not only making services available but also making them acceptable to young people. At present, even where good syndromic treatment is in place, young people are far too frightened to make use of it: they fear abusive attitudes of health workers, and often experience a lack of privacy and confidentiality.

In many of the countries mentioned above, STD treatment is still perceived as an issue to be handled by the clinical expert. But most dermatovenereologists find it very difficult to talk to national AIDS control programme officers (and vice versa), and thus opportunities are lost again and again, while the HIV epidemic sequentially spreads through one risk group after the other and then slowly but steadily creeps into all niches of the society.

There are also a number of conclusions which must *not* be drawn from the Rakai trial results, although many have jumped to them already: firstly, that the mass treatment of STDs is in general a useless thing to do. Mass treatment did not work under the circumstances met in Rakai, but it is perfectly possible that mass treatment (maybe in a more feasible single round strategy), when combined with improved routine services for symptomatic STDs (thus controlling reinfections and STDs in those who are mobile and do not participate in the campaign), may lead to a substantial reduction of both STD and HIV transmission. This question can be approached through modelling exercises; but a definite answer may require further randomised controlled trials. In the face of the looming epidemics in Asia and elsewhere, too much is at stake for this option to be shelved a priori.

Secondly, some will draw the conclusion that STD treatment doesn't prevent HIV transmission in *all* populations, and that therefore funds should no longer be allocated to it, as it diverts resources away from behavioural interventions against AIDS. Such discussions are already going on in the donor community. For those entrapped in this kind of philosophy it may be of help to remember that such a view is unthinkable in other areas of preventive medicine: nobody interested in reducing mortality from coronary heart disease at the population level would suggest concentrating on the control of hypertension, while neglecting hyperlipaemia or smoking.

We will hear again that STD control is not "a magic bullet", and that the Rakai trial results confirm these doubts. In fact, STD treatment has never been a magic bullet, but it is a human right. According to the World Development Report of 1993, STDs are the second most important group of diseases in terms of the loss of healthy life years in women of child bearing age worldwide.[19] Anyone who has worked as a primary healthcare officer or hospital doctor in a developing country knows about the countless women who suffer from chronic pelvic inflammatory disease, become socially ostracised because of infertility, or die even today from ectopic pregnancies.

Thanks to the various intervention studies we have learned many lessons. Thanks to Rakai we have also learned that there are still more questions than answers. What is the role that asymptomatic STDs play in HIV transmission, and what is their role in keeping STDs at a high level of endemicity? What is the role of bacterial vaginosis and genital herpes in HIV transmission in mature HIV epidemics? There are good reasons to assume that HIV related immunodeficiency increases the incidence and the duration of herpetic episodes, that herpes lesions enhance HIV transmission, and that both these phenomena together may lead to a vicious circle which drives populations deeper and deeper into an HIV epidemic. Epidemiological data addressing this issue are scarce, and there is presently no simple solution for the control of genital herpes at the population level.

Clearly, if we want to be more successful in controlling the AIDS epidemics in Asia, Latin America, and eastern Europe than we have so far been in Africa, policy makers will need to put STD control even higher on the agenda, donor agencies will need to support these efforts more decisively, and scientists will need to address the many unanswered research questions with urgency.

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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