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.

The review by Flemming and Wasserheit, 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. 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.

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.

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.

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, 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, or in the general rural population from Mwanza Region, Tanzania, as shown in the context of a community based randomised controlled trial. 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 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, 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. 1 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 dermatovenerologists 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 epidemic 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 classicSTDs 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 underestimated 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.3–5 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.6–12 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.16 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.17 Studies among pregnant women in several European countries found prevalence rates ranging from 9.7% to 27.9%.18 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%.19 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.19–21 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.19 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
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 maintain a significant cause of genital ulcerations in sub-Saharan Africa though 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.

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Is nucleoside analogue monotherapy sufficient for treatment of HBV infection? Lessons from HIV

Interferon has until very recently been the sole licensed treatment for hepatitis B virus (HBV). It is effective in only a minority of patients and there is an urgent requirement for new therapies. A number of nucleoside/nucleotide analogues are in clinical trials, including BMS-200475, famciclovir (both guanosine analogues), adefovir, and finally lamivudine, which has recently been approved for treatment of HBV by the Food and Drug Administration in the United States. Similar licensing in Europe for HBV monotherapy is imminent. (Clinical trials of lobucavir, another potent anti-HBV compound, have recently been suspended in the light of animal toxicity data, and the long term future of this drug is therefore in doubt.) New quantitative assays for HBV DNA in serum are available to assess more precisely the antiviral effects of these drugs, as well as allowing insights into the dynamics of infection. This is of course reminiscent of advances in our understanding of HIV infection a few years ago. Against this background, what principles should govern the use of these new antiviral agents?

**Potency**

The estimated daily production of HBV within an infected individual is 10^{11} (compared with 10^9 for HIV), with typical viral loads of up to 10^{-6} copies/ml serum, and highly potent antiviral activity will be required for effective suppression of virus replication. Although not formally demonstrated, it is assumed that viral load reductions will be associated with longer term clinical benefit. Lamivudine, lobucavir, and adefovir lead to 2–4 log reductions in HBV viral load (by contrast, HIV viral load is reduced by 1–1.5 log, by lamivudine monotherapy, before the rapid emergence of resistance) and animal data suggest that BMS-200475 will also be a highly potent drug. Although these reductions are impressive, monotherapy rarely suppresses serum viral load to undetectable levels, as defined by the most sensitive commercial assay (current limit of detection 400 copies/ml). Combinations of nucleoside analogues demonstrate additive or synergistic antiviral effects in vitro, and we await similar data from clinical studies.

**Drug failure/resistance**

An increase in HBV viral load back towards baseline on lamivudine monotherapy, associated with mutations in the viral polymerase gene, occurs with a 1 year incidence of approximately 14% in chronic hepatitis, rising to around 40% at 2 years. A similar rate is observed in HIV/HBV coinfected patients. The incidence appears substantially higher, and resistance occurs more quickly, in liver transplant recipients receiving lamivudine before and after transplantation as prophylaxis against graft reinfection. All lamivudine resistant viruses described to date have a mutation at polymerase amino acid position 184 (M184V) (analogous to the 184 position in HIV reverse transcriptase that is also the locus for lamivudine resistance). HBV polymerase containing these mutations appears to have reduced inherent enzyme activity in vitro and some clinical data suggest that lamivudine resistance associated viral rebounds do not reach pretreatment levels of viraemia. Nevertheless, failure of prophylaxis in transplant recipients owing to drug resistance can lead to fatal hepatitis, and it is therefore premature to suggest that lamivudine resistant viruses are less pathogenic in vivo. Mathematical modelling of the growth characteristics of lamivudine resistant virus following transplantation suggests that these species pre-exist within the virus quasispecies. Resistance is more likely to emerge in patients with high pretreatment viral load, presumably reflecting a greater frequency of these pre-existing single or double mutation species. Emergence of resistance is therefore likely to be reduced by use of drug combinations that require multiple mutations within the viral polymerase to generate high level resistance. Of particular note is the observation that HBV polymerase containing the classic lamivudine resistance mutations retains sensitivity to the nucleotide analogue, adefovir. Similar data are observed for HIV, where viruses containing the M184V lamivudine resistance mutation demonstrate an increased susceptibility to adefovir. Clearly, the lamivudine/adefovir combination deserves study within the HBV setting. By contrast, lamivudine resistant HBV species that do not encode famciclovir resistance mutations rapidly develop cross resistance when famciclovir is added to the drug regimen (unpublished data). This illustrates the difficulty in predicting resistance patterns to combination therapies based on monotherapy resistance data, and the potential dangers of suboptimal sequential therapy, as has been gleaned from the study of HIV. A second determinant of emergence of resistant virus is the turnover of infected hepatocytes, since there is a requirement for such viruses to infect sufficient numbers of susceptible (uninfected) hepatocytes to become the majority species. Infected hepatocytes have an estimated half life of 10–100 days compared with 2 days for HIV infected CD4 cells, and this difference may explain why the time to emergence of lamivudine resistance is longer for HBV than for HIV during monotherapy. It also explains the rapid development of resistance following transplantation, whereby an uninfected liver is provided for reinfection with circulating resistant virus.

**Immune modulators and eradication of virus**

The majority of acute HBV infections in adults are “cleared,” in association with a vigorous cell mediated immune response targeted at infected hepatocytes. Such cytotoxic T lymphocyte responses are deficient in chronically infected individuals, although spontaneous or interferon induced resolution of infection (as may occur in up to 40% of selected patient groups) is associated with an increase in this factor. Thus, reduction in the large and long lasting infected hepatocyte population is most likely to be achieved by a combination of potent antiviral and immunostimulatory therapy. Parallels can again be drawn with HIV, for which the role of immune based therapies such as IL-2 to increase infected cell turnover in antiretroviral treated patients is being explored. Of interest, proliferative responses to HBV antigens are enhanced by lamivudine treatment, possibly related to a reduction in viral load. However, new immunostimulatory compounds in addition to antiviral agents will be required; it remains unclear how such combinations should be evaluated within different patient groups. Whether chronic HBV infection can be reliably controlled to the extent of “clearance” awaits the outcome of such trials.

Despite differences in the virology and dynamics of these two infections, many of the principles guiding HIV therapy are pertinent to HBV. Drug combinations, with or without...
immunostimulants, will be required to effectively suppress viral replication and reduce the risk of resistance. The benefits of long term nucleoside analogue therapy must also be balanced against potential drug toxicity, as tragically observed for fialuridine. Trials are required to identify optimal regimens in different patient groups, and at different stages of infection. It is likely that emergence of resistance to drug monotherapy will compromise subsequent antiviral responses, and we therefore suggest that monotherapy arms of clinical trials are no longer appropriate. These issues should also be carefully considered before initiating monotherapy in clinical practice. The history of HIV therapy teaches us that the evolution of HBV drug resistance should not be determined by the evolution of drug treatment options.

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New technologies, old challenges?

New technologies have the ability to transform the practice of medicine, including in the field of sexually transmitted infections. Diagnostic methods using more complex markers and DNA amplification techniques have the potential to reveal previously invisible infection. Genetic typing of causative organisms may facilitate epidemiological investigation, with the potential to map transmission through the population by providing a measure of genetic distance between pathogens. Genetic typing of the host will enhance our understanding of natural history and the range of pathogenic responses to infection. New techniques have already led to potentially revolutionary advances in therapy, vaccine development, and new methods for the prevention of sexual transmission including microbicides.

There is a danger of “biological reductionism” in some applications of new technologies; investigating molecular relations may be seen as less challenging than investigating social and sexual relationships that contribute to transmission and control of infection. The two disciplinary approaches should not, of course, be seen as competing, but rather complementary tools in the common endeavour of improving the health of the population.1 While workers on the front line of research ponder these complex questions, those on the front line of infection control and service delivery often have other concerns. Populations with the highest burden of infection frequently have the poorest access to existing, let alone new, diagnostic and treatment technologies. In recognition of this problem, Sexually Transmitted Infections devoted a whole supplement in 1998 to the “Syndromic approach to STD management”.5 This publication revealed that simple algorithms for diagnosis have proved to have poor validity and syndromic treatment, although potentially very effective, has been difficult to implement consistently. At best it will treat the minority of patients who are both symptomatic and present to healthcare facilities.

Can this gap be bridged? New technologies promise much to the practice of medicine, to the development of science, and to the control of infectious disease—for example, in the development of simple diagnostic tests and effective vaccines. They also promise substantial profits to those pharmaceutical companies that win the race for commercial applications. But will this simply deepen the ravine that separates those with access to resources and those without, or can the technologies be harnessed appropriately?2

Call for papers

This year editors from medical journals around the world have chosen to focus on the impact of new technologies in medicine. A number of journals will produce a special “Global theme issue” in 1999. Sexually Transmitted Infections, along with several journals from the BMJ Publishing Group, is inviting contributions for this issue. If you have original articles or commentaries that relate to the issues raised above, or more broadly related to new technologies in medicine, please submit them according to the usual instructions for authors.3 Papers will be subject to standard peer review, and we hope to include these articles in the December issue.
Anniversary year

Sexually Transmitted Infections is celebrating its 75th anniversary. We have marked the occasion by asking eminent sexually transmitted disease (STD) physicians across the globe to comment on articles which appeared in the journal in its two previous incarnations as British Journal of Venereology and Genitourinary Medicine, and which significantly changed their understanding or clinical practice. These will appear as a supplement later this year, finances permitting.

In this issue Richard Pattman inaugurates a new series “Clinical knots”, where we will invite experts to help us through problematic clinical and diagnostic issues. Subsequent articles in this series will discuss the management of HIV associated itchy maculopapular rash and recurrent or persistent problems such as warts, vulvovaginal candidosis, bacterial vaginosis, and non-gonococcal urethritis. We would welcome suggestions, both in terms of “knots” and authors.

Another series planned for later this year will be directed at those doing research in sexually transmitted infections. Everyone working in this field will have encountered problems that are specific to our specialty such as: What is a disease episode? What to do with repeat infections. What controls to use, and from what age band. What is successful contact tracing? How to use census data. Which deprivation indices are best for population studies? What is ethnicity? What are the limitations of clinic based data with regard to sampling and populations? How to define sexual activity in questionnaire investigations. Uses and limitations of structured interviews. What statistics package to buy. Use of decision analysis. Again we invite you to share with us the problems you encountered in your own researches.

Two further series are also in progress. Basic science for the clinician has already been launched. It aims to introduce clinicians to basic science research which underpins and elucidates common clinical practice. The other will be on tropical STDs edited by Moses Kapembwa. Review articles will address both the most advanced diagnostic tests and treatments available, but also “best practice” in resource-poor settings.

Last year we rejected one quarter of the papers submitted. The introduction of a hanging committee dramatically reduced rejection time to a mean of 18 days. Unfortunately we were less successful in reducing time to publication which was a median of 10 months. The delay was partly attributable to the reviewing process and partly to the time to revision by authors. Accepted manuscripts were normally published within 4 months.

The impact factor of Sexually Transmitted Infections continues to rise (fig 1). Despite the various shortcomings, funding bodies and policy makers in research are increasingly using this imperfect measure to influence their decision making. In 1994 the mean impact factor for 4400 biomedical journals was 1.6 and the median 0.66. With an impact factor of nearly 1.782 in 1997 Sexually Transmitted Infections (as Genitourinary Medicine) was well within the top 25%. Of course with the change in name confusion will set in.

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