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From the editorial board

This is the newsletter of the DFID* Knowledge Programme on HIV/AIDS and STIs. The Programme is funded by the Department for International Development, UK, and based at the London School of Hygiene and Tropical Medicine (LSHTM) and the Medical Research Council (MRC), Social and Public Health Sciences Unit (SPHSU), University of Glasgow. It has five Knowledge Areas: 1) Determinants of sexual behaviour; 2) Biological risk factors for HIV and STI transmission; 3) Factors affecting use and effectiveness of care and prevention services for HIV/AIDS and STIs; 4) Impact and cost-effectiveness of interventions against HIV and STIs; and 5) HIV/AIDS and STI prevention and care priorities and policies.

These newsletters provide a forum for the exchange of research within the Programme and introduce other relevant research from Programme members. They form a useful means to exchange information such as updates on projects underway, conferences, new grants, etc. Selected articles reflect the contents of our bi-annual scientific meetings.

Contributions from Programme members are invited. Please email comments and suggestions to: Tamsin.Kelk@lshtm.ac.uk. Also see the Programme's website at: http://www.lshtm.ac.uk/dfid/aids/

Philippe Mayaud, David Mabey, Graham Hart and Tamsin Kelk

In this issue

- We report on notable issues raised at the 16th Biennial meeting of the ISSTDR held in Amsterdam in July 2005. Reports are provided by Programme members who received Programme funding to attend.

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ISSTDR 2005: Re-Emerging STI: The Challenge

Introduction

The 16th Biennial Meeting of the International Society for Sexually Transmitted Disease Research took place in Amsterdam, The Netherlands, from 10 to 13 July 2005. The theme of the conference was "Re-emerging STI: the challenge" (http://www.isstdr.org).

In this newsletter, 7 members of the Knowledge Programme give their impressions of the conference, and highlight presentations they found of particular interest.

Re-emerging STI

Philippe Mayaud, CRU, LSHTM

The theme of the ISSTDR conference, *"Re-Emerging STI: The Challenge",* was particularly fitting, as the conference was for me the tale of two infectious agents (or diseases) currently causing epidemics of genital ulcerations in settings where previously each one would not have featured prominently.

Lymphogranuloma venereum (LGV) outbreaks in industrialised countries

LGV, a genital ulcerative disease (GUD) caused by serovars L1-L3 of *Chlamydia trachomatis*, has been a rare occurrence in industrialised countries since the mid-1960s. Therefore, it came as a shock when the report of a first large outbreak of anorectal LGV among men who have sex with men (MSM) in Amsterdam in 2003 [1] was quickly followed by an epidemic of similar reports from across Europe and North America [Martin MP-132; McLean MP-138; Mann J MP-140].

van der Laar [MP-201] described the epidemiology of the LGV outbreaks following the launch of an international surveillance alert through the European STI Surveillance Network in October 2004. Over 300 cases have been reported in Europe, mainly from The Netherlands [150 cases, van der Laar MW-201], France [142 cases, Herida MP-142] and the UK [Ward MW-205], with many cases identified retrospectively.

A notable epidemiological feature of these outbreaks was that most cases comprised Caucasian men belonging to large sexual networks associated with the sex party scene, and were not obviously linked with known endemic countries. Between 45-90% of these men were HIV-seropositive and presented high rates of co-infection with other STI (syphilis, gonorrhoea) or hepatitis C infection [van der Bij MP-137; McLean MP-138; Vandenbruane MP-139; Mann MP-140; McDonald MP-141]. Worryingly, a quarter of 11 recent LGV cases in Amsterdam had sex with both men and women, making transmission outside the MSM community possible [de Vries MW-203].

Recent developments of molecular diagnostic techniques for LGV have greatly facilitated thorough investigation of these outbreaks and will improve our knowledge of LGV epidemiology [Ballard MW-201]. It has been shown that all European outbreaks have been caused by serovar L2, and many of the isolated strains have exhibited a common mutation named L2b, already demonstrated in the original L2 strains from Amsterdam [Herida MP142]. However, Martin [MP-132] showed that the UK outbreak was not due to a single L2 strain, suggesting that multiple transmission networks are contributing to the outbreak.

Genital ulcers in developing countries: the increasing importance of Herpes

In contrast to industrialised nations, LGV has been endemic in several developing countries. The proportion of GUD that can be attributed to LGV in such settings varies from <1% to around 10%. The lack of specific diagnostic tools for LGV and the relatively poor degree of clinical suspicion for this condition, even in endemic countries, may have biased these estimates.

Since the development of the HIV epidemic in Africa, the

epidemiology of aetiologies of GUD has been changing. In general, the proportion of ulcers due to chancroid has decreased from 40–50% 10 years ago to 15% or less now, while HSV-2 has risen from 5–10% to 40% [2]. The prevalence of LGV, however, has remained stable and has not exceeded 5% of GUD, although a study from Durban, South Africa, reported a rising prevalence of LGV from 2% to 10% over a 10-year period [3]. Published work [4] and presentations by the same group [Sturm AW MP-133; Sturm PDJ MP-134] confirmed that prevalence of LGV may even be higher in Durban. In 276 patients presenting with GUD and/or genital/inguinal swellings, the authors identified LGV in ulcer specimens or lymph node aspirates in 20% of cases. They confirmed the already known limitations of specific micro-immunofluorescence (MIF) serology, which had only 25% sensitivity.

Elsewhere, studies of GUD patients have confirmed the increasing importance of *Herpes simplex* virus type 2 (HSV-2) as the predominant aetiological factor: in a study of 103 GU patients in Karnataka, India, HSV-2 was identified in 22% of men and 17% of women whilst only 1 case of *Treponema pallidum* (TP) and none of *Haemophilus ducreyi* (HD) were demonstrated, with 76% and 83% of men and women having no aetiology, respectively [Becker TP-13]. A study among commercial sex workers in Ibadan, Nigeria, showed that 20% had GUD and the most common aetiologies were HSV-2 (10%), followed by HD (6%), TP and LGV (4% each); LGV was not associated with HIV serostatus, whilst HSV-2, HD and TP were [Fayemiwo TP-123].

In Ghana and the Central African Republic, trials are underway to evaluate the impact on HIV and HSV shedding and ulcer healing rates of episodic treatment with acyclovir as a supplement to standard syndromic management of GUD. Baseline information from these trials includes data on ulcer aetiology, which again showed that HSV-2 dominates GU aetiologies (53%), whilst bacterial aetiologies have almost totally disappeared. HIV-positive women were significantly more likely to have HSV-2 ulcers, ulcers of longer duration, more ulcers and ulcers which take longer to heal [Gresenguet MO-605]. In a nested study, the authors described the clinical and epidemiological characteristics of 8 women with primary or first episode genital herpes (PGH), one of the first such African series [Mayaud TP-010]. In contrast to women with recurrent HSV-2 ulcers, women with PGH were more likely to have had a new partner in the past 3 months, to have short duration of infection before presentation and smaller size, blister-like ulcers; and were less likely to be HIV seropositive. Considering that such episodes could put women at increased risk of HIV acquisition, early treatment of such episodes may represent a useful strategy for HSV and HIV control.

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Performance of type-specific serological assays to detect anti-HSV-2 antibodies in various populations

Maria Claudia Nascimento, CRU, LSHTM

The study of HSV-2 infection has gained increasing importance because a number of epidemiologic studies have reported that previous infection with HSV-2 increases the risk of HIV infection. For example, in a meta-analysis of longitudinal studies, Freeman et al (MO-607) demonstrated that the risk of HIV infection is 3 times higher for male and female subjects who are HSV-2 infected compared with those who are HSV-2 uninfected. Furthermore, Freeman et al. (MO-606) found that between 34% and 38% of new HIV infections could be attributable to HSV-2 infection in 4 different cities in Kenya, Zambia, Cameroon and Benin.

Thus, the accurate diagnosis of type-specific HSV infection is of public health concern. The FDA has approved 3 type-specific diagnostic tests to detect anti-HSV-2 antibodies in adult populations: HerpeSelect® ELISA assay (Focus Technologies, Inc. [formerly MRL Diagnostics]), HerpeSelect Immunoblot (Focus Technologies) and POCkit rapid test (Diagnology Inc.). The use of new type-specific serological assays to detect anti-HSV-2 antibodies has been reviewed after controversial results with HerpeSelect® were found in sera samples from sub-Saharan Africa. Alternatively, Kalon® (Kalon Biologicals, UK) is a newer type-specific serological assay which has been accurate to detect anti-HSV-2 antibodies at lower cost in comparison with FDA-approved commercial ELISA assays [1].

During the ISSTDR, there were 4 poster presentations on the evaluation of HerpeSelect® to detect anti-HSV-2 antibodies in sera samples from Brazil (Nascimento TP 003), the US (Ashley-Morrow TP 004) and Africa (Legoff TP008; Delany TP 0011). In summary, the authors concluded that Kalon® is a sensitive and specific test to accurately detect HSV-2 infection at a lower cost, and the specificity of HerpeSelect® can be improved when the manufacturer's cut-off index is increased from 1.1 to 3.5.

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Male circumcision snippets

Richard White, CPS, LSHTM

Male circumcision has long been associated with lower STI and HIV rates in sub-Saharan Africa [1-3]. A number of studies presented at the ISSTDR conference further explored the role of male circumcision in STI and HIV transmission, in an atmosphere of unexpected excitement. The *Wall Street Journal,* that well known and trusted scientific source, had run a circumcision story just prior to the conference [4]. It reported that Bertran Auvert's circumcision trial in South Africa had been stopped prematurely. Not due to problems, but because circumcision had been shown to be so protective that it was deemed unethical not to immediately offer the intervention to the men in the comparison group. That was, if you believed the rumours… Could it be true that circumcision had been so effective at preventing HIV infection in a country with the most desperate need for effective intervention?

Any impact of circumcision on HIV incidence may be partly due to the protective effect of circumcision on other STI. Helen Weiss [MO-103] presented the first systematic review and meta-analyses of associations between circumcision and chancroid, syphilis and HSV-2. The results showed that circumcised males were at substantially reduced risk of chancroid (6 out of 7 studies, no meta-analysis performed) and syphilis (adjusted risk ratio (aRR) = 0.67, 95% CI 0.54–0.83). The association with HSV-2 was weaker, and of borderline significance (aRR = 0.88, 95% CI 0.77–1.01). In line with these findings, Bertran Auvert [TO-704] presented some very preliminary results from his circumcision trial in South Africa.

He found a non-significant but lower risk of HSV-2 incidence among recently circumcised males (aRR = 0.75, 0.52–1.08) in an intention-to-treat analysis.

Our team presented some results from our ongoing modelling project, set up to try to explain the differing HIV epidemics in 4 cities in East and West Africa [5]. In the two Eastern cities, Kisumu in Kenya and Ndola in Zambia, HIV has risen to much higher prevalences than in the Western cities, Cotonou in Benin and Yaounde in Cameroon. Despite modelling higher-risk sexual behaviour in the lower HIV prevalence Western cities, as measured empirically, by modelling the observed male circumcision rates in the 4 sites, and assuming that lack of circumcision doubled male susceptibility to HIV, syphilis and chancroid infection, we were able to fit the trend in HIV prevalence in the 4 sites well.

Further, by modelling counterfactual scenarios in which we varied the prevalence of male circumcision from that observed (Yaounde and Cotonou = 100%, Kisumu = 25%, and Ndola = 10%), we predicted that if the proportion of males circumcised in Ndola was 100%, rather than the measured 10%, HIV prevalence in 1997 in Ndola would have remained much lower, and at a similar prevalence to that observed in Yaounde. The converse was predicted for Yaounde. We concluded that circumcision may have had an important role in explaining the differing HIV epidemics across sub-Saharan Africa [5].

The rumours turned out to be true. Auvert's trial did show a strongly protective effect of circumcision on HIV incidence among young males in South Africa. Results of an intention-to-treat analysis presented subsequently show the incidence rate ratio was 0.40 (95% CI = 0.24–0.68) [6]. Needless to say, UNAIDS/WHO is advising caution in interpretation of the results, until results of the other two ongoing trials in Uganda and Kenya are reported. Nevertheless, this is a very exciting result.

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STI control and prevention in developing countries: ensuring effective interventions are implemented

Louise Knight, IDEU, LSHTM and NIMR, Mwanza, Tanzania

I was particularly interested in presentations on STI control and prevention in developing countries. The following is a summary of sessions with a focus on the theme of ensuring that effective interventions are implemented.

The Sunday sessions introduced the importance of understanding sexual networks and the epidemic phase in a population for successful STI prevention, the use of counter-factual modelling of the spread of HIV to help understand what would happen in the absence of interventions, and the challenges of evaluating a national prevention programme. The latter highlighted the need for multi-disciplinary collaboration to adopt alterative methods to evaluate such programmes.

The Monday session on 'STI prevention: the life course perspective' included presentations on: 1) **Resource allocation and programme evaluation**: on costs and benefits of social investments in safer sex and the importance of behavioural responses; 2) **Efficacy to effectiveness**: on the process by which providers adopt model interventions; 3) **Policy challenges**: on the evidence base for effective interventions including issues of cost-effectiveness and timeliness.

Tuesday's session on strategies for STI prevention and control included a presentation on eradication of chancroid. This summarised an approach for successful interventions: firstly knowing the baseline in a country, then to plan, do, assess and scale-up. Another presentation was on periodic presumptive treatment as a strategy to control STIs, which included hypothesized reasons for the lack of impact in example African studies. Factors included insufficient understanding of sexual networks and their dynamics, changing economics and insufficiently implemented or targeted interventions.

Wednesday's workshop on disease control prevention priorities for STIs and HIV in developing counties brought together some of the issues highlighted in the previous sessions, leaving us with key messages regarding prevention interventions. The presentation on "What has worked?" highlighted difficulties in quality STI service provision and reiterated that improvements would decrease prevalence and incidence of STIs. It was also presented that declines in STIs may be attributable to widespread interventions such as syndromic management and interventions in target groups. In summary some of the key messages were:

- **Development of prevention interventions**: The importance of understanding: (1) sexual network structures, cost effectiveness, the epidemic phase, different country settings, population and targeted interventions, behaviour responses, involvement of end users at an early stage, and (2) how all these factors interlink to inform tailored interventions.
- **Evaluation of prevention interventions**: (1) Use of modelling to understand what would happen in the absence of interventions and the impact of interventions that change risk behaviour; (2) Review what has worked and how this can be improved on by increased knowledge of factors mentioned above; (3) The importance of evaluation and of measuring effectiveness to inform future intervention planning.

Conference highlights

Mary Rusizoka, AMREF, Mwanza, Tanzania

The Mwanza HSV project team gave an oral presentation and presented 2 posters: (1) A randomized HSV2 suppressive treatment trial for HIV prevention, design, enrolment and follow-up [TO-703]; (2) Prevalence and risk factors for bacterial vaginosis in high risk women Tanzania [WP-122]; (3) Risk factors for HIV and HSV in high risk women Tanzania [TP-016].

It was a real challenge, as the conference theme itself says. Over 1000 scientists and researchers tried hard to explore it via numerous posters and oral presentations on the different research under way. I found the presentations presented by our AMREF team particularly exciting.

The following important issues were highlighted in the closing lectures:

1) The incidence and prevalence of STIs are high and increasing the disease burden on health services, communities and individuals.
2) Symptomatic and asymptomatic STIs cause serious complications to women, men, neonates and foetus.
3) STIs are a burden to national economies.
4) Social stigma and taboos still make control difficult.
5) STIs and HIV share the same transmission routes and thus the same risk behaviours and similar preventive strategies.
6) STIs increase HIV infectiousness, HIV viraemia and HIV shedding.

A breath of fresh air…

Peter Vickerman, HPU, LSHTM

My attendance of the ISSTDR conference was very fruitful. After attending the AIDS conference a number of times, it was a breath of fresh air to attend a smaller conference that was based much more on the science and epidemiology of STIs. It was quite a learning experience for me because of the range of research areas covered in the different sessions and because of the conversations I had with other STI researchers. Particular sessions I found very useful for my research included:

- **'Prevention strategies for STI and HIV prevention: what, where and when'**: There was a wealth of good presentations in this all-day symposium, mainly of a review nature, with many focusing on areas of modelling.
- **'Congenital syphilis'**: This was particularly useful for some research I am doing for WHO. The session from South Africa gave me some estimates for model parameters values that have been useful in that work. It also gave me some ideas for possible areas of additional research or extra analyses.
- **'New network theory and its implications for the prevention of STIs'**: Some of the modelling theory here was new to me and very insightful. It gave me some ideas for further research in modelling of HIV transmission in IDU populations. These have already been incorporated into a PhD scholarship submission to MRC – a collaborative project with IDU epidemiologists from Imperial College.

What have we learned from STI research in sub-Saharan Africa?

David Mabey, CRU, LSHTM

Africa has been in the news a lot this year, mostly for the wrong reasons. The press like to tell us about famines, wars and other disasters. They often forget to say that Africa is full of wonderful people, enjoying life, sometimes under difficult circumstances. In the field of STI research, we have learned more in the past 25 years from studies in Africa than from any other continent (with the possible exception of North America). In my closing address at the ISSTDR meeting, I summarised what we have learned in Africa, and tried to identify the reasons why research there has been so productive.

African researchers and their international collaborators have taught us:

- The value of syndromic management of STIs/RTIs
- - and its limitations
- How to diagnose and treat chancroid
- How to prevent gonococcal ophthalmia neonatorum
- How to prevent congenital syphilis
- How to control STIs in high risk groups
- The importance of STI control for HIV prevention
- The growing importance of *Herpes simplex* virus type 2 in facilitating HIV transmission.

Syndromic management of STIs was introduced in the primary health care programme in Zimbabwe in the 1970s, and promoted through the WHO by Ahmed Latif and Andre Meheus in particular. In the 1990s a number of evaluations of the WHO syndromic management flowcharts were conducted [1], nearly all of them in Africa. They confirmed that the flowcharts for genital ulcer disease and urethral discharge performed well in a variety of clinical settings, whereas the algorithm for vaginal discharge was less satisfactory in terms of sensitivity and specificity.

A series of definitive studies on the diagnosis and treatment of **chancroid** was published by collaborators from the Universities of Manitoba and Nairobi in the 1980s. Studies on the prevention and treatment of gonococcal **ophthalmia neonatorum** were also done at the University of Nairobi, in collaboration with the Institute of Tropical Medicine (ITM), Antwerp. They showed that single dose ceftriaxone is an effective treatment, and that 1% tetracycline ointment was as effective as the time-honoured silver nitrate method for prophylaxis [2–3]. A single dose of benzathine penicillin was shown to prevent adverse pregnancy outcomes due to **syphilis** in Mwanza, by researchers at the Tanzanian National Institute for Medical Research, in collaboration with the LSHTM [4].

A number of collaborative projects in Africa have shown that education and screening programmes can reduce the prevalence of STIs in sex workers and their clients. Particularly successful programmes have been run by the ITM and collaborating institutions in Kinshasa and Abidjan; by the University of Nairobi and collaborating institutions; and by the University of Laval, Canada and collaborators in Cotonou [5–8].

The work of the Nairobi group, in collaboration with the University of Manitoba, was among the first to flag up the role of curable STIs in facilitating HIV transmission. Three community-randomised intervention trials, all conducted by Lake Victoria, have looked at the effect of improved STI control programmes on the incidence of HIV infection. The first, in Mwanza (NIMR and LSHTM), showed that improving syndromic management in health centres reduced HIV incidence by 40%. The other two trials, in Uganda, failed to show an impact on HIV incidence (Makerere University, Johns Hopkins, University of Columbia; Uganda Virus Research Institute, LSHTM). Collaborative modelling studies by the groups responsible for the 3 trials suggested that this was because the HIV epidemic was more mature in Uganda, so that most transmission was between regular rather than casual partners. STIs play a less important role in these circumstances [9–11].

Sub-Saharan Africa has been at the forefront of STI research for the past two decades. Successful research has depended on a few inspirational individuals, on long term and carefully nurtured partnerships and collaborations, and on the willingness of African research groups and their collaborators to share their methodology and results.

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Publications

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