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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. Initially, the selected articles reflect the contents of our bi-annual scientific meetings in London (or Glasgow). 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/

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In this issue

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Microbicides

Introduction

The global HIV pandemic continues to expand, the total number infected increasing from 35 million in 2001 to 40 million in 2004. Of 5 million new HIV infections in 2004, an estimated 3.1 million occurred in sub-Saharan Africa and there were 2.3 million deaths from HIV in this region. Most HIV infections in Africa are due to heterosexual transmission, and women suffer disproportionately, with 1.3 women infected for each infected man.

While much effort is rightly being put into extending access to antiretroviral treatment in Africa and other developing regions, primary prevention of HIV infection remains an urgent public health priority. Consistent condom use offers effective protection from heterosexually acquired HIV, but women are not always able to negotiate condom use, particularly in their primary partnerships. There is an urgent need for preventive methods that women can use to protect themselves.

Vaginal microbicides are being developed in response to this need. These are products in the form of gels, creams, foams or films that women can use before sex and which are designed to prevent HIV infection (and possibly other STIs) either by forming a physical barrier to the virus, by disrupting or destroying the virus before it infects the host, or by blocking entry of the virus into host cells.

Initial research focused on nonoxynol-9 (N-9), a detergent chemical used for many years as a contraceptive lubricant on condoms. Trials were carried out in Africa and elsewhere, but unfortunately demonstrated unacceptable levels of toxicity. A systematic review of these trials showed a non-significant increase in HIV incidence and a significant increase in genital lesions. These results have emphasised the importance of finding products with a more favourable toxicity profile. Several products are coming through the pipeline, and at least four are now entering Phase III trials.

Working with international and national partners, members of the Knowledge Programme are working on many aspects of microbicide research, including: design and implementation of a Phase III trial of one microbicide product (MDP, described below); modelling analyses of the potential impact of an efficacious microbicide in different settings (including the analysis from Karnataka presented below); analyses of the potential changes in condom use that could occur following microbicide introduction without increasing HIV risk; economic analyses of the potential costs of widespread microbicide distribution and the role of different methods of distribution; and social science research on microbicide acceptability and to support Phase III trials (including work on coital diaries presented below).

Microbicides Development Programme

The Microbicides Development Programme (MDP) was set up 3 years ago supported by a grant of £16 million from DFID. MDP is a partnership of Northern and Southern institutions. It is coordinated centrally by the MRC Clinical Trials Unit and Imperial College in London, but LSHTM is also closely involved, and other collaborators include the University of Southampton, the MRC Social and Public Health Sciences Unit in Glasgow and research institutions in Uganda, South Africa, Zambia and Tanzania. The primary objective of MDP is to carry out a Phase III trial of a candidate microbicide among women in Africa. Additional objectives are to carry out laboratory, pre-clinical and Phase I/II safety studies of new

products, and research on the implementation and marketing of potential microbicides through work on mathematical modelling, health economics and behavioural science.

The field trial

Focusing on the field trial, MDP has spent the past 2–3 years establishing six field sites in Africa. A multicentre study will be needed to accumulate sufficient person-years of observation to obtain reliable results on efficacy, given that incidence rates of HIV are relatively low even in highly endemic populations. A study spread over several countries also helps to ensure generalisability of the findings. Of the field sites, three are in South Africa (at the Wellcome Trust Africa Centre in KwaZulu Natal, the Reproductive Health and HIV Research Unit in Johannesburg, and the South African MRC in Durban), one in Zambia (University Teaching Hospital, Lusaka), one in Uganda (UVRI/MRC Research Programme on AIDS) and one in Tanzania (LSHTM/NIMR/AMREF Collaborative Projects, Mwanza). LSHTM is directly involved in the field site in Mwanza (the Project Leader, Andrew Vallely, is a member of School staff) and we collaborate with the groups in Johannesburg and Uganda. Richard Hayes is also playing a role in the central coordination of the trial with colleagues at the Clinical Trials Unit.

Feasibility studies have been carried out in these six sites to evaluate whether they are suitable to carry out the Phase III trial. These have established how many women can be recruited from the selected study populations, what proportions can be successfully followed up, and what are the incidence and prevalence of HIV and other STIs. Different study populations have been recruited in different sites, including women attending outpatient and family planning clinics in South Africa, women living on a sugar plantation in Zambia, women working in bars, guesthouses and other food and recreational facilities in Mwanza, and women in HIV-discordant partnerships in Uganda. Annual HIV incidence was 4% or above, and follow-up rates after 9–12 months were around 70–80%. On the basis of these data, it has been estimated that we need to recruit around 12,000 HIV-negative women and follow them up for at least 9 months to have sufficient power to detect a 35% reduction in HIV incidence. Steps are being taken to add extra sites in Swaziland and Cameroon so that additional women can be recruited.

We have just heard that DFID and the MRC have awarded an additional £26 million so that the MDP trial can be successfully completed. The trial should now start recruitment in the next 3 months, and will be a 3-arm trial comparing two alternative doses of the microbicide Pro2000 with a placebo gel. This will be the largest trial of a microbicide product carried out anywhere in the world. Results should be available in 2008–9, and if the gel is found to be effective this will be a major step forward for HIV prevention efforts.

Richard Hayes
Infectious Diseases Epidemiology Unit, LSHTM

The potential impact of microbicides in Bagalkot District, Karnataka, India: model projections

Background

Much of the international debate on microbicides has focused on their importance in sub-Saharan Africa. There has been less discussion of their potential role in settings where the HIV epidemic is less generalised. After South Africa, India has the highest number of people living with HIV. The National AIDS Control Organisation (NACO) estimates that 5.1 million people were living with HIV in India in 2003. As part of a larger collaborative project between LSHTM, the Global Campaign on Microbicides, and International Family Health, mathematical modelling analysis was used to explore whether a partially effective microbicide could potentially impact on HIV transmission in an Indian setting. For the analysis we consider the impact of a microbicide that is made widely accessible in the urban areas of three sub-districts within Bagalkot District, in the southern Indian State of Karnataka – a setting where the HIV epidemic is starting to become generalised, with an estimated 2% of the general population being HIV infected.

Methods

Behavioural research suggests that, in this setting, commercial and casual sex are commonly reported by men, and that some groups have concurrent sexual partnerships, with some married men having other partners, and over a third of sex workers being married or having other non-commercial partners. Sex workers report very high levels of condom use with their last client (90%), but use is much lower in marital partnerships, with 4% of males reporting using a condom at last sex with their wife.

The impact of microbicide use was simulated using a dynamic mathematical model and site-specific data. The model simulates HIV and STI transmission between sex workers and their clients, and from sex workers and clients to their non-commercial sex partners. The model is used to project how HIV transmission may change over 4 years if an efficacious microbicide was made accessible to 75% of sex workers, clients or non-commercial partners of either. The baseline scenario considers the impact of a 40% HIV and STI efficacious microbicide (assuming that they are used in 90% of commercial sex acts, 70% of non-condom-protected sex acts between sex workers and their non-commercial partners, and 50% of non-condom-protected sex acts between clients and their non-commercial partners). Microbicide users are assumed to reduce their level of condom use by 5%.

Results

In this setting, for the specific baseline assumptions about microbicide distribution and use:

- A 40% HIV and STI efficacious microbicide would avert 18% of the expected HIV infections – mostly averting infections among clients and their non-commercial sexual partners;
- A 60% HIV and STI efficacious microbicide would avert 35% of expected HIV infections – almost twice the impact of a 40% efficacious microbicide.

Microbicides reduce the extent to which the non-commercial partners of clients become infected both directly (by their own use of microbicides) and indirectly (by reducing the rate at which clients become infected). Reductions in condom use following microbicide introduction – termed 'condom migration' – will primarily be a concern if sex workers are using condoms with very high consistency (90%), microbicide efficacy is low (40%) and microbicide use is low (50% of non-condom-protected sex acts).

Conclusions

Microbicides could be an important addition to current HIV prevention options in India. In settings such as Karnataka, where HIV is largely concentrated in the most vulnerable populations, microbicide use could help reduce transmission to the wider population. If there is little condom migration then, even when condom use in commercial sex is high, microbicides used as a fall-back to condoms with commercial and non-commercial partners could have a substantial impact on HIV transmission, particularly among clients and their non-commercial partners. Condom migration could be a concern among groups who are able to use condoms with high levels of consistency, such as those engaging in

commercial sex, particularly if microbicide efficacy and uptake are low. The impact of microbicides will depend upon the extent to which women find them accessible, and easy and convenient to use consistently.

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The reliability of coital diaries in collecting sexual behaviour data in a microbicides trial feasibility study in Tanzania

Introduction

Coital diaries (CDs) have supposed advantages in researching sexual behaviour, such as reductions in recall and social acceptability bias. Very few studies have used them in developing countries, where they may have advantages with less literate populations. CD studies in developing countries may require higher levels of face-to-face contact with researchers than in Northern countries, given less access to phones and postal services and different norms of social interaction. This study explored the reliability of CDs compared with questionnaires using face-to-face interviews, and also compared reporting patterns according to levels of support and interaction with researchers.

Background

A feasibility study was carried out in Mwanza, Tanzania, to explore whether women at high risk of HIV were a suitable study population for clinical trials of vaginal microbicides. Around 1500 women in Mwanza City, who worked in bars, guesthouses, local brew shops, food or recreational facilities, were enrolled over a 14-month period between August 2002 and September 2003. Among the objectives was to pilot sexual behaviour collection methods, including CDs that were developed specifically for Mwanza. Initially, five different designs of CD were pre-tested with 35 women selected from the feasibility study cohort, in order to assess the acceptability of coital diaries, and to provide information on diary type preferences. This revealed that CDs were acceptable to study participants, and those that were pictorial only were easier to understand than those using words and pictures.

Coital diary study methods

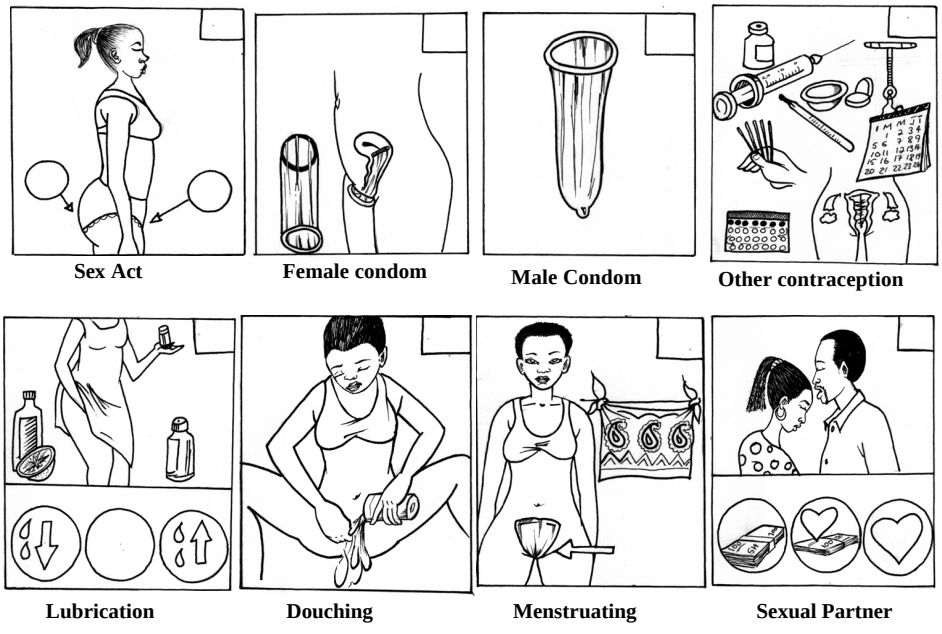
Following the pre-test, we explored the reliability of CDs in measuring sexual behaviour and assessed the level of support that women need from researchers to achieve reliable data. In this study, 150 women were randomly selected from the feasibility study cohort following stratification by the geographical ward in which they worked. Weekly CDs were provided to all the study participants to complete on a daily basis over a 4-week period. The CD used was a modified version of the most acceptable diary in the pre-test. It was spiral bound, approximately a quarter A4 size (to fit into a pocket or handbag), and contained seven data entry sheets for each day of the week, a laminated information sheet and diagram sheet with explanations for each picture. All diary booklets and instructions were translated and back translated into Kiswahili before production. Each page contained pictures (see below) depicting different sexual behaviours including vaginal or anal sex act, condom use, contraceptive use, lubrication, douching, sex during menstruation and type of sexual partner (regular partner, irregular partner or partner for gifts or money only), with tick boxes for women to record any of these sexual behaviours on a daily basis up to four times.

The women were randomly allocated to three groups, each provided with different levels of support by the researchers. All the women received a scheduled visit from a fieldworker at their home or facility on a weekly basis for 4 weeks, during which the CD for the previous week was collected and the CD for the following week was delivered. At these visits, those with medium and intensive support were given time to discuss any concerns. Those with intensive support received an extra, unscheduled visit each week, during which the woman's concerns or questions could also be discussed. Women who received medium and intensive support were also administered a recall questionnaire at the end of each week, which collected sexual behaviour information for the previous week (process evaluation – PE). All the women were administered a recall questionnaire at the end of the 4 weeks, which collected sexual behaviour information for the whole period (exit interview – EI).

Study findings

The findings showed a significantly higher number of reported vaginal sex acts on CDs than on either type of recall

Coital diary pictures depicting sexual behaviour with tick boxes



questionnaire, both for the 4-week period as a whole and for individual weeks. On average over the 4 weeks the women reported 13 sex acts in the CDs compared with 10 at the PE and 8 at the EI. The findings also revealed that less socially acceptable behaviours, such as male condom use (38% compared with 26%) and sex with an irregular partner (14% compared with 6%) were reported by more respondents on the CD than on the EI, but there were no significant differences in such reporting between the CD and the PE. However, the number of respondents reporting vaginal sex at all was not affected by data collection method.

These findings can be interpreted in two main ways. First, respondents are more willing to disclose higher numbers of sexual acts on CDs completed in private than at face-to-face interviews. Second, proximity to time of the act itself makes CDs more accurate in picking up each additional sexual act. This seems to be confirmed by the fact that there were fewer differences between the CD and the weekly PE data than between the CD and the EI completed at the end of 4 weeks. The wording of questions on the PE and EI was identical (apart from reference periods) so the discrepancies between recall methods were not associated with question design.

The findings also revealed that whilst higher levels of support appear not to affect frequencies of sexual acts reported in CDs, levels of support impacted on numbers of women reporting sex at all (65% minimum, 79% medium and 90% intensive reported at least one sex act). Higher levels of support also impacted on reporting at the EI, being associated with higher reported: experience of vaginal sex, frequencies of sex, douching and sex with an irregular partner. These findings suggest that presentation bias had more influence on reporting patterns for the face-to-face interviews than for the CD self-completion method.

For vaginal sex and sex in exchange for money or gifts, the disparity in reported frequencies between CDs and exit interviews fell as the level of support grew. Higher levels of support resulted in higher inter-method reliability.

Conclusion

As biological or observational confirmation is not possible, there is no 'gold standard' to show that CDs are more accurate than the recall methods. Our *a priori* assumption was that higher reported frequencies of sensitive or socially stigmatised activities are more accurate. Based on this assumption, CDs are a more accurate method than recall methods for collecting sexual behaviour data among food and recreational facility workers in Mwanza.

Intensive support appears to have built up trust towards the research team and to have encouraged higher reporting in face-to-face interviews, in terms of both frequency and number of people reporting. Higher levels of support improved consistency in reporting between data collection methods. The implementation of CD studies should therefore be accompanied by intensive support from fieldworkers, involving a weekly scheduled visit to check their responses using a questionnaire and an unscheduled visit during the week to help respondents with any concerns or problems in completing the diary.

Thus we conclude that it is acceptable and feasible to use CDs to collect relatively reliable sexual behaviour data.

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Useful websites

Microbicides Development Programme:
http://www.mdp.mrc.ac.uk/

Global Campaign for Microbicides:
http://www.global-campaign.org/

Alliance for Microbicide Development:
http://www.microbicide.org/

International Partnership for Microbicides:
http://www.ipm-microbicides.org/

Selected New Publications

Foss A, Watts C, Vickerman P, Heise L (2004) Condoms and prevention of HIV. *BMJ* 329: 185–6.

Korenromp EL, White RG, Orroth KK, Bakker R, Kamali A, Serwadda D, Gray RH, Grosskurth H, Habbema JD, Hayes RJ (2005) Determinants of the impact of sexually transmitted infection treatment on prevention of HIV infection: a synthesis of evidence from the Mwanza, Rakai, and Masaka intervention trials. *J Infect Dis* 191 (Suppl 1): S168–78.

Mayaud P, Mabey D (2004) Approaches to the control of sexually transmitted infections in developing countries: old problems and modern challenges. *Sex Transm Infect* 80: 174–82.

Nascimento MC, Wilder N, Pannuti CS, Weiss HA, Mayaud P (2005) Molecular characterization of Kaposi's sarcoma associated herpesvirus (KSHV) from patients with AIDS-associated Kaposi's sarcoma in Sao Paulo, Brazil. *J Clin Virol* 33: 52–9.

Plummer ML, Ross DA, Wight D, Changalucha J, Mshana G, Wamoyi J, Todd J, Anemona A, Mosha FF, Obasi A, Hayes R (2004) "A bit more truthful": The validity of adolescent sexual behaviour data collected in rural northern Tanzania using five methods. *Sex Transm Infect* 80 (Suppl 2): ii49–56.

A more extensive list of publications is available on our website: http://www.lshtm.ac.uk/dfid/aids/

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