Challenges in the conduct of vaginal microbicide effectiveness trials in the developing world

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Conducting a phase III trial of a vaginal microbicide in a developing country poses several important and complex ethical challenges. As part of a process to bridge the gap between ethical theory and practice, we share our experiences in performing a phase III trial of Col 1492 (Advantage S) among female sex workers at four sites worldwide; Durban, Abidjan, Cotonou and Hat Yai. The ethical challenges included: (i) difficulties in obtaining informed consent. Participants were unable to grasp the concepts of a clinical trial for several weeks to months. In Cotonou, 30% of the women did not know the gel was tested for HIV prevention. Only 25% understood what a placebo was. In Durban, 70% of the women did not fully understand the study after 3 months; (ii) in sustaining the use of known HIV prevention strategies. Participants at the Durban site had difficulty in sustaining condom use due to financial and client preferences. Sex without condoms was worth more ($20) than sex with condoms ($10); (iii) in maintaining the confidentiality of the subject's HIV status. Novel approaches such as role plays and emphasis on other exclusion criteria were needed to maintain the confidentiality of women not included in the trial due to their HIV status; (iv) in providing care and support to the subjects who became infected with HIV during the trial. Women could only be offered routine sexually transmitted disease treatment and counselling. Anti-retrovirals were not offered. The successes and failures of the solutions attempted are described.

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Introduction

A number of potential microbicides have reached the stage of human clinical trials to assess their tolerance, preliminary safety and acceptance (phase I), expanded safety, acceptability and preliminary effectiveness (phase II) and effectiveness (phase III). Whereas phase I trials are usually conducted in the country where the microbicide was developed (i.e. industrialized countries), efficiency considerations dictate that some phase II and all phase III trials be conducted among women in the developing world, where the incidence rates of HIV and other sexually transmitted diseases (STDs) are higher.

The United Nations Joint programme on AIDS sponsored a multicentre trial of a vaginal microbicide COL 1492 (Advantage S; Columbia Laboratories, Paris, France) in the prevention of male to female transmission of HIV and other STDs in female sex workers.

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The study was conducted at four sites worldwide: Durban (South Africa), Cotonou (Benin), Hat Yai (Thailand) and Abidjan (Côte d'Ivoire).

In Durban, the women were recruited from truck stops along the main trucking route between the port city of Durban and the commercial capital Johannesburg. They were recruited using participatory methods, by using one sex worker at each truck stop as a community liaison person. Details of the recruitment procedure are described elsewhere [1]. Most women were Zulu speaking and were migrants from rural areas in the province of Kwazulu-Natal. They travelled every month to Durban (300 Km) for their clinic visit. A total of 198 women were enrolled in the study.

In contrast, women in Cotonou were recruited from a clinic dedicated to female sex workers at a primary health care centre in the heart of the city. Most sex workers at this site were foreigners, mainly from Nigeria, Ghana and Togo. Only 15% were Beninese. A total of 235 women were recruited in the study.

In Thailand, Thai sex workers were recruited from a STD clinic located in the city of Songkla, in the south of Thailand. The clients were fishermen and blue collar workers. The women often worked in brothels, bars and restaurants. A total of 194 women participated in the study.

Women in Abidjan were recruited from a confidential clinic for female sex workers and their partners, which has offered diagnosis and treatment for STDs since 1992. Women were contacted by peer health educators and through group health education sessions. The majority of the women were Nigerians. A total of 129 women were recruited into the study.

This article discusses some of the practical difficulties we have encountered in implementing a phase III protocol in developing countries, with special reference to informed consent, condom promotion and care and support for HIV-positive participants. Our aim is to outline the strategies developed by us to overcome some of the obstacles and ethical dilemmas faced by many investigators, in the hope of bridging the gap between theory and practice in vaginal microbicide clinical trials.

Informed consent

Trial participants are required to sign an informed consent form after receiving detailed information on the study aims, methods, anticipated benefits, potential hazards, discomfort, and the voluntary nature of participation in the trial [2]. However, in practice, obtaining truly informed consent was difficult to achieve. Despite extensive counselling and explanation of the study, some of the study subjects at all sites did not fully understand the details of the study procedures and the full implications of study participation when the informed consent was initially administered.

At the Durban site, assessment of the women's knowledge of the study and its procedures at 3 months revealed that up to 70% of the women did not understand the study fully. While many (90%) understood that there were two types of products, namely placebo and experimental product, and that they had a 50% chance of receiving either, data from the acceptability questionnaire suggested that most (98%) did not appreciate that the potential effect of each of the two products against HIV and STDs might differ. The most frequent misconception was that the gels, placebo and experimental, protected them from STDs. For example, when women were asked for the reason why they liked the gel, most responded that the gel they were allocated protected them from STDs. This belief had further credence because women in both arms of the study experienced fewer symptoms of STD (such as vaginal discharge and lower abdominal pain) since their enrolment in the trial, and this was attributed to the gel rather than to their increased condom use or the STD syndromic treatment they received at every study visit. Similar experiences were reported from the other two sites.

To overcome the literacy problems in Durban, more Zulu-speaking staff (counsellors and translators) were employed to provide longer, more detailed and repeated counselling to the subjects. The liaison persons were trained to explain scientific terms such as 'placebo', 'randomization' and 'double-blind' in several different ways. For example, we explained that if the women had a headache they could either be randomized to receive an aspirin or a vitamin tablet, which looks similar to aspirin. The aspirin will have an effect on the headache but the vitamin tablet will not. In addition, we used role-plays to determine the women's understanding of the informed consent form. The women were asked to obtain informed consent from the study staff. They were asked to explain the study procedures, placebo versus active product, the purpose of the HIV test and speculum examination etc.

A study was conducted at the Cotonou site to assess the internalization of the contents of informed consent and to evaluate a field intervention aiming at increasing the women's understanding of the study. Data were collected on a subset of the cohort by field workers by means of a questionnaire and after administration of the informed consent form. At the first visit, 58.1% of the women did not remember the name of the gel under study; 30% of the women did not fully understand that

the gel was being tested to prevent HIV and STD; only 25% of the women could understand what a placebo was and 35% understood the importance of remembering their study and randomization number, which identified the gel they were receiving. Forty-seven per cent did not know why the doctor was requesting to use the gel and a condom during sexual intercourse. Of the women, 48.5% had completed primary level or less (6 years or less) and low education was associated with poor understanding. The intervention of reiterating the informed consent procedure at each visit was effective (although not 100%) in increasing understanding. At the fifth follow-up (5 months later), 82.5% of the women were able to explain the notion of a placebo and 85.4% knew the name of the gel.

In Thailand, it was initially believed that the information in the informed consent form was understood. However, testing of the women's knowledge by the study co-ordinator revealed that women did not understand many aspects of the trial. The study team set up colourful charts with graphic presentations to explain the trial concepts. This method proved to be successful.

In Abidjan, the informed consent procedure was conducted twice at enrolment and thereafter at every visit. Unfortunately the women's understanding of different issues was not evaluated.

Condom promotion

The study protocol stated that the subjects should be encouraged to use condoms during each sexual act, in keeping with the Council for International Organizations of Medical Sciences guideline [3]. At baseline, prior to screening for the trial, a questionnaire survey showed that condom use at the Durban site was low; on average about 25% of sexual acts were protected by condoms [1]. In contrast, condom use with clients was already high at the other centres, 70% in Cotonou, 95% in Hat Yai and 80% in Abidjan.

In order to strengthen condom use in Durban, the subjects were asked to attend a workshop on prevention methods for HIV and STD prior to trial admission. Despite these efforts, post-enrolment increases in condom use were seldom ($< 50\%$ of sexual acts) sustained. Although condom use increased from $< 25\%$ to 50%, one of the major problems in sustaining this was condom negotiation. Face-to-face interviews with sex workers suggested that financial and client preference resulted in poor condom use. Clients perceive condoms as barriers to sexual pleasure and therefore pay less for vaginal or anal sex when condoms are used. Unprotected vaginal sex commands a price of Rand 120 (US$20) whereas vaginal sex with a condom is worth only Rand 60 (US$10). In the context of sex work at the truck stops, our efforts to maintain sustained high levels of condom use have had only limited success. More effort, well beyond that available in a trial, is needed to organize these women (who compete with each other for clients on a daily basis) so that they can set prices and refuse clients who will not use condoms.

Confidentiality of HIV test results at baseline

Because HIV seroconversion was the study's primary endpoint, only HIV-negative women were included in the study. At baseline, all potential participants were tested for HIV infection in the strictest confidence with pre- and post-test counselling.

In practice, it was difficult to maintain the confidentiality of HIV results at screening in some centres. Each site had to develop strategies to overcome this dilemma.

In Durban, because the women in our cohort lived and worked together and knew who was included in the trial, the issue of confidentiality posed as a major problem. As there were several exclusion criteria in addition to HIV positivity (e.g. wanting to become pregnant, pregnancy, genital abnormality etc.) the approach of saying that there were several criteria for eligibility and that a participant had to satisfy all of them to be included seemed best. For example, a women could tell her peers that 'her vagina was unhealthy', 'she intends to have a baby soon' etc. In addition, role-plays were used to help HIV-positive women to discuss their exclusion from the study. The women were counselled individually on how to deal with the issue of confidentiality. This strategy appears to have been successful as none of the women have reported any violence or stigmatization.

In Cotonou, only women who were prepared to receive their results were enrolled (this was not done at the other centres). As the physician individually counselled the women in Cotonou, and as the women were from neighbouring countries, excluding HIV-positive women from the study was not a major problem. In addition, as in Durban, women were informed about the other exclusion criteria used in the study and were counselled on how to deal with the issue of confidentiality.

In Thailand, the HIV prevalence was lower (11.4%). Women who tested HIV positive often returned back to their home town mainly to the north and north-east

of the country thus restricting their interaction with other participants in the trial.

In Abidjan, the decision was made to include HIV-positive women in the study (external funding had to be sought for this). In this way all women screened could be enrolled if they satisfied the other inclusion criteria.

Care and support for HIV seroconverters

Besides the women found to be HIV-positive on pre-enrolment screening, women who seroconverted during the study also needed support and assistance to deal with their HIV status and maintain their confidentiality. Experiences in providing post-test counselling to HIV-positive women on screening was totally different to those who seroconverted during the trial.

For women who seroconverted during the trial in Durban, the HIV results were not divulged until after at least two consecutive visits with a positive test result. During this time, general counselling was conducted to determine the preparedness of a woman to accept a HIV-positive result. This was achieved by exploring the support networks accessible to the woman, whether assistance was needed to disclose her status to her partner and family members and her attitude to safe sex. HIV status was not disclosed to women who did not want to know, but the implications of being HIV infected were continually emphasised.

In keeping with the protocol, women who seroconverted during the trial were not required to leave the study. All HIV-positive women received the routinely available standard of care at KwaZulu-Natal Provincial Hospitals. This did not include antiretroviral drugs.

In Cotonou, the women were informed of their HIV status after every HIV test. As the women were told at the outset that their HIV status would be revealed to them, the investigators did not experience similar problems as in other centres. Further, the women were offered routine STD care and counselling.

Thailand had minimal seroconversions. These women were given conventional management such as tuberculosis prophylaxis and were offered a choice of a permanent or long-term contraception (Norplant). Antiretroviral agents were not provided. The women left the study once they seroconverted.

In Abidjan, there were very few women who seroconverted. Despite intensive counselling, the women left the study as soon as they became aware of their infection. All HIV positive women were referred to other organisations of HIV positive people. These organisations could help the women to get access to antiretroviral therapy at a reduced rate.

Discussion

Our findings suggest that informed consent is not a once-off event, but an ongoing process. It may take several weeks or even months before the women understand the concepts of a clinical trial. We recommend that future trials have a short 'run-in' period prior to implementation of the study to allow for difficulties in the understanding of the trial procedures. In this way the participants will have enough time to think and consult their peers before they agree to enrol in the trial. In addition, women should be asked of their knowledge of the study, their reasons for participation and whether their participation was voluntary.

Current Good Clinical Practice [2] guidelines do not provide such information to investigators. Our study clearly suggests that the mechanism and guidelines of achieving informed consent need to be extensively revised.

Provision of routine STD care for participants recruited from non-clinic facilities such as in Durban, poses a major dilemma. Involvement of a local HIV prevention and care organization in providing additional ongoing HIV prevention, education and counselling at a hospital closer to the truck stop has not been very successful. The women were reluctant to go to these clinics for fear of being stigmatized. One of the difficulties in actively promoting condom use in a population reluctant to use it is that the women are likely to lie to the study members about their condom use.

Partnerships with HIV prevention organizations need to be fostered prior to and after the study, to avoid the ethical dilemma faced by the investigators who may have limited facilities for intensive counselling necessary in high HIV prevalence areas. Further, if the participants become familiar with the representatives of external organizations, the transition from one caregiver to another would not be difficult.

Dealing with issues of confidentiality was a learning curve for all of us. As researchers we need to take cognisance of the impact of HIV testing on the individual and her community, specifically if we are going to draw the population under study from the same geographic location or community.

Disclosure of the HIV-positive result to a trial partici-

pant takes time and can only be done if the participant wishes to know her HIV status. Our findings suggest that it is not always possible to disclose an individual's HIV status immediately. Many women felt that as treatment for HIV was not affordable to them, life would be less stressful not knowing their results. Like informed consent, it is a process to prepare the women to receive a positive result. As effectiveness clinical trials are now moving away from high risk individuals such as sex workers to women who may not have many sexual partners, community awareness and participation in clinical trials will be essential. Lack of preparedness in the community being investigated may result in tension and uncertainties for both the investigators and trial participants.

Conclusion

The HIV epidemic has thrown up many new challenges in the ethical conduct of research. Cultures, traditions, and beliefs from different countries worldwide, have thus in a unique way been brought into an international forum. A critical mass of scientists in the developing countries is urgently needed to foster partnerships in research with the developed countries at all levels. Further, investigators from resource-poor countries should be encouraged to become involved in biomedical research ethical guidelines in order to close the gap in standards between countries. Appropriate guidelines for research in resource poor countries are limited and need to be developed together with a system for implementing them.

This multicentre trial has underscored the difficulties in standardizing non-clinical procedures. Vigilant co-ordination was required to strive for scientific excellence without compromising traditions and beliefs at various centres world-wide. Since phase III vaginal microbicide trials are just beginning, with only one study having been completed to date [4], this is a good opportunity for us to reflect on the challenges we have faced and the approaches and solutions we have tried. One of the main lessons learned is that there needs to be ongoing vigilance for the ethical conduct of microbicide trials and that there is a need for a close partnership between the investigators, local health service providers, HIV support organizations and the community for practical implementation of the trial. These partnerships serve as the building blocks that bridge the gap between scientific knowledge, ethical standards and practice.

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Appendix

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