Preventing for efficacy trials of vaginal microbicides in Indian women

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Vaginal microbicides are topical compounds that are expected to protect against vaginal transmission of HIV and other sexually transmitted pathogens. A large number of compounds are being evaluated as possible microbicides. Considering the spread of the HIV epidemic among women in India, clinical trials on microbicides starting from the Phase I safety and acceptability studies to Phase III efficacy trials are important. Conducting efficacy trials is a major endeavor and this review discusses challenges and issues and the preparatory steps to make such efficacy trials possible in India.

Key words: Efficacy trials - vaginal microbicides

The human immunodeficiency virus (HIV) epidemic continues to spread worldwide, mainly in the developing countries in spite of two decades of preventive efforts. According to the estimates of UNAIDS, 42 million persons were living with HIV infection by the end of 2003 and women accounted for nearly 50 per cent of the total global HIV burden. Heterosexual transmission is the dominant route of HIV spread in the developing world. Women are more vulnerable to HIV infection than men because of specific biological and socio-demographic factors. Many women experience difficulties in negotiating the use of male condoms and trusting their partners’ fidelity. Women desperately need protection against HIV through female controlled-options, such as microbicides and female condoms. Microbicides are topical compounds that could render protection against vaginal or anal transmission of HIV and other sexually transmitted pathogens. Microbicides might be available in the form of a cream, gel, foam, etc. Preferably these should be undetectable by the partner and ideally should not reduce the sexual pleasure. Some microbicides might not have contraceptive properties so that women and couples using such products can protect themselves against sexually transmitted infections (STIs) and still have children.

Essential early steps in development of vaginal microbicides include the determination of antiviral activity, cytotoxicity, mechanism of action, pathways to resistance, cross-resistance to approved drugs, effects on vaginal microflora and pathogens that cause sexually transmitted diseases. Inflammation of the female reproductive tract increases susceptibility to HIV infection and other viral infections. Pro-inflammatory cytokines can predict mucosal toxicity and it becomes a serious liability to select out candidate vaginal products that cause local inflammation and may enhance HIV transmission. Table I describes various stages of clinical trials on microbicides in humans that follow traditional drug development phases.
Nonoxynol-9 (N-9), available as a contraceptive for the last 50 yr has been extensively evaluated as a microbicide initially. However, four randomized controlled trials have shown that the use of N-9 did not protect against HIV infection. This has prompted the search for other products as possible microbicides and currently 65 such products are being evaluated. A total of 18 candidate products are in various phases of clinical trials (Table II) and six products (BufferGel, PRO 2000 gel, Cellulose sulphate, Dextrin-2 Sulphate, Carraguard™ and C31G) are entering large-scale effectiveness trials in Africa and Asia, as well as in the United States. It is unlikely that the first generation of microbicides would be 100 per cent efficacious. However, it is estimated that a partially effective microbicide used by 20 per cent of women in half of all the sex acts that do not involve a male condom, would avert 2.5 million new HIV infections over 3 yr.

Indian scenario of HIV infection among women and the role of microbicides

Heterosexual contact is the dominant route of HIV transmission in India. Initially, the HIV epidemic in Indian women was concentrated among commercial sex workers. However, studies have also reported higher rates of HIV infection among married, monogamous women reporting to sexually transmitted infection (STI) clinics in Pune who have a high-risk husband and do not have HIV risk behaviour of their own. Similarly in Chennai, India, among 134 HIV positive women who sought care for HIV infection, 82 per cent were married, monogamous women whose risk factor for HIV infection was sexual intercourse with their HIV-infected spouses. In a study in Manipur, 45 per cent wives of HIV-infected injection drug users were detected to be HIV positive, despite not being injection drug users themselves. The incidence of HIV-1 infection among heterosexual couples has been reported to range between 4.6 and 11.8 per 100 person-years world wide and a study is currently underway for the incidence estimation among HIV discordant couples in Pune. Married women in India are getting infected with HIV mainly from their infected male partners and microbicides are expected to be useful to women in the discordant couples’ setting when condom use cannot be negotiated. In spite of mass awareness programs for population control and HIV prevention, male condom use was as low as 3 per cent in India, as per the National Family Health Survey-2 (NFHS-2), conducted in 1998-99. Therefore, microbicides having contraceptive properties would provide female controlled options for prevention of unwanted pregnancy as well as HIV infection.

Although the HIV epidemic in India is more than 18 yr old, limited studies have been conducted on microbicides so far. A Phase I safety and acceptability study of a nonoxynol-9 vaginal pessary which acts by dissolving the lipid membrane of microorganisms, was conducted in 1998, as was a Phase I study of BufferGel, a compound that acts by maintaining an acidic vaginal pH, which renders protection against HIV. Subsequently Phase I safety studies of Praneem polyherbal tablet (unpublished observation) (unclassified mechanism of action) and cellulose sulphate (a polyanion inhibitor of HIV binding), have been done. A Phase I safety and acceptability study of 0.5 per cent of PRO 2000 vaginal gel (another inhibitor of HIV binding) has been recently completed (unpublished data) and a Phase II study using Praneem polyherbal vaginal tablet is currently ongoing in Pune. However, Phase III efficacy trials have not been conducted so far in India.

Considering the spread of HIV infection among women, field evaluation of microbicides for safety, acceptability and efficacy among women is a priority. Indian settings are important for conducting efficacy trials because there is a clinical and laboratory capacity and information and technology expertise required for data management. Additionally there is a large population of “at-risk” women and the cost of conducting clinical trials is low. However, conducting large-scale Phase III trials is a major endeavour because this would require clinical, laboratory and community environment at multiple sites that would facilitate the conduct of microbicides clinical trials. Indian Council of Medical Research (ICMR) and National AIDS Control Organisation (NACO), New Delhi, India are keen to pursue research on vaginal microbicides and addressing likely challenges and issues in their conduct might make such trials possible in India in the immediate future.
Finding resources and ensuring support

Developing candidate microbicides and then conducting efficacy trials costs several hundred million US dollars and warrants sustained allocation, since the process of going from in vitro tests of concepts to animal studies to human trials can take more than a decade. Efficacy trials require large resources in terms of finance, scientific contributions, human resources and monitoring of the trial. The cost of a large clinical trial is dependent upon the number of study sites, sample size, accrual and retention period and sensitive laboratory assays for incident STIs and clinical management of incident HIV infections.

Protocol development and partnership building

Developing a Phase III study protocol itself may require more than a year since a lot of trial intricacies,
ethical issues, statistical considerations, study monitoring, safety issues and laboratory tests have to be incorporated in the protocol. The primary endpoint of such trials is HIV seroconversion and secondary end points might include other incident STIs, as well as ongoing safety and acceptability assessment. Partnerships should be developed within and outside India for developing a good study design as well as efficient system of data management, quality control and laboratory support for sophisticated laboratory assays, etc., would eventually help in scientifically sound conclusions. These may also help in strengthening laboratory infrastructure, developing site capacity and ensuring support. In case of products developed outside India, intellectual property rights need to be discussed between the international trial partners and the site investigators.

**Regulatory requirements in India**

Before initiating any clinical trial, the study protocol, the informed consent form, case report forms and all study related information materials for participants have to be approved by the Institutional Ethics Committee (EC) / Institutional Review Board (IRB). If the institute conducting the trial has a Scientific Advisory Committee (SAC), it must approve the study protocol. In case of trials receiving foreign funding, ICMR approves the study protocol for its scientific contents and ethical considerations and forwards the same to the Health Ministry Screening Committee (HMSC). Drug Controller General of India governs the import and availability of any investigational drug/ medicinal products in India and provides permission to conduct the clinical trial after reviewing the study protocol, reports of previous *in vitro*, *in vivo* animal studies and data from previous clinical trials. Usually all the regulatory approvals require a minimum of eight to twelve months.

**Ethical guidelines for conducting clinical trials**

The ICMR has published a set of guidelines for biomedical research on human subjects that are at par with other international guidelines and are applicable to microbicides trials. There are international guidelines for ethical conduct of research and clinical trials. Although international trials are sometimes reviewed by international ethics committees, ethical review has to be done in the country hosting the trial.

**Preparedness of researchers**

The development and maintenance of adequate clinical and laboratory infrastructure is necessary for the conduct of clinical trials. Clinical research facilities required include counselling facilities, facilities for pelvic examination and colposcopy (generally for Phase I and II trials only), as well as trained clinicians, laboratory technicians, nurses and study co-ordinators. The counselling staff involved in clinical trials need to be trained to counsel participants about the study objectives, informed consent issues about HIV testing, specifics involved in study participation, ways to optimize participant adherence and retention. In large efficacy trials, the counselling staff may experience “burn out” because of the repetitive nature of the work. Therefore, the leadership of any large trial should anticipate such problems and develop comprehensive staffing plans and vary staff responsibilities to enhance morale and avoid monotony.

To conduct microbicide studies, the laboratory infrastructure requires HIV testing facilities along with the capacity to perform routine biochemistry and haematology studies as part of product safety monitoring. Laboratories also have to be proficient in the diagnosis of STIs in order to screen women to decide their eligibility as well as to diagnose incident STIs during study participation. Ongoing quality control and quality assurance in laboratory and clinical procedures are important research components. Appropriate data management and analysis infrastructure is required to manage randomization procedures, ongoing monitoring of safety and assessment of primary and secondary end points in addition to data entry, verification and periodic report generation. Many randomized clinical trials include a data and safety monitoring board (DSMB), that is responsible for reviewing accruing data, monitoring performance of the trial, assuring safety of the participants in the trial, and assessing the efficacy of treatment.
Preparedness of the community in which microbicide trials will be conducted

Women in India are still not aware of the risk of HIV infection and that options could exist to protect them against HIV and STDs. Therefore, large-scale awareness and advocacy will help in sensitization of the community. Phase III trials require enrollment of a large number of participants at high risk of HIV infection and this will not be possible unless the community is well informed and prepared for the trial. Hence education becomes a crucial issue in optimizing active participation of the community.

Researchers have an obligation to protect participants from any study-related harms and to maximize their individual benefits. However, the actual benefits of a specific research study will hopefully help the society in future and not necessarily the individuals who participated in the study. Therefore, individual participation will be maximized when the community understands the need of specific research studies. Awareness programmes and advocacy help in creating perception of this need among the vulnerable populations.

The commitment for research on microbicides will increase at the policy level when the recognition of the vital need for female-controlled options comes from the community. The involvement of non-governmental organizations (NGOs) in research from the outset can help the researchers gain confidence of the community. A partnership between NGOs and researchers can ensure and increase community participation in the development and implementation of research protocols.

One of the most important approaches to community education is the development and involvement of a Community Advisory Board (CAB). CAB is an independent panel of representatives of the stakeholders in community-based research and is a new concept in India. In the context of microbicides trials, CAB members may include women’s organizations, sex workers, truckers, people living with HIV, NGO representatives, grass root level workers, lawyers, etc., all of whom are likely to be interested in the development of microbicides and might include prospective beneficiaries. The CAB is expected to bridge the community on one side and the researchers on the other side. The membership of CAB can be specific, study-oriented and the CAB can increase interaction with the community, translation of the consents in the local language and developing study specific information material for creating awareness on microbicides.

Key scientific issues in conducting efficacy trials

Identifying sites and participants for conducting clinical trials: Efficacy trials have to be conducted in the population of women who are at risk of HIV infection. Although a large number of Indian adults are at potential risk for HIV infection, it might represent a smaller percentage of the general population, therefore, finding such “at-risk” population is a challenging task.

Conventional methods of incidence estimation are cohort studies which are lengthy, difficult to coordinate and face the most important challenge of retaining the enrolled participants to the study end point. Newer methods are becoming available for HIV incidence estimation such as BED-Capture EIA (BED-CEIA), which can be an important tool for identifying cohorts for prevention trials (microbicides, vaccine) and for monitoring and evaluating programmes. The BED-CEIA determines whether a person who presents with HIV infection acquired his infection recently, and so this test enables researchers to identify the communities where the HIV incidence is high and HIV is spreading rapidly.

The sample size requirement of effectiveness trials is quite large in order to achieve adequate number of primary study end points, that is incident HIV infections. Hence such trials are possible with a reasonable sample size only if the HIV incidence in the population is high. For the effectiveness trials to be conclusive, HIV uninfected women at high risk of getting infected with HIV (women with STIs, with multiple partners, with a partner who is having STI/HIV infection/multiple partners) need to be enrolled. There is lack of understanding and many misconceptions about STIs in the community, which affect the health seeking behaviour of women and
their risk perception. Because of the Indian socio-cultural settings, women are often not willing to disclose their partner’s risky behaviour or their own sexual history and multi-partner relationships. Facilities for laboratory diagnosis of STIs are lacking in many health care settings and therefore it may be a challenge to find women who could be at high risk of getting infected with HIV and hence appropriate to participate in efficacy trials.

Though sex workers are at the highest risk of HIV infection, some of the recent microbicide trials are not being planned among sex workers. Most of the available data on failure of N-9 in protecting against STIs and HIV have emerged from studies among sex workers wherein the product was used more frequently than it would be used by other women, and frequent use of N-9 in these trials resulted in increased micro-ulcerations and abrasions resulting in increased risk of HIV transmission.

A large number of women get HIV infected from their husbands and it is possible that some products may be protective for women who do not have multiple daily sexual partners like sex workers. Therefore it is important to evaluate safety, acceptability and efficacy of vaginal microbicides among other women also.

Product adherence and retention: Adherence to the long-term treatment regimen (at least one year) is important to see the effectiveness of the product. Therefore adherence needs to be stressed at each clinic visit. In microbicide research it is necessary to assess actual use of the product, which is mostly dependent on self reports by the participants. Newer techniques are being developed to assess compliance in vaginal microbicide trials such as use of stained applicators which could be identified as being inserted in the vagina. Adherence to product use is dependent on understanding the importance and meaning of research, consent comprehension, perceived risk and the acceptability of the product.

In order to get adequate study end point results, it is necessary that majority (> 80%) of the participants complete all their scheduled visits. In efficacy trials, participants are required to be followed for a minimum of twelve months to assess incident HIV/STI infections. Participants’ retention is very challenging since they have to be reminded of their scheduled follow up visits, which become difficult when majority of the population does not have access to telephonic facility. Often home visits have to be conducted by the study staff to remind participants of their missed visits, and they have to agree to this type of contact in the informed consent. In conducting such home visits, there is a risk of leakage of information about the individual’s decision to participate in the trial to the family and other community members. Therefore, home visits have to be conducted by trained and experienced staff according to a well-practiced and well-rehearsed protocol. Participants are sometimes unable or unwilling to give correct residential address at enrollment and tracing such participants who miss their follow up visit or are lost to follow up, becomes difficult.

Key ethical issues in conducting effectiveness trials

Informed consent: As per the 2001 census of India, around 44 per cent of the adult female population is illiterate. Administering an informed consent for study participation is a challenge when majority of the study population is illiterate. As compared to nuclear families in most of the other countries, the joint family structure predominates in India and lot of decision-making is dependant on the male partner as well as other family members. Therefore involvement of male partner since the beginning of the study can help to avoid domestic problems. Informed consent is a continuous process throughout the study and does not stop after signing the consent document. Study participation means that potential participants must understand the risks and benefits of participation and decide to participate with complete understanding and without any coercion. Participants must understand the meaning of research, clinical trials, their purpose and objectives, the concept of randomization into active product arm vs a placebo arm and their rights and responsibilities. Participants in the placebo arm must be assured that they will not be denied access to the best treatment otherwise available. Study participants should be of legal age to be able to provide voluntary consent. In many instances, participants are
often unable to give their exact age and the counselor is required to estimate the age mainly based on their reproductive history.

The consents of clinical trials may be lengthy. In order to increase consent comprehension, brochures, fact sheets, pictorial booklets, etc., may be provided to ensure adequate understanding of the participants. Participants should be made aware that they are participating in a research trial and the product may or may not have any preventive properties and they should not have any false sense of security. Since the study products do not have proven efficacy, it is unethical to withhold known methods of protection. Therefore, condom counselling for risk reduction must be stressed at each clinic visit. HIV testing should be voluntary with necessary pre-and post-test counselling facility.

Reimbursement of trial participants: Participants should be reimbursed for their travel and time spent for the visit to the clinic and the amount of compensation should cover the actual costs but should not be so high and lucrative as to eliminate the option of refusal to participate. The amount should not be too large to be considered as undue inducement for trial participation. This amount should be approved by the local EC / IRB.

Care and treatment of study participants: Study volunteers need to have a 24 h contact number of the study clinician in order to be able to contact in case of any adverse event. Referral services should be available for potential participants who become ineligible at the screening process. The institution that conducts the trial should also develop appropriate policies and provide adequate funding to support the provision of antiretroviral therapy whenever required to the participants who become HIV infected during the trial. Post trial access of the product at an affordable price is an important issue and should be aggressively negotiated by the host country.

Overview and challenges in the context of efficacy trials on microbicides

Microbicides would provide an option to thousands of women who are at risk of HIV but are unable to negotiate condom use because of gender inequality, illiteracy, cultural resistance and poverty. There is increasing commitment globally as well as nationally in India for research on safe and effective microbicides.

In summary, the following points are important: (i) Conducting efficacy trials on microbicides is a major endeavour; (ii) There is a need for capacity building of institutes for conducting clinical trials. Ongoing training of research staff would certainly help in improving the quality of research; (iii) Large-scale community awareness and advocacy for microbicides will increase community participation; (iv) Regulatory requirements should be strictly followed; (v) Efficacy trials are conclusive when baseline prevalence and incidence of HIV is high. Therefore, it is essential to identify appropriate sites that can provide access to appropriate study population and should have adequate clinical and laboratory infrastructure. Feasibility studies for participant recruitment and retention would help in planning for future clinical trials; (vi) Obtaining informed consent is a major challenge when majority of the population is illiterate. Participants should not remain under the perception of false sense of security; (vii) Product adherence and retention require lot of training and skills building in counselling; (viii) Ongoing quality control has to be an integral part of any research study to ensure high standards of research; and (ix) Post-trial access to the product at an affordable price and post marketing surveillance of the new product is a public health responsibility of the country.

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