Methods for Improving Reproductive Health in Africa

Overview

This multi-site randomized, controlled trial measured the effectiveness of the diaphragm and Replens® gel in preventing heterosexual acquisition of HIV infection among women. The study was powered to detect effectiveness (biological efficacy combined with adherence) of 33 percent. We enrolled sexually active seronegative women in South Africa and Zimbabwe (N=5,045); and followed them for 12-24 months (median of 21 months). The study began enrollment in August 2003, and completed follow-up in December 2006, for a total study duration of 3 years. All trial participants received voluntary counseling and testing, safer-sex counseling, free male condoms and diagnosis and treatment of curable sexually transmitted infections (STIs). Half of the participants were randomly selected to receive, in addition, an Ortho All-Flex® latex diaphragm and a non-contraceptive lubricant (Replens® gel). We evaluated the effect of providing the diaphragm, lubricant gel and condoms (intervention) compared to condoms-alone (control) on HIV incidence in women. The trial also investigated the acceptability of the diaphragm in this study population.

Partners

The study is supported by a grant from the Bill and Melinda Gates Foundation. Dr. Nancy Padian of the Women's Global Health Imperative at UCSF is the trial's principal investigator, and the collaborating institutions and co-investigators are:

- UCSF, Women's Global Health Imperative (Dr. Nancy Padian, Dr. Ariane van der Straten) www.wghi.org
- Ibis Reproductive Health (Kelly Blanchard) www.ibisreproductivehealth.org
- University of Zimbabwe-UCSF Collaborative Research Programme (Dr. Tsungai Chipato) www.uz-ucsf.zw
- Medical Research Council of South Africa (Dr. Gita Ramjee) www.mrc.ac.za/hiv/hiv.htm
- Perinatal HIV Research Unit of South Africa (Dr. Guy De Bruyn) www.hivsa.com/phru

Primary Objective

To determine the effectiveness of the diaphragm with Replens® gel in preventing heterosexual HIV transmission in women.

Secondary Objectives

1. To determine the effectiveness of the diaphragm with lubricant gel in preventing cervical infections with *Chlamydia trachomatis* (CT) and *Neisseria gonorrhoeae* (NG).
2. To assess the long-term acceptability of diaphragms with lubricant gel for use as an HIV prevention method.
3. To examine the effect of using the diaphragm and lubricant gel on *Trichomonas vaginalis* (TV) and herpes simplex virus type 2 (HSV-2) infection and to evaluate *Treponema pallidum*, TV, and HSV-2 as potential effect modifiers of a diaphragm-HIV relationship.
4. To examine the feasibility of the diaphragm and lubricant gel as a sustainable HIV prevention strategy, including logistical factors such as: access to product in a timely fashion, hygiene and diaphragm washing and reuse, problems associated with use, ability to use the diaphragm covertly when so desired, and other related acceptability issues.

Sub-Studies and Ancillary Projects

Several sub-studies and ancillary projects were also incorporated into the MIRA Trial. The objectives were:

- To evaluate the effect of Replens® gel on cervical HPV testing, urine PCR testing for chlamydia and gonorrhea, and cervical cytology quality. This pilot study was conducted at UCSF only.
- To evaluate whether diaphragm and Replens® gel can decrease the incidence and persistence of HPV, and hence reduce the risk of cervical cancer; the study also evaluates whether HPV infection and high HPV viral load increase the risk of male-to-female vaginal HIV transmission. This sub-study was conducted in Zimbabwe only.
- To evaluate whether the diaphragm and Replens® gel can decrease the incidence and persistence of Bacterial Vaginosis. This sub-study was conducted in Zimbabwe only.
- To determine the prevalence of HSV-2 in the study screening population. This sub-study was conducted in Durban, South Africa only.
- To determine whether women in the intervention arm have a reduced incidence of Pelvic Inflammatory Disease.
- To educate and train participants of clinical trials to become peer educators as a way to increase STI/HIV awareness and knowledge in the target communities. This project was conducted in Durban, South Africa only.
- To assess the effect of male involvement on women's diaphragm, gel and condom adherence and acceptability. This sub-study was conducted in Zimbabwe only.
- To investigate the social context of diaphragm and Replens® gel use and the trial experience of participants through focus group discussions and in-depth interviews with women and their male partners (social science component).
- To determine time requirements for diaphragm education and counseling, fitting and practice at study visits.
- To determine the prevalence of recent HSV-2 infection in a cohort of HIV negative women as measured by avidity index score ≤40. This sub-study was conducted in Johannesburg, South Africa only.

Policy and Advocacy
The MIRA trial also undertook a number of activities to support the trial in the policy and advocacy arena as follows:

- Establish partnerships in the family planning and STI/HIV/AIDS fields and serve as a key resource on cervical barriers, including the establishment of the Cervical Barrier Advancement Society www.cervicalbarriers.org.
- Build awareness of cervical barriers and the MIRA trial among researchers, providers and policy makers.
- Investigate the legal and regulatory issues relevant to cervical barriers in the U.S., South Africa and Zimbabwe.

Standard of Care
The MIRA trial established relationships with community referral sites and facilitated treatment and care for HIV-positive trial participants through these sites. The MIRA team also elicited feedback regarding trial-referral site relationships and assessed the impact of the trial and its referral system on the community referral service providers.

MIRA Project Timeline

Aug-03 — **UZ-UCSF began enrollment (Sites: Chitungwiza & Epworth, Harare, Zimbabwe)**

UZ-UCSF Collaborative Research Program Staff

Nov-03 — **Medical Research Council began enrollment (Sites: Umkomaas & Bothas Hill, Durban, South Africa)**

Medical Research Council & Ibis Reproductive Health MIRA Staff

Apr-04 — **PHRU began enrollment (Site: Soweto, Johannesburg, South Africa)**

Aug-05 — **First participants began exiting study**

Sep-05 — **Enrollment completed; participant follow-up ongoing**

Perinatal HIV Research Unit and UCSF Staff

UZ-UCSF:	**2502**
Medical Research Council:	**1515**
Perinatal HIV Research Unit:	**1028**
Total enrolled participants:	**5045**

Dec-06 — **Participant follow-up completed**

Apr-07 — **Data collection for social science component completed**

May-07 — **Standard of Care activities completed. Sites closed**

Jul-07 — **Main study results disseminated and published in the journal, *The Lancet***

- **Findings presented at International AIDS Society conference, Sydney, Australia**