



METHODS FOR IMPROVING REPRODUCTIVE HEALTH IN AFRICA: A phase III trial of the diaphragm and lubricant gel for HIV prevention in women

The Methods for Improving Reproductive Health in Africa (MIRA) trial was a multi-site, open-label, randomized controlled trial to determine the effectiveness of the diaphragm and Replens[®] lubricant gel in preventing heterosexual acquisition of HIV and other STI infections in Zimbabwean and South African women. Both products evaluated in this study are commercially available; the diaphragm has been used by women for decades.



Summary

Enrollment of participants began in August 2003 and the study was completed in December 2006; 5,045 HIV-negative, sexually active women were recruited from clinics and community-based organizations at three sites in South Africa and Zimbabwe. Women attended study clinics for quarterly follow up visits for up to 24 months (median was 21 months of follow-up). All participants received a comprehensive HIV prevention package consisting of pre-test and post-test counseling about HIV and sexually transmitted infections, testing, treatment of curable sexually transmitted infections, intensive risk-reduction counseling, and provision of condoms. During the trial, free hormonal contraceptives were made available to participants. Half of the participants were randomly selected to receive, in addition, an Ortho All-Flex[®] latex diaphragm and a non-contraceptive lubricant (Replens[®] gel). The primary outcome of the MIRA trial was incident HIV infection.

KEY FINDINGS

HIV outcome:

- Overall HIV annual incidence in the trial was 4.0%. There was no statistical difference in the rate of new HIV infections in the two study groups: in the intervention group (those who received a diaphragm plus lubricant along with male condoms) 158 out of 2472 women became HIV infected (a 4.1% HIV incidence per 100 woman-years) whereas in the control group (those who received male condoms only) 151 out of 2476 women became HIV infected (a 3.9% HIV incidence per 100 woman-years). Therefore, the study findings do not support the addition of the diaphragm to current HIV prevention strategies.
- While there was high condom uptake among all study participants, uptake was lower in the intervention group than in the control group. On average, the proportion of last sex acts where women reported using male condoms was 54% in the intervention group compared to 85% in the control group ($p < 0.0001$). However, the lower reported condom use among women provided with diaphragms did not result in increased infection, a finding which merits further research.
- Reporting of adverse events was similar between the two groups, confirming that the study products are safe. Rates of pregnancy were the same in both groups, with an overall annual incidence of first pregnancy of 13.1%.

Other STI infections outcome:

- There were 471 first *Chlamydia trachomatis* (CT) infections and 192 first *Neisseria gonorrhoeae* (GC) infections among the 4,968 participants who had at least one follow-up urine sample for CT/GC analysis; overall incidence of CT and GC in the trial was 6.2 and 2.4 per 100 woman-years, respectively. Intention-to-treat analysis found no statistical difference in the rate of new CT or GC infections in the two groups. However, in a separate analysis that examined the effect of the intervention among those who reported “always use” of the diaphragm since the last quarterly visit as compared to those who reported use less than always, there was a statistically significant reduction in the incidence of GC among women in the intervention group as compared to those in the control group (RH 0.61, 95% CI: 0.41-0.91). These findings do not support the addition of the diaphragm to current STI prevention strategies, though they do suggest that consistent use of the diaphragm may reduce GC acquisition.

MAIN STUDY PUBLICATIONS

Padian NS, van der Straten A, Ramjee G, Chipato T, de Bruyn G, Blanchard K, Shiboski S, Montgomery ET, Fancher H, Cheng H, Rosenblum M, van der Laan M, Jewell N, McIntyre J, the MIRA Team. Diaphragm and lubricant gel for prevention of HIV acquisition in Southern African women: a randomized controlled trial. *Lancet*. July 2007; 370(9583):251-261.

Ramjee G, van der Straten A, Chipato T, de Bruyn G, Blanchard K, Shiboski S, Cheng H, Montgomery E, Padian N. The diaphragm and lubricant gel for prevention of cervical sexually transmitted infections: results of a randomized controlled trial. *PLoS ONE*. October 2008; 3(10):e3488.

OTHER PUBLICATIONS

Fukuchi E, Sawaya GF, Chirenje M, Magure T, Tuveson J, Ma Y, Shiboski S, da Costa M, Palefsky J, Moscicki AB, Makunike-Mutasa R, Chipato T, Smith-McCune KK. Cervical human papillomavirus incidence and persistence in a cohort of HIV-negative women in Zimbabwe. *Sex Transm Dis*. May 2009; 36(5):305-11.

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Jewell N, van der Straten A, Montgomery E, Rosenblum M, Padian N. Diaphragms and lubricant gel for prevention of HIV—Authors' reply. *Lancet*. December 2007; 370(9602):1823–1824.

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Sawaya GF, Chirenje MZ, Magure MT, Tuveson JL, Ma Y, Shiboski SC, da Costa MM, Palefsky JM, Moscicki AB, Mutasa RM, Chipato T, Smith-McCune KK. Effect of diaphragm and lubricant gel provision on human papillomavirus infection among women provided with condoms: a randomized controlled trial. *Obstet Gynecol*. November 2008; 112(5):990–997.

Smith-McCune K, Tuveson J, Rubin M, da Costa M, Darraugh T, Shiboski S, van der Pol B, Moscicki A, Palefsky J, Sawaya G. Effect of Replens gel used with a diaphragm on tests for human papillomavirus and other lower genital tract infections. *Journal of Lower Genital Tract Disease*. October 2006; 10(4):213-218.

van der Straten A, Cheng H, Moore J, Kacaneck D, Blanchard K, de Bruyn G, Ramjee G, Chipato T, Montgomery ET, Padian N, the MIRA Team. The use of the diaphragm instead of condoms in a phase III diaphragm trial. *AIDS Behav*. December 2008; 13(3):564-572.

van der Straten A, Moore J, Shiboski S, Montgomery ET, de Bruyn G, Ramjee G, Chidanyika A, Kacaneck D, Padian N. Patterns and predictors of adherence in a Phase III diaphragm trial in Sub-Saharan Africa: a trajectory analysis. *J Acquire Immune Defic Syndr*. April 2009; 50(4):419-426.

PARTNERS

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- UCSF, Women's Global Health Imperative (Dr. Nancy Padian, Dr. Ariane van der Straten)
- Ibis Reproductive Health (Kelly Blanchard) www.ibisreproductivehealth.org
- University of Zimbabwe-UCSF Collaborative Research Programme (Dr. Tsungai Chipato) www.uz-ucsf.co.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

This fact sheet will be updated on an ongoing basis as analysis of the MIRA data continues and publications become available. For more details about the MIRA trial visit the Cervical Barrier Advancement Society (CBAS) at www.cervicalbarriers.org. At CBAS you'll also find more background information, fact sheets, and explanatory documents about clinical trials and cervical barrier methods.