# Trial shows microbicide is safe but not effective

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## Nevertheless, much useful information comes out of trial

*(The source for this article, unless otherwise stated, was an online presentation delivered by the Population Council. See the Population Council's press statement here.)*

The Population Council has released the results of a microbicide trial conducted in South Africa with the Medical Research Council, University of Cape Town (UCT) and Medical University of South Africa (MEDUNSA) in Isipingo (near Durban), Gugulethu (in Cape Town) and Soshanguve (near Pretoria). The trial found that the microbicide Carraguard was no more effective at reducing HIV transmissions than a placebo. Carraguard was however found to be safe. Participants in both the placebo and Carraguard arms of the trial were given counselling on safer sex and the need to use condoms. Women who sero-converted were offered "a monitoring visit, including CD4 count, viral load, pap smear, physical exam and direct referrals to ARV programs for those eligible."

Unfortunately, the trial's primary objective failed. From the publicly available evidence, the trial was conducted to high ethical standards and the trial participants were given extensive support. Microbicides are still in an early phase of their development. There are likely to be more failures than successes ahead; this is the nature of scientific discovery.

Nevertheless, we urge microbicide scientists to co-operate and choose optimally which products should be tested in future clinical trials. In 2004, Dr Michael Gross, writing in the American Journal of Public Health, raised a concern that five of the six microbicide products entering large-scale trials were in the same class. He wrote "Paradoxically, entering more candidates into more trials may confuse or compromise efforts to identify an effective product. Instead, a single trial of the most promising product(s) best serves the current candidates while also preserving resources needed to promptly advance innovative new protective concepts into future large-scale trials." (Am J Public Health. 2004;94:1085?1089) Dr Gross's advice is still relevant in 2008.

A wealth of useful information has come out of the trial. It was conducted over a three year period (March 2004 to March 2007). Over 9,500 women were screened for HIV before the trial started. About 2,600 women were HIV-positive at screening and consequently excluded from the trial. Slightly more than 6,200 women were enrolled, with approximately 3,100 assigned to each arm. This was a massive study and some interesting results have come out of it, which might improve our understanding of the epidemic. For example:

- The overall HIV incidence rate was 3.5 per 100 woman-years (285 women contracted HIV during the trial. The Carraguard arm had a statistically insignificant lower incidence rate than the placebo one.) This is very high. Given the counselling, information and support trial participants had, it is likely that the incidence rate in

the general population of women of the same average age is even higher. Indeed, "prevalence of STIs decreased during the trial [and] reported condom use increased from 33% at baseline to 64% during the trial." This demonstrates how much more needs to be done to improve prevention efforts in South Africa. The Isipingo arm's incidence rate of 5.9 per 100 woman-years is extraordinary and deeply disturbing.

- Yet, the vast majority of participants reported being in steady relationships with only one partner. The average number of times women in the Isipingo arm reported having sex (1.9 times) was lower than than the other arms (2.6 times), contrary to what one would expect given the higher incidence rate in Isipingo. Of course, since these statistics are based on participant feedback, they have to be treated with caution.
- 41% reported experiencing abuse from their partners. Most of this was emotional abuse, which is possibly a key factor in whether women are able to negotiate condom use. 11% reported being forced to have sex, usually by their steady partner.

From the perspective of future microbicide research, based on participant reports, use of Carraguard was too infrequent. The researchers calculate that only 44% of sex acts would have been covered by the microbicide. It is entirely possible that Carraguard's failure went beyond poor uptake, i.e. it simply might not be effective for biological reasons, but the poor uptake is sobering news for the likely effectiveness of microbicides applied topically. It points to the need for massive public education around prevention strategies, including proven strategies such as condom use and male circumcision.

There is a long way to go in the search for more effective means of preventing HIV transmission. Behavioural change models have had very limited success; there are no known well-defined behavioural interventions that have been proven on a large-scale in high incidence countries. Currently post-exposure prophylaxis, male medical circumcision and, of course, consistent condom use are the only known biological mechanisms for reducing sexually transmitted HIV transmission. The TAC supports substantial and increased investment in prevention research, especially efforts aimed at giving women more power to have safer sex. There needs to be much more visible leadership on prevention, and particularly campaigns against domestic violence and rape so that women who know about their risk of HIV and want to protect themselves can do so. But it is also vital that investment continues to be directed at the most effective current intervention: ensuring that people with advanced HIV infection have access to highly active antiretroviral treatment. This means building sustainable health-care infrastructures in developing countries with high HIV prevalence and ensuring sufficient health workers, medicines and monitoring tests are available so that more people can benefit from appropriately administered treatment.

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