

Answering Hard Questions on the Savvy Trial Results



On September 19, 2007 Family Health International (FHI) provided an update on the data obtained through their trials of Savvy (C31G) in Ghana and Nigeria. The letter provides a summary of these data and on-going secondary analyses that they are conducting to learn as much as possible from them. This fact sheet seeks to provide easily accessible answers to some of the difficult questions that people may have in connection with the findings described in the FHI letter.

If you have questions that are not addressed in this brief, please forward them to info@global-campaign.org and we will do our best to track down the answer.

It seems like all the microbicide trials are showing that the products don't work and may cause harm. Is that true?

That is not actually true. So far, the field has obtained efficacy results on three products: Nonoxynol-9, Cellulose Sulfate and Savvy. The results so far have been mixed:

N-9: two trials of N-9 containing gels or films were completed. Of these, one showed increased risk and one did not.

Cellulose Sulfate (CS): Two studies were stopped before completion. One showed no difference in the rates of infection among those who used cellulose sulfate and those who used a placebo. The other suggested a trend toward more infections among CS users, but the result could have occurred by chance (i.e. it was not statistically significant)¹.

Savvy: Two studies were stopped before completion. Again, one suggested no difference in HIV risk among those who used Savvy and those who used a placebo. A second suggested the possibility of increased risk but, again, it is possible that the result could have occurred by chance.

It is very unfortunate that the field has not yet produced more helpful results. But it is important to remember that the field errs on the side of caution by eliminating microbicide candidates where there is any evidence of possible increased risk – even if that evidence is weak. Participant safety is always put before the pursuit of any particular microbicide candidate.

How many women sero-converted in the trials where the product may have caused risk?

In the N-9 trials: Of 1005 women enrolled, 59 sero-converted in the N-9 arm and 45 in the placebo arm.

¹ In every-day English, "significant" means important, while in Statistics "significant" means probably true (not due to chance). In the case of trials, a "statistically significant" result means that there is probably a real difference in number of infections observed among those using the product compared to those using the placebo. It does not mean that the difference is necessarily large, important or significant in the usual sense of the word. Also, when studies include small numbers, a result could indicate a real difference, even if it is not "statistically significant." If a larger study were done with more participants, our confidence in the truth of the finding would increase.

In CONRAD's Cellulose Sulfate trial: Of 1425 women enrolled, 25 in CS arm and 16 in the placebo arm.

In the Savvy study in Nigeria: Of 2153 women enrolled, 21 in Savvy arm and 12 in placebo arm.

Every single infection is a human tragedy, but we must also bear in mind that these trials were done in countries and communities hard-hit by the HIV pandemic. In South Africa, for example, 48% of the women who volunteered for CS trial participation were unable to participate because they were already HIV positive at the time of their screening visit. In Uganda, the rate was 32% at screening, and in Nigerian recruitment for the Savvy trial, it was 12%. Thus, each new infection that occurs during a trial must also be viewed in the context of women's pre-existing risk in their communities.

What happened to the women who sero-converted in the Savvy trial?

They received counseling and were connected with local providers of HIV care and support services, including antiretroviral treatment as needed. The Nigerian study sites had established referral agreements with PEPFAR (President's Emergency Plan for AIDS Relief)-funded programs providing access to antiretroviral drugs and HIV care. Study staff accompanied the women to the PEPFAR program office to make sure they got appropriate evaluation and services and were assured that they could return for these services on an on-going basis. The Ghanaian Savvy study contracted with local care and treatment organizations to provide access to treatment for women who sero-converted during their trial participation.

The numbers indicate that almost twice as many women got infected in the Savvy arm of the trial than the placebo arm—isn't this worrisome?

When numbers are small, it is harder to be sure that a difference observed is true and not due to chance. Researchers are currently conducting further analyses to see if there could be other reasons for the appearance of increased risk. For example, they will look at whether the risk of HIV infection is higher among women who reported using the product more frequently or having sex more often – which would make sense if the product did increase risk. Although not certain, these results do suggest there may be a problem with Savvy. At minimum, we now know that it is very unlikely to be protective against HIV.

What was done to help women stay uninfected during the trial?

Extensive measures were taken at all trial sites to help women understand that they should not rely on the test product to protect them from HIV. All participants went through comprehensive informed consent procedures in their own languages. Key messages were reinforced at every visit, including the fact that they should not count on the gel for protection, that half were receiving the placebo gel (known to be ineffective), and that they had the right to withdraw from the trial at any time. All participants received HIV prevention counseling each month, as well as free condoms, and diagnosis and treatment for any curable sexually transmitted infections.

What would have happened to these women if they hadn't been in the trial?

Of course, it is impossible to know what would have happened to any individual person. But it is likely that some of these women would have become HIV infected. HIV incidence is the term used for the number of people who become HIV infected in a given area within a given year. Unfortunately, it is

very difficult to measure because sero-conversion rates vary widely, even among groups of people living in the same city or geographic region. Sero-conversion rates can also go up or go down within a short time period, depending on what is happening in a community. Public health entities don't have "up to the minute" rates and looking at HIV incidence rates that are even a year or two old may not tell you what the current rates are.

There is very little data available about HIV incidence in Nigeria, but one study done among college students at the University of Jos in 2000 showed that their incidence rate was 1% per year². Let's just imagine for a moment what the numbers would look like if the incidence rate in the communities where the Savvy trial was conducted was also 1%. The Nigerian Savvy trial ran for two years, from September 2004 until it closed in August 2006. If the communities where the participants lived had a 1% incidence rate, then it is likely 22 women (1% of the 2153 women enrolled) might have gotten HIV each year -- or 44 altogether during the two years.

Compare this to the 33 women who actually did become infected during the two years of the Savvy trial. We do not know if this is a valid comparison or not because we do not have incidence data for the wider population of women at the Savvy study sites. But it provides an example of how the number of sero-conversions in the study might actually be lower than what would have happened to the participants if they had not enrolled in the study.

HIV prevention trial networks are testing different techniques to learn how to get the most accurate possible information about the sero-conversion rate in a trial community at the time the trial starts. The most reliable way to do this is by doing a prospective cohort study, in which researchers enroll participants and test them regularly for HIV for at least six months before any of them start using either the test product or the placebo. Clearly, this is time-consuming and very expensive to do.

Another way to gather important information is to measure condom use rates among women at the time they enroll in the trial (before they have had any condom counseling) and then compare that information to the condom use rates the women report throughout the trial. This would at least show the extent to which being in the trial helps women reduce their frequency of unprotected sex.

Still, it is alarming that this is the third time a product has appeared to have increased women's risk – even if we don't know for sure whether it did or not. What are the researchers doing to make sure this doesn't keep happening?

What makes this really difficult is that determining safety is not as simple as testing women in the Phase 1 and Phase 2 safety trials for minor side effects (such as mild vaginal irritation, soreness, etc.) that could come from using the gel. Both Cellulose Sulfate and Savvy appeared to be very safe in the early safety trials. If they had not, they would not have been moved into Phase 3 trials.

But safety evaluation of candidate microbicides is an evolving science. Scientists are working hard to develop new screening tests that could indicate that a product might increase HIV risk. They look at a large range of bio-markers -- factors like specific chemical changes in the vaginal environment that are much harder to see than detectable vaginal irritation but that might signal increased vulnerability. It is hard to tell which of the many detectable changes could actually be warning flags -- signals that the product is disturbing the vagina in a way that might increase risk.

² Harvard School of Public Health AIDS Initiative, Vaccine Think Tank, 2000
http://www.aids.harvard.edu/conferences_events/Recurrent/vaccine_development/2000/vacdev-14.html

After trials close, researchers focus intensively on going back through all the data they have and looking for those warning flags. Their goal is to detect any patterns that appear in the data collected from the women who sero-converted and do not appear at the same levels in the data collected from the women who did not sero-convert. Finding this kind of information is the key to knowing what to look for in safety trials. For more information on how scientists evaluate safety, please see the GCM issue brief: [Evaluating Microbicide Safety](http://www.global-campaign.org/clientfiles/GCMBrief-Safety-Evaluation-Fundamentals.pdf) (Available at <http://www.global-campaign.org/clientfiles/GCMBrief-Safety-Evaluation-Fundamentals.pdf>). This can also be down-loaded at <http://www.global-campaign.org/briefing.htm>.)