Advocates' Frequently Asked Questions About HPTN 035

Produced by the Global Campaign for Microbicides (www.global-campaign.org)

Please note: *The Microbicides Trials Network has developed very comprehensive fact sheets about this trial that are available on their website, http://www.mtnstopshiv.org/news/studies/17. We strongly suggest that you consult those materials for background information about the mechanics of the trial, how it was implemented, what governmental approvals were required for the trial, etc. The following information is provided to address other issues regarding this trial that may arise from an advocate's perspective*

On 9 February, 2009, the US National Institutes of Health announced the results of HPTN 035, a clinical trial of PRO 2000 and BufferGel, two candidate microbicides.

What did this trial actually tell us?

In this study, women who were offered PRO 2000 gel plus condoms had 30% fewer HIV infections than those offered only condoms or condoms plus a placebo gel. HPTN 035 is the first study yielding promising data that a candidate microbicide might actually work in women.

Another candidate product, BufferGel, was also tested in this trial but did not show any protective effect. Women using BufferGel had basically same rate of infection as those using the placebo gel or no gel at all. All the women in the trial were provided with free condoms and safer sex counseling encouraging them to use condoms every time, along with the gel if they received one.

Does this mean we know for sure that PRO 2000 gel works?

No. The 30% reduction in HIV seroconversions among the women using PRO 2000 did not reach the level of statistical significance. In the language of research statistics, "significance" is a measurement used to answer the question: "what is the likelihood that we could be wrong about finding an effect?" In this case, we are asking: "is it possible that the difference between the number of women who became HIV positive in the PRO 2000 arm and the number who became infected in the control arms could have occurred just by chance?"

A statistically significant result, in this case, would have been supported by data showing that the odds were less than one in twenty that the lower number of HIV infections among the PRO 2000 users could have occurred by random chance.

To see whether the trial data showed that, the researchers did calculations based on the number of seroconversions, the number of women in the trial and several other factors. What they found was a one in ten chance that the lower number of seroconversions in the PRO 2000 arm might have occurred by chance. Since those odds are higher than one in twenty, this trial result cannot

be considered statistically significant. This does not mean that PRO 2000 does not work; only that we cannot say for sure whether it works or not until more data are collected.

Fortunately, another effectiveness trial of PRO 2000 will soon be completed in South Africa, Tanzania, Uganda and Zambia. This trial—known as MDP 301—has enrolled nearly 9,400 women, three times the number enrolled in HPTN 035. The results of MDP 301 are scheduled to be released in November 2009. Because they will be based on so much more data, they will hopefully tell us more clearly how effective PRO 2000 really is.

If the MDP 301 results in November confirm that PRO 2000 reduces women's risk of HIV, the developers of PRO 2000 will likely take steps toward governmental licensing and distribution in at least some of the countries hardest hit by AIDS now. Each government, together with other stakeholders, will need to decide whether it makes sense to introduce the product in their country given their local epidemic and the effectiveness of the final product.

It is important to note that, when used consistently and correctly, male or female condoms will provide better protection against HIV and STIs than a partially effective microbicide. Thus, it will remain important to strongly encourage condom use whenever possible, recognizing that microbicides (when introduced) can be used with condoms for extra protection or by people who are not using condoms (for whatever reason) as a way of reducing their risk of HIV.

How many women got infected during HPTN 035?
Of the 3,099 HIV negative women enrolled in the trial, a total of 194 became HIV positive during the trial. It is important to remember that all of the women in the trial were offered free condoms and received safer sex counseling. Both the participants and their partners were provided, free of charge, testing and treatment for sexually transmitted infections. Women were encouraged *not* to trust the gel to protect them (if they received gel) and to use condoms every time they had sex. Even with this support, some women were still at risk of HIV infection.

The number of women infected in each arm of the trial breaks out this way:

53 women who did not receive a gel of any kind
51 women who received the placebo gel
54 women who received BufferGel
36 women who received PRO 2000

You can see that these women are a small percentage of the 3,099 women who enrolled in the trial. Because the difference in numbers between the PRO 2000 arm and the other trial arms is so small, it could possibly have occurred by chance. This is why the trial results are viewed as "not statistically significant"

Every single infection is a human tragedy, but we must also bear in mind that these trials took place in countries and communities hard-hit by the HIV pandemic. All the women who volunteered to be in the trial went through a screening process which included giving their informed consent to be tested for HIV. At the African trial sites, the percentage of women volunteering for the trial who were already HIV positive at their screening test ranged from 18% to 28%. So we need to think about each woman who became infected during the trial in the context of the risk in her community.

What happened to the women who found out they were positive at screening? And those who become HIV positive during the trial?
Women who tested HIV positive at screening were could not enroll in the trial but were offered extra post-test counseling and referral to programs providing antiretroviral (ARV) treatment and other support services. The Microbicide Trials Network (MTN), who conducted the study, reports that, "Women who acquired HIV during the study were counseled and referred by study staff to local medical care and support programs offering psychosocial services and HIV care, including antiretroviral therapy. Some MTN research sites are part of health care institutions where HIV care and support is provided, while other sites have established referral agreements with programs such as those funded by the U.S. President's Emergency Plan for AIDS Relief."[1]

The Global Campaign for Microbicides is urging all research networks to monitor how frequently women follow through with these referrals to treatment and actually get connected successfully with on-going care and support. Some sites are already monitoring this. Some also offer study-assisted referrals—where clinical trial staff help women to schedule appointments and accompany them to referral centers, when necessary.

Why did this trial have a "no gel" arm (in which participants received no gel at all) in addition to a BufferGel arm, a PRO 2000 arm and a placebo arm?
In addition to testing the two candidates, this trial also sought to test whether the neutral placebo was, in fact, neutral (i.e., had no effect on HIV risk). This is a key question in microbicide trials. If the placebo (sometimes called the comparator gel) provides even a small measure of protection against HIV, it could skew the result of the trial and potentially make the product being tested appear to be less effective than it really is.

After the Nonoxynol-9 gel study results came out in 2000, many scientists questioned whether Replens (a vaginal moisturizer that was used as the comparator gel in that study) was truly neutral or whether it may have reduced HIV risk slightly among the women in the control arm of the study. These questions led to the development of a product called HEC, a gel that is supposed to be truly neutral and that is now used as the "universal placebo" in microbicide trials.

HPTN 035 was designed with a "no gel" (or condom only) arm in an effort to see if it was possible to detect any difference between this arm and the arm using HEC. The difference between the number of women infected in the "no gel" arm and the number in the "placebo" arm turned out to be so small that is appears that HEC *is* truly neutral and has no effect on women's risk.

What happens next?
As described above, more data on PRO 2000 will be available in November, 2009. Indevus Pharmaceuticals, the company than makes PRO 2000, announced today that if PRO 2000 is proven to be safe and effective, they will "seek worldwide marketing approvals, and plan to

[1] This is from MTN's "Backgrounder" fact sheet. It is available on-line at *http://www.mtnstopshiv.org/news/studies/17*

work with government agencies and other organizations to help ensure affordable access to the product in resource-limited settings where the need is greatest."[2]

Other clinical trials are also underway to explore the safety and possible effectiveness of microbicide candidates that contain antiretrovirals (ARV) that specifically target HIV. These candidates are created by taking some of the same drugs that people living with HIV use to treat their disease and adapting them for use as gels, films or other topically applied forms to see if they might also work to prevent HIV transmission. Many people think that these ARV-based microbicide candidates may have an even greater chance of successfully blocking HIV transmission than the non-ARV-based candidates tested to date. Five of these ARV-based candidates are already in early clinical trials and the first is expected to produce effectiveness results by 2010.

Why are scientists pursuing non-ARV-based candidates like PRO 2000 if the ARV-based candidate microbicides are likely to be more effective?

It is important to fully explore non-ARV-based candidates for a number of reasons:

1. If effective, they could provide an alternative for people who cannot or do not want to use an ARV-based microbicide. It is possible that using ARV-based microbicides may put a person at risk if developing drug-resistant virus if she/he becomes HIV infected while using it. Some people may not want a product if it carries that risk.

2. Since it will only be appropriate for HIV negative people to use an ARV-based microbicide, they will likely only be available by prescription to people who have recently been tested for HIV. A non-ARV-based microbicide could be provided without a prescription, since it will likely be appropriate for both HIV positive and HIV negative people to use.

3. HIV positive women have said very clearly that they want a microbicide they can use to help prevent re-infection. Many would especially like to have a non-contraceptive microbicide that they could use to reduce their partner's risk of HIV exposure when they are trying to become pregnant. It is completely unknown at this point as to whether any microbicide will be able to help protect a woman's partner during sex. Much more testing would be needed to assess that.

   But it is clear that ARV-based microbicides will not be appropriate for use by HIV positive women because of the potential drug resistance issue. PRO 2000 is non-contraceptive so, if it is ultimately proven effective, it could be a potential option for both HIV positive and HIV negative women who need to reduce their risk of HIV but still want to become pregnant.

[2] Indevus Press Release, *CNN Money,* 9 February, 2009. Available on-line at http://www.prnewswire.com/news/index_mail.shtml?ACCT=104&STORY=/www/story/02-09-2009/0004968465&EDATE=