Global Campaign for Microbicides
Fast Facts

In August 2009, GCM launched a new series to complement our existing resources: The GCM Fast Facts . Each month, the Fast Facts are responses in "everyday" language to a common question in the field of HIV prevention research. They are intended to enable advocates and trial staff to better understand and explain to others the intricacies of the field.

*These GCM Fast Facts were inspired by the Contraceptive Pearls series focused on family planning that was circulated from 1998 to 2007 by Dr. James D. Shelton from the Office of Population, at the United Stated Agency for International Development (**http://www.jhuccp.org/pearls/parchive.shtml**).*

*If you have questions to suggest for the series, please send them to: **info@global-campaign.org***

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August 2009

What does it mean when a product looks as if it is more effective than a placebo but the results are not 'statistically significant'? Why can we not begin to license a product like this?

In every-day English, **"significant"** means important. But in statistics (the field of mathematics used to analyse research data), **"significance"** is an answer to the question: *"what is the likelihood that we could be wrong in saying that a difference between two outcomes was caused by a specific factor – and not just something that occurred by chance?"*

In the case of a microbicide effectiveness trial, a **"statistically significant"** result is one in which the **difference** between:

1) the number of new HIV infections among women using the trial product; and
2) the number observed among women using the placebo (or comparator) product

is big enough that it is highly unlikely to be the result of chance. The odds of this must be one in twenty or less in order for the trial results to be called **"significant"**. When the odds are that low, scientists feel confident in saying the decrease in the number of new HIV infections was caused by the product and, therefore, are real evidence of its effectiveness.

When the difference between the two trial arms is small, the odds that it could have occurred by chance are often greater than one in twenty. The results are not considered statistically significant, but this does not mean that the product **does not** work. It simply means that the scientists cannot say for sure if it works or not until more data are collected. Regulators require trial results that are clearly statistically significant before they will consider licensing products.

September 2009

Why are women physically more vulnerable to HIV infection?

Suppose a man and a woman have vaginal intercourse without a condom and one of them is HIV positive. If the woman is HIV negative and the man in HIV positive, she is **2-3 times** more likely to become HIV infected than if the situation is reversed. Why? Because:

- HIV cannot survive when the fluid it lives in dries up. Vaginal secretions coating the penis start dying right away unless they are under the foreskin (if he is uncircumcised) or they get into his blood through a scratch on his penis. **But semen does not dry out inside the vagina**, which means that the amount of time a woman is exposed to HIV is longer than that of a man. Also, the vaginal lining is a larger surface so HIV spreads out and comes into contact with lots of cells.
- Semen generally contains more HIV than vaginal fluids. How much virus an HIV positive person has depends on many factors. But usually, **a woman is exposed to more HIV from semen** than a man is from vaginal secretions.
- HIV infects particular target cells and large numbers of these live under the vaginal lining. On the penis, most of these cells live in the foreskin—another reason that circumcision helps to protect men from HIV infection. **It's easier for HIV to find cells to infect inside a woman than on a man**.

Having sexually transmitted infections (STI) or using anything but water to clean out the vagina can damage the vaginal lining and raise a woman's HIV risk. Young women whose bodies are not fully mature are also at higher risk. So are women whose vaginas are not lubricated during sex, either by their own secretions or by using a lubricant product, because tearing and inflammation only increase the ability of HIV to find cells to infect.

Economics, social customs and violence are external factors affecting women's HIV risk. But even without these, **women are at higher risk just for physical reasons**.

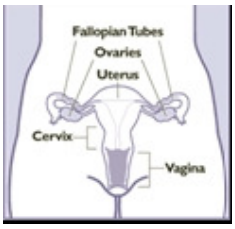
Check out the Microbicides Essentials Course for images that explain these physical vulnerabilities—in module 2 at http://www.hivpreventionresearch.org.

October 2009

Will we be able to use the microbicides developed for vaginal use in the rectum?

The rectum is more vulnerable to HIV infection than the vagina. Although estimates vary, unprotected receptive anal intercourse with an infected partner **is probably 5-20 times more likely to transmit HIV** than receptive vaginal sex. It is about **100 times more risky than receptive oral sex**.

Why? Key physical differences between the rectum and vagina make the rectum more vulnerable to HIV infection:



- The rectal epithelium (lining) consists of a **single layer of cells** and is highly susceptible to tearing. By contrast, the vaginal epithelium and the part of the cervix facing the vagina (see diagram) is normally around **40** cell layers thick. But this is not true for all women. In younger women, the face of the cervix can be a single layer thick. And after menopause, the vaginal epithelium thins and weakens. The cervical canal leading to the uterus (or womb) is always a single layer thick.
- The target cells that HIV most likes to infect are immediately underneath the epithelial layer in both the vagina and rectum. Since the rectal epithelium is generally thinner and more fragile, **it is easier for HIV to come into contact with target cells in the rectum**. While HIV can still reach target cells in the vagina, especially if there is a break or tear in the vaginal epithelium, the thicker lining provides a bit more of a protective barrier.
- The vagina is shaped like a pouch. The cervical opening is very small and restricts access to the uterus. The rectum, however, **is part of the intestinal tract**. This means HIV can travel up into colon and has **access to a bigger surface area** than it does in the vagina.

Thus, it may be **unsafe** to use a microbicides developed for vaginal use in the rectum. Since the lining of the rectum is more delicate than vaginal lining, a substance that works as an effective vaginal microbicide could actually be **harmful** if used rectally. At one point, for example, Nonoxynol-9 (a contraceptive substance that is still used to coat some condoms) was being tested as a candidate microbicide. It failed because frequent use of it irritated vaginal tissue but it turned out to be even more damaging to rectal tissue.

Both women and men who have anal sex need safe and effective rectal microbicides. Research to assess the safety of current microbicides candidates for rectal use is on-going, as is research to develop microbicides specifically for rectal use. For more information please see: http://www.global-campaign.org/clientfiles/RMbasicsfactsheet2008.pdf.

With thanks to the Jeanie Schottenstein Center for Advanced Torah Study for the use of this diagram

If trial participants are asked to use condoms every time they have sex, how can researchers know whether new intervention being tested works or not?

The reality is that even when given free condoms and lots of risk reduction counseling and support, ***many women are not able to convince their partners to use condoms***. If they could, we wouldn't need a product like microbicides.

An effectiveness trial basically compares the overall number of seroconversions (people becoming HIV positive) in the two groups of trial participants. Everyone in each of the two groups receives the same counseling, medical services, testing, etc. The only difference is that people in one group get the product (e.g. candidate microbicide or PrEP pills) that is being tested and people in the other group get the placebo -- something that looks exactly like the test product but does not contain any active ingredient.

Researchers assume that the rates of condom use, test product use, etc. will be about the same in each group. So, if more people seroconvert in the group using the placebo than in the group using the test product, the difference is assumed to be the result of the test product's protective effect.

HIV prevention trials measure whether use of the active product offers protection among people ***who do not use condoms 100% of the time*** during the trial. This condition is set up to mimic real life – since many people do not use condoms 100% of the time in real life, either.

Even though a successful microbicide has not yet been identified, the evidence gathered during microbicide trials indicates that:

- Condom use generally **goes up during a trial**. As a result, the rate of seroconversions among people enrolled in an HIV prevention trial is generally lower than the rate among their peers who are not enrolled in the trial, even in the placebo group. So, generally all the women in the trial are better off than had they not enrolled.
- Nonetheless, **some acts remain unprotected** by condoms and so some seroconversions do occur.
- In microbicide trials, **significant numbers of women report that they can and do use the gel,** even when their male partners do not use condoms. In the HPTN 035 trial, for example, participants said they used their assigned gels for 81 percent of their sex acts and reported using condoms during 72 percent of their sex acts.

What is a double-blind trial and why is it important?

A **double-blind trial** is a study design that ensures that neither the participants nor the researchers know which participants are receiving the experimental product, for example, a **microbicide**, and which are receiving **placebo**—that is, they are **"double-blinded"**.

This type of study design means that there is **less potential for bias** so that neither the participants nor the researchers can directly affect the outcome of the prevention method. For example, if the investigator knew who received the placebo, he or she might try harder to get those participants to use a condom. Likewise, a participant who knew she received the experimental agent, for example a candidate microbicide, might feel protected and **be less likely** to use a condom. As a result, double-blind trials tend to yield the most accurate results.

A third party, such as the Data Safety Monitoring Board (DSMB), holds the **"key"** that identifies the participants and the group to which they belong. This key is released to the researchers once the study has been completed, or if unexpected safety concerns emerge or the results are so much better than anticipated that it would be unethical to continue with the trial.

After all of the data have been recorded (and in some cases, analysed), the researchers discover which participants received the microbicide, or agent being tested, and which participants received the placebo. Essentially, the results are **"unblinded"** at this point.

Double-blind trials are considered particularly important in prevention research as **they reduce the possibility of bias** in the study.