Microbicide Success Story: What It Means and Where We Go Next

July 21, 2010 By David Evans

Undoubtedly, the big scene-stealer at the XVIII International AIDS Conference (IAC)—taking place July 18 to 23 in Vienna—was a presentation Tuesday morning on the successful results of the CAPRISA 004 tenofovir microbicide trial. As reported here and elsewhere, the study found that women who used the tenofovir gel were far less likely to become infected with HIV than women using a placebo gel. (People living with HIV take an oral version of tenofovir to treat the infection; as such, tenofovir is marketed and included in the meds Viread, Truvada and Atripla.)

Specifically the tenofovir gel users were 39 percent less likely, overall, to become infected with HIV than women who received a placebo gel. For women who used the tenofovir gel correctly more than 80 percent of the time, HIV infection was 54 percent less likely. Researchers also found that the tenofovir gel cut the rate of new genital herpes infections in half.

What received less attention, however, are the additional facts that were learned from the trial, and what all of this means for when a microbicide will finally be approved and available and what it will take to get there. To help answer those questions, two presenters—Angela Kashuba, PharmD, a clinical pharmacologist at the University of North Carolina in Chapel Hill, and Sheena McCormack, MSc, FRCP, a clinical epidemiologist from the Medical Research Council in London—offered additional data and perspectives at the Tuesday morning session where the CAPRISA 004 efficacy data were presented.

More Tenofovir Equals More Protection

Kashuba, who led a research team in analyzing blood and genital tissue samples, explained their findings about the relationship between tenofovir levels in the blood, cervicovaginal fluid (CVF), and vaginal and cervical tissue and the likelihood of infection with HIV or herpes.

Kashuba found that tenofovir concentrations in blood and CVF were much lower in women on tenofovir who became infected, compared with those who did not. In fact, there was a strong linear relationship between the level of tenofovir in CVF and the likelihood of infection—with the lowest levels showing the highest risk of infection and the highest tenofovir levels showing almost no HIV infections.

Kashuba explained that her results greatly strengthen two of the CAPRISA 004 efficacy findings:

first that it was the gel, rather than some other random occurrence, that explains the efficacy results, and second, that adherence was a powerful influence on efficacy. Kashuba's interpretation was that women with low tenofovir levels probably had low adherence levels.

Kashuba said that these results are the first in humans to directly link tenofovir levels with efficacy. These results, combined with another ongoing trial that is testing daily tenofovir gel use, called the VOICES study, will greatly aid researchers in devising new tools and strategies to make microbicides even more effective.

A Small Window of Opportunity

McCormack presented a snap shot of all the biomedical prevention trials that have been reported to date, and compared them to CAPRISA 004. She celebrated the fact that CAPRISA 004 offers the first totally unambiguous efficacy results of any trials conducted thus far, with the exception of several male circumcision studies.

Unlike the circumcision studies, where three of the studies were running at the same time and which reported their results within about a year of each other, there is currently only one other large microbicide test underway, and it is testing tenofovir gel in a different manner than CAPRISA 004. This difference could have a profound influence on how we conduct further microbicide studies and how a tenofovir microbicide might get rolled out if it is approved.

Specifically, McCormack explained that the CAPRISA 004 study suggests that the VOICES study—testing daily tenofovir get use—will also likely find at least some protective benefit. In the interim, researchers believe that it is still ethical to initiate studies where the tenofovir is compared to a placebo.

If VOICES does prove protection, all further prevention studies will probably have to use tenofovir gel (in women), as a means of baseline protection along with condoms, and a placebo will no longer be acceptable: not only with microbicide studies, but also for women in PrEP and other types of prevention studies. As McCormack points out, this leaves a very "small window of opportunity" to generate data about tenofovir compared with a placebo.

One of the big unanswered questions is how or whether a tenofovir gel might protect women and men during anal intercourse. Early studies are underway to explore this question, but much remains unknown.

With PrEP, where an oral drug is already licensed and approved for use for another purpose, McCormack explained that immediate roll out is technically possible, should the results of PrEP trials show strong efficacy. With a microbicide, where there currently is no approved product on the market, it's likely to take much longer for a product to make it over all the regulatory hurdles that stand in its way.

"[CAPRISA 004] is a step in the right direction, but it is a step on a path," McCormack explained

during her conclusion. “Are we excited? Yes! Are we ready for roll out? We’re not quite there yet.”

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http://beta.docker.poz.com/article/hiv-caprisa-microbicide-18794-7889