First Rectal Gel Studies Show Real Promise

March 1, 2011 By David Evans

Microbicide researchers announced success with a new rectal gel designed to cut HIV transmission, saying that early data suggests it could work quite well provided that they can figure out how to make it more compatible with the fragile cells that line the rectum. Those important tweaks are already in the works and were also reported Monday, February 28, at the 18th Conference on Retroviruses and Opportunistic Infections (CROI) in Boston.

In the first study, Peter Anton, MD, from the David Geffen School of Medicine at the University of California in Los Angeles presented data on behalf of his colleagues from the Microbicide Trials Network 006 (MTN-006) study. MTN-006 was designed to test how well a vaginal gel that demonstrated a roughly 40 percent reduction in new infection in women might work as a rectal gel for people who have anal sex.

The vaginal gel, manufactured by a company called CONRAD and containing a 1 percent solution of the antiretroviral (ARV) drug tenofovir—found in Viread, Truvada and Atripla—demonstrated superiority to a placebo in the CAPRISA 004 trial in 2010. Women who used the gel intermittently were about 39 percent less likely to become infected with HIV than women who used a gel that contained a placebo.

Researchers have been eager to fast-track an effective microbicide for rectal use, given that rates of HIV infection are so high among men who have sex with men in many parts of the world, and since anal sex—which plenty of women engage in as well—confers such a high risk for HIV transmission.

The first step in the process was to demonstrate whether the same gel that worked vaginally would have any potential as a rectal gel. To determine this, Anton and his colleagues recruited 14 men and 4 women, all HIV-negative, to try the gel rectally and see whether the it was safe and whether cells taken from participants' rectums after the gel was applied would be resistant to HIV infection. Anton's team were also curious how likely people who tried the gel would be to use it for anal sex in the future.

In terms of potential effectiveness, Anton's group first looked at how well the gel got into the cells of the rectum and to the blood stream, and compared this with tenofovir taken orally, which is also being tested for its HIV-prevention potential. The group found that while very little of the drug in

gel form made it into the blood stream—which is actually a good thing as this could increase the risk of side effects—concentrations in the rectum were many times higher with the gel compared with people who took the oral version.

Anton and his colleagues next looked at cells taken from the rectums of people who used the gel or the oral form of tenofovir and examined whether those cells were either more or less susceptible to being infected with HIV in test tubes.

Strikingly, the team found that when people took the oral version of tenofovir, their cells were not resistant to infection. The same was true when they looked at cells taken after only a single application of the gel rectally. When people applied the gel every day for seven days, however, the cells taken from their rectums were much more resistant to infection. This, said Anton, offers strong signals that the gel could work for anal sex as it did for vaginal sex.

All didn't go smoothly, however. Only 25 percent of the people who used the tenofovir gel said they liked it, compared with 50 percent of the people who received a placebo gel—though most indicated that they would still use it if it were shown to be effective. Also, the tenofovir gel caused some unpleasant side effects in some of the participants' lower intestinal tract.

"These results tell us that tenofovir gel was relatively safe to use in the rectum for most participants, but we need to address side effects to make it more acceptable to use," Anton said. "Even though three quarters of the participants reported they didn't like the gel, we are very encouraged that the majority would consider using such a product in the future."

When the group looked for an explanation for the side effects, Anton and his colleagues realized that the tenofovir gel was causing an imbalance in the chemicals inside and outside of the rectal cells, causing those cells to expel water and become damaged (a process called osmolality). This meant that the specific tenofovir gel used in the study really couldn't ever be offered in real world conditions.

Fortunately, one of Anton's colleagues, Charlene Dezzutti, PhD, from the University of Pittsburgh, is already working on an improved version of the tenofovir gel. Her team published a poster at CROI documenting their progress on the improved gel so far in test tubes.

By reducing the amount of silicon in the gel, Dezzutti's team reduced the osmolality of the gel and made it potentially much safer and less irritating for rectal cells. The new formulation, however, is just as effective at fighting HIV as the old gel. The next step, according to the Microbicide Trials Network, will be to study the new gel formulation under the same conditions as the old one, and that study is already underway at three sites in the United States.

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