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When prophecy fails: How to better predict success in HIV prevention clinical trials

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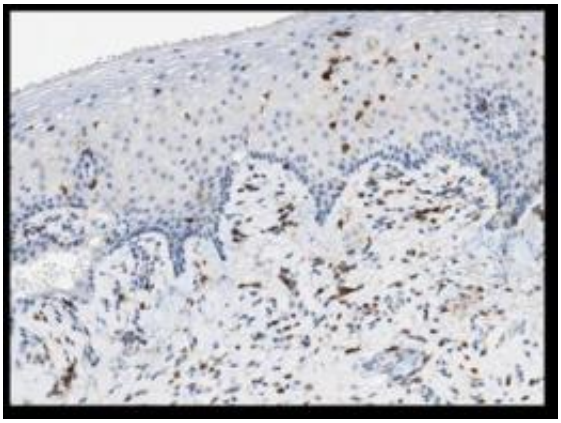

Vaginal tissue stained for cells containing CD4 receptors, which are susceptible to HIV infection. A new study shows that antiretroviral drug concentrations vary widely across different types of tissue. This has important implications for the use of ARVs for the prevention of HIV transmission. Credit: Source: Kashuba Laboratory, UNC Eshelman School of Pharmacy

New research from the University of North Carolina at Chapel Hill schools of medicine and pharmacy may help explain the failure of some recent clinical trials of prevention of HIV infection, compared to the success of others that used the same drugs.

The study published online December 7, 2011 in the journal *Science Translational Medicine*, also suggests how to improve the chances for success, even before the research begins. These suggestions are

reinforced in an editorial by several of the UNC authors writing in The Lancet, also published online December 7, 2011.

Over the past two years, results from several clinical trials involving pre-exposure prophylaxis (PrEP) for HIV infection have been a mixed bag of successful prevention and futility. Reports described varying degrees of successful HIV infection prevention in four trials and failure in two others. In all the PrEP trials, the drugs used were tenofovir (TFV) and emtricitabine (FTC) in daily oral and/or gel combinations.

These drugs have been shown to be protective against HIV infection in animal PrEP studies and are now being used clinically, and tenofovir is considered the backbone of HIV therapy, both used orally and topically.

The new UNC study looked at drug concentrations in the mucus membrane tissues that are most susceptible to HIV infection: the tissue lining the vagina, cervix and rectum. The study was led by Angela D.M. Kashuba, PharmD, professor in the UNC Eshelman School of Pharmacy and director of the UNC Center for AIDS Research Clinical Pharmacology and Analytic Chemistry Core. She also is a member of the UNC Institute for Global Health & Infectious Diseases.

"We did this study to understand how much drug got into these tissues and how long they lasted over two weeks," Kashuba said. And after giving normal, healthy volunteers a single pill combination of TFV/FTC, "What we found over the next 14 days was somewhat surprising. When a person takes a drug, it doesn't end up in the same concentration in different tissues."

Indeed, concentrations of tenofovir were 100 times higher in rectal tissue than in vaginal or cervical tissue. "And FTC achieved concentrations 10 to 15 times higher in vaginal and cervical tissue than they were in rectal tissue," Kashuba said. "And this raised some

questions: because of these discrepancies can the two drugs be used equally well in both populations – women at risk for HIV infection and men at risk for HIV infection? And are the concentrations achieved even after a single dose high enough to prevent HIV infections?"

According to Kashuba, it's clear from the recent clinical studies that drug concentration in tissue may make a difference in effectiveness. For example, in one of the placebo-controlled PrEP clinical trials involving men who have sex with men, the combination of these drugs provided about 44 percent effectiveness overall.

But the half the men given the active form of the drugs had no detectable drug in their system when they were sampled during the study and, therefore, were not taking it consistently every day. Thus, the high tenofovir concentrations in rectal tissue could explain the relatively high efficacy of 44 percent.

Results of a PrEP clinical trial (VOICE) conducted in heterosexual women in Uganda, South Africa and Zimbabwe, also paralleled the UNC findings. The daily tenofovir arm was stopped because no protection was seen for the drug taken daily. "If these women did not take the drug every single day, we think our study supports the fact there would not be good efficacy because tenofovir drug concentrations in the vagina and cervix are so much lower than what we see in rectal tissue, Kashuba said."

The authors of the study and the editorial say adherence to taking the drug as prescribed is crucial. They lament that the only prospective means of measuring adherence now available is what the patient reports. "And so if you ask someone did you take all your doses, most will say yes," Kashuba said "People want to be considered good study participants, and sometimes they just can't remember how many doses they took last week, or in the last month, be it almost all of the doses or

half of them."

The UNC researcher points to lessons learned: "Before delving into a clinical trial, we need to keep in mind that when someone takes a pill, you can't assume that the drug gets in all places at the same amount. And before we can select the drugs and the right doses for a clinical trial, we need to know what concentrations in tissue prevent HIV infection. They could be different."

And along with the above, the authors emphasize the need to develop ways to objectively measure drug-taking behavior in clinical studies so that the research can be designed and interpreted correctly.

Provided by University of North Carolina School of Medicine

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