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The North Carolina Contribution to the CAPRISA 004 Study:

The Global Health Initiative in Action

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The results of the CAPRISA (Centre for the AIDS Programme of Research in South Africa) 004 study have invigorated the world of human immunodeficiency virus (HIV) infection prevention [1]. This trial is promising step toward giving women a new tool to protect themselves against HIV infection because it is the first in which a topical pre-exposure prophylactic (PrEP) agent (ie, 1% tenofovir gel) showed a statistically significant decrease in the risk of HIV infection. The tenofovir gel yielded a 39% reduction in risk among all users and a 54% reduction among the most frequent users. Encouragingly, tenofovir gel also showed an overall 51% decrease in the risk of new herpes simplex virus type 2 (HSV-2) infections [1].

The premise of PrEP was developed in part from the observations that tenofovir and similar antiretroviral drugs can disrupt the life cycle of HIV in HIV-positive individuals. HIV prevention scientists who conducted various trials of topical and oral PrEP formulations hypothesized that if a drug such as tenofovir was in the blood stream or genital tract on exposure to HIV, the virus might be destroyed before it could infiltrate host cells. Thus, an individual exposed to the virus would be protected from becoming acquiring HIV infection.

The CAPRISA 004 study was conducted during 2007–2010 in the rural village of Vulindlela and in Durban, both of which are in the South African province of KwaZulu-Natal. The study recruited sexually active women who were randomly assigned to 2 study arms; in one, participants received 1% tenofovir gel, and in the other, participants received placebo gel. Tenofovir gel is a clear, colorless, and odorless viscous gel, packaged in single-dose plastic applicators. Women were instructed to use an intermittent, coitally dependent, vaginal dosing strategy, known as BAT-24, which involves insertion of 1 gel up to 12 hours *B*efore sex, insertion of 1 gel as soon as possible within 12 hours *A*fter sex, and use of no more than *T*wo doses in 24-hour period. A total of 889 women were enrolled and randomized; 445 were in the tenofovir gel arm, and 444 were in the placebo arm. One indicator of the study's high quality is the low loss to follow-up—nearly 95% of participants completed the study.

After years of disappointing findings from trials of hopeful HIV vaccine and PrEP candidates, the scientific, medical, and advocacy community waited eagerly for the results of the CAPRISA 004 study. The results were met with a standing ovation at the Vienna International AIDS Conference in July 2010. The success of topical PrEP in this trial represents new possibilities for abating the HIV epidemic. One of the most important features of PrEP is that it empowers women who often cannot negotiate safe sex practices with their partners to take HIV prevention into their own hands. A woman at risk for HIV infection could insert the gel before and after sex or could take a pill daily (different trials test these different models) without her partner's involvement.

The Global Health Initiative: In-Country Ownership

The importance of the trial, however, is greater than its results. The study espoused the principles of country ownership and capacity building well before their emphasis in the president's Global Health Initiative [2]. It also demonstrated the value added by North Carolina institutions in facilitating high-quality science in low-resource settings.

The CAPRISA 004 study was led by a South African institution, a global first. The Centre for the AIDS Programme of Research in South Africa at the University of KwaZulu-Natal (Durban) spearheaded the trial. The study was the product of highly talented South African investigators, who designed a methodologically rigorous randomized trial, chose an appropriate antiretroviral product, designed a creative dosing regimen that served the trial participants' situation, analyzed their data in robust fashion, presented their findings to an international audience, and published their results in one of the most influential scientific journals [1].

The North Carolina/CAPRISA 004 Connection

Two North Carolina institutions, FHI and the University of North Carolina (UNC)–Chapel Hill, were among the US-based partners that collaborated with the CAPRISA 004 study team. These 2 organizations are also active members of the Triangle Global Health Consortium [3]. The CAPRISA team was able to leverage FHI's organizational strengths in science facilitation and its long tradition of managing high-quality clinical trials in low-resource settings. Likewise, the Clinical Pharmacology and Analytical Chemistry Core at the UNC–Chapel Hill Center for AIDS Research added the essential biologic data to complete the etiologic puzzle and conclusively demonstrate that 1% topical tenofovir gel prevented HIV infection. The state of North Carolina is proud to have had a role in this landmark undertaking.

FHI contributed to the CAPRISA 004 study in a number of ways. FHI's director of biostatistics worked with the CAPRISA statistical team, helping them develop the analytic plan and assisting in the primary analysis of trial results, and was a coauthor of the article by Abdool Kareem and colleagues [1]. A senior FHI behavioral scientist helped design the innovative intermittent-dosing regimen used in the study. She also designed and oversaw the ancillary case-control study that was performed to assess factors associated with infection. FHI scientists helped assess the endocrinologic characteristics of different contraceptives used to prevent pregnancy during the trial. An FHI clinician served as the medical reviewer. FHI's senior research informatics scientist assessed the data management site before the study was started. Throughout the trial, FHI staff provided monitoring and quality-control assistance to CAPRISA investigators, to ensure adherence to internationally accepted guidelines for Good Clinical Practice. FHI's Protection of Human Subjects Committee reviewed, approved, and monitored the trial. FHI staff also facilitated meetings of the study's data safety and monitoring board, which reviewed the ongoing conduct of the trial. The results dissemination plan was guided by senior FHI communications advisors.

The UNC–Chapel Hill Center for AIDS Research also contributed to the CAPRISA 004 study in multiple ways. The Clinical Pharmacology and Analytical Chemistry Core worked closely with CAPRISA 004 investigators to develop the clinical protocol for measuring the tenofovir concentration in the genital tract and blood of study volunteers. The Center for AIDS Research also provided tools and techniques that allowed the CAPRISA 004 investigators to obtain samples in a minimally invasive and minimally labor-intensive fashion. The Clinical Pharmacology and Analytical Chemistry Core developed highly sensitive and specific assays to measure levels of tenofovir and its active metabolite tenofovir-diphosphate in specimens of blood, vaginal secretions, and vaginal and cervical

tissues collected from study participants. Finally, the Center for AIDS Research provided pharmacokinetic expertise for data analysis and interpretation of the tenofovir concentrations in the context of gel adherence and efficacy against HIV type 1 and HSV-2 infection.

Conclusion

The results of the CAPRISA 004 study have changed the field of HIV infection prevention. The CAPRISA 004 trial set a high bar for research conducted in any setting, let alone an institution based in a developing country. The trial's promising results provide hope for a new female-controlled prevention tool. If these results are replicated in the National Institutes of Health–funded VOICE (Vaginal and Oral Interventions to Control the Epidemic) trial, women worldwide will have an effective means of protecting themselves against HIV and HSV-2 infection. Two North Carolina organizations, FHI and UNC–Chapel Hill, were partners to the South African investigators leading the CAPRISA 004 study. This is one of many examples of how North Carolina contributes to global health.

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