CAPRISA
CENTRE FOR THE AIDS PROGRAMME OF RESEARCH IN SOUTH AFRICA

Newsletter

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Genital inflammation reduces efficacy of tenofovir gel:

Shedding new light on why topical PrEP effectiveness varies in women

Why do some women get HIV infection, even though they are using tenofovir gel for prophylaxis? A new study by scientists at the CAPRISA, published in *Nature Medicine* this week, shows that genital inflammation significantly reduces the effectiveness of tenofovir gel in preventing HIV infection in women. These findings indicate that both genital inflammation and adherence need to be addressed to improve the effectiveness of topical pre-exposure prophylaxis strategies for HIV prevention in women.

The researchers measured small proteins, known as cytokines, in the vagina. Raised cytokines levels in the vagina indicate the presence of inflammatory immune responses, even in the absence of clinical symptoms. In this study, HIV infection rates and cytokine levels as a marker of genital inflammation were studied longitudinally in 774 women over 2.5 years. Lead authors of the study, Dr Lyle McKinnon and Dr Lenine Liebenberg, found that women with genital inflammation were at higher risk of subsequently contracting HIV compared to women without inflammation. The study further showed that tenofovir gel provided 57% protection against HIV acquisition in women who had no evidence of vaginal inflammation but provided no protection in women with genital inflammation, even if they used the gel consistently.

"This study gives us an important clue to enhance HIV prevention in women. It is not only adherence-related behaviours, but also biological processes in the vaginal that need to be addressed to prevent HIV and enhance the effectiveness of topical PrEP," said Professor Salim Abdool Karim, Director of CAPRISA and CAPRISA Professor of Global Health at Columbia University.

In this study, 9 pro-inflammatory cytokines were measured in specimens collected at over 2,139 clinic visits by 774 women at a rural and urban clinic in KwaZulu-Natal, South Africa to define the levels of genital inflammation. In women who had no genital inflammation, women assigned to tenofovir gel had a HIV incidence rate of 2.3 per 100 person-years (95% CI: 1.0–4.4) compared to 5.4 per 100 person-years (95% CI: 3.4–8.2) in women assigned to placebo gel. Conversely, in women with genital inflammation, the HIV incidence rate in those assigned to tenofovir gel was 6.8 per 100 person-years (95% CI: 3.8–11.1) compared to 7.0 per 100 person-years (95% CI: 3.7–11.9) in women assigned to placebo gel. The study found that among women who used the gel most of the time (≥ 50% of sex acts), tenofovir gel was 75% protective (95% CI 25–92%, P = 0.014) in those women who had no genital inflammation as compared to no protection (-10%; 95% CI −184–57%, P = 0.844) in women with evidence of genital inflammation.

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In this Issue

Our feature story this month reports on the study published in Nature Medicine that shows that genital inflammation undermines the effectiveness of tenofovir gel in preventing HIV acquisition in women.

On page 2 we highlight the visit and lecture by Prof Madhukar Pai, the Canada Research Chair in Epidemiology & Global Health at McGill University.

We feature the presentations made by CAPRISA affiliated students and staff at the NICD, at the recent HVTN meeting held in Cape Town, we provide a summary of Prof Jerome Singh's contributions to the review that examined the challenges adolescents faced in accessing SRHS and we also report on the visit by newly appointed OSCO Programme Officer, Blanca Castillo on page 3.

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...(*from p1*) Genital inflammation reduces efficacy of tenofovir gel

In 2010, the CAPRISA 004 trial provided the first evidence that tenofovir can prevent sexual transmission of HIV. Tenofovir gel reduced HIV acquisition by 39% overall. Two subsequent studies found that tenofovir gel was not effective, most likely because most of the women in the trials did not use the gel consistently. A sub-group analysis of the FACTS001 and the MTN 003 trials showed that the gel was just over 50% effective in consistent users, highlighting the importance of high adherence. The new evidence emerging from this genital inflammation study indicates that there may be a biological basis for the differing results as well. The causes of genital inflammation are not well understood at present. Previous studies have shown that there are many possible causes of genital inflammation in women, including imbalances in the bacteria of the vaginal microbiome, sexually transmitted infections and vaginal practices.

Commenting on the study, Dr Jo-Ann Passmore (in the photo), Head of the CAPRISA mucosal immunology laboratory and a Professor at the University of Cape Town, said: "Genital inflammation, which is present in up to a third of women, makes it harder to protect women from HIV infection." She said that, "…the next step is to expand our results to assess how genital inflammation might affect the efficacy in HIV prevention trials of vaccines, passive immunization with antibodies and antiretroviral PrEP administered through pills, rings and implants." Dr Passmore is the Principal Investigator of this research, which was funded by the US National Institutes of Health. The original CAPRISA 004 study was funded by The US Agency for International Development and was conducted by CAPRISA in partnership with FHI360, CONRAD and Gilead Sciences.

According to Dr Mckinnon, who is also a researcher at the University of Manitoba, "Reducing inflammation of the genital tract in women may augment the HIV prevention in women." "The study highlights the major role of genital inflammation in HIV risk and in modifying the efficacy of HIV prevention strategies," said Dr Liebenberg. "Current and future attempts to improve topical PrEP efficacy would benefit from knowing the causes of inflammation, and developing new strategies to treat genital inflammation."

One such effort is currently underway at the University of Manitoba, where a study is being led by Dr Keith Fowke to use the anti-inflammatory, Acetylsalicylic acid (known commonly as aspirin), to reduce inflammatory responses in the female genital tract. (ClinicalTrials.gov: NCT02079077).

Access the scientific paper at: http://dx.doi.org/10.1038/nm.4506

Strengthen primary health care to reduce the burden of TB says epidemiologist

(L-R):Dr Nesri Padayatchi Deputy Director CAPRISA, Dr Satvinder Singh WHO, Prof Madhukar Pai McGill University and Dr Kogie Naidoo Head: HIV & TB Treatment at CAPRISA. Pai is also the Associate Director of the McGill International TB Centre.

CAPRISA hosted Professor Madhukar Pai, the Canada Research Chair in Epidemiology & Global Health at McGill University and Dr Satvinder Singh Treatment and Care, in the HIV Department at WHO on 23 February. Pai's lecture titled, Primary care: the weakest link in TB control, was well attended and raised critical issues that impede effective TB treatment. He said that in most countries, 'TB is a vertical program, and poorly integrated into the general health system and most primary care providers do a poor job of managing TB'. He called for the strengthening of primary care and the integration of TB into Universal Health Coverage. Commenting on his presentation Dr Kogie Naidoo, head of CAPRISA HIV and Treatment said, "Pai's primary research focus is on improving the diagnosis and treatment of tuberculosis, particularly in India and South Africa where the burden of disease is extremely high."

International Review on access to SRHS by adolescents

CAPRISA's head of Ethics, Professor Jerome Singh, was a key contributor to a collaborative international review by the United Nations Children Fund (UNICEF) and the Southern African AIDS Trust, to assess the challenges that adolescents experience globally, in accessing sexual and reproductive healthcare services (SRHS). CAPRISA's Faadiela Jogee and Samantha Chareka also contributed to the report.

The review, The *Age of Consent: Legal, Ethical, Cultural and Social Review Project*, explored the ethical, social and cultural factors that impact adolescents in relation to: the age of consent for sex and sexual debut, adolescent sexuality, contraception and abortion, ART, PrEP, HIV counselling and testing (HCT). The review was undertaken in 11 countries globally. "The project lends itself to a broader initiative that endeavors to ignite social change and foster advocacy at national and international levels via UNICEF and UNAIDS's 'ALL IN' initiative," said Singh. The initiative strives to put an end to the AIDS epidemic in those most vulnerable to the disease, adolescents.

He said that the key findings included the average age of consent for sex and sexual debut globally is 16 years – however, there are exceptions with cultural and religious factors. HIV/AIDS related stigma and discrimination, the absence of adolescent-friendly youth services, and cultural and religious attitudes towards sexuality and gender are the principal factors that challenge adolescents' access to SRHS, particularly contraception and HCT worldwide.

Access the link at: http://www.satregional.org/downloads/

Presentations at HVTN meeting of a 'very high standard'

Seated from left are Dr Nono Mkhize (NICD), Dieter Mielke (UCT), Ms Anneta Naidoo (CHIL), Ms One Dintwe (CHIL), Dr Zanele Ditse (NICD) and Ms Simone Richardson (NICD).

Four staff and students, from the CAPRISA Centre of Excellence in HIV Prevention based at National Institutes of Communicable Diseases (NICD) and University of Cape Town, presented their work in a session for Early Stage Investigator in Basic Science at the recent HVTN meeting held in Cape Town from 21-22 Feb.

The session was chaired by Dr Julie McElrath, head of the Laboratory Program for the HVTN (far right in the photograph).

"All the presentations were of very high standard and generated a lot of discussion", said Professor Lynn Morris, interim Executive Director of NICD.

Newly appointed OCSO official visits CAPRISA

Photo: at the CAPRISA eThekwini Research Clinic (L-R) Front Row: Leila Mansoor, Blanca Castillo, Anushka Naidoo, Kogie Naidoo.Back Row: Kathy Mngadi, Charlene Harichand, Yajna Duki, Kalendri Naidoo

Blanca Castillo the newly appointed Programme officer, in the Office of Clinical Site Oversight (OCSO), in the Division of AIDS, National Institutes of Allergy and Infectious Diseases (NIAID) at the National Institutes of Health, spent three days at CAPRISA from 26 – 28 February to gain insight into CAPRISA's strategic operations. She was hosted by Dr Nesri Padayatchi, Deputy Director CAPRISA. Castillo visited the CAPRISA research clinics at Vulindlela, Umlazi, eThekwini and at the King Dinuzulu Hospital where she held discussions with study PIs and study coordinators. At the CAPRISA headquarters, in the DDMRI she met the support core team and had a tour of the newly refurbished laboratory equipped with a BD Fortessa, the Abbott SP and the Roche Ampliprep.

Scientific papers published in 2018

1 Abdool Karim SS, Passmore J-AS, Cheryl Baxter. The Microbiome and HIV Prevention Strategies in Women. Current *Opinion in HIV and AIDS* 2018; 13(1):81–87.

2 Dorward J, Drain PK, Garrett N. Point-of-care viral load testing and differentiated HIV care. *Lancet HIV* 2018; 5(1): e8-e9. doi: 10.1016/S2352-3018(17)30211-4.

3 Naidoo A, Ramsuran V, Chirehwa M, Denti P, McIlleron H, Naidoo K, Yende-Zuma N, Singh R, Ngcapu S, Chaudhry M, Pepper MS, Padayatchi N. Effect of genetic variation in UGT1A and ABCB1 on moxifloxacin pharmacokinetics in South African patients with tuberculosis. *Pharmacogenomics* 2018; 19(1):17-29.

4 Ramsuran V, Naranbhai V, Horowitz A, Qi Y, Martin MP, Yuki Y, Gao X, Walker-Sperling V, Del Prete GQ, Schneider DK, Lifson JD, Fellay J, Deeks SG, Martin JN, Goedert JJ, Wolinsky SM, Michael NL, Kirk GD, Buchbinder S, Haas D, Ndung'u T, Goulder P, Parham P, Walker BD, Carlson JM, Carrington M. Elevated HLA-A expression impairs HIV control through inhibition of NKG2A-expressing cells. *Science* 2018; 359(6371):86-90.

5 Reimers P, Israel-Ballard K, Craig M, SpiesL, Thior I, Tanser F, Coutsoudis A. A Cluster Randomised Trial to Determine the Efficacy of the "Feeding Buddies" Programme in Improving Exclusive Breastfeeding Rates Among HIV-Infected Women in Rural KwaZulu-Natal, South Africa. *AIDS and Behavior* 2018; 22(1):212-223.

6 Vandormael A, de Oliveira T, Tanser F, Barnighausen T, Herbeck JT. High percentage of undiagnosed HIV cases within a hyperendemic South African community: a population-based study. Journal of Epidemiol Community Health 2018 Feb;72 (2):168-172.

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8 Dlova NC, Chateau A, Khoza N, Skenjane A, Mkhize M, Katibi OS, Grobler A, Gwegweni JT, Mosam A. Prevalence of skin diseases treated at public referral hospitals in KwaZulu-Natal, South Africa. *British Journal Dermatology* 2018;178(1):e1-e2. doi: 10.1111/bjd.15534.

9 McKinnon LR, Liebenberg LJ, Yende-Zuma N, Archary D, Ngcapu S, Sivro A, Nagelkerke N, Garcia Lerma JG, Kashuba AD, Masson L, Mansoor LE, Abdool Karim Q, Abdool Karim SS, Passmore JS. Genital inflammation undermines the effectiveness of tenofovir gel in preventing HIV acquisition in women. *Nature Medicine* 2018 Feb 26. doi: 10.1038/nm.4506. https://www.ncbi.nlm.nih.gov/pubmed/29480895

*continuation from previous newsletter

Scientific Reviews

Abstracts submitted for review		Manuscripts submitted for review		Ancillary studies submitted for review	
Total#	Cumulative^	Total#	Cumulative^	Total#	Cumulative^
5	395	1	230	0	84

 # for month, ^ since committee initiation