



# CAPRISA

CENTRE FOR THE AIDS PROGRAMME OF RESEARCH IN SOUTH AFRICA

Newsletter

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## Biological mechanisms of hormonal contraceptive effects on HIV acquisition

### In this Issue

The feature story this month focuses on research assessing the biological mechanisms of a hormone contraceptive and the effect of HIV acquisition.

On page 2, we report on a PrEP demonstration project in South Africa; an EDCTP Early Career Fellowship awarded to a CAPRISA Research Associate; and the best poster prize won by a CAPRISA PhD Fellow.

We report on two new studies that have been awarded grants by the NIH and SAMRC; a CAPRISA scientist's participation at the House of Lords Science & Technology committee; and the virtual H3 Africa Consortium Meeting, on page 3.

We congratulate CAPRISA Honorary Scientist, who was awarded the prestigious JoPPP Award on page 4.

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Research on the biological mechanisms that potentially link the injectable hormonal contraceptive, DMPA, with an increased risk in HIV acquisition was recently published in *Mucosal Immunology*.

To better define the mucosal impact of DMPA, researchers from CAPRISA, AHRI and the University of Manitoba developed a mass spectrometry assay to measure DMPA, norethisterone enanthate (NET-EN), and progesterone concentrations in plasma samples. The assay was applied to longitudinal samples obtained from South African women enrolled in the CAPRISA004 study (n = 664), with parallel quantification of 48 cytokines and >500 host proteins in cervicovaginal lavage.

The researchers found higher DMPA levels that were associated with reduced CVL concentrations of numerous cytokines including GCSF, MCSF, IL-16, CTACK, LIF, IL-1 $\alpha$ , and SCGF- $\beta$  in adjusted statistical models (Figure). Dose-dependent relationships between DMPA concentration and genital cytokines were frequently observed, particularly for reduced concentrations of growth factors such as GCSF and MCSF supervised clustering of host proteins by DMPA concentration suggest that women with low DMPA had increases in proteins associated with mucosal fluid function, growth factors, and keratinization.

Although DMPA was not broadly pro-inflammatory, it was associated with increased IP-10 in HSV-2 seropositive and older women. DMPA-cytokine associations frequently differed by vaginal microbiome; in non-Lactobacillus-dominant women, DMPA was associated with ele-

vated IL-8, MCP-1, and IP-10 concentrations. This could mean that DMPA alone is not broadly pro-inflammatory, but has different effects in different sub-groups of women.

The biological effects of DMPA may vary depending on age, HSV-2 status, and vaginal microbiome composition and have important implications for understanding the biological effects of injectable hormonal contraceptives in women at high risk of HIV infection.

### For further reading see:

Molathegi RP, et al. Plasma Concentration of Injectable Contraceptive Correlates With Reduced Cervicovaginal Growth Factor Expression in South African Women. *Mucosal Immunology* 2020; 13(3):449-459. <https://www.ncbi.nlm.nih.gov/pubmed/31896762>

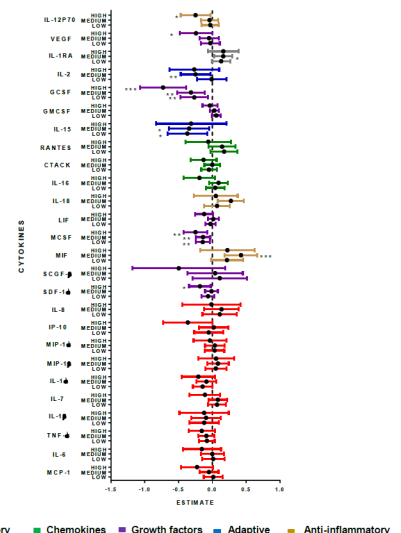


Figure: The effect of MPA levels on cervicovaginal cytokines milieu stratified by pro-inflammatory cytokines (red), chemokines (green), growth factors (purple), adaptive factors (blue), and anti-inflammatory cytokines (gray).



## PrEP breakthrough infections

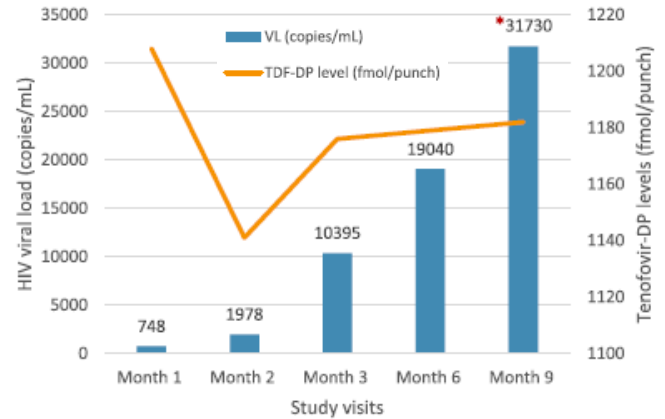
A case study detailing a breakthrough infection while on oral pre-exposure prophylaxis (PrEP) was recently published in *BMC Infectious Diseases*. The report highlights the importance of appropriate HIV screening during wider oral PrEP scale-up to circumvent the consequences of prolonged dual therapy in an undiagnosed HIV infection and in turn prevent ARV resistance.

This report describes a 20-year-old woman in a HIV sero-discordant relationship who initiated oral PrEP through a demonstration project (CAPRISA 084) in October 2017. Despite good adherence throughout her PrEP use, she tested HIV antibody positive at month nine of study participation. Retrospective testing showed increasing HIV viral load over time (Figure), and retrospective use of fourth-generation rapid HIV tests showed HIV detection (positive antigen/antibody) at month one.

Sequencing confirmed a dominant wild type at month one with dual therapy resistance patterns emerging by month three (M184V and K65R mutations), which suggests protracted PrEP use during an undetected HIV infection.

The participant was referred to the infectious diseases department for further management and was initiated on a first line, tenofovir-sparing regimen. In January 2020, the participant had been on ARV-therapy for 13 months and had no signs of either clinical, immunologic or virologic failure. This case provides evidence that supports a recommendation for the use of fourth-generation HIV rapid tests for routine HIV screening for PrEP use. Findings show the importance of prompt ARV resistance testing once HIV infection is identified, initia-

tion on the appropriate ART-regimen and subsequent follow-up of both participant and partner/s for early detection of ART-regimen failure.



**Figure:** Participant HIV viral load and TDF-DP levels at different time-points in study participation. \*All 3rd generation HIV rapid tests were negative until month 9, where both HIV rapid tests were positive

### For further reading see:

CL Naicker\*, LE Mansoor\*, et al. *Importance of early identification of PrEP breakthrough infections in generalized HIV epidemic settings: A case study from a PrEP Demonstration Project in South Africa. BMC Infect Dis 2020; 20(1):532. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7374822/> Equal contribution – Joint first author*

## EDCTP Early Career Fellowship awarded



CAPRISA congratulates Dr Nikita Naicker, a Research Associate at CAPRISA, who was awarded an European and Developing Countries Clinical Trials Partnership (EDCTP) Career Development Award aimed at providing individual training to talented early-career scientists to develop as independent researchers and team leaders at host institutions in sub-Saharan Africa for long-term conti-

nity, networking and research ownership in the region. Naicker was awarded the funding of €141 500 over a 3-year period.

The overall aim of the fellowship said Naicker was to 'investigate metformin as a repurposed agent for improving TB treatment outcomes and better understanding of immune responses and host containment of TB'.

## PhD Fellow scoops best oral presentation award



CAPRISA PhD fellow, Andile Mtshali, scooped the best oral award at the University of KwaZulu-Natal School of Laboratory Medicine and Medical Sciences for her presentation titled "Temporal changes in vaginal microbiota and cytokines in women treated for bacterial vaginosis". She found that metronidazole for the treatment of BV induced short-term shifts in the vaginal micro-

biota and mucosal cytokines, while treatment failures promoted long-term elevation of pro-inflammatory cytokine concentrations at the genital tract.

Andile plans to submit her PhD Thesis by end of October 2020 and is grateful to CAPRISA and her PhD supervisors for the support.



## Examining the immunological and metabolic effects of maternal ARVs

**D**r Sinaye Ngcapu, CAPRISA scientist, was awarded an R01 research grant earlier this year by the NIH-SAMRC Joint Call.

The 5 year study will determine whether specific vaginal anaerobic microbes and associated inflammation can influence preterm deliveries or the acquisition of HIV infections.

The study will also examine the immunological and metabolic effects of maternal ARV use during pregnancy on in-



fant health without HIV exposure. This will inform the risk-benefit analysis of maternal PrEP explained Ngcapu.

“This study has the potential to lead to more refined interventions to mitigate risks of adverse birth outcomes, HIV acquisition and neonatal morbidity,” he said.

## COVID studies awarded SAMRC Grant



**P**rofessor Penny Moore of NICD/CAPRISA was awarded an SAMRC grant to define SARS-CoV-2 neutralizing responses and Fc effector function in COVID-19 convalescent sera in South Africa.

This grant brings together a team of CAPRISA affiliates including Dr Simone Richardson, Dr Thandeka Moyo, Dr Nono Mkhize, Professors Carolyn Williamson and Lynn Morris, and Dr Jinal Bhiman to redeploy expertise and technical platforms developed for CAPRISA HIV studies towards SARS-CoV-2 studies.

In the last 6 months, the NICD HIV Virology Section has established serological, neutralization and Fc effector assays for COVID-19 work supported by this grant.

## Scientist invited to the House of Lords Science & Technology Committee

**C**APRISA scientist in the Mucosal Immunology Laboratory, Dr Lenine Liebenberg, was one of three experts invited to speak to the House of Lords Science and Technology Committee on 29<sup>th</sup> September to discuss the human microbiome, the potential of research in this area, and where action is needed to help realise this. The Committee is made up of members of the UK House of Lords that conduct deep dive inquiries



into areas of science and its conduct, taking written evidence and inviting experts to speak with them. Dr Liebenberg, along with Dr Patrick Varga-Weisz (University of Essex, University of Campinas, Cambridge) and Professor Julian Parkhill FRS FMedSci (University of Cambridge), collectively outlined the links between the microbiome and human health, and the benefits and concerns related to developing a *biome-bank*.

## H3Africa Consortium Meeting

**T**he NICD's Dr Cathrine Scheepers, chaired a COVID-19 session within the virtual H3Africa consortium meeting. During this session talks were given by Dr John Nkengasong (Director of Africa CDC), Prof. Mark Daly (Director of the Institute of Molecular Medicine in Finland and leader of the COVID-19 Host Genetics Initiative) and Prof. Gavin Churchyard (Founder and CEO of the Aurum Institute).

These talks covered topics rang-

ing from Africa CDC's strategy for defeating COVID-19 on the continent, the influence of host genetics on disease severity and the COVID-19 vaccine initiative and current vaccine strategies. Talks were also given by H3Africa PIs and Co-Investigators, including Dr. Simone Richardson from the NICD. Simone's talk focused on studying antibody responses to COVID-19 and using this information to inform on vaccine efficacy. The session concluded with a panel discussion,

including Prof. Lynn Morris of the NICD/CAPRISA on “Why Africa needs to be actively engaged in the search for a COVID vaccine”.





## Scientific papers published in 2020

- 48\* **Dorward J**, Sookrajh Y, Gate K, Khubone T, Mtshaka N, Mlisana K, Ngobese H, **Yende-Zuma N, Garrett N**. HIV treatment outcomes among people with initiation CD4 counts >500 cells/ $\mu$ L after implementation of Treat All in South African public clinics: a retrospective cohort study. *Journal of the International AIDS Society* 2020; 23(4): e25479
- 49 **Tanser F**, Kim HY, Vandormael A, Iwuji C, Bärnighausen T. Opportunities and Challenges in HIV Treatment as Prevention Research: Results from the ANRS 12249 Cluster-Randomized Trial and Associated Population Cohort. *Current HIV/AIDS Reports* 2020; 17(2):97-108.
- 50 **Dorward J, Msimango L**, Gibbs A, **Shozi H**, Tonkin-Crine S, Hayward G, Butler CC, Ngobese H, Drain PK, **Garrett N**. Understanding how community antiretroviral delivery influences engagement in HIV care: a qualitative assessment of the Centralised Chronic Medication Dispensing and Distribution programme in South Africa. *BMJ Open* 2020; 10(5):e035412. doi: 10.1136/bmjopen-2019-035412.
- 51 **Naicker N**, Sigal A, **Naidoo K**. Metformin as Host-Directed Therapy for TB Treatment: Scoping Review. *Frontiers in Microbiology* 2020; 11:435. doi: 10.3389/fmicb.2020.
- 52 Penn-Nicholson A, Mbandi SK, Thompson E, Mendelsohn SC, Suliman S, Chegou NN, Malherbe ST, Darboe F, Erasmus M, Hanekom WA, Bilek N, Fisher M, Kaufmann SHE, Winter J, Murphy M, Wood R, Morrow C, Van Rhijn I, Moody B, Murray M, Andrade BB, Sterling TR, Sutherland J, **Naidoo K, Pa-dayatchi N**, Walzl G, Hatherill M, Zak D, Scriba TJ; Adolescent Cohort Study team; GC6-74 Consortium; SATVI Clinical and Laboratory Team; ScreenTB Consortium; AE-TBC Consortium; RePORT Brazil Team; Peruvian Household Contacts Cohort Team; CAPRISA IMPRESS team. RISK6, a 6-gene transcriptomic signature of TB disease risk, diagnosis and treatment response. *Scientific Reports* 2020; 10(1):8629. doi: 10.1038/s41598-020-65043-8.
- 53 Moyo T, Kitchin D, **Moore PL**. Targeting the N332-supersite of the HIV-1 envelope for vaccine design. *Expert Opinion on Therapeutic Targets* 2020; 24(6):499-509.
- 54 Brault MA, Spiegelman D, **Abdool Karim SS**, Vermund SH. Integrating and Interpreting Findings from the Latest Treatment as Prevention Trials. *Current HIV/AIDS Reports* 2020; 17(3):249-258.
- 55 **Naicker\* CL, Mansoor\* LE, Dawood H, Naidoo K**, Singo D, Matten D, **Williamson C, Abdool Karim Q**. Importance of early identification of PrEP breakthrough infections in a generalized HIV epidemic: a case report from a PrEP demonstration project in South Africa. *BMC Infectious Diseases* 2020; 20(1):532. doi: 10.1186/s12879-020-05255-5.

\*continuation from previous newsletter

## Pharmacy researcher receives the prestigious JoPPP award

**W**e congratulate Mr Andy Gray MSc (Pharm), CAPRISA Honorary senior scientist who is one of three winners of the prestigious Helen-Clark-Journal of Pharmaceutical Policy and Practice Research (JoPPP) award which recognizes the talents of exceptional researchers who are making a significant contribution to the field of pharmaceutical policy and practice.



Gray joins Dr Birna Trap, Denmark; and Prof Paul Newton, University of Oxford as winners of the award presented on the 'scientific merit of their work, as well as the impact of their work on patients, decisions makers and on governments'. "This year's Award Winners have made a significant contribution to the advancement of pharmaceutical policy research, said the Editor-in-Chief of the Journal.



CAPRISA hosts a DST-NRF Centre of Excellence in HIV Prevention



**UNAIDS**  
CAPRISA is the UNAIDS Collaborating Centre for HIV Research and Policy



CAPRISA hosts a MRC HIV-TB Pathogenesis and Treatment Research Unit

CAPRISA hosts a DoH-MRC Special Initiative for HIV Prevention Technology



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