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CENTRE FOR THE AIDS PROGRAMME OF RESEARCH IN SOUTH AFRICA

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VOICE trial stops gel arm

The announcement that the VOICE (Vaginal and Oral Interventions to Control the Epidemic) study did not demonstrate protection against HIV in women prescribed daily tenofovir gel is a grave disappointment to CAPRISA.

Professor Salim Abdool Karim, Director of CAPRISA, and Pro Vice-Chancellor (Research) at the University of KwaZulu-Natal, who is a site investigator in the VOICE trial, said that "These results were totally unexpected as there is good evidence from laboratory research, animal studies and human trials showing that tenofovir gel prevents HIV. However, science does not always produce the answer we hope for. This is particularly pertinent when a drug's effectiveness is dependent on a complex combination of the biological activity of the drug and the human behaviour influencing use of the drug as prescribed during the study. I look forward to seeing the complete results and, in particular, an analysis of whether the drug levels in the female genital tract provides any clues to the study's outcome."

The VOICE study is designed to test whether antiretrovirals, either as tablets or as gels, are safe and effective in preventing sexual transmission of HIV in women from South Africa, Zimbabwe and Uganda. CAPRISA enrolled 623 of the 5029 women in the VOICE study; 360 at the CAPRISA eThekwini clinic in Durban, which was also one of the sites where the CAPRISA 004 study was conducted, and 263 at the Aurum clinic in Klerksdorp.

On 16 September 2011, the tenofovir tablet component of the VOICE study was discontinued after interim results showed that it was no better than placebo in preventing HIV in the study women, in contrast to results of a study (PartnersPrEP) which reported 62% reduction in HIV incidence in HIV discordant couples using tenofovir tablets daily as prophylaxis. Two months later, on 17 November 2011, a scheduled review of the VOICE study's data by the independent Data Safety and Monitoring Board (DSMB) revealed that the incidence rate of HIV infection in the women assigned to daily tenofovir gel was 6.0% compared to 6.1% in women assigned to placebo gel. Based on this latest review, the tenofovir gel component of the VOICE study is being discontinued while the tenofovir/emtricitabine tablet component is continuing to study completion.

Following the announcement in July 2010 that the CAPRISA 004 study demonstrated that tenofovir gel used before and after sex reduced HIV infection by 39% and genital herpes by 51%, there was high hope that the VOICE study of daily tenofovir gel would show similar promising results. As highlighted in previous microbicide studies, to be able to demonstrate effectiveness of a microbicide gel, women have to consistently use the right amount of the right drug to get the right drug levels in the right cells at the right time. At present, it is unclear whether the VOICE study's unexpected outcome could be due to inadequate or non-use of the gel by women in the study, to insufficient drug levels in women at the time of HIV exposure during sex, or to some other reason. A detailed analysis of the study data, anticipated in late 2012, will be critical to understanding the reasons for these perplexing tenofovir gel results as well as the VOICE trial's recently announced surprising results that tenofovir tablets also did not prevent HIV infection.

There is a substantial body of evidence on the effect of tenofovir on HIV infection – some of which contributed to the compelling rationale for undertaking the VOICE

In this issue...

The lead story for this issue of the newsletter focuses on the discontinuation of the tenofovir gel arm in the NIH-funded VOICE trial.

On page 2 we highlight the UNICEF HIV prevention meeting focusing on effective HIV prevention in adolescents.

We also congratulate Jerome Singh on being appointed to the inaugural high-level advisory panel of the Critical Path to TB Drug Regimens and Sengeziwe Sibeko on receiving the Oxford Nuffield Medical Fellowship and the Discovery Foundation Academic Fellowship to support her studies at Oxford University on page 3.

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UNICEF HIV Prevention Meeting

Tanuja Gengiah (CAPRISA), Suzanne LeClerc-Madlala (USAID), Susan Kasedde (UNICEF)

UNITD NATIONS, New York - a two day internal meeting of regional UNICEF HIV prevention advisors and field staff, preceded by a 2 day consultation with key researchers and implementers focusing on the evidence for effective HIV prevention in adolescents, was held at UNICEF House, 10-14 October 2011. Tanuja Gengiah, representing CAPRISA's prevention efforts, participated in the consultation along with other experts in the HIV Prevention and Adolescent health fields. Tanuja's presentation focused on microbicides overall, results of the CAPRISA 004 trial and implications for programmes to make 1% tenofovir gel available to young women. Her presentation expanded on what the likely safety and regulatory challenges to access might be and ways to address these. The overall focus of the meeting was for UNICEF to take stock of the major lessons from recent research on HIV prevention and their implications for prevention work targeting adolescents and young people in different regions and epidemic contexts, to review UNICEF's work on HIV prevention; and to define UNICEF's global vision, strategy and priorities. The meeting and discussions with the UNICEF staff included robust discussions on scaling up prevention efforts for young people and the atmosphere was that of hope for the future and pragmatism.

study - which is the only trial to study both tenofovir tablets and tenofovir gel. Research on tenofovir gel to date has shown that:

- Tenofovir gel prescribed for use before and after sex reduced the chance of acquiring HIV by 39%. Different types of analyses in the CAPRISA 004 study showed consistent results ranging from 39% to 45% protection.

- Tenofovir gel prescribed for use before and after sex reduced genital herpes acquisition by 51%. A recent laboratory study confirmed the mechanism of action of high doses of tenofovir, which is seen with gel but not tablets, against HSV -2 and provided further evidence from tissue culture and animal models for this effect.

- Tenofovir gel demonstrated a clear dose-response relationship - the higher the adherence, the higher the level of HIV protection, reaching 54% protection against HIV in the most consistent gel users.

- Tenofovir gel showed a strong correlation between tissue concentrations of the drug and the level of protection against HIV infection. The higher the level of drug detected in the genital compartment of women in the CAPRISA 004 trial, the greater the level of protection against HIV infection.

- Tenofovir gel has been shown repeatedly to be highly effective in the cervical explant tissue challenge model and in monkeys - in the recent monkey challenge study conducted by the CDC, not a single monkey exposed to SIV after application of tenofovir gel became infected.

Taken together, this set of promising findings makes continued research on tenofovir gel imperative and provides a strong rationale for the ongoing FACTS 001 study, which is being conducted by a consortium of South African researchers to assess the effectiveness of coital use of tenofovir gel in 2200 women in South Africa. It is anticipated that the FACTS 001 study, together with the VOICE study, is well placed to provide new insights into tenofovir gel and HIV infection in women. In light of these new results from the VOICE study, CAPRISA has initiated a review of its portfolio of tenofovir gel studies including CAPRISA 008, which provides post-trial access to tenofovir gel for women from the CAPRISA 004 trial and assesses implementation of tenofovir gel through family planning clinics. As additional data from the VOICE trial become available, CAPRISA will continually assess its tenofovir gel research plans – with the overall goal of empowering women with a safe and effective microbicide.

Young women in Africa bear the brunt of the HIV epidemic, with HIV rates up to 8 higher than the rates in their male counterparts. For women unable to assure mutual monogamy or consistent condom use, microbicides are a critically important technology. The need for a woman-controlled HIV prevention technology remains urgent.

Jerome Singh appointed to TB drug development committee

Professor Jerome Singh is congratulated on being appointed to the inaugural high-level advisory panel of the Critical Path to TB Drug Regimens (CPTR). This committee is CPTR's senior advisory body. The Advisory Panel will provide guidance to CPTR's Coordinating Group – helping CPTR navigate the complicated technical, political, and economic challenges that challenge the field of TB drug development. Members will also help catalyze global support for TB drug combination testing and champion the new regulatory pathways and other tools needed to accelerate the development and delivery of dramatically improved treatment to TB patients worldwide.

The inaugural members of the Advisory Panel are among the most well-respected thought leaders in the TB field, and include regulators, donors, bioethicists, advocates, industry representatives and others from around the world. Each inaugural Advisory Panel member will advise the initiative for at least a one-year term.

"The CPTR Advisory Panel offers a broad array of expertise that is necessary to advance a new paradigm for TB drug development," said Raymond Woosley, MD, PhD, President and CEO of C-PATH and a member of CPTR's Coordinating Group. "The members of CPTR look forward to working with the Advisory Panel to speed development and delivery of new TB regimens."

The CPTR initiative aims to speed the development of new and markedly improved drug regimens for tuberculosis. This partnership brings together the world's leading pharmaceutical and other drug developers, global regulatory agencies, and civil society organizations to support advances in regulatory science, the development of infrastructure, and other progress needed to facilitate the development and availability of new TB drug treatments. Co-founded by the Bill & Melinda Gates Foundation, the Critical Path Institute, and the TB Alliance and launched in March 2010, CPTR is working with stakeholders around the world to advance a new paradigm that dramatically speeds new TB drug regimens to patients.

Sengeziwe Sibeko to complete DPhil degree at Oxford

Dr Sengeziwe Sibeko will be leaving CAPRISA at the beginning of 2012 to pursue her studies towards her DPhil degree at Oxford University. Dr Sebiko secured two prestigious scholarships—the Oxford Nuffield Medical Fellowship and the Discovery Foundation Academic Fellowship - to fund her research on the function of dendritic cells in mucosal infection, comparing HIV-1 and HIV-2 infection at Oxford University.

Dr Sibeko is a specialist Obstetrician and Gynaecologist and the Project Director and protocol co-chair for CAPRISA's Acute Infection Study. Dr Sibeko's research interests are in enhancing our understanding of mucosal immunity. Dr Sibeko joined CAPRISA in 2006 as a post-doctoral trainee under the mentorship of Prof. Quarraisha Abdool Karim and has also been supported by EcoBio for Clinical Trials Training in preparation for the CAPRISA 004 microbicide study. Dr Sibeko was the recipient of the prestigious Columbia University Southern African Fogarty AIDS international training and Research Program traineeship and completed her Masters in Epidemiology at Columbia University in 2008. During her time at CAPRISA she has worked as co-investigator as the study gynaecologist on the CAPRISA 004 tenofovir gel trial, and was responsible for the development and implementation of a contraceptive counselling curriculum for this study. More recently she has been leading the development and implementation of a basic science study program, TRAPS (Tenofovir gel research for advancing HIV prevention science), at CAPRISA that aims to enhance our understanding of the impact of tenofovir pre-exposure prophylaxis on the immune processes at cellular level and clinical disease progression among women that seroconvert to HIV having been exposed to this antiretroviral drug.

CAPRISA congratulates Dr Sibeko on this prestigious achievement and wish her well with her degree.

CAPRISA Scientific Publications in 2011

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**this list continues from the previous newsletter - providing all CAPRISA publications in 2011*

Upcoming Conference & Workshop Reminders

Conference	dates	Deadlines Abstracts	Registration	website
Microbicides 2012	April 2012	17 Nov 2011	15 Mar 2012	http://www.microbicides2010.org/microbicides-2012
19th CROI	5-8 Mar 2012	5 Oct 2011	3 Feb 2012	http://retroconference.org/
3rd SA TB Conference	12-15 Jun 2012	20 Jan 2012	18 May 2012	http://www.tbconference.co.za/

CAPRISA is an official research institute of the University of KwaZulu-Natal.
CAPRISA was established in 2002 through a CIPRA grant from the NIH, as a multi-institutional collaboration, incorporated as an independent non-profit AIDS Research Organization

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