



CAPRISA

CENTRE FOR THE AIDS PROGRAMME OF RESEARCH IN SOUTH AFRICA



CAPRISA IS A UNAIDS
COLLABORATING CENTRE
FOR HIV PREVENTION RESEARCH

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In this issue...

Our front page story in the April issue of the newsletter we congratulate Dr Sengeziwe Sibeko, a Fogarty AITRP Fellow, on her recent award from the Department of Epidemiology at the Mailman School of Public Health.

Our main story on inadvertent enrollment of ineligible participants in the CAPRISA 004 tenofovir gel trial and the MTN statement on co-enrollments in HPTN 035 and CAPRISA 004 is on page 2 and 3.

On page 4 we cover the highlights from the 3rd International Conference on HIV Treatment Adherence that was held in New Jersey, in March 2008.



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FOGARTY Fellow receives Sydney Kark Award

Dr Sengeziwe Sibeko, a specialist Obstetrician and Gynaecologist, who is currently completing her Fogarty-sponsored Masters in Epidemiology degree at the Department of Epidemiology at the Mailman School of Public Health, Columbia University, is congratulated for her recent achievement in being nominated to receive the Sydney Kark Award in epidemiology for 2008. Only those students whom best represent some of the icons of their field, as decided by their departments, qualify for this award. The award which is named after the late Professor Sydney Kark who successfully initiated and practiced the Community Orientated Primary Health Care concept (COPHC) in Pholela community South Africa. Dr Sibeko will receive her award at the Columbia University Graduation week on May 20 2008.



Dr Sengeziwe Sibeko, recipient of the Sydney Kark award for 2008



Mailman School of Public Health recognised for AIDS research

CAPRISA also takes this opportunity to congratulate our collaborating partners from the Columbia University Medical Center for being rated in the April 7-14, 2008, issue of U.S. News & World Report's "America's Best Graduate Schools.". The Mailman School of Public Health achieved an overall ranking of # 6 while the College of Physicians and Surgeons' received an overall ranking of # 11 with their medical special-

ties of drug/alcohol abuse, AIDS, pediatrics, and internal medicine achieving rankings of #2, #7, #10, #10 respectively. These rankings, based on the 2007 data, are determined by medical school deans and senior faculty throughout USA and are a reflection of the researchers strong performance in research, education, and clinical care in these areas.

Inadvertent enrollment of ineligible participants in CAPRISA 004

Scientists at CAPRISA and the Medical Research Council (MRC) HIV Prevention Research Unit recently discovered that a number of CAPRISA 004 participants had also enrolled in MRC microbicide studies. This brief note describes this discovery and its effects on the trial.

The CAPRISA 004 trial, which started in May 2007, is being conducted at two sites in South Africa: eThekweni and Vulindlela. The eThekweni site is in the Durban city centre, attached to a municipal clinic for the treatment of sexually transmitted infections and tuberculosis. The Vulindlela site is in a rural community about 90 minutes from Durban. To date, the Vulindlela site has enrolled 407 participants and the eThekweni site has enrolled 381 participants.

The Discoveries

In mid-February, CAPRISA staff discovered that two of the CAPRISA 004 participants at eThekweni were co-enrolled in the HPTN 035 trial—which is being conducted by the MRC at a site about 25 kilometers away. In response to this discovery, both study teams began to cross-check their records to avoid additional co-enrollments.

These procedures turned out to be inadequate—it was subsequently determined that additional co-enrollments had taken place. This new discovery led to a comprehensive review by both study teams to identify all possible co-enrollments.

This detailed review revealed that 131 participants were taking part in an MRC study at the time they enrolled in CAPRISA 004, and that 49 others had at some time in the last 12 months taken part in an MRC study before they enrolled in CAPRISA 004. Of the 131 participants, 96 were co-enrolled in HPTN 035 and CAPRISA 004. The remaining 35 were enrolled in other MRC studies being conducted at sites outside of Durban.

Ineligible Enrollments

As a condition for enrollment in CAPRISA 004, a woman must not have participated in any research related to a vaginally applied product in the past 12 months. A total of 180 participants at eThekweni are considered to have been ineligible when they enrolled in CAPRISA 004. They will no longer participate in CAPRISA 004, but the co-enrolled participants will continue to be part of the MRC trials.

Another four participants were found to have enrolled in an MRC study after they enrolled in CAPRISA 004. These co-enrolled women were eligible at the time they enrolled in CAPRISA 004, so they will continue their participation in the trial. However, they will no longer be taking part in the MRC study. The Vulindlela site had no ineligible enrollments.

The ineligible women did not disclose their participation in other trials during the screening and enrollment process. The MRC and CAPRISA teams are now trying

to establish the circumstances that led to the co-enrollment of these women. This information will help us prevent future occurrences.

Scientific Impact

Although the number of ineligible participants at the eThekweni site was substantial, most had been in the CAPRISA 004 trial for a short period of time—which constitutes only about 3% of the total person-time that is being accrued in the trial. This will have little, if any, effect on the scientific validity of the trial. These participants did not meet the study's entry criteria and so will not be included in the primary data analyses of the CAPRISA 004 trial, but they will be included in a sensitivity analysis to assess their potential impact on the study's outcome.

If left unchanged, the CAPRISA 004 study will now take 5 months longer to complete. At the request of the independent data safety and monitoring board (DSMB) that oversees CAPRISA 004, the study's investigators and statisticians are modeling various options regarding the trial's sample size and the duration of the follow-up studies needed to meet the study's objectives in a timely manner.

Participant Safety

The participants who were co-enrolled have been carefully followed for safety in the CAPRISA and MRC studies. The DSMB that oversees CAPRISA 004 met on 5 May to review the safety monitoring data and “found no safety concerns in both groups of ineligible participants—the co-enrolled participants as well as in the ineligible participants who were not co-enrolled.”

Several official bodies have been notified of the ineligible participants, including the University of KwaZulu-Natal's Biomedical Research Ethics Committee, Family Health International's Protection of Human Subjects Committee, and the South African Medicines Control Council.

The Future

HIV-prevention trials are fraught with challenges. A recent report from the US Institute of Medicine highlighted several challenges in these trials, including product discontinuation during pregnancy, participant adherence, and an adequate incidence of HIV to achieve the study's goals. The co-enrollment of participants in microbicide, vaccine, and other HIV-prevention studies is yet another challenge that clinical scientists must seriously consider.

CAPRISA and the MRC have introduced new measures to avoid co-enrollments in future studies. For example, the study teams are now cross-checking records *before* they consider potential participants for enrollment in CAPRISA 004 and MRC trials. The two organizations will continue to develop and enhance these new safeguards in the interests of participant safety and the scientific integrity of the trials.



Statement from the MTN regarding co enrolment of participants in HPTN 035 and CAPRISA 004

HPTN 035 is a safety and effectiveness study of two candidate vaginal microbicides, BufferGel and 0.5% PRO 2000 Gel. The study began in January 2005, completed enrollment of 3100 participants in July 2007, and will complete follow-up in September 2008. We are looking forward to the successful completion of the study later this year and release of its results in the first quarter of 2009.

On April 24, 2008 the MTN leadership became aware of a serious situation concerning the co-enrollment of approximately 96 HPTN 035 participants into the CAPRISA 004 study. I can assure you that we are working diligently to better understand exactly how this occurred and we are actively considering measures to prevent future co-enrollment of participants in HIV prevention trials. Although some questions still remain unanswered, based on the information we have to date, the impact of these co-enrollments on the scientific integrity of HPTN 035 is likely to be minimal, resulting in a loss of less than 1 percent of the total follow-up time for the 3100 women on the HPTN 035 study. The data accumulated during the period of time when women were co-enrolled on both studies when product exposure is unknown will not be used in the analysis being done to evaluate the effectiveness of the products.

At the PrEP Collaborative Meeting held in Atlanta on May 2, 2008, Quarraisha Abdool Karim reported that some women had co-enrolled into both CAPRISA 004 and HPTN 035, and additional women enrolled in the CAPRISA 004 study within a year of completing HPTN 035, a violation of the CAPRISA protocol. Many at that meeting had legitimate questions about this situation and how it would impact HPTN 035 – how was this problem detected? When did the research teams first learn of the problem? What specific measures are being employed to prevent this from happening again in the future? The purpose of this letter is to provide some insight into how this problem was detected, and the measures that are being employed to ensure that it does not happen again.

To the best of our knowledge, 96 HPTN 035 participants at the South African Medical Research Council (MRC) in Durban, South Africa, co-enrolled in the Centre for AIDS Prevention and Research in South Africa (CAPRISA) study. The two study sites are approximately 25 km. from each other. The study teams first came to suspect the possibility of co-enrollment on February 12, 2008. By February 20th, 14 co-enrollments had been identified across the two studies, based on a records crosscheck between HPTN 035 and CAPRISA 004. At that time, the MRC HPTN 035 and CAPRISA study teams instituted additional procedures to avoid any additional co-enrollments. However, when it was recognized that additional co-enrollments had occurred, a concerted effort was undertaken by both study teams to complete a comprehensive review of MRC HPTN 035 and CAPRISA 004 study records to identify all possible co-enrollments. NIAID Division of AIDS and MTN leadership were notified of the situation on April 24. The review was completed April 30, at which time the 96 co-

enrollments were confirmed by the two study teams, although we are awaiting a final confirmation of the numbers from our data center at SCHARP.

At the core of the problem is that women who joined both studies did not disclose to either study team that they were also enrolled in another microbicide study. These co-enrolled participants are being discontinued from CAPRISA 004. They will, however, continue their participation in HPTN 035 through their scheduled study exit date and, at all remaining HPTN 035 visits, will be counseled on the importance of not taking part concurrently in other studies. Within the next one to two weeks, our HPTN 035 protocol statisticians at SCHARP will have more fully assessed the implications of these co-enrollments and will advise the HPTN 035 protocol team accordingly. In addition, the MRC and CAPRISA teams are conducting bilateral cross-checking across organizations to ensure that additional co-enrollments do not occur while CAPRISA completes its accrual.

I would like to extend my support to both the HPTN 035 and CAPRISA 004 study teams as they work toward understanding and addressing the co-enrollment of study participants. I also look forward to working with these teams to apply the lessons learned from this series of events to the design and implementation of future MTN studies. First and foremost, we are fully and firmly committed to ensuring the safety of the women in our studies. When women participate in more than one study, they are exposed to more than one investigational product, which raises issues of safety that can be consequential. Secondly, multiple product exposure also compromises study validity, since it makes it difficult to assess which side effects or other problems women experience during a study are due to which drug agent being evaluated.

For all of us engaged in HIV prevention research, particularly in the conduct of clinical trials, there are indeed important lessons here. Clearly, as a general matter, we need to do a much better job monitoring enrollment practices and patterns across studies and study sites within the same geographic regions. We must also develop and implement more stringent surveillance techniques and processes for verifying participant identities, in order to prevent co-enrollment or ineligible enrollment into multiple studies. We must also train clinic staff meticulously in the use of any new approaches emerging from the learning derived from this present dilemma.

Every single clinical trial of any product presents challenges, often unanticipated, despite careful planning and preparation. However, these challenges also offer opportunities to craft best practices to apply to future HIV prevention research. As we move forward, transparency and cooperation among clinical trial groups will be essential to protecting the scientific integrity of any study and, most critically, the safety of study participants.

- Sharon Hillier



Discussing adherence issues

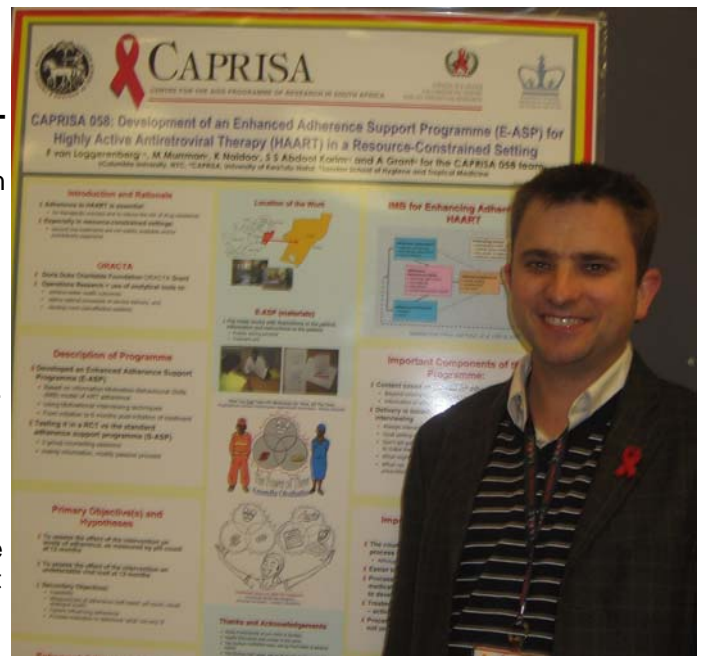
Francois van Loggerenberg and Tanuja Gengiah recently attended the 3rd International Conference on HIV Treatment Adherence followed by the Doris Duke Foundation's ORACTA Grantees Meeting in March in Jersey City.

Francois, who is a recipient of an ORACTA grant, did an oral presentation on "CAPRISA 058: Development of an Enhanced Adherence Support Programme (E-ASP) for Highly Active Antiretroviral Therapy (HAART) in a Resource-Constrained Setting".

The International Adherence Conference, co-hosted by NIMH and IAPAC, covered areas including the relationship between adherence and viral load, assessing patient readiness to initiate antiretroviral therapy, adherence in African settings (in which the CAPRISA 058 presentation was included), and adherence measurement in resource-poor settings. Highlights included a presentation on the relationship between adherence and class-specific drug resistance by Dr Edward Gardner, a presentation on NNRTI treatment interruptions and their association with viral rebound by Dr Jean-Jacques Parienti, as well as a very well-received presentation on the gold standards of adherence measurement by leading adherence researcher, Dr Margaret Chesney.

The keynote address by Dr Richard Laing of the World Health Organisation was on the global implications of HIV treatment adherence, and he suggested that work to understand the factors associated with ART adherence was critical to the success of the rollout of treatment across the world. The conference ended with a panel discussion by Drs David Bangsberg, Edward Gardner, Robert Goss and Jean-Jacques Parienti which looked at whether or not the newer boosted regimens which showed less susceptibility to viral rebound and resistance meant that the traditional goal of greater than 95% adherence could be shifted.

At the ORACTA meeting, Francois presented the challenges of implementing the CAPRISA 058 study and took



Francois van Loggerenberg presented data from his adherence study at the recent International Conference on HIV Treatment Adherence

part in a workshop facilitated by CAPRISA collaborator, Dr Wafaa El-Sadr.

Two key learning points emerged from both meetings; firstly, challenges of measuring, assessing and ultimately optimizing adherence to care and treatment are shared across the world and secondly, that regardless of the setting, pharmacy refill data are reliable, easy to access and may be more predictive of good adherence than CD4 count, as data presented at the conference showed.

- Francois van Loggerenberg, CAPRISA

UKZN-CAPRISA CTU: Current status & progress

ACTG—DAIDS RCC has granted provisional approval for the study - pending the verification of the accuracy of the English back translation of the Zulu informed consent. The provisional approval does not allow the site to commence enrolment, but does enable the site to order study drugs. Full site readiness is anticipated mid May 2008.

HVTN—The HVTN study continues with follow up of the enrolled participants. All 53 enrolled participants have been unblinded and unblinding procedures done except for the 2 LTFU. We are currently following 50 participants as we had a termination in addition to the 2 LTFUs. All participants are now on 6 monthly visits and we await a protocol amendment for more frequent visits

IMPACT—The HPTN046 protocol Version 3.0 for implementation at the Umlazi CRS has been registered with DAIDS. Site activation is still pending. The delay is due to the outstanding review of the pharmacy SOPs and Pharmacy Plan by PAB which is underway. The HPTN 046 study (version 3.0) has not commenced at any of the international sites, but is scheduled to commence sometime in April.

MTN— A detailed set of milestones is being developed by MTN CORE, SCHARP, and DAIDS for the Umbilo/eThekweni, Durban site to meet in order to achieve activation of VOICE. Implementation activities are moving forward to achieve site activation. The Site is currently reviewing the behavioral data collection instruments.

Research update - March 2008

Study	Site	Screened		No. Enrolled	
		Total	Cumulative	Total	Cumulative
Acute Infection	Umbilo (Phase II)	2	68	2	68
CAT	Vulindlela	17	2764	10	1082
	eThekwini	5	1996	6	609
SAPIT	eThekwini	49	1158	27	561
START	eThekwini	0	147	0	58*
CHAVI	eThekwini	589	8141	1	21
HEPS	Umbilo	-	-	0	122*
HVTN	eThekwini	0	114	0	53*
Microbicide	eThekwini	91	747	62	339
	Vulindlela	91	617	40	346
EASP	eThekwini	-	-	14	171

* enrolment stopped

CSRC update - March 2008

Abstracts submitted for review		Manuscripts submitted for review		Ancillary studies submitted for review	
Total [#]	Cumulative [^]	Total [#]	Cumulative [^]	Total [#]	Cumulative [^]
1	113	0	35	1	10

for month, ^since committee initiation

Upcoming Conference & Workshop Reminders

Conference	dates	Deadlines		website
		Abstracts	Registration	
6th European HIV Drug Resistance Workshop	26-28 Mar, 2008	1 Feb 2008	1 Mar 2008	www.virology-education.com
15th Int Symp on HIV & Emerging Infect Dis (ISHEID)	28-30 May 2008	15 Feb 2008	15 Feb 2008	www.isheid.com
HISA 2008	17-20 Jun 2008	12 Mar 2008	12 Mar 2008	www.hisa.co.za
TB conference	1-4 Jul 2008	TBA	31 Jan 2008	www.tbconference.co.za
XVII IAS Conference	3-8 Aug 2008	19 Feb 2008	19 Feb 2008	www.aids2008.org
AIIDS Vaccine 2008	13-16 Oct 2008	May 2008	Jun 2008	www.hivvaccineenterprise.org
15th 2008 Int Conf on AIDS and STIs in Africa	3-7 Dec 2008	14 Apr 2008		www.icasadakar2008.org/en.php

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