



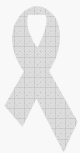
In this issue...

Our main story summarises the discussions between Salim Abdool Karim and Robin Shattock on the dosing of Tenofovir gel.

CAPRISA was privileged to host two international pharmacokinetics experts who spend a week with CAPRISA researchers reviewing current data on tenofovir pK, gel dosing strategies and developing ancillary studies to the CAPRISA 004 trial to measure tenofovir levels in the vaginal lumen, tissues and blood (See page 3 for details).

On page 4 Beth Robinson from Family Health International interviews Janet Frohlich on the involvement of the Vulindlela community in the CAPRISA tenofovir gel trial.

The Targeted AIDS Intervention (TAI) Aunts and Uncles Project is making an appeal for support for 90 orphans and vulnerable children from the Mafakathini area. Read more about this "adoption" project on page 5.



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Joint summary: Salim Abdool Karim & Robin Shattock discuss tenofovir gel dosing

Following a news article in *Nature* in July on the dosing strategy in the CAPRISA 004 trial, Salim Abdool Karim and Robin Shattock committed themselves to discussing the differences of opinion and resolving them. They met through conference calls and then spent several hours in a face-to-face meeting in London reviewing and discussing the existing preclinical and clinical data relating to the use of tenofovir for pre and post exposure prophylaxis.

In releasing this joint summary of their discussions, they commented: "Throughout, the discussions were very constructive and proved to be both interesting and informative with substantial common ground. We would like to thank everyone for your support. Like you, we are deeply committed to the important goal of a safe and effective microbicide and believe that our common purpose in achieving this goal has enabled us to find common ground and a clear way forward."

Below is a summary of their discussions:

The scientific rationale for the design of the CAPRISA 004 study is based on the concept of antiretrovirals, specifically single dose nevirapine, to prevent mother-to-child transmission, findings from several macaque challenge studies using both local and systemic administration of tenofovir by either intravenous or subcutaneous routes and human safety and pK studies. The broad trend identified from these data is that a single pre-exposure dose is able to prevent infection in macaques when administered subcutaneously (vanRompay, 2001), vaginally (IB Study 2) or rectally (Cranage, CROI, 2007).

The determination of the timing of the pre-exposure dose in the CAPRISA 004 study is based on available human safety data on two doses per day (Mayer, 2006), duration of tenofovir in cervico-vaginal lavages in women (Vourvahis, 2006), and on a macaque vaginal tissue pK study of radio-labeled tenofovir gel which showed that "Radioactivity was detected starting at 15 minutes post application. The peak concentration of tenofovir in the tissue is at 8 hours and remains high at 12 hours." (IB, table 6-1). These data suggested that tenofovir may have a long duration of activity and that both pre and post exposure doses may be important in providing protection.

It was agreed that while the studies of systemic administration may be informative, they could only provide an indication of potential activity derived

from vaginal administration. In addition, caution needs to be exercised in interpreting monkey data as no evidence exists that tenofovir levels or protection in monkeys correlates with tenofovir levels or protection in humans. Macaque data are limited by, amongst others, small numbers of monkeys in studies, differences in challenge virus and dose, use of progesterone, inability to mimic coitus during challenge and methods for determining presence of infection. Other supportive data suggesting a long duration of activity for tenofovir are based on in vitro studies showing that the drug can protect cells from infection for prolonged periods of time, again these are supportive but are not definitive for vaginal use of product.

Current data based on macaque challenge studies following vaginal gel application, performed under sub-contract from NIH, were extensively discussed. These studies had been performed over a wide time span and by different investigators and are presented in the HTPN059 protocol. It was agreed that only studies 1,2 and 6 were interpretable as studies 3,4 and 5 were flawed due to lack of consistent infection in untreated control animals. Study 2 indicates that protection could be achieved by treatment of the animals 24 hours before, 15 minutes before and 24 hours post-challenge: this protected 4 out of 5 animals.

Continued on page 2.....



Joint summary on Tenofovir gel dosing strategy..... continued

.....Continued from page 1

Similarly a single 15 minute pretreatment with tenofovir gel provided protection in 3 out of 5 animals in the same study; statistically there is no difference between either dosing regime, suggesting that the majority of protection was provided by the 15 minute dose. While these data may indicate benefit to dosing either side of exposure, it does not provide any scientific basis for once daily administration of the product. Study 6 explored single dosing either 24 hours or 12 hours prior to exposure. In this study there was no protection with 24 hour dosing, and only 2 out of 8 animals were protected with 12 hour dosing. This again is not supportive of once daily dosing and suggests that the window of protection or the ideal window of protection may be less than 12 hours. One caveat relating to the study 6 is that it used the progesterone macaque model where the dose of input virus may have been higher than that used in the earlier studies. However, data from a number of other groups show good protection in this model using compounds that protect target cells, examples of which are PRO2000, PSC-RANTES, and CMPD-167. It is expected that tenofovir should be at least as good as these other compounds. The conclusion from this wide ranging discussion of current preclinical and clinical data was that the majority of evidence is supportive of coitally dependent use of this product.

However, the window of protection provided by the use of tenofovir gel has not been fully determined. A number of ongoing studies have the potential to inform the use of tenofovir gel and interpretation of the current CAPRISA study. The first of these are the human PK studies of vaginal administration of tenofovir gel, which will provide comprehensive data on the vaginal and systemic pK following vaginal application. The second is a planned animal pK study. The third study is a planned animal challenge experiment study to define more accurately the window of protection provided by a single pre challenge vaginal dose of tenofovir. This study would determine the level of protection provided at time points between 15 minutes and 24 hours post dosing. These 3 studies will relate animal efficacy to drug PK and potentially allow greater interpretation of human pK studies. This will provide the most accurate prediction of the window of protection that may be achieved by pre coital dosing with tenofovir gel in macaques and potentially in humans, but they will not inform on any potential benefit of an additional post coital dose.

The CAPRISA 004 study is collecting detailed data about product use, current analysis suggests that the majority of women ($\pm 80\%$) are using the product within 6 hours of exposure. If the window of protection is shown to be less than 12 hours by macaque challenge studies, the totality of the available data will be reviewed. If the weight of evidence suggests a shorter window of pre-exposure application may be warranted, an interim analysis will be carried out on timing of gel use in CAPRISA 004 to determine whether enough subjects are using the product within the time frame of protection indicated by macaque challenge studies. If this is the case it may be sufficient to proceed without any alteration in the protocol. If there is strong evidence to show that the window of protection is limited to a time frame of less than 12 hours, careful consideration will be given to a protocol amendment to ensure adequate numbers of subsequent participants use the gel within a tighter time-frame surrounding intercourse.

One constraint for the initial design of the CAPRISA study was that no more than two doses of gel should be given within a 24 hour period. Should the window of protection be short, a limitation of 2 doses per 24 hours might compromise coital dosing where multiple sex acts occurred during a weekend. Therefore, consideration should be given to determining the safety of up to four applications of gel per day.

Further discussion and data are required to determine appropriate dosing and usefulness of any post coital dose.

UKZN-CAPRISA CTU: Current status & progress

ACTG

Ethics approval has been received from the Biomedical Research Ethics Committee for the conduct of ACTG 5221. The outcome of the amendment submitted to the MCC to include the CAPRISA eThekweni Clinical Research Site (CRS) as an additional implementing site, with additional investigators is still pending.

Kogie Naidoo and Lucky Barnabus attended the ACTG Meeting in Washington DC in October 2007. Both delegates from CAPRISA found the training sessions, CAB and investigator meetings to be useful and informative. The eThekweni site plans to commence screening for ACTG A5221 in November pending the various regulatory approvals.

HVTN

Subsequent to the HVTN 503 trial being put on hold after the release of the results of the STEP study, the HVTN 503 DSMB met and reviewed the STEP data as there is not enough data from the Phambili study to analyse. The following recommendations were made by the HVTN 503 Oversight Committee in accordance with the DSMB

- permanently discontinue enrolment and vaccinations in the Phambili study
- continue to follow-up participants who were already enrolled onto the study
- unblind participants as to which arm of the study they were enrolled into

The eThekweni and Aurum Health Research sites are currently contacting participants and scheduling them for unblinding visits. PPD came to do a site initiation assessment for Umbilo CRS on the 17 - 18 September 2007 and this went well.

The Aurum site has completed follow up of the last participant in HVTN 204

IMPAACT

Regulatory approval from the MCC is still pending for HPTN 046. Protocol specific training is going to be conducted in December by FHI. The Site Pharmacy was visited by Scharla Estep on 19 October.

MTN

The VOICE trial held a protocol team meeting in Durban, attended by all the sites involved in conducting the trial. The 3 day workshop reviewed the protocol in detail. Ayesha Kharasany and Tanuja Gengiah attended on behalf of the CAPRISA site.



US Experts on Tenofovir pharmacokinetics visit CAPRISA



The tenofovir pharmacokinetics protocol development team included: from L-R: Ayesha Kharsany, Salim Abdoool Karim, Craig Hendrix, Angela Kashuba, Cheryl Baxter, Tanuja Gengiah and Leila Mansoor

CAPRISA were privileged to host two pharmacokinetic experts in October; Dr Angela Kashuba from the University of North Carolina and Dr Craig Hendrix from Johns Hopkins University. Drs Kashuba and Hendrix were invited to CAPRISA to collaborate in developing an ancillary study that is part of the CAPRISA 004 protocol, focusing on measuring tenofovir in the vaginal lumen, intracellularly and in the plasma in order to determine concentrations of tenofovir that may be associated with protection against HIV infection following vaginal application of the 1% tenofovir gel.

At present the optimal levels of tenofovir in the genital tract to protect against HIV infection is not known. This ancillary study aims to advance the field by providing a description of tenofovir levels in various compartments in the genital tract. The week-long programme focused on understanding the existing pharmacokinetic data in both human and animal models and provided an opportunity to refine the most appropriate specimen collection techniques and laboratory processing methods for the specimens that will be collected during the study. The specimens that are collected mostly in the genital tract will be processed by the CAPRISA laboratory in a short space of time and immediately put into storage for analysis when the study has ended. By the end of the visit the exhausted ancillary research study team was successful in achieving their goal of creating

a clear understanding of how to proceed with meeting the objectives of this important ancillary study

Also during their visit the experts had the opportunity to visit the CAPRISA eThekweni Research site where they interacted with study staff to get a better insight into the implementation of the CAPRISA 004 trial. The Medical School Community was fortunate to attend a Doris Duke Distinguished Lecture where; Dr Kashuba presented data on the pharmacokinetics of antiretrovirals in the female genital tract and the implications for HIV pre- and post-exposure prophylaxis while Dr Hendrix spoke on his research on the distribution of microbicide and HIV surrogates in the rectum and distal colon to inform rational rectal microbicide development.

Dr Kashuba is an Associate Professor at the School of Pharmacy and Director of both the, UNC Center for AIDS Research Clinical Pharmacology/Analytical Chemistry Core and Verne S Caviness General Clinical Research Center Analytical Chemistry Laboratory. Dr Hendrix is currently an Associate Professor of Medicine, Pharmacology, and Epidemiology and serves as Director of the Drug Development Unit and Co-Chair of one of the institutional review boards that provides oversight for human subjects research at Johns Hopkins University.



Beth Robinson in conversation with Janet Frohlich about the involvement of the Vulindlela community in CAPRISA 004

What is the CAPRISA Vulindlela Community Research Support Group (CRSG) and how do you involve them in the research?

The Vulindlela CRSG is a structure that ensures an ongoing dialogue between the CAPRISA investigators and the community, and serves as a two-way information conduit between the site and the local community. Members of the CRSG are elected from the traditional leadership structure, community opinion leaders, religious and women's organisations, as well as from among the youth. The CRSG assists in ensuring that there is community involvement in studies and informed participation of its members through protocol development, data collection and dissemination of information to the community. Members also provide regular input to the CAPRISA investigators on cultural factors and norms that may affect the study, advise on appropriate recruitment and retention strategies, and keep the investigators informed about emerging issues of concern in the community. Training sessions are provided to build understanding of research, the informed consent process, and the ethics that underpin microbicide trials.

How do you proactively go about community outreach? Which elements of your approach are especially important in helping counter rumors or misinformation?

Through the establishment of a community fellowship programme, the CRSG helped identify and select 32 community members who were trained and then financially supported to serve as community educators. These community educators actively promote knowledge of issues related to HIV prevention and research, including the importance of determining one's HIV status, reducing stigma and discrimination, and the benefits of participation in CAPRISA projects. Every household in the catchment area for recruitment was visited to inform the community of CAPRISA projects and to identify community priorities and concerns. Simultaneously, community mapping was conducted by key informants from the community and CRSG members, and data was collected to identify demographic and social characteristics, establish willingness to participate in HIV prevention and treatment research, and identify experiences of stigma and discrimination. This type of face-to-face encounter facilitated the development of a trust relationship and working alliance with community members. Skills-building workshops are also arranged to advocate for community support and participation in research. These workshops include discussion and debate on informed consent, and ethical, legal and human rights issues. They provide an opportunity for collaborative and collective planning for broader community awareness and education. Community gatherings and targeted, consultative group meetings are

held regularly to disseminate information and counter rumors -- i.e., misinformation about early closure of study trials, HIV and AIDS issues emerging in the press, and feedback received from CRSG members.

When issues emerge, how do you talk to the community?

We are very fortunate in having an astute and active CRSG who will report myths and concerns emerging from the community and sensational stories appearing in the local media. We address these issues in a collegial manner through open dialogue. Meetings with different community stakeholders are held to elicit concerns and to put these into perspective. A CRSG member is present at these meetings to dispel any mistrust that may emerge from the community towards the research team. If needed, relevant training is organized to address the issues. With the closure of the cellulose sulphate microbicide trial in January, for example, there was a need for re-training CRSG members on the differences between types of microbicides.

On an ongoing basis, the community liaison officer plays a vital role in keeping the CRSG members informed about current issues in the field of microbicide research. Pertinent information is collected from relevant websites and journals, and these are summarized and printed in the CAPRISA newsletter, as well as translated into non-scientific language for the CRSG. Community events are used to update the broader community and dispel myths. Information sessions are also held with participants and they are encouraged to discuss any concerns with their nearest CRSG member. Study participants are also invited to raise any concerns or to share information they are hearing in the community through the suggestion box.

How did you explain to the community why Vulindlela was chosen for this trial?

This is such an important question in the context of the ongoing debate that "communities are over-researched." We have been conducting annual antenatal surveys since 2002 in this community and so have data on trends in HIV prevalence over time. These findings are presented annually to traditional leaders, local health service providers and the CRSG, so the community has become very aware of the magnitude of the epidemic, and that it has shown no signs of stabilization. We were constantly being encouraged by the CRSG, the District Health Department, and the traditional leadership to explore interventions that could have an impact on the epidemic.





Beth in conversation with Janet continued.....

The Inkosi (the head of the traditional leadership) of this community said if there was no abatement in this epidemic, he “would not have a people to lead.” We also collaborated with the Faculty of Education at the University of KwaZulu Natal, which had a very innovative project -- “Learning Together” -- using visual methodology to sensitize the community to HIV and AIDS. Learners and community health workers were taught how to use a camera and documented through pictures how the epidemic was affecting their community. A video was developed and community members were invited to validate that the video was a true reflection of what was happening in their community. The success of our treatment programme has also led to an increase in the number of people wanting to know their HIV status. This community is very aware of the urgency of conducting prevention trials and we have received overwhelming support for CAPRISA 004.

How do you build partnership between providers and the community?

A cooperative research partnership is built on four pillars: mutual trust and shared decision-making, capacity development of relevant partners, identification and ownership of the problem, and dissemination of information and research findings. At Vulindlela this partnership is promoted through a collaborative approach and collegial acknowledgment among the CRSG, investigators and site research team. The CRSG members, as partners, have helped inform the consenting process by advising on culturally sensitive and linguistically correct terminology. When illiterate participants in our trial request it, CRSG members are able to serve as an impartial witness to the consent process. The community fellowship programme has consolidated the partnership between the community and the site, thereby actively promoting a supportive environment for the conduct of high quality microbicide trials. Quarterly meetings with health service providers have included general information around microbicides, in-service training on prevention modalities, and updates on microbicides trials in the field and the progress of CAPRISA 004. These regular meetings have strengthened the partnership between the District Health Service and CAPRISA. Participants in our preparedness study for CAPRISA 004 requested certificates of participation that would acknowledge their contribution to making a difference to the HIV and AIDS epidemic in their community. We carefully chose wording for a certificate we provide to study participants that would protect their privacy (not reveal their study participation) but still convey the message that they are a community champion. The certificate says, “This certificate of appreciation is awarded to [name here] for her contributions to HIV prevention in her community.” Each certificate is signed by the community Inkosi, the chairperson of the CRSG, and the project director, acknowledging that research at the CAPRISA Vulindlela site is conducted through partnerships.

“Adopt” an orphan



The Target AIDS Intervention (TAI), a non governmental organisation based in Pietermaritzburg, is making an appeal for support for their Aunts and Uncles Project which aims to provide increased psycho-social support for the 90 orphans and vulnerable children (OVC) that they work with. This project strives to make the children feel valuable and a part of a society that cares for them.

The Aunts and Uncles Project is headed by Brad Gibbs, also known as Jabulani Buthelezi to his host family in South Africa. Jabulani is a Peace Corps Volunteer from New York now living in Mafakathini, about a 30 minute walk uphill from the Vulindlela CAPRISA site. He lives with one of the Zulu families in Mafakathini who have embraced him as one of their own. “Lots of laughter follows whenever my host father says, “Yes, he’s my first born son!”” said Jabulani.

The Aunts and Uncle’s Project is looking for individuals interested in “adopting” one of these children. Here’s how you can help:

- **Birthday & Christmas presents:** Purchase and wrap a gift for the child’s birthday and for Christmas (each worth R100).
- **Birthday Parties:** All are welcome to attend the two birthday parties that we have each year; one for children whose birthday falls between January and June, and the other for birthdays that fall between July and December. If you are unable to make the party, arrangements can be made to give your child his or her present. Arrangements will also be made to give your Christmas present to your child.
- **Material Support:** If you are interested in buying groceries for your child’s family or clothes for your child (although not required), TAI can certainly help you with this process.
- **Any other way you like:** You can also come up with other creative ways to support your child. Any ideas are welcome!

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Research update - September 2007

Study	Site	Screened		No. Enrolled	
		Total	Cumulative	Total	Cumulative
Acute Infection	Umbilo (Phase II)	0	57	0	57
CAT	Vulindlela	5	2668	4	1021
	eThekwini	14	1877	4	578
SAPIT	eThekwini	34	895	27	419
START	eThekwini	0	147	0	58*
CHAVI	eThekwini	567	4993	1	16
HEPS	Umbilo	-	-	0	122
HVTN	eThekwini	48	114	23	44*
Microbicide	eThekwini	75	208	28	56
	Vulindlela	52	123	23	70
EASP	eThekwini	-	-	14	31

* enrolment stopped



CSRC update - September 2007

Abstracts submitted for review		Manuscripts submitted for review		Ancillary studies submitted for review	
Total [#]	Cumulative [^]	Total [#]	Cumulative [^]	Total [#]	Cumulative [^]
0	84	2	34	0	8

for month, ^since committee initiation



Upcoming Conference & Workshop Reminders

Confer- ence	dates	Deadlines		website
		Abstracts	Registra- tion	
Microbicide 2008	24-27 Feb 2008	30 Sept 2007	30 Oct 2007	www.microbicides2008.com
HISA 2008	17-20 Jun 2008	TBA	TBA	www.hisa.co.za



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