

**International Rectal Microbicide Working Group
Conference Call
Monday, October 30, 2006
Duration: approximately 90 minutes
Minutes taken by Linda Hughes (many thanks to Linda!)**

Jim Pickett welcomed participants to the call and thanked amfAR for sponsoring today's conference call.

There was some discussion of required slides of upcoming presentations and Jim responded to email requests for those recipients who still needed them. Slides are currently posted on www.lifelube.org.

Roll call (done by Jim Pickett --- please send him corrections, affiliations):

1. Dr. Rowena Johnston – amfAR (Steering Committee member)
2. Dr. Sharon Hillier – presenter – Microbicide Trials Network
3. Dr. Robin Shattock – presenter – St. Georges
4. Cheryl Gardiner – PA Campaign for Microbicides
5. James Sykes – The AIDS Institute
6. Polly Harrison – Alliance for Microbicide Development
7. Lori Heise – Global Campaign for Microbicides (GCM)
8. Martin Methot – International Partnership for Microbicides
9. Jen Heitel Yakush- SIECUS
10. Kevin Fischer – AIDS Vaccine Advocacy Coalition (AVAC)
11. Brian Green – Safeguards Project
12. Rachel Jankowski - AIDS Alliance for Children, Youth & Families
13. Dierdre Grant – AVAC
14. Anna Ford – AIDS Action
15. Kim Mulji – NAZ Foundation International (Steering Committee member)
16. Rick Jones – GNP+ (Steering Committee member)
17. Dr. Ian McGowan – UCLA (Steering Committee member)
18. Roy Wadia – British Columbia Centre for Disease Control (Steering Committee member)
19. Robert Reinhard
20. Linda Hughes – Polydex
21. Jerry Galea – UCLA (Steering Committee member)
22. MarcAndre LeBlanc – GCM (Steering Committee member)
23. Dr. Ron Stall – U of Pittsburgh
24. Trina Nelson – AIDS Foundation of Chicago
25. Jessica Terlikowski - AFC
26. Jim Pickett – AFC (Steering Committee member)

Dr. Rowena Johnston, Research Director at amfAR acted as moderator for the rest of the call and provided an introduction for Dr. Hillier.

Dr. Sharon Hillier presented first and presented an excellent set of slides for following along. Since it is fairly new, she began with an introduction of the Microbicide Trials Network and mentioned that she would fill us in on the Network Mission, what they are working on, and how that relates to potentially concurrent stealth study of rectal microbicide development.

The Mission of the MTN is to reduce the sexual transmission of HIV through the evaluation of products applied topically to mucosal surfaces or administered orally.

Dr. Hillier reviewed why the MTN asked the NIH for support of the Microbicide Trials Network, noting that there are limited prevention options available, there is notable feminization of HIV/AIDS, there is a strong pipeline of candidates showing efficacy in simian models, and even though our studies focus largely on the vagina, we recognize that anal sex happens among both sexes and it is an important HIV transmission option.

The MTN's Plan of Action will be to collect and move forward a variety of products. A bit like a pharma company, MTN has enhanced laboratory facilities and specialists paying close attention to the safety data and have recognized that behavioral studies are key to the research (how people have sex, how they use various products, etc.)

The MTN plans to do 15 clinical trials over the next 7 years. This is a fairly aggressive development objective.

In the first year of funding the MTN has taken over the trials known as HPTN035, which is a Phase II / IIB study of Buffergel and Pro2000 in the US and in Africa, and HPTN059, the topical tenofovir trials in India and the US. These trials will utilize approximately 90% of the MTN funding.

Two new studies (MTN-004 and MTN-015) are new studies being developed and will utilize the remaining 10% of the funding budget. More on these later but first to discuss the HPTN trials.

HPTN 035 is a two armed Phase II / IIB study wherein 800 women will be enrolled in the safety assessment and 3,200 women will participate in the effectiveness arm of the trial. We have just completed a safety monitoring of the trials and determined good safety data at this point in the trials, which is good news because the trials continue without interruption so long as the compounds maintain no harm.

At this time 1,700 women are enrolled, 3,400 have been screened. Full enrollment is expected by May 2007 and the trial should be completed by May of 2008.

MTN is enrolling about 800-900 women per quarter in the Tenofovir (used as a topical microbicide) and PMPA trials assessing prevention of acquisition of SIV on mucosal surfaces of female rhesus macaques.

HPTN059 is a Phase II expanded safety study of the Tenofovir microbicide has a primary objective to assess local and systemic safety of Tenofovir in HIV un-infected women over 24 weeks and daily and coital dependent use.

This study will determine whether the product is safe and whether women will use it. To date approximately 50 women have enrolled and should be completely enrolled (200) by Spring. Dr. Hillier said they want to look carefully at Tenofovir for vaginal and rectal transmission of HIV, they want to determine what kind of systemic absorption will there be, and whether or not a topical antiretroviral is as acceptable as oral antiretrovirals, and suggests that ultimately we will need both options to provide a stronger prevention method.

With these trials MTN is also hoping to answer some of the ART resistance questions. Is it better to have topical or systemic use? Will resistance have a higher risk from oral than topical?

Vivagel is also being considered for Phase I safety clinical trials but arrangements have not been finalized. Perhaps a start date of mid-2007.

MTN003 is a proposed three arm Phase 2B trial to determine effectiveness utilizing placebo, topical vaginal PMPA and oral tenofovir. We need to determine if women can adhere to coital dependent topical use versus systemic administration. We need these trials to assess delivery methods, for instance will an oral administration offer rectal protection? Will oral delivery of ART's be more acceptable than coital dependent topical formulations?

MTN has a high level of interest and is very committed to the development of rectal microbicides. Although expertise has thus far been in the study of women, we certainly appreciate the need for rectal studies. We have developed rectal study safety models in monkeys. Connie Celum was the first to publish rectal safety information. Also Dr. Anton and Dr. McGowan are developing protocols for rectal studies of UC781 and other compounds and so there is some focus on this important research.

Discussions with the FDA have been ongoing to determine a regulatory framework for microbicide studies. A streamlined clinical trial design will be necessary for the rectal microbicide studies, and since microbicides developed for vaginal use will likely be used in the rectum, microbicides that are currently in late-stage vaginal trials must be separately studied for rectal safety use. We have to parallel develop rectal microbicides along with better-supported vaginal microbicides and we are looking at some of the major candidates.

Funding remains a crucial issue to the expansion and development of current and new microbicide candidates.

Dr. Johnston postponed questions for Dr. Hillier from members until after the following presentation by Dr. Shattock. Dr. Johnston introduced Dr. Shattock.

Dr. Shattock begins by saying that his area of research is more focused at the earlier end and not in the late-stage studies.

In the first slide of Dr. Shattock's presentation he points out the wide number of cells that can be infected in the rectal cavity. The thin epithelial layer in the rectum will make safety trials paramount in the development of any microbicide that will be used rectally. Some products (protein based for instance, and surfactants) might work in the vagina but not in the rectal compartment. Also absorption might be different. And so various formulations and forms of rectal microbicide candidates must be carefully studied.

They must be safe. They must have high degree of efficacy. They must be inexpensive and easy to use to ensure the likelihood that a product will be used reliably in real world situations.

A review of the current pipeline identifies candidate polyanionic substances currently engaged in Phase III vaginal efficacy trials. The antiretroviral products in development as microbicides follow closely, in Phase II trials. Other entry inhibitors and other compounds are emerging in preclinical trials.

The current leading compounds may have the advantage of being inexpensive to produce and may also possess a broad range of prevention capabilities but we still don't have proof of concept on any of them. Some of these have been studied for rectal safety but not to the result of any comprehensive data. A high degree of efficacy is likely going to be necessary for the prevention of transmission of HIV in the rectal compartment and since these leading compounds can boast a broad spectrum of prevention, they may not be as potent as newer, second-generation

candidates. That might mean that the first generation candidates might have to be used every time to maximize efficacy, or large volumes of the product may be needed and therefore may not be suitable for some users.

The ARV's currently in development as microbicide candidates might offer some advantage in that they are also fairly inexpensive, may be highly potent, and might be formulated for sustained release dosage. Dr. McGowan is planning safety trials of ARV microbicide candidates.

Some of the disadvantages associated with ARV microbicides are the existing potential for resistance development, the current lack of safety and animal data, and the narrow spectrum of activity that would limit its use to HIV prevention. We may have to look at marketing a product that goes beyond just HIV prevention, for instance one that might include claims of sexual pleasure or other indications to influence users.

NNRTI studies exposed rectal tissue before challenge with virus. Protection was noted in vitro for up to 6 days. More in vivo studies are required.

Entry inhibitor microbicides have demonstrated a high activity in vitro and could also be formulated for sustained release. Again we are short on animal and safety studies and need to consider all options in looking for a highly effective and safe candidate. There are some production issues with cyanovirin right now but when those are resolved we plan to go into further clinical trials with that compound.

In looking at various animal studies we found some surprising information. The cyanovirin was highly potent, and with Tenofovir we might be able to enhance effectiveness but we need more animal studies. E. Coli infused with C peptide provided 50% effectiveness at prevention.

Currently there is insufficient funding for novel formulation studies and the very expensive animal studies needed to go forward.

Moving beyond safety issues, what is it going to take to demonstrate effectiveness of a rectal microbicide candidate? Like vaginal microbicide candidates, the rectal effectiveness trials will need approximately 5,000 to 12,000 participants in several areas where HIV incidence rates are high, and consistent use of the microbicide throughout the trial period. We don't know yet to what extent the safe-sex counseling will have on HIV incidence rates and, as has been demonstrated by some of the vaginal candidates, participants in trials who adhere to safe sex practices and condom use can have a dramatic effect on the local incidence rate, making data collected in those areas less statistically significant resulting in enrollment cessation and pursuit of other more suitable locations for completion of those trials. We will need to plan for potential failure of certain sites, based on the effect on incidence rate of participants who accept safe sex counseling and utilize condoms provided.

Dr. Shattock is often asked why there aren't more microbicide products moving into clinical trials at a faster rate. The response is that there are currently so few viable products in development. 1st generation microbicides are unlikely to be effective in rectal use, ARV's might work, but they require a lot of consideration of the resistance issues and the entry inhibitors will require animal studies to determine effectiveness in rectal use.

What's worse, should some of these vaginal product concepts fail, it could be detrimental to developing forward moving strategies with rectal microbicide candidates. The "knock-on" effect. We may have to develop rectal microbicides in concert with other prevention options such as PREP and circumcision to maintain relevance as a prevention option and not be so closely tied with potential adverse effects in vaginal trials.

We will need to look at designing the right type of product that will be used and will affect incidences. And like the vaginal microbicide trials we still need to determine the economic factors to develop a rectal microbicide. How much would these trials cost? How many new infections would a partially effective microbicide avert? What level of health care benefit will be derived from prevention and what level of population should be targeted for use of a rectal microbicide?

As Dr. Shattock has completed his presentation, the Dr. Johnston moves to take questions from conference call participants.

The first Member's question was posed to Dr. Hillier (sorry I didn't get the question verbatim but it was about the implication of vaginal trials on potential rectal trials). Vaginal microbicides might be damaging to the rectum and unrecognized use of a vaginal microbicide rectally during trials could also be damaging. A microbicide that is safe for vaginal use may create excessive levels of toxicity in the rectal environment and that could be a show-stopper. Rectal microbicide candidates will require comprehensive safety studies and we will need to develop minimal safety guidelines. In order to accomplish this we will have to look at use patterns (lubricants, HIV prevention, etc.)

Are there any candidates in the clinical trial pipeline being tested for rectal safety?

Vivagel is about to enter Phase I rectal safety study.

Do the applications for funding at the MTN represent any rectal trial sites and in Europe are there any objections to funding of rectal microbicide trials?

At MTN we do not yet have a full list of our clinical trial sites, we anticipate having that in about a month. We do pay attention to whether or not the applicants have the necessary facilities including the skills of the clinicians and access to the necessary population to do rectal studies. It is very hard to estimate the cost. Vaccine developers have utilized behavioral studies to get an early read on potential effectiveness before embarking upon costly Phase III studies.

European funders don't seem to be culturally challenged so much as they want to know to the cost benefit ratio before pledging trial support. Even the small studies are going to be expensive.

Of the candidates in late-stage efficacy trials, do we have any rectal safety studies from any of those compounds? NO

A rectal safety study for PRO2000 is planned to start early next year, sponsored by the UK Microbicide Development Program and will be held in the U.K.

Vivagel is the only other compound with rectal safety studies planned that we know of. No rectal safety data is available on Carraguard, Cellulose Sulphate, Buffergel or PRO2000. although it was reported (by Dr. McGowan) that five years ago he had completed the protocol for a rectal safety study of cellulose sulphate but that CONRAD determined that the trial would not be undertaken at that time.

Regarding the women currently in trials in Africa, India, US, etc., how can we be assured that they are not using the product rectally?

There is no way to be sure, we just try and collect our data and remain sensitive to the participants; we try to give them a comfortable setting where they feel safe and free to speak

truthfully about their sexual practices. Up to this time, women have reported low usage of microbicides and anal sex practices.

Are there any products in development for sustained delivery in the rectum? Obviously a vaginal ring isn't going to work.

Yes, the technology is being developed – we are thinking more along the lines of varying formulations, for instance epithelial retaining gels that might stick in place and release microbicidal agents over time or drug formulations that might be easily absorbed by healthy cells and hold the drug for sustained protection. In this regard PMPA might be too readily absorbed and so we could consider changing the formulation to address that, and we could also use entry inhibitors. Of course, funding for improved formulation development is challenging and a number of researchers are working on the logistics of formulation development.

Are current studies of the developing vaginal microbicides informing the study of the vaginal ecology, etc.? Is there anything published?

Dr. Hillier says yes to the question but suggested that that query be sent to her via email so that she can look at addressing specifics. She knew of no current publications to support the response.

After no further questions were posed, Jim Pickett thanked Dr. Hillier and Dr. Shattock for sharing their time and expertise with the IRMWG.

Jim followed up with a brief overview of the process of establishing a Steering Committee for the International Rectal Microbicide Working Group, and named the 17 members of the newly formed Steering Committee. With over 300 members of the IRMWG located in 33 countries, Jim reminds us all that together we are the working group and that suggestions and input is important for the Steering Committee - so don't hesitate to put forth your ideas and also to sign up (and refer others) to the IRMWG Listserve to stay current. The Steering Committee will have a closed listserv to facilitate communication among this far-flung group and will be up and running in about a week.

Jim (and everyone) thanks amfAR for hosting and Dr. Johnston for expertly moderating today's conference call.

Here is the list of the Steering Committee members once again:

1. Jonathan Berger, AIDS Law Project, Braamfontein/South Africa
2. Manju Chatani, African Microbicides Advocacy Group, Accra/Ghana
3. Julie Davids, Community HIV/AIDS Mobilization Project, Providence/RI/US
4. Jerome Galea, University of California Los Angeles Program in Global Health, Lima/Peru
5. Dr. Pamina Gorbach, University of California Los Angeles, Los Angeles/CA/US
6. Bridget Haire, Australian Federation of AIDS Organisations, Sydney/Australia
7. Anuchit Jitrathanakul, Population Services International, Bangkok/Thailand
8. Dr. Rowena Johnston, American Foundation for AIDS Research, NYC/US
9. Rick Jones, GNP+, Amsterdam/Netherlands
10. Jeremy Kwan, PT Foundation - MSM Programme, Kuala Lumpur/Malaysia
11. MarcAndre LeBlanc, Global Campaign for Microbicides, Ottawa/Canada

12. Dr. Ian McGowan, University of California Los Angeles, Los Angeles/CA/US
13. Dr. Ken Mayer, Brown University, Fenway Community Health, Boston/MA/US
14. Kim Mulji, NAZ Foundation International, London/UK
15. Jim Pickett, AIDS Foundation of Chicago, Chicago/IL/US
16. John Shaw, advocate, San Francisco/CA/US
17. Roy Wadia, British Columbia Centre for Disease Control, Vancouver/BC/Canada

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