

International Rectal Microbicide Working Group  
Teleconference – December 7, 2006  
Notes provided by Linda Hughes

Today's call is centered around Dr. Ian McGowan's slide presentation, which will be archived and can be referenced at [www.lifelube.org](http://www.lifelube.org)

Jim Pickett thanks UCLA and the Microbicide Trial Network for hosting today's web and teleconference.

Roll-call

1. Bridget Haire from Australian Federation of AIDS Organizations (special kudos for attending at 2:30 am her time!! Wow – in Sydney)
2. Kim Mulji from NAZ Foundation in London
3. Rick Jones from GNP in the Netherlands
4. Dr. Ian McGowan, UCLA, calling in from London
5. Julie Davids, from CHAMP in New Orleans
6. Dr. Rowena Johnston from AMFAR in New York
7. Lori Heise, Global Campaign for Microbicides, in D.C.
8. Carolyn Plescia, Alliance for Microbicide Development from D.C.
9. Manju Chatani from African Microbicides Advocacy Group (Ghana) calling in from Northampton
10. Jerry Galea, from University of California (normally in Peru) calling from Miami
11. Deidre Grant from AVAC in New York
12. Bindya Patel, Global Campaign for Microbicides, in D.C.
13. Jim Pickett, AIDS Foundation of Chicago (AFC) in Chicago
14. Trina Nelson (AFC)
15. Jessica Terlikowski (AFC)
16. Nisha Haniff, University of Michigan, from Ann Arbor, MI
17. Wakefield, HIV Vaccine Trials Network, from Seattle
18. Linda Hughes, Polydex, from Point Roberts, WA
19. John Shaw from San Francisco
20. Charles Price, UCLA
21. Dr. Pamina Gorbach, UCLA
22. Dr. Peter Anton from UCLA
23. Marc-Andre LeBlanc from Global Campaign for Microbicides in Ottawa
24. Roy Wadia, from BC Centre for Disease Control in Vancouver
25. Shaleena Theophilus from Canadian AIDS Society in Ottawa
26. Edd Lee from AVAC, NY

Jim thanked everyone on the call for attending from such a wide variety of time zones, and provided an overview of today's agenda, introducing Dr. Ian McGowan and his presentation on Rectal Microbicide Safety, and Julie Davids as the moderator for the question period.

Ian had dropped off the call momentarily and so Marc-Andre utilized this moment to ask everyone to consider hosting future teleconferences in the New Year and suggested that willing organizations could drop him ([maleblanc27@yahoo.ca](mailto:maleblanc27@yahoo.ca)) or Jim ([jpickett@aidschicago.org](mailto:jpickett@aidschicago.org)) an email to so indicate a willingness to host a call, and then a roster of sponsor organizations could be prepared. Jim added that sponsorship of the call means paying for it, and providing access information and pass codes. There are a number of variables that determine costs etc., such as the number of participants, length of call, etc., but normally run a couple of hundred dollars per teleconference. Marc-Andre followed up by saying that approximately 6 – 8 calls were sponsored this year and that we might expect as many as 10 calls next year and called for IRMWG organizations to share the burden, share the love.

Ian is back on the call and opens with brief comments on his slide presentation, looking into the safety and development of rectal microbicides. He noted that the rectal microbicide development field is becoming more respectable by the day, and this good news is evidenced by the various meetings and strategy groups that are inviting RM developers to the table for discussions, looking for answers to the question of how rectal microbicides will fit into the overall microbicide development picture.

The HIV Prevention Trials Network held a safety meeting in March of '06 and DAIDS held a meeting in November where toxicity issues were discussed, along with other key aspects of microbicide development.

Some of these important issues were the rising awareness in the general population regarding microbicide development and the notable conclusions that vaginal microbicides will most certainly be used rectally when they are rolled out. At the moment the only safety data on file is from animal (primate) studies, and the PMPA and Cyanorivin studies are advancing toward Phase II. There is a confluence of different issues surrounding how we approach rectal safety.

Two years ago we heard mostly concept conversations, back when N-9 was the most widely known microbicide product in development, but slowly the pipeline is becoming richer and rectal microbicide candidate products are beginning to move forward in clinical studies. Dr. Anton at UCLA has begun screening for the UC781 rectal safety study. This rectal study is part of the U19 grant assessing UC781 as a vaginal microbicide.

Ian is now developing the protocol for a Phase I rectal safety study of Vivagel and expects to run this study on women in Puerto Rico next year.

PRO2000 will likely be next approved for rectal study and certainly we are asking how are we going to conduct these studies.

The HPTN Microbicide Safety meeting held last March discussed safety issues of these trials, starting with the preclinical trials and moving onto discussion of the Phase I vaginal microbicide safety and then Phase II and III studies and included a session on rectal safety. These discussions involved diverse representation including from CDC, WHO, and the FDA who really helped with the discussion around regulatory issues. The list of delegates is included in the slide show (accompanying this presentation) and it is evident and encouraging that contributions to this discussion came from researchers, clinicians, regulators, federal agencies, pharmaceutical companies, and communities.

Rectal safety was an issue discussed at this meeting and a manuscript is being prepared from it.

Currently there are no FDA guidelines for rectal microbicide studies. We will probably need two approaches, one conducting rectal safety studies using vaginal microbicides approaching licensure (because they most certainly will be used rectally) and then for products that will be designed specifically for rectal use.

These trials will likely be designed similar to the vaginal microbicide trials, first with sexually abstinent HIV negative participants, then with sexually active HIV negative participants and then with sexually active HIV positive patients etc.

A list of safety measures was devised for the studies, and a number of considerations must be recognized, one being that the rectum is quite adept at absorption, which makes it quite different than the vagina. Systemic exposure might also be different from the vaginal studies than in the rectal studies. A list of these safety measures is on slide 9 of the 32 in this presentation and includes required safety measures and those that are strongly recommended, including histology and lavage (which was the main index Patton (?) used in monkey studies. In the histology studies they extensively counted cells, etc., and found that was inconclusive in some ways.

Could a product be administered rectally that does not present symptoms but is in fact absorbed and ultimately affects other areas in the body, the kidneys, liver, etc.?

We have also looked at the influence of HIV drugs on shedding, sloughing, etc.

In the UC781 study, the timeline design is shown on slide 10, indicating that an 8-week period is the total involvement period, beginning with initial screening, an initial dosing and then follow up with 7 daily doses, clinical evaluation and telephone interview follow ups continue through the duration of the trial design.

The primary endpoints of the trial design are to determine the frequency of greater than Grade 2 adverse events and the acceptability of the product to participants. We want to make sure there are no untoward signs or symptoms and that users find the product acceptable enough to use. Surrogate endpoints will look at whether individuals experience sloughing or other epithelial reactions. Fecal calprotectin study will help us determine the level of absorption in the rectal cavity. As the colon is designed to absorb liquid into the body and leave behind the formed feces, it will be important to determine if absorption of a microbicide compound will create adverse effects elsewhere in the body, not necessarily visible in rectal examination alone.

The most exciting part of the trial will be the biopsies taken after administration of the microbicide doses that are then combined with the virus in a test tube to determine some idea of efficacy. We should be screening in January for this.

We also talked about labeling at this meeting since no product is yet licensed and therefore labeling requirements are yet to be determined. The labeling refers to the insert that is packaged with prescribed drugs, which is very specific in content and is always mandated. Will rectal safety studies be included in the labeling of vaginal microbicides? The FDA felt that they would not agree to have the label say the product is safe rectally, based on preclinical and one safety trial, but would include indications that the product is unsafe rectally if there are markers in the studies.

At the DAIDS meeting, we talked about devising a Toxicity Table for measurement of adverse events in rectal studies. What is a Toxicity Table? It's meant to be a Go-To guide for a clinician looking after a patient. If something does happen, and things do happen, then the clinician needs to provide a report of the adverse event, whether it is a mild symptom, moderate or severe and reporting of these events needs to be consistent. A toxicity table should be a guide; a comprehensive grading system that is easy to read, understand and use. If it's not easy, clinicians won't use it.

Therefore, various grades of adverse events need to be determined and consistently defined for use across all trials. We looked at existing toxicity measurements used in vaginal studies, including adverse effects like pregnancy and pain and the use of colposcopy for consistency in measurement.

A Rectal Team, consisting of clinicians, researchers and FDA representation began a conversation on how to grade a variety of symptoms and devise a Toxicity Table. Such a table presents a number of challenges as it is well known that benign anal conditions are highly prevalent in the general population, more than 1.5 million prescriptions are dispensed yearly for anal symptomology and 80% of the US population with anal symptoms self-medicate their conditions. Symptoms may not be indicative of an adverse effect from participation in a clinical trial. Also the rectum and anus are separate and distinct compartments (see slide 19 of 32) each with potentially different reactions and symptoms to a variety of conditions.

Also, very similar symptoms may present even when the diagnosis of conditions differ (slides 20 and 21 of 32). Itching and pain are common reactions to several diagnoses, including STD's, and it will be challenging to separate common conditions from reactions to microbicide use. Perhaps a microbicide will induce similar effects as STI's or other conditions. We need to make sure our Toxicity Table can be interpreted consistently across a variety of training.

We are using high resolution Anoscopy technology to obtain clear and identifiable images for measurement of symptoms (similar to colposcopy technology) and provide diagnoses. For instance Irritable Bowel Syndrome is extremely common and presents with a number of symptoms that might interfere with observance and diagnosis of symptoms related to microbicide use. Should we exclude patients with a history of IBS into microbicide trials? These are some of the questions we need to address while developing the rectal toxicity table. It will need to be comprehensive, relevant for all phases of rectal microbicide trials and easy to use.

Slides 27 to 30 outline various grades of symptoms that together create a model benchmark for future trials.

Topics not addressed here, histological toxicity scales and emerging endpoints of uncertain validity will be more appropriately addressed after a couple of years when more data is available.

Julie Davids suggested to the IRMWG participants that we should open the floor to questions and would like to start with any clarifying questions to Dr. McGowan arising from his presentation.

Kim Mulji from London asked about the safety labs, and asking if a check for blood toxicity could be more comprehensive?

Dr. McGowan referred to his earlier comments about high rectal absorption, defining that compounds absorbed into the system may not present symptoms in

the rectum itself and therefore warrant further investigation into potential adverse effects, potentially in the liver, kidneys, etc.

Nesha asked for a re-definition of the difference between the rectum and anus.

Dr. McGowan gave a description of development of the area from the time of birth but ultimately where these two types of cells meet and fuse, there is an extreme difference in cellular structure where the anal tissue can be 15 to 20 cells thick but the rectal mucosa is only 1 cell layer thick.

Another caller wanted to re-visit the toxicity issues and how they differ in the rectum from the vagina.

Dr. McGowan explained that the rectum/colon's main job is to absorb fluid, creating the firm feces. The vagina is not designed to absorb at all and therefore a microbicide designed for the vagina does not need to consider this absorption factor. If a vaginal microbicide is absorbed into the system through the rectum, then adverse effects may not be visible on external inspection and a more thorough examination of the liver, kidneys, etc., may be necessary.

Rowena from amfAR asked what is the mechanism of action of Vivagel?

Dr. McGowan said that Vivagel is a polyanion that essentially acts as a fusion inhibitor.

Do you have faith in polyanions?

There is some very good in-vitro evidence. For the herpes indication the data is quite convincing and for the HIV we will simply have to wait and see.

Lori Heise says that in the vaginal studies there seems to be very little concordance between colposcopic findings and symptoms. Where are we in terms of understanding signs and symptoms – other potential markers – rectal compared to vaginal?

Dr. McGowan responds that we are really at the very beginning of the learning curve and acknowledges that this very good question should be asked again in about one year's time. He agrees that there is a lack of concordance in the vaginal trials (symptoms vs. diagnosis) and with the rectal studies we are very early in the development track. The studies being carried out at UCLA are very comprehensive and fortunately they have a very high retention rate. This should create the opportunity to study these issues over time.

Question: Nonoxynol-9 is clearly toxic. If this irritant were to be used in studies wouldn't we then be able to measure response? Can we use N-9 as a positive control?

Dr. McGowan says it would be a good positive control in a study of non sexually active participants.

Someone asked Dr. McGowan to define positive control.

He explained that a new test would tell you if a microbicide is toxic. If you were to use a bland compound then it would not create any reaction and you wouldn't know if your test will pick up reactions to potentially toxic compounds but if you use something that you know will have a positive impact (ie cause inflammation) then you would know the cause of that inflammation was the positive control compound.

Julie asks if there are any more clarifying questions, and in the interest of time left for this call proposes that we move to the three questions posed by Jim Pickett. The first question there proposes discussion of the necessity to advocate with funders and regulators around the (mandatory?) inclusion of rectal studies for vaginal products.

To further the discussion on this topic, Marc-Andre began by asking how likely are these scenarios? What kind of testing is being done on current first and second generation vaginal microbicides. How likely/unlikely is it that a first generation product will be safe?

Dr. McGowan said that the only data available right now is from the monkey studies or the explant data (the removal of tissues from humans after microbicide dosage and then exposure to pathogens within a test tube to determine adverse effects on the cells) In this explant data, the product is not associated with coitus. None of the current first generation products have been tested for rectal safety in humans (other than the explant study mentioned above)

Lori Heise asks what can we say once we have Phase I rectal safety study data? We can't say that a product is safe after Phase I data is available in a vaginal study, so what information will the rectal Phase I data give us?

Dr. McGowan: Very limited data. These trials are done over a very limited time period, for instance 7 days. Is it safe? All we know is that after just one dose of N-9 it is clear that changes occur and adverse effects can be measured. Perhaps we can use this information to say something like - even after 7 days use

rectally, no adverse effects were observed, in comparison with the use of N-9, which causes notable irritation after just one use.

Kim asked whether all vaginal microbicide products in Phase III will have been tested for rectal safety before being rolled out.

Dr. McGowan says he knows of no human rectal safety studies in any of the current Phase III compounds.

Someone mentioned having heard that if there is an indication of effectiveness in the Carraguard Phase III trial then Pop Council intended to conduct rectal safety studies before roll-out of the product.

Lori mentioned that only two of the products in Phase III are trials of licensure size – PRO2000 and Carraguard. She added that the trials of other compounds in Phase III trials will require additional trials before licensure as they were not of the appropriate size to be considered for licensure.

Dr. McGowan said that he was not sure that was so. He also mentioned that some sponsors simply don't consider rectal studies part of their program and there is a sense of ambivalence among some – those saying they may and others saying they may not consider rectal studies.

Julie Davids brought us back to the question of whether we should advocate for mandatory rectal safety studies prior to the roll-out of any vaginal microbicide product.

Bridget indicated in the affirmative.

Nesha reminded us that a vaginal product will most certainly be used rectally. John indicated that since it will be used rectally, safety trials should be mandatory.

Linda asked whether it should be mandatory, considering that a failed rectal safety study might jeopardize the microbicide pipeline (people's overall perception of safety).

Julie responded to this with a recollection of how the devastating setback of the N-9 trials did not have a lasting impact on the rest of the microbicide pipeline.

Marc-Andre pointed out that according to what Ian said earlier, we are unlikely to see problems at the severity level of N9. And with one safety trial, labeling is unlikely to say a product is safe rectally, but might say it is unsafe for rectal use if the trial shows indications that this is the case.

Lori said that she has come across a lot of support for rectal microbicides safety studies and mentions that sponsors want to have some control over that study

data. Regulatory involvement is not desirable, but field studies have a lot of support. It's dangerous to imply that education won't be necessary and a Phase I study will not give us proof of safety.

Julie and Lori both agree that a variety of terms can more accurately reflect a product's ability to "do no harm" as opposed to being "safe" or "doesn't appear to show harm" and also "potentially helps"

Manju asks if the second generation products are all considering rectal studies.

Dr. McGowan says let's assume you mean RTI's when you say second generation (like PMPA and Tenofovir) and says that the funding of rectal studies is going to depend on whether trial sponsors like CONRAD and IPM are interested in rectal studies. Not sure whether IPM is considering prioritizing rectal trials on TMC120 (anyone on the line from IPM?) but feels that CONRAD might be open to consideration of funding rectal studies. UC781 is in a rectal study now and not sure whether Pop Council is considering rectal trials with MIV150 (combo Carraguard compound)

Marc-Andre asks if anyone in Phase III trials is on record saying they would do rectal studies?

Dr. McGowan says no, no one is on record but it is in the early stages of discussion among a number of trial sponsors.

Marc-Andre asks if we should contact these groups with compounds in Phase II or higher and ask them the question on whether they would do rectal studies.

Dr. McGowan says that there are primarily two issues – One being that most sponsors are small companies that are very short on cash for clinical trials. A phase I safety study will surely cost in the neighborhood of \$1 to 2 million. And secondly, these sponsors feel that some of the science is simply not ready and that is not unreasonable, we are just getting started in the rectal study of microbicides. The pace of the pipeline is actually OK right now, by the time we complete these early safety studies we will have learned a lot and can look to further development of microbicides for rectal use.

Jim asks why anyone would want trial sponsors to do rectal studies outside the FDA regulatory oversight?

Lori answered by saying that the FDA commonly approves compounds for one indication and not another and that sponsors who may want to do what's right don't want to end up caught in the FDA quagmire of regulatory procedures.

Lori continued that we should try and think in terms of stages. Carraguard might show some reduction in their vaginal trials and if so wondered whether we should hold up the roll-out in the absence of rectal safety data - and recently presented that very question to Dr. Hillier. Dr. Hillier reportedly said that she would not support holding up Carraguard's roll-out in South Africa.

Marc-Andre points out that there will be challenges and suggests that perhaps the IRMWG can advocate for rectal studies, encouraging studies and focus on helping sponsors overcome some of the obstacles Ian mentioned earlier.

Bridget asked whether there is a strategic benefit in NOT mandating rectal studies.

Lori answered Yes, saying that she thinks we can get the data we want with less angst if we work with the sponsors rather than involving regulators. She mentioned also that these studies are typically quite short and presumes that the prep time is the lengthiest part of the timeline with protocol design, presentation to IRB's etc., does that take about a year?

Dr. McGowan agrees with Dr. Hillier that no product roll-out should be delayed in the absence of rectal studies. With respect to the timeline question, he says that depends on who is paying for the study. For instance the NIH takes longer due to the number of steps in their protocols. IRB designed protocols would be quicker to commence the study. In our current trial we expect to enroll 45 patients, 1 or 2 a week, so this trial could take a year to complete, plus the preclinical time and the toxicology to screening time...

Julies asks if we need to set up separate groups to 1-continue to clarify issues or 2-draft language. Do we want to push toward mandatory rectal studies?

More discussion – several responses flood in that we need more discussion. Maybe not mandated but FDA provided guidance might be helpful.

Anyone willing to join a group to continue looking at these issues, and eventually draft language?

Marc-Andre

John Shaw

Bridget Haire

Jim Pickett

Roy Wadia

Lori Heise

Ian McGowan – will be happy to consult but is unable to be deeply involved

Manju Chatani

In closing the teleconference Julie mentioned that a number of the IRMWG Steering Committee will be at the Conference on Retroviruses and Opportunistic Infections in Los Angeles in February '07 and suggests that we plan a "gathering" of those that will be available for a meet and greet and some discussion – no statements, policies or decisions – just a gathering. Let her know if you will be there.

Thanks all around, this is our last teleconference until the New Year.