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**4th IAS Conference on
HIV Pathogenesis, Treatment and Prevention
Emerging Challenges in Designing
Prevention Research
International AIDS Society and
Australasian Society for HIV Medicine
July 23, 2007**

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RENEE RIDZON, M.D.: Hi, my name is Renee Ridzon. I'm from the Bill and Melinda Gates Foundation where my responsibilities include working on the Foundation funded work on non-vaccine HIV prevention. I'm delighted to be a part of this important symposium and actually to be a part of an increase attention and looking at prevention in these conferences. I want to acknowledge Gita Ramji [misspelled?] for putting this session today. Thank you very much. I think this is an important session. We have several large-scale phase III HIV prevention trials finishing up and ongoing in the field right now. These trials are teaching us many lessons are proving to be exceedingly more complex and expensive than anyone anticipated with challenges of lower expected incidence and higher than expected pregnancy rates requiring a product to be stopped, a decrease retention and many other challenges, which has necessitated a very good look at how these trials need to proceed and so hopefully we will have some important information, observation and lessons in this session. I would like to introduce my co-chair, Mitchell Warren, who is the Executive Director of the AIDS Vaccine Advocacy Coalition and doing a lot of advocacy around vaccines, but also around other non-vaccine prevention/interventions and the facilitator for this afternoon is Kim Dickson from WHO, who has been working on

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[inaudible] and male circumcision. I would like to introduce Mitchell at this point who will make introduction of the first couple of speakers.

MITCHELL WARREN: Great. Thanks very much, Renee, and it is tremendously exciting for a number of reasons both in terms of content but also in terms of friendship. One of the nice things is challenging as this field is, there are a lot of great people working in it and a great deal of collegiality, and it's my great pleasure to introduce first and foremost Quarraisha Abdool Karmin, with whom I personally had the chance to work for many years when we didn't talk about research as much as we talked about actually preventing new infections, and it's been an evolving piece of work in her own career in South Africa and internationally. She currently is the Scientific Director of the Center for the AIDS Program of Research in South Africa, better known to many of you as CAPRSA, and is also the Co-PI of the HPTN, the HIV Prevention Trial Network Leadership Group, the NIH funded leadership group. So, I'm going to turn it over to Quarraisha, who is going to talk about current challenges in HIV prevention research.

QUARRAISHA ABDOOL KARMIN, PH.D.: Thanks very much, Mitchell, for that warm introduction. Good afternoon ladies and gentlemen. I sort of feel like a very distinct disadvantage. My body is here and my mind is telling me

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something else, you know, it should be sleep time or something, but anyways it gives me, I want to thank the organizers for the opportunity to address you. I had a [inaudible] invitation that gave me one title and then I saw the program so I tried to mix a little bit of some of the prevention challenges with some of the research challenges so hopefully this works. If not, I'm sure between Ward and Drew and Veronica there'll be some compensation.

So in terms of my presentation this afternoon, I want to talk very briefly about the evidence pyramid, some of the prevention challenges to, if you needed any convincing that prevention actually does work, and then some of the timeline for the current prevention trials and the issue of getting research into policy and practice indeed a complex phenomena.

So, Mitchell and I were chatting a little bit about we have been hearing repeatedly over the course of this conference and in other settings about the need for evidence, and I wanted to share briefly this evidence pyramid where the value, least valued of evidence is that affects opinion and some people, you know, if you like what they saying then expert opinion counts very highly, but seriously in terms of good understanding of what is making a difference? Does an intervention work or not? The randomized control trial is about the best evidence you can get for informing policy and practice and then beyond the

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individual randomized controlled trials net analyses of multiple randomized controlled trials through systematic reviews, et cetera.

So, here in terms of knowledge generation you can have expert opinion moving on to in vitro research, animal research, case series and case reports, case controlled studies, cohorts that is, and then evidence sufficient to design and implement a randomized controlled trial and from thereon systematic previews [misspelled?].

So, in terms of prevention challenges more broadly, I think one of the first issues is that we are not dealing with one simple pandemic, but what we are dealing with is a complex mosaic of multiple epidemics that are diverse in terms of modes of transmission, but also in terms of burden of disease. So, when we are thinking prevention and we are thinking about effective prevention, we can't be thinking about one solution to eradicating HIV we can get to be that lucky, but certainly in our response knowledge of the epidemic is really an important stopping point from thereon identifying the target populations that would benefit and what is the most effective interventions to target at those groups.

So, an additional challenge that we have in terms of prevention is a fair amount of scientific uncertainty in terms of transmission, in terms of replication, et cetera, but one of

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the bigger ones facing us in terms of intervention research is that we have no surrogate markers of protection and at this time the most reliable marker we have is HIV infection upon infected people. So, in the context of this huge amount of scientific uncertainty, we at the same time have a parallel imperative, a public health imperative, to respond to the epidemic and this has been a tension over many years is, how much more basic science do we need before we act? And what is the balance between a knowledge that we divide in terms of basic science, clinical science and then implementation and design of interventions? That's not one that's easily resolved and this debate continues today, and we see particularly in terms of microbicide trials, we see that with vaccine trials, but also in light of the most recent trial data that was released in terms of MERA [misspelled?] and the early closure of the cellulose sulfate trials, and I'm sure it's something that we will continue to discuss and debate and those debates and discussions as far as they are constructive will move us forward, but there is no right answer about how much basic science do we need to have before we proceed to testing these interventions in clinical trials?

The knowledge general process in terms of, in the context of HIV is a lot more complex. As scientists working in other areas, we are used to sitting in our labs or offices or

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wherever it is we do our research and quietly getting on with what we need to do and most of the world is not interested in what are the outcomes of stem cell research as something as esoteric as that, but with AIDS having such an immediate impact, public opinion matters, public need for information, public need for accountability and transparency in decision making is really quite unprecedented in the context of the HIV AIDS epidemic, and our responses to that. And this need for information flow communication of ideas is not what we usually do, which is publish our paper through a peer review process and then discuss it has really led to some novel ways of science in our generation particularly I want to highlight the synergy that has evolved between science and activism.

I think more recently what we've seen is the emergence of politics and media as I won't call [inaudible], but new challenges in the way we do research, and I think that transformation of those two other players in the way we do research is one that needs to develop and be refined a lot more to take the science forward as opposed to paralyzing science, which is sensationalizing science. And lastly that HIV-AIDS is more than a medical issue, and I think most of us sitting here understand its development context, its need for a multi-sexual [misspelled?] approach and that if we are going to be effective, we need to partner with a whole lot of people that

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we don't usually partner when doing biomedical or medical research.

One of the newer challenges that, or I actually see it as an opportunity is with increasing access to anti-retroviral treatment. What we are seeing is the integration of prevention and care and this is while it is an evolving and emerging opportunity for improving intervention efforts, to date there have been few successful sustained efforts to integrate prevention into clear programs and prevention interventions have traditionally concentrated on particularly those at risk of infection and this integration of prevention with care demands a refocus and an expansion of prevention efforts to target those already affected. To date, we have very few new models in this regard, but these are starting to emerge, and I think this is one of the newer and more exciting developments.

To move on to what evidence that prevention works. I think quite often when the UN AIDS data is released, we are oh, we are just not succeeding, and the reality is that there are countries and here we have Uganda – I won't go through the details of that – we have Thailand with 100-percent condom promotion program, and we have this country where we are all gathered in Australia that has really shown the way in terms of country-level responses with leadership with multi-sector approaches knowing the details of the epidemic, targeting the

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interventions that the groups to benefit most have been able to demonstrate with very limited prevention options behavior change, condom promotion, VCT, injecting supportive harm reduction interventions that you can make a difference at a country level to epidemic trajectories, but the reality in most parts of the world is that we have failed to scale our prevention, and this slide is a little bit dated, but it gives you some clue and indication of how unsuccessful we have been to target these known interventions to the level, to the magnitude and to those who need to benefit most.

So this I've fidgeted so many times with this particular slide because as I prepared for this talk, more trial results became available, and I think we have all been very disappointed with what we have been hearing and seeing on the one hand, but on the other hand I think also that for each of these trials that have not given us the outcome we want, we've had other important valuable lessons and the other speakers in the panel will be addressing it, but this gives you some idea. Color coded microbicide trials, barrier methods, behavior, treatment, PMGCD vaccines. One of the long roads we have ahead, and anything can happen, you know, for example, we have the MERA [misspelled?] trial results. Moved on hearing about it earlier, but negative and, but we are learning a whole bunch of other things that's the important piece, and if we

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have the answer already there would be no need for these trials. That's the important thing to remember, and a lot of this is really the public setting [inaudible], all the trials we have seen here or really all of the trials occurring, and I think that's a sad indictment in terms of the prevention research field in terms of investment other than vaccines for shorter timeline interventions to alter the epidemic trajectories.

I'll turn briefly to some of these trials and as these results come out, they all have certain things in common with exception of some of the vaccine trials, which is that they require some kind of chronic use of the intervention or medication in otherwise healthy and uninfected persons, and the same thing is increase in health systems focus in terms of these prevention interventions. Also the importance of knowledge of HIV status and some concern as we have many partially affective or many new interventions. When you introduce a new intervention, it's going to lead to migration from other methods.

So, as we think about this as we await these trial results, one of the things we need to start thinking about is getting research into policy and practice, and now I want to dwell a little bit in terms of what are the lessons we have learned to date? A couple of experiences that may inform the

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scale up of these new trial findings as in when they emerge. The first lesson is that from scaling up anti-retroviral treatment access and they highlight lots of issues, but in particular, issues around politics and capacity and how that impacts on policy formulation and programmatic scalar.

The issue of promotion of knowledge of HIV status beyond a client-initiated one to provider initiated, all kinds of other permeations [inaudible] in this conference will deal with, but particularly a human rights dimension that's highlighted, the issue of introducing the female condom and particularly migration from other methods and also ethical issues and then male circumcision trials.

So, this is a [inaudible] diagram in terms of impact of mortality with introduction of anti-retroviral treatment. Industrialized countries served as a huge impetus for scaling up anti-retroviral treatment access in resource constrained settings has led to some [inaudible] interventions, PETFAR, the Global Fund for AIDS, TB and malaria, et cetera, but what is the reality? The reality in Africa, for example, is there has been a slow scaling up of anti-retroviral treatment, and if you focus on the last slide, so I have displayed by techofobic [misspelled?] [inaudible], if you look at the total, there are just over three million people who need to be on treatment and about 351,000 on treatment representing less than 10-percent.

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In large parts of Africa, there were concerns. People don't own clocks so they won't be able to adhere to medication. I think there's lots of data that have come out to show that's the least of our concerns.

Adherence, in fact, in Africa exceeds much of what we see in industrialized countries, but one of the bigger bottlenecks besides the political [inaudible] in some of our countries has been the shortage of health care personnel. Health care services in Africa are struggling to cope with the additional burden of AIDS care. We have overworked and stressed staff. Deborah Ward [misspelled?] mentioned that this morning. Those are concerns about accidental HIV exposure leading to low moral given the high HIV burden that we see and limited barrier method access, et cetera, but importantly Africa doesn't just have AIDS that's a problem. It has many, many health problems and what AIDS is doing is taking away some very limited resources away from other care and this has to shift. This balance needs to get back so we don't address the AIDS issue and then find we are lagging behind, and we have already seen that with our immunization coverage rates are low. We are looking at female mortality going down, infant mortality rates going up, some of that is AIDS related. Some of it is about other care being compromised with the increase in focus and while there's a dire and humanitarian need to scale up

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anti-retroviral treatment access, there's some balance here that needs to be [inaudible]. And for many years, again, the point Deborah made this morning is for years we have been struggling to retain our skilled health care professionals. The work secret in Africa is that our biggest import – export rather – is health care workers. So, you go around the world you see people trained in Africa who are nurses, pharmacists, clinicians, et cetera, and just to give you one example over the last 35 years at the University of Witwatersrand in South Africa, 44-percent of the graduates have immigrated and most of the medical or health care worker training is done with public sector funds. So, there's these public sector funds subsidizing export of skills to other parts of the world. This is a serious issue that needs to be addressed.

Okay, we all know that knowledge HIV status is an important gateway both for prevention and for treatment. Huge amounts of stigma, real or perceived, has been a huge bottleneck for people seeking to know their HIV status. Some of it has also been the models of VCT provision that we have, and I emphasize VCT because this has been shown repeatedly as an important component and dimension for testing. We do now have evidence from countries that have chosen to go with just testing and we've seen very little impact of that particular mode of HIV testing in terms of uptake testing, as well as the

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impact of knowledge of HIV status. Here we have several examples of trials underway or interventions at an ecological level. For example, family-based VCT in Uganda has made an enormous difference over an 18-month period increasing knowledge of HIV status from about 80-percent to greater than 84-percent and many people now who know the epidemic from the early 90s attribute this as one of the more important interventions in terms of altering the epidemic trajectory in Uganda. In ten years we have good examples of provider initiated VCT in the total universal HIV testing with VCT and then a trial, a very exciting trial in South Africa at the moment, a community-based one, which is really one of the few structure level interventions to promote knowledge of HIV status.

So, I want to focus now on female condoms intervention programs and fortunately the Brazilian government when they decided to introduce the female condom, sort of anticipate those nay-sayers that say when you introduce something new, people will migrate from other things. So, they tried different permutations where they introduced the female condom in the community through health care settings and then randomized some communities to get a combined community and health care intervention and what you see uniformly here is contrary to popular belief that when you introduce something

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new in a setting, you actually increase the number of protected [inaudible] acts compared to when you just have a single intervention. And I think this is really important because our goal is not to promote one intervention or the other. We need a panoply of interventions and here introducing new interventions actually increases the probability of exposure to the virus in [inaudible] sexual acts in this particular case.

I want to turn to male circumcision and Mitchell said this, and I'm going to say it again, I think you are going to hear it over and over again, this is one of the best pieces of good news that we've had in almost a decade and not only good news from the Orange Foundator [misspelled?], which became available just over two years ago, but consistent data from the [inaudible] study trial and also [inaudible]. So, if we think in terms of the evidence pyramid that I started off with, you can't get better than this. Three randomized control trials all with consistent data and what more do we need? I mean this is very clear that male circumcision is an opportunity to impact on HIV trajectories in low circumcision countries with high prevalence, HIV prevalence, it involves consenting adult men some of the discourse gets conflated with what about adolescents? What about infants? What about rights? What about culture? But their trials are very specific. They were all conducted in adult consenting men. We are not

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extrapolating the data beyond that. These are settings where male circumcision is not common, and here is an opportunity to integrate safe male circumcision with other sexual and reproductive health services for men. We keep hearing about the vulnerability of women in countries where women are vulnerable. Men who have power and have the ability to make decisions have not been taking the responsibility or making those decisions. So here is a wonderful opportunity to choose that for promoting greater male responsibility but importantly modeling data is saying that it could reduce incidence in adult men by 50- to 60-percent.

So, we've had an unprecedented rapid recommendation on scaling up from [inaudible] in AIDS, but there is still some lack of consensus in the scientific community is also ambivalent to make policy decisions at a country level and also mixed feelings in other quarters.

So, to summarize, translating RCT findings to policy and practice is complex. Partly because HIV-AIDS is more than a health issue, and we've learned over the years that social mobilization is a very effective tool. This is something as scientists we don't think about much more, but there's certainly evidence from the country level interventions are far significant and important and impact social mobilization. We also know that RCT evidence is not sufficient for policy

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formulation. It's important as we think about and prepare for some of the trial findings that within the timeline that we need to start strengthening health care delivery systems. We also need to be thinking of combination interventions that combine biomedical and behavior or social interventions to have a more substantive impact on the pandemic even as we think about access issues and design of new trials. We need to address stigma and discrimination to promote uptake of HIV testing. It's one of the few hopes we have with increasing access to treatment that we can have a more classic infectious disease impact on this epidemic by dealing both with those infected and uninfected and at risk and those recently infected. I think what we have some evidence for, and I'm sure increasing as the number of interventions we have increase is that the concern that the introduction of new intervention will lead to migration of known and available interventions is misplaced. Indeed, we need a plately [misspelled?] of options to address the complex and diverse pandemic and its challenges it causes to us. Thank you. [Applause]

MITCHELL WARREN: Thank you very much, Quarraisha. Our intent is to engage in a dialogue after all four presenters. I will open it for any questions of clarification. I see none. We will move to our next presenter. I don't see any truly. Okay. I really don't. Next it's my great pleasure to

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introduce a great friend and colleague, Ward Cates. I think for any of us that work in this field we know that there are, if we don't know there are going to be setbacks and challenges, we are in the wrong line of work, and in my darkest, most cynical days, I'm always just able to look at Ward and remember that there's optimism in this field because he keeps us all optimistic and that's true of his days at the Center for Disease Control and for the last several years, many years, running programs at Family Health International. So, I'll turn it over to you, Ward, to talk about the optimist view, which I did not know was your title when I said those things about you.

WILLARD CATES, JR., M.D., M.P.H.: Well, I knew that you were going to introduce me, Mitchell, so I couldn't resist this particular title. It takes one to know one and truly this is a time even with discouraging results from trials, to be optimistic about what we learned from them about stronger future trials and that's going to be the bottom line. Now, all of us seem to have this rainbow series whether it's Mitchell's or whether it's Quarraisha's, whether it's Kate Hankins [misspelled?], whether it's Veronica's, but this is one that I've been using that just show when we might have anticipated trial results including one even today regarding acyclovir for both acquisition and infectious, at least, shedding in poster prevention 011. So, we have had both late breaking news and so

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on, and we have to keep in mind that the past decade have brought two new biomedical approaches whether it be nevirapine or whether it be male circumcision as Quarraisha pointed out, and we've really had ten valuable lessons learned about how to do the trials that we are talking about awaiting the results for and these are just my sort of breakdown of the ten, Ward's ten top lessons, but because of timing and so on I'm going to only focus on five of those. Some of them were touched upon at a macroscopic viewpoint by Quarraisha.

Now, adherence is the most crucial aspect of all of our prevention trials. We've learned about the role of social desirability bias in terms of the self-reports that we get not matching up at least with the objective biologic results we get when we test it. So, we've really learned by having some new approaches to refine and improve our accuracy whether they are computer assisted, CASI [misspelled?] methods, whether there's some applicator testing that I'll show you in a moment, whether there are MIMS [misspelled?] pack exposure to, you know, packets that pills are actually dispersed, both of those talk about the applicator or the packaging. It doesn't actually tell you about the actual use, but then there's drug levels which sort of spot checks of either urine or blood at particular visits. PSA or Y-chromosomes to look for sexual activity, unprotected sexual activity, and then a creative

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approach directly observed adherence or directly observed protection that's being planned for future studies. And finally, we've even redesigned counseling messages during the course of trials when we started saying that the type of adherence in specific groups we wanted was not happening.

A couple of examples. I personally think this is one of the real five top breakthroughs in the microbicide field that we've had and it happens to be with at least a measure of adherence by the POP [misspelled?] Counsel Group and their Care-A-Guard [misspelled?] study these are the applicators. What you do is they ask for the applicators are brought back. Very inexpensive blue dye is applied to the tip, run under water. If their applicators were not used, look to the left you'll see some clear applicator tips. If they were used, you'll see some residual blue dye. Now, some have been skeptical as whether or not that assay has been, can be used, can be validated, number one, and used in the field. Just published a month ago Andrea Wallace [misspelled?] and her counsel crew did studies in a very tightly controlled clinical setting in the United States and actually found for both true insertion and true non-insertion high levels of accuracy and that same methodology played out when it was done in the actual trial settings of Care-A-Guard [misspelled?], which indicates that if future trials want to use this either as a spot check

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or as a continued check for their applicators, it is one way to add at least an indicator to complement the self-reports.

Then in terms of reinforced counseling, within the HPTNO-35, we found early on in the study that there's sort of a concordance that those who were more likely to use condoms were also more likely to use gel when they used condoms and the discordancy to some extent if you want to think of it that without condoms those were also less likely to use gel. Now this far right hand column is the column we want to enhance most. It's those who are not using condoms, we want the most used gel. The counseling messages were changed and over the course of time, over the course of about 20 months at least the self-reports, and again, the skeptics are saying social desirability bias, but the self-reports showed an increase in terms of use of gel in those last action, which condoms weren't used. So there have been creative approaches to the question of adherence and there'll be even more as we go forward in the future. This is crucial.

What about the prevention standard of care? And I want to read to you from a wonderful document that Mitchell, Kate and others have put forth called, "Good Participatory Practice," and one of the essential principles of good participatory practice is a standard of prevention that says researchers, research site staff and trial sponsors have an

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ethical responsibility to ensure that appropriate risk reduction counseling and access to proven HIV prevention methods and the emphasis there is on proven. So, what are our traditional approaches for counseling people as our prevention standard of care? Well, number one, there is this reinforcing prevention counseling for which the evidence is somewhat there if you look at the Explora trial [misspelled?], but I would not say it's that strong as far as level one evidence. There [inaudible] of male condoms for which we have no level one evidence because it's unethical actually to do a randomized trial with male condoms, but we provide those, and we give STI treatment. Now, these are, for which there's one level one and four level one, that is positive, four level ones have shown no effect. Now, are these proven interventions? We use them and they may even work. Quarraisha brought up the female condom for which there's biologic plausibility and for which increasingly in some of our trials those have been also included as our standard prevention standard of care package. And then the male circumcision results, which are incontrovertible how do we get those into our prevention standard of care? Well, there are some evidence, there is some evidence that these trials are interventions of their own, and I had shown for years the evidence from the Ron Roddy's Cameroon [misspelled?] film trial, which showed at least using

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limited pre-trial estimates relatively high incidence levels in the population being studied had during the trial and then in a couple of follow up studies showing that it stayed relatively low or even lower afterwards.

Well, in Kenya, Elizabeth Amgooby [misspelled?] just published in JADS, her results from her Nairobi Female Sex Worker Cohort in the early part of the millennium that had also the same sort of trend data in terms of incidence during a trial and even after the trial with rather minimal continued community intervention and peer support. So it is sort of interesting that the trial whether it's because of a selection phenomena for those who choose to participate in trials and continue to get reinforced during the trial, but there is some evidence that these trials themselves are interventions – prevention standard of care. But what about male circumcision? This is now what we are wrestling with in doing the future trials not only counseling patients, but what must we offer to all participants if we are doing a prevention trial of men in recruiting uncircumcised men or if we are doing prevention trials in women and they have uncircumcised partners? Is it at least as protective for the women as a preventive standard of care to offer to circumcise their partners as it is to offer the male or female condoms? Think of it. Level one evidence on one hand. Okay, and then how else do we handle this in the

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analysis and then how will it actually affect our study validity?

Now is going to some fun part, which I thought how was I going to present anything new to this audience from these people that I talk with weekly? And so I thought what we would do is to present some cost elements across some of these trials because it is as Quarraisha said expensive to do these trials, and we ought to learn just like we are learning lessons in methodology, we have to learn lessons in cost and then there's the effect of what is planned? What are the budgets we put in and get some of the people sitting in this audience to say "yes" to? And then what does it actually cost once we do the trial and then there are whole elements of sequencing. How much does it cost before the trial begins? Okay, how much during the trial and then how much after the trial, which frequently isn't even built in to the typical study estimate. And this is just the operations timeline that shows what we could sort of count as total trial costs, but frequently what we talk about are the cost from first participant in to last participant out. Just to show you the cost considerations, but there's much more than that. And this is the wonderful layer cake that Kate McQueen [misspelled?] designed and has the whole aspects if you just look at the middle layer the typical trial that we would talk about, but when you start adding policy

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development and advocacy, community elements, acceptability, and at different stages in operations and operations research and implementation, you build a lot more cost into the trial and it really takes a total village to run these prevention trials right now.

Let me just start to wrap up because Renee is telling me this when I'm halfway through, okay, but what are the components of these costs? And I'll go through very quickly. It depends upon what are some studies? Are there the prep studies, preparatory studies beforehand? What behavior laboratory or sera converters are involved? Are product expenses actually, does the trial itself have to pay for the product or is this going to be donated? What are the community activities that are going to be built pre, during and post? Communication support and then central versus field. We are used to networks where we might have force of four for operations statistical and laboratory versus site costs in the field getting that and then monitoring visits within, for example, NIH costs, those monitoring visits are not built into the type of budgets that the networks have to provide because NIH picks that up through PPD. All of these are sort of considerations in trying to compare different costs. So what do we have? Well, these are six microbicide studies labeled anonymously A through F and these total estimated costs come

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from the investigators themselves asking how much did it cost? So there is nothing validated about this. There's more of a qualitative estimate. What I want you to do is look at the column from the second from the right and then the far right. That there is not only a huge range of the total estimated costs even in our microbicide trials with some difference in number of participants and lots of difference in number of end points, but we have a range of cost per participant from very low to very high, but I shouldn't say from very low to very high, from low to slightly higher. Ah, but we also have very interesting ranges that are not even necessarily correlated with a cost per participant, which is a cost per end points, and I'm just showing you that because of the range of costs as we are starting to zero in on what is really what we should budget for these trials.

Now, I want to show a good news story. Remember, circumcision is a great news in terms of scientific validity when you look at trials A, B and C for the circumcision trials and you look at cost per participant and cost per end point, there's some variability, but it's much lower than, and I just showed my [inaudible] I could show any of the other non-circumcision trials and they'd all be in the exact same ballpark as microbicides, but so what is the summary of our cost effort if I can get this thing to move? Okay, first of all

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there are many components. What I have just shown you is really comparing apples and oranges, which produces a wide range of estimates. The cost per participant factor is most necessary for budgeting trials. Those are the number of people that you have to plan on seeing, but the cost per end point is actually the most important for determining effectiveness in the trial and something we are going to have to keep in mind and then the best buy is, of course, male circumcision at all levels as a scientific consistency, as a cost per trial, and as a scale up.

I have two others I was going to go into, but we are short of time and we are going, they weren't even partially covered. I'm just going to, I'm just going to hold this down and go through these as quickly as we can here, but it has to do with community engagement. It doesn't go as fast as I would like it to. I'm trying. [Laughter] Okay. I just want you to know that. Okay, but our multiple communities we've talked about research literacy for the community, research and community literacy for researchers. You've heard several of us talk about this before. We have to start it early and set aside our resources and extend beyond local community and though we have great well-meaning efforts at formative research and it's moved trials ahead, it's necessary but not sufficient. This is about how you do [inaudible]. This is one curriculum

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FHI has done for research ethics. I show you the good participatory practice guidelines that WHO mix all others and put together and then there's the communication's planning as we've learned. The fastest thing to stop a trial is communication to get out of control. We've had the plan for that. We've had to pick sites with established relationships investigators who are, who have some ability to intervene and then practice and practice and prepare and practice when this comes into play. This is Lee Peterson at the Toronto Conference giving the final results of the tenofovir trial actually encouraging at the end and the most widely cited abstract out of Toronto and had a good ending.

So, in conclusion, nature, I mean research by its nature is going to be evolving all the time. They are going to have a lot of complexities with lots of lessons learned, disagreements are going to be common, and we have to move ahead and our current generation, the ones that we are going forward for future rainbow series are in a much stronger methodologic foundation and operational foundation than they were before. Thanks. [Applause]

MITCHELL WARREN: Thank you so much, Ward. Are there questions for clarification for Ward? Alright, that's great. I'll turn it over to Renee.

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RENEE RIDON, M.D.: Okay. Thank you and well done, Ward. Thank you. I'm sorry. We were getting a bit late in started. Our next speaker is Dr. Andrew Nunn, who is an Investigator from the Microbicide Development Project from the UKMRC. He works on the phase III trial examining microbicide candidate Pro 2000. He is also the Associate Director for the Clinical Trials Unit for the MRC, and he's going to give us a talk on challenges in microbicide trial design.

ANDREW NUNN, M.SC., M.SC.: Thanks, Renee, and thank you for the opportunity to talk about this subject. As a clinical trialist, I believe that one, that the best trials are very often the large and the simple trials, but I'm, I did tend to think that when we started doing trials in microbicides, they would be simple. They are simple in some ways, but I don't think they are simple at all and indeed, the challenges that I want to talk about are the challenges, not the challenges that we might face in the future, but the challenges that we face now. I realize it's not a complete list and when we come to discussion later on there'll be people who will want to address some of those things perhaps that I haven't mentioned, and indeed the solutions that I might be proposing to some of those challenges will by no means be unique, and indeed, some of you may wish to disagree with them.

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Some of the areas that – it doesn't press very well does it? That's better. Some of the areas I want to talk about is shared on this slide. I won't go through this slide now, but we will pick the points up as we go along. I want to begin with the question about biomarkers. How can they help? Well, maybe the question is not so much how can they help, but can they help? Can they provide the information on safety and/or efficacy, will enable us to identify a winner? In other words, to make life a little bit easier in our selection of products. Results from current phase III trials and those that are finishing right now, was that they have produced positive or negative results together with the lab data that went before them and the early phase clinical studies, they need to be critically evaluated and that's going to be so important in order to be able to make an assessment as to whether we can make use of the pre-phase three data in our choice of products.

Biomarkers are, however, I believe most likely to help to identify potentially unsafe microbicides. In other words, ones that we don't want to use rather than ones that we do want to use. Quarraisha has already indicated that there are no good, there are no surrogates of HIV acquisition. At the end of the day, we have no intermediate marker. As in trials of cancer treatment, for example, where you might look at progression of the tumor as an intermediate as to what is

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happening, we don't have that luxury and so we are much more likely to be able to eliminate unsuccessful or possibly potentially dangerous products rather than, in fact, pick on ones that you think are going to be very good.

We also have to be aware of the fact that markers are identified in one class of microbicides cannot be assumed necessarily to be useful in the assessment of new classes. A word of caution, even if we could accept or reject the candidates for phase III solely on the basis of activity in vitro and in the McCant [misspelled?] studies, the most effective products in these models may not be the safest in the long-term, and indeed, activity in these models will not necessarily translate into effectiveness because of biological differences and [inaudible] effects in the presence of semen. And probably one of the most important factors of all at the end of the day is the acceptability of the product and adherence will be critical determinants of effectiveness in women. It's a great relief to us that MVP301 we are finding women who are taking part in that study are so thrilled with the product they are very disappointed to get to the end of the study and not to be able to continue using it not thinking so much necessarily about whether it's protecting them, but the fact they are enjoying using it.

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A word about phase II-b studies. This has been discussed in a number of different arenas. First of all the case in favor. Well, of course, it is the way to help us to select if we've got multiple products. We are not in that position right at this present time of having a lot of new products to look at, but it does offer the opportunity to eliminate ineffective products and should there be amongst that group of products a highly effective one, it could provide us with a fast answer. That, of course, would go with a substantial reduction in cost, but only if no further trials were indicated. If we didn't get a product out of the trial, one thing we would get, of course, would be insights on the design of the trial and site preparedness, but the case against it is also something we need to think about because a phase II-b can result in a longer and most costly process at the end of the day because if we only find a moderately effective microbicide, then our subsequent phase III trial will be required and we run the risk, I believe, in eliminating potentially effective microbicides we perhaps don't run too well in that early study.

An important consideration I think we do need to think about, and we need to think about this if we are doing a phase II-b at the time we are doing it and not after we've done it, if we get a positive finding whether it's statistically

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significant or not, it could make it more difficult to conduct a pivotal phase III trial because if we've got to go on and do that trial afterwards, participants and possibly ethics committees might consider it unethical to conduct another placebo controlled trial if the product has already been shown to have some effect.

A long time ago Erasmus said, "Prevention is better than cure," and it's something that most of us would agree with, but proving the effectiveness of a preventive therapy is often much harder than proving the effectiveness of a cure. Here's a quote from Nancy Padden's [misspelled?] paper in the [inaudible] just over, just under two weeks ago, to date 25 randomized control trials for HIV prevention have reported and four, only four, have shown a perfected [misspelled?] effect. Three trials of circumcision and one trial treating STI's whereas 19 showed no effect and two had a potentially deleterious effect. That's where we are right now. It is more difficult to conduct trials of prevention than trials of treatment. If you are assessing treatment, you can target the people that you want to treat. You know who you are looking for, and you could determine from your criteria of eligibility who you want in the study. If, on the other hand, you are doing prevention, you don't really know who are the people you want to treat, indeed, you've found a very good change of

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perhaps missing them and working on the population where there are very few people, in fact, who actually need your preventive treatment in the first place. And just to make things even more complicated, because of the ethical constraint on us to make sure that we give and deliver good counseling for condom use and so on, it's quite possible, even if we could identify our target population, that they will move off and we will miss them yet again.

So there is a real challenge of how we can efficiently conduct a trial, when we don't really know who the people we want to target. Well, one way of doing that, of course, is to study discordant couples. NHTM study, and I've probably got the number wrong here, is a placebo controlled trial, which has successfully enrolled three, nearly three and a half discordant couples in 14 sub Saharan African countries, to assess whether insight to their suppression in HIV2 positives induces the chance of HIV transmission. So it can be done, and indeed, at MDP, we have one of our sites, the site in Valsartan [misspelled?], Uganda, which is on target right now to enroll 620 serum negative women, whose main partner is an HIV positive man.

There are, of course, pluses and minuses, with the case for discordant couple's studies. Yes, we have a high incident group, yes it could be useful also to evaluate by direction

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effects, we could have a look at, we could see the effect not only on a negative women from a positive man, but from the other direction as well. But we also need to be aware that when those in the trial become aware of their mutual status on enrollment in the study, that may result in good adherence to study product, but at the same time, result in substantially increased condom use. And, of course, it goes without saying, a study like this provides very large numbers, as both of the two studies I've already referred to have shown.

We already had brief reference made to the idea of DOT. Now DOT, of course, is something which, in fact, has been shown to work extremely well in the treatment of particularly tuberculosis, and the suggestion has been made that, well, if we wanted to demonstrate proof of concept, not to do this as something which we can deliver as a regular way of doing things, but if we wanted to demonstrate proof of concept, than this could be a way, perhaps one of the most quick, effective ways to do so with microbicides. And this is a study which, in fact, is currently being planned by IPM.

He's gone to sleep again. Why don't we move on to talking about the choice between a short and a long term follow-up? In the beginning, we had a long discussion about whether it would be appropriate to perhaps give a shorter follow-up than we might originally have chosen to do in the

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designed study. One of the advantages of a short follow-up is, because there is a likelihood that over time there will be a lots to follow-up and increased pregnancy rates, that is a real concern. And indeed, adherence is also likely to fall over time. Now as a trialist, obviously we're not just concerned that numbers will, in fact, the power of the study may be reduced if, in fact, we have more women dropping out of the study, but also what the results may mean if, in fact, they are limited to a smaller proportion of the total number enrolled. If we had a shorter follow-up there is a possibility that we'd have an increased chance to develop to demonstrate proof of concept.

On the other hand, there are disadvantages, because we clearly again need to screen and recruit more women, and there will be increased costs to go with that. We will only have short term data on adverse events and the data may no longer be useful for licensing purposes, and indeed there will be no data on long term acceptability or effectiveness. And indeed, there is the bottom line that is possible, and we will only know this when our trials have been completed, that adherence could improve with time. I don't know how I'm doing for time, but how am I doing?

FEMALE SPEAKER: [Inaudible].

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ANDREW NUNN, B.SC., M.SC.: We'll go through this one very quickly. There has been a discussion amongst a number of researchers recently about the possibility of what we call the super [inaudible], to help enable earlier detection of adverse outcome. This is a very important concern amongst receptors because of cross, increased the possibility of increased serum conversions in the Triphed [misspelled?] arm over the placebo, is something which could do an awful lot of damage if it occurs. And we want to be able to stop that in the early stage. We don't want to stop it too early, and this is something which could be done without the threat to the integrity to the study, and it's important, I believe, to maintain public confidence.

We come right down in parallel trials of the same product or of different products of the same class. How would it work? Well, serum conversion data from each of the trials would be sent to independent center. The program would be run to see whether in fact a particular threshold had been crossed. No more looking at the data, this data would actually go into a computer program. If the threshold is crossed, then that monitoring board would meet to decide whether they need to make recommendations to the individual BSRB's.

Data to look at monitor, if efficacy is not such a good idea, and I won't go into this slide now, but in fact, certainly it's something which is generally frowned upon

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amongst researchers. So how are we going to improve tri efficacy? I believe one of the most important things is selection of our population. We need to get populations with fairly high incidence. Some of our trials have had to close simply because they didn't have incidence which was sufficiently high. If you just look at these figures here, you'll see that the difference that you, the numbers that are acquired for study where the incidence rates are only one to two percent, and for those where they are perhaps four to five, four, five, or six percent. Interestingly, this comparative difference between the four and five percent, compared to the one, two, and three percent, so there are the sort of figures we should be aiming for. And if we look at age difference to the cost of the trial and how long it takes to do, there are other factors, of course. We need to be able to choose a stable population, we need to consider the option of DOT if we want to show proof of concept, as I've indicated earlier. We need to minimize loss to follow-up, possibly through short, follow-up duration. Involving male partners is particularly important and ensuring participants who are aware of the commitment that we require of them. We need, and I have to confess, this is only just a fleeting mention of that very important area, behavioral data. We need to have a better understanding of the participant's behavior. Behavioral data

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is important, and we need to learn from experience of completed trials.

This is my last slide. In conclusion, I don't believe there are any magic bullets which will actually help to face up to the challenges that we have to deal with today. Improving trial efficiency is probably the best option that we've got, but we do need to learn from all that we can from the results of the completed and current phase III trials, particularly in regard to identifying unsuccessful interventions.

Thank you very much.

FEMALE SPEAKER: Any clarifying questions for Dr. Nunn? Alright, yes, I see hands, Dr. Paydian.

DR. PAYDIAN: One really quickly, a comment and then a question. I think another essential difference between prevention and treatment is assurance, and that is if you know you're sick, you're likelihood to take whatever it is, obviously were different than if you were well. A question about couples, about discordant couples, and that is insofar as there's individual variation in susceptibility, I wondered what you thought about the likelihood of, unless you're getting the index partner with huge infection, getting couples where transmission, if it had occurred, would have occurred, and then you sort of shoot yourself in the foot.

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ANDREW NUNN, B.SC., M.SC.: I suppose the answer to that is we don't know until we analyze the first of our studies. It's a very good point, it's not something we've really given a lot of thought to.

FEMALE SPEAKER: Dr. Baldo [misspelled?]

DR. BALDO: Just a comment that the [inaudible] has been proven in real life to work, even at the last minute, the CS trials came together and then three days it caused them to look at it, and it worked for both of us together, which I shared also with [inaudible].

FEMALE SPEAKER: Thank you. I will now introduce our next speaker, who is Dr. Veronica Miller. She is the Director of the Forum for Collaborative HIV Research, in Washington DC. She's also professor of research at George Washington University in Washington DC, and she is going to be talking about what needs to be done to move prevention research forward.

VERONICA MILLER, PH.D.: Thank you. So I think as the last person on this panel all I really have to do is keep what everybody else has said and just reshuffle it a little bit, and maybe it will all sound somewhat different. But, anyway here we go. So I thought if I wanted to acknowledge The Forum of my medical prevention of working group and I've given you the what side for the information that will list all of the participants

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and all of the various presentations and work that went into clean out our first report that is also available on our website. So I guess that the first statement that I would like to make is that effective research really does require the effective translation of research results into implementation at the community level. And I hadn't really realized, as I was preparing this talk, how much this was going to be a theme of this conference here. So I think we've all been sort of singing the same song, maybe in different voices, but I think that's been very exciting to see that happening at this conference. So this is just sort of my kind of schematic view of the research cycle. We start with basic research here, whatever clinical trials that provide results, they get confirmed, there needs to be some kind of acceptability at the community level to actually do that. And then of course some of these errors go back and forth, this is just very schematic. Anyway, at some point that there needs to be developed into policy, which then gets implemented in that will hopefully provide effectiveness at the community level. If that prevention really is effective at the implementation level, just as it was in the clinical trial stage, that will then build more confidence in the community regarding the research process and will support for the research. So this is really sort of the schematic. But, you guys wrecked this, now it

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doesn't work at all. But, you know what I really want to point out that in this whole field of research we're not really starting from zero at all, we have a lot of experience in prevention, both in the HIV field and in other fields. And there is a couple up here that use drugs, for example, prevention of mother-to-child transmission, preventing opportunistic infections, or from Malaria. I got this one is because I guess you could kind of compare that to something—so it's basically not a chemo-therapeutic prevention, [inaudible] method, and of course we also have vaccines. So part of the theme is that we always need to keep remembering the lessons we have already learned and try and maximize on those as we move forward in HIV. So this is my view of the current research landscape. I've changed the slides slightly from what we used that are my medical form by the working group. So basically once we get into policy development and we do have a couple of, so this basically the research timeline. And there's a couple of things that have already kind of come down as like cascade and have been developed into policies, a certain adult exchange programs [inaudible] prevention mother-to-child transmission for example. And I'm just going to go through these fairly quickly. [Inaudible] and I don't [inaudible] space in here to be anything that you should measure and figure out how many years this is going to take, but basically prevention vaccines

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won't be out at somewhat longer time in coming. I think most people would agree with that, and maybe there's some third generation like herbicides and it's not a card or treatment. But we already have some data available, for example, safety data on some second-generation microbicides and for some vaccine studies. We have data available, four PREP studies for example, the safety data. And of course we'll hope to have additional PREP studies that are designs likely different or use different drugs or formations of drugs, more data that will be available later, HSV2. And then is the one study that was actually stopped, male circumcision. We've heard a lot about the three studies were so conclusive, and there was another study that was ongoing that was actually stopped. And I was looking at the effective male circumcision in terms of preventing acquisition of HIV in females if the male was HIV positive. So that is we have some data or basically don't have much data available but we do have a study going on that was stopped because it wasn't likely to show any [inaudible] effect. And then we have those where we do have Phase 3 data available. Not all the studies have been positive, VAXGEN for example is not likely to be converted into policy, the CS study, the mirror study, which we will hear more about at this meeting. And of course one of the recent studies that is being

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developed into policy of course is the male circumcision for the protection of men in acquisition.

But I wanted to illustrate here is that this does not happen in a vacuum, so when we talk about all of this prevention research landscape, it really happens in the presence of the [inaudible] for factors and how behavior influences the research and how research influences behavior. We all of the various social cultural factors, for example, gender issues, and really just giving one example here, there's many more. Structural factors such as access to school and how that determines what the individual person's risk is. In policy environment, for example, will the policy environment accept or not accept the research findings. And we have had many examples where positive research findings are not being accepted by the policy makers. But what's missing in the landscape is research on combination approaches, and that just lists that a couple of here for example, microbicides and vaccines are HSV2, we also [inaudible] and that data will be available later, later.

So just a few thoughts regarding effective research and how this will actually be moved forward. Well I think one of the first things that does need to be sustainable. So we need funding and sustainability in funding. If we just have spurts of funding, for every now and then, that's not really going to

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develop in any effective research agenda. So we need communication between the funders and sponsors. We need better integration of the funding mechanisms, for example, and I'll get back to that later to program funding versus research streams. And really find work more in the question about how we can most out of the research dollar. We also need to work much more on the sustainable of research science and I think that's already been alluded to actually in all of the talks before. The real challenge of finding the right sites and being able to actually carry the studies to a completion. Just my editorial comment here, turf wars will not build community support. Because I think again this mantra that's been repeated by all the speakers already that we really need to have community buy-in and community support.

Cooperation, coordination and collaboration: So we really need to work on this. There are many, many cost cutting issues between the different approaches in terms of the trials, and we need to find common solutions. But basically cooperation, collaboration is a better business mode then going it alone or silo approaches, and any person that is successful in business will tell you that. And in this situation, just one comment here, airing things out in the press is not the best place for expert discourse. And I'm just mentioning this recent editorial that appeared, and each are not because I want

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to highlight the controversy or draw it out again, but basically to really use that as an opportunity to talk about some of the lessons learned. And I think what that particular discussion showed is that the urgency of the HIV pandemic and the passions that are unleashed by that urgency are definitely real. Everybody's really very much concerned about doing the right thing as quickly as possible. But what it really does show is a need for a mechanism where we can really review the protocol discussions and not that we should be shy about voicing different opinions, but it needs to be able to happen in a safe and collegial environment. And also I think it highlighted the need for review process for prevention clinical trials that are transparent.

So just a few comments here that prevention research practice basically are available resources both in finances and in kinds of sites and patients we can involve etcetera, are really kind of at odds with the trial size requirements and I think Ward really highlighted that very nicely also Andrew Dunn. And it's not just a matter of resources, because each prevention trial will impact on every other trial and I think that the package of prevention care really illustrates that. So in terms of they're both are changing standard of prevention care, but also just simply because the sciences are so interconnected, so none of these approaches really work totally

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independently of each other. So we really need to find a way to approach prevention research that's much more kind of an open dialogue with each other in finding of ways to move forward that really mean win-win situations for everyone.

In terms of the community importance, I think the community really needs to have confidence in the research, and we have seen many situations where that has happened, we've seen somewhere that wasn't happening but now I think we have some positive examples. And if the community doesn't trust what's going on it's going to have a very negative effect. But the community also does need to be able trust in the scientific rigor when choosing products for large-scaled trials. So if they say yes we're really going to go into this with you, that really the scientists have done their homework in terms of what they're actually going to take into study. And so counts on [inaudible] will not constitute community ownership, and I've just listed some examples here of some of the circumcision trials of the Rakai Study and on very strong research programs, on a different model setting through strong research programs embedded in local centers of excellence. But these are just some examples of where community involvement was really made a priority and I think it had really, really paid off.

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And just a few comments on research and policy, and again that's been addressed so I'll go through this quickly. So translation to the policy, once the positive results are available, is obviously necessary. And I also wanted to highlight, because there was a very interesting talk that Don Smith gave at the IAS-ILF Symposium on Sunday, which really had a very good outline for how you plan for implementation. And just as an example of where this happens, or doesn't happen, for example, the research that we have clearly demonstrated effective interventions to prevent mother-to-child transmission. Yet when we look at what's actually being implemented, and this comes from the global prevention-working group, it is estimated that only 11-percent of HIV infected pregnant women receive the necessary antivirals to reduce the risk of infection. So here's something where we have very, very clear evidence and the policies have been developed, and yet they are not being implemented. And that's not just for MTCT but for the rest. Just a few more comments about policy makers. So basically this whole communication between researchers and policy makers I think is something that we need to work on further, and I'm just going to—some examples were that clearly demonstrate that policy makers are not always been data-driven.

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A few comments on biomedical and behavioral research, and again this has been addressed so we can't really leave it out of the equation although it's a very complex thing and it's sometimes difficult to figure out how that is going to work. But I think the basic to bottom line is the problem with behaviors as that it happens or not depending on whether we're talking about risk behavior or preventive behavior. So that's always going to be a part of the equation. And then prevention and treatment go hand-in-hand. Now this is one of our brand slides that I thought was just absolutely fantastic. When we talk all about what is the poor researcher to do, so there you're quite completely being overburdened with all the extra work. So just maybe just as a way of solution basically these things appear as what we think of traditionally in the research camp, in that much of this down here really can be built into the program camp. And even if we do that effectively we can actually develop the happy camper, so that that poor guy doesn't have to be so overburdened. Different models of integrating programs in a research. And then just basically the conclusion, let's not ignore the lessons that we have already learned. Let's work on translation of research and effective policy implementation. Let's find ways to make sure that research in research sites are sustainable cooperation, coordination, collaboration. Community ownership and

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confidence in the research are very important and find better ways to integrate by medical and behavioral research and treatment and prevention research. Thank you.

FEMALE SPEAKER: Thank you Veronica. So if there are any quick, clarifying questions for Veronica, and then we would like to move into a little bit more of a longer discussion or a discussion for all of the panelists that will be facilitated by Kim Dickson. And we may actually go a few minutes over because we started a bit late. Yes, in the back.

FEMALE SPEAKER: I'm Dr. [inaudible] from [inaudible]. This is my question to Dr. Miller. Dr. Miller I am just trying to understand what you would imply by sustainability of the research and research sites. Can you explain to me what would that imply?

VERONICA MILLER, PH.D.: If I understand the question correctly it was about sustainability of research sites.

FEMALE SPEAKER: Yes it is [inaudible] the research of the research sites that you have been talking about. If you could just further explain that point.

VERONICA MILLER, PH.D.: Yes, so it's just basically the idea that if you're going to fly in every time you have a trial and then have to basically just set up a site from scratch. And that site then disappears when that particular trial is finished, but maybe another program has research going

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on where they could also maybe use that site. So basically trying to find ways to build up site capacity and get maximum use out of the those sites, that doesn't necessarily depend on just one particular agency or one particular program.

FEMALE SPEAKER: I just wanted to share like I think you are basically showing us slides and a researcher basically. So I would like definitely think burden what is like in that to show the lack of response to do that [inaudible]. And there basically into the [inaudible]doing research and [inaudible] of which to [inaudible]the research and the implementation part like how do you explain the things you have [inaudible] and how do they then translate into the information the [inaudible] and everything of that sort. So [inaudible] as a researcher I would [inaudible] things which will help me and I have to [inaudible]. How do I identify and measure the program communicators of which I should be tracking down from time to time? And then how do I do know definitely and who [inaudible] research which gets [inaudible] back of the program [inaudible] and about evaluation of the programs that we [inaudible]. So that researchers [inaudible]. Thank you so much.

KIM DICKSON, M.D.: Thank you. My task now is now to try to facilitate a discussion on some of the emerging challenges that we have. So thanks to all the speakers. May I ask that if you want to make a question or you want to make a

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comment or ask a question, if you could line up by the speakers? And please could you make your input short and succinct. And what I would like us to focus on really is taking from what the speakers have said around our CT evidence not being sufficient for policy formulation and effective research requiring translation of results into program implementation. That we look at some of the challenges and we try and address how we actually design our prevention research so that we can get it translated into policy and programs. But also to caution that we don't expect the researchers to do everything even as we carry out the research. And so if we can try and open the discussion around some of those issues. Thank you very much. Can I take the first comment up there please?

FEMALE SPEAKER: I have one question. I would like to ask the question about [inaudible]. As far as I see from the presentations that there were three trials in Kenya most probably. I just want to know that was there any problem doing male circumcision, the adult population and what was the barriers of community who took it or just a little bit deeper understanding of how it was accepted in the community?

KIM DICKSON, M.D.: Just to summarize very quickly, tomorrow there will be a pillory that will address male circumcision. But to say that no there were not any real barriers but also to point out that Professor Bombay is in the

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audience so I would suggest you grab him after this session
and-

FEMALE SPEAKER: Raise your hand Bombay.

KIM DICKSON, M.D.: Bob, if you don't mind, yes. And
then he can tell you exactly what went on in Kenya. But there
were also trials in Uganda and South Africa. Can I take, is
that Judy? Can I just ask if Judy can give her question and
then we allow other people, and then we'll come back to you,
thank you?

FEMALE SPEAKER: Well Judy is actually going to make a
comment and it's not directed to the panel, it's directed to
the conference. Just to note that prevention research is much
broader than randomized controlled trials and biomedical
technologies. And I understand that the track for this
conference is very focused on biomedical technologies and I was
invited to be a part of that track committee. But part of my
role was to remind others that there's a lot more in prevention
research than just biomedical technologies and randomized
controlled trials. That being said, I was struck—so my point
is I'm sure your charge was limited to that, so this is not
an accusation to the panel—but I think it is really important
for us to remember that the field is much broader than that
which is being discussed right here. In part because some of
the challenges and limitations you all identified are precisely

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because we've been very narrow in our approach to prevention research. Typically with regard to the things that are most funded and accepted as being able to provide real evidence. And I think that the thing that struck me the most—and Veronica I'm not going to pick on you, it's just your slide that sort of jumped out at me to help me make the point—that when you had the boxes that showed the different biomedical technology trials. That it went on to the circles about social, cultural and environmental factors, that hover around these trials. As a sociologist and social scientist I would say those little circles ought to be the object of our research as much as the biomedical technologies. And even individual behavior and behavior change. They're not [inaudible] or just sort of factors hovering about. I'm reminded—and I will be finished in just a second—I'm reminded of something that we all said very early in the field and now it's kind of a chuckle moment. That if we actually spent more time and energy studying the behavioral change or behavior of decision makers and policy makers, and attempted to change that, we might have a greater impact on the epidemic than focusing on individuals and communities we judge as more vulnerable. And if you think about it, it may sound a little goofy. But in fact it may be true, that if we could change social attitudes and institutions to mitigate stigma, to mitigate lack of access to healthcare,

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could do all those social things that everybody now recognizes as important, to facilitate HIV prevention we might actually have a very significant impact. So my point is simply to say let's not keep treating these things as if they're sort of handmade or off on the side, or not relevant for prevention research. They ought to really be a big part of this.

KIM DICKSON, M.D.: Okay, thank you very much for the important reminder Judy. I think we've got it. Can I ask Brazy [misspelled?] because I think Brazy might want to emphasize that point? And then I'll come back to the lady up there.

FEMALE SPEAKER: Well actually I think Judy said it perfectly so I'm not even going to go there. I wanted to make a prevention lead in I think would be that several of the speakers brought forward the issue of the timeline on research and the investments required before, during and after. I wanted to propose—I don't know who the repertoire is for this track—but word slide about the pre, the during and the post part of the prevention trials. I hope that goes into the final summary because I think it's really important. Costing a whole package, planning for the whole package and not just for the slice in the middle. But I think it would be valuable to disaggregate what goes on, the issue of research versus program. Who funds it? And an issue of quality, because it's

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been a very public secret for a long time that in many low resource settings participating in a study is the best way to get services that are the higher quality than you might get elsewhere. And I think where I'm going with this is that particularly in the area of behavioral interventions, I think we're only learning to have to discover what high quality intervention costs. If you don't really know what high quality behavioral interventions cost because we have been much more careful and let's say concrete about defining quality standards in the clinical interventions than in terms of the content and the basic requirements of the behavioral interventions. Often we get the best of both in the clinical trials and then when we try to move into the programs afterwards we haven't defined that, the patient behavior where it's long enough to be able to roll it out into practice.

KIM DICKSON, M.D.: Thank you. So we go back to the lady up there.

DR. MANI CHOVIK: Thank you. I'd want to introduce myself. I'm Dr. Mani Chovik [misspelled?] from Bangladesh and I have the next question about microcide gel. That if this is targeted and we get the chance to use it for the sex workers because we know that are the people who are more infected because a condom is not used by the clients, would it be a [inaudible] only that they can use the microcide gel? Or would

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there be a problem telling them to use the gel without the condom?

KIM DICKSON, M.D.: Okay, thank you. We'll ask the speakers to note the question and we can answer it at the end as we wrap up. Thank you.

VIRGIT HAY: I'm Virgit [misspelled?] Hay from the [inaudible] Federation of AIDS Organizations. And the question that I want to ask is about [inaudible]. Specifically how would you accurately ensure something, explain to a man for example who is considering circumcision as a prevention intervention, what exactly [inaudible] efficacy modeling to him in his particular circumstance?

KIM DICKSON, M.D.: Okay, I'll ask for some comments to the last two questions and not just about male circumcision because we're going to have partial efficacy with all the other products. So would the speakers, Quarraisha?

QUARRAISHA ABDOOL KARIM, PH.D.: Sure, right the question from Dr. Chandry on use of gel without condoms. And I think the ethical issue is, are you talking about it in the context of a trial or are talking about it in the context of a gel that has already proven efficacy. So I think if you're talking about it the context of a gel already has proven efficacy. It's an ethical obligation to promote condoms although it's very unlikely that if we do have a microbicide

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that is efficacious it's likely to be partially efficacious not a 100-percent efficacious. So the messaging needs to be very carefully thought through as with the male circumcision that this is the level. And I can't predict or project what that is, whatever that level is and you have to talk about other means and methods. It's important to remember though in the context of microbicide promotion that it has a very specific niche market. And it's for women who are unable to get their partners, or their clients to use a condom. And so this would offer them some protection in that sort of context. So don't think the messages are all so clean and clear-cut. I think we need to be looking at who the target population is and how best to do that messaging.

MALE SPEAKER: It's really interesting to try and sort of form a timeline on what we've learned about communicating partial effectiveness, really. My grading, from the contraceptive field and to the HIV prevention field, we're doing this type of communicating all the time in terms of relative protection, in terms of choice of methods, and not perfect protection. But at any rate, as part of [inaudible], developing as clear messages as we can that will allow us to communicate to both participants number one, and then in the really world number two, that we're talking about procedures to lower risks, but frequently not eliminate risks. And perhaps

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by using multiple methods you can lower those risks even more. This is sometimes a tough message to take, number one communicate and probably even a tougher message to act on at the individual level. But it needs to be reinforced.

QUARRAISHA ABDOOL KARIM, PH.D.: I think you've defined the problem, but you haven't actually answered the question. What would you actually tell people?

MALE SPEAKER: You mean about male circumcision? Well, for number one I'd turn to that person right behind you and say what do you tell you people? But I would say that studies that have shown that it reduces your risk of becoming infected by approximately 50-60-percent and by making this decision to have that surgical procedure you give yourself that degree of lower risk. You can further build on your ability to lower that risk by using condoms after you've had that surgical procedure. I don't know if that's clear enough for you.

QUARRAISHA ABDOOL KARIM, PH.D.: It's a start.

KIM DICKSON, M.D.: It's a start, yes. But I think we have to understand that the issue of partial efficacy, partial effectiveness, is a complicated one and even in the reproductive health field we try to communicate this and talk about real protection. But we've got some experience from there. What I'll do is I'll take the last few comments. We've go three people on the floor, and I think they might even

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address this issue about partial effectiveness as a sector. So we've got Bob, we've got Likeness [misspelled?] and then Nancy. And then we'll sum up.

MALE SPEAKER: [Inaudible] I was needless to say intrigued by your table that showed that male circumcision trials were relatively inexpensive. And I was wondering if there's anything behind that? So did you get any data on what contributes to the variation in the cost per endpoint or per participant? Why were the circumcision trials less expensive than some of the other trials, and why were some of the other trials so much more expensive?

MALE SPEAKER: There are a couple of speculations but what would be really fun to do would be to get all of the investigators together actually at a roundtable to find the elements of what they used to make those cost projections. Dissect those out and then find out, as best we can comparing apples with apples, as to why that is. One of my speculations is that there was a heavy investment in the intervention upfront but there weren't as many visits and as much participant interaction as might happen in terms of the other types of prevention trials. That's pure speculation, and it would really be fun to get the individuals together to try and come up with up a systematic approach to what goes into a

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prevention trial. Especially now that there have been further expectations to it.

KIM DICKSON, M.D.: Okay, the chair for the facilitators has been asked to wrap up. So I'll ask [inaudible] and Nancy to make very short comments and then I'm sorry we have to close.

MALE SPEAKER: Did I just hear that the case suggested that we could include male circumcision as one of the interventions given in the standard of prevention?

MALE SPEAKER: Yes.

FEMALE SPEAKER: With regard to partial effectiveness or partial efficacy, I just think it's very important that we don't hold HIV prevention to a standard that pretty much doesn't exist. There are very few things in this world that are, as far as health goes, public health, that are really are 100-percent efficacious. And even seatbelts aren't. And I'm not saying that you can't have different levels of efficacy, but that is reality.

KIM DICKSON, M.D.: Thank you, that's a very lovely way to end this session. So I apologize we don't have more time for discussion, but we've been told to close. Thank you very much.

[END RECORDING]

