

**4th IAS Conference on HIV Pathogenesis, Treatment, and
Prevention
IAS Industry Liaison Forum (ILF): Are We Prepared for PrEP?
Challenges of Implementing Proven Biomedical Prevention
Technologies
International AIDS Society
and Australian Society for HIV Medicine
July 22, 2007**

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[START RECORDING]

ELLY KATABIRA, M.B., Ch.B., M.Med: Tell them to give us feedback because without your feedback, we wouldn't be able to improve what we are doing, and look forward [inaudible] performance period that we have presented to one of our [inaudible - mic problem].

So it starts right away, and we will start with Dr. Dawn Smith. Dawn is a medical epidemiologist at the CDC, and she had begun her International HIV Research experience in my country, Uganda, and also in South Africa, and has recently returned to Atlanta after four years in Botswana establishing a clinical trial site and getting the PrEP trials on the way. She got into the research for providing guidance to the CDC on international and domestic proprietors and has the lead in the planning and coordination from preparational PrEP when actually it goes. Dawn will be addressing the question, how prepared are we for PrEP? Dawn.

DAWN SMITH, M.D., M.S., M.P.H.: Hello. Can I have the first slide, please?

ELLY KATABIRA, M.B., Ch.B., M.Med: Can we have the first slide?

DAWN SMITH, M.D., M.S., M.P.H.: Okay. As the professor said, we are really here to open a conversation, and so I am going to talk to you a little bit about what the conversations have been like at the CDC about implementation,

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about really looking forward to the comments from you here and to the ideas that you will have about implementation.

The first thing I just wanted to run through was just sort of where we are with the PrEP Trials. The trial in Thailand in injection drug users using tenofovir expects to have its first interim analysis in the spring of next year. That was part of the impetus for having these kinds of conversations. That's not very far away, and the final analysis will be approximately a year after that. And when you think about the challenges that will be involved in implementing PrEP having a year or two to think through those things and come to some consensus about what we would do if it proves efficacious that's not very much time.

As you can see, there are also trials underway among heterosexual men and women in Botswana, and now among MSM in Peru and Ecuador. Congratulations to Bob Grant for actually getting his first participants enrolled. We are very excited about that. And then there are a number of efficacy trials that are being discussed that are still in development. There is the safety trial underway in the United States and an additional safety trial that's in development potentially for women in Thailand.

So one question that came up at CDC was, why should we start planning before the trial results are in? Shouldn't we wait and see if this works before we put a lot of time and

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energy into that? But I think there is sort of two reasons that we decided to go ahead and start thinking about it. One is that we have reasons to be optimistic that these trials will be successful, and we know that it will take time to plan effectively. In the U.S., a new biomedical intervention for HIV/AIDS is a process that we haven't really done. We have been focusing on community engagement and behavior change strategies, and so having to think about how CDC would work with a biomedical intervention is a little bit complicated. There are lots of factors that we need to take into account in planning for this, and we need to consider the viewpoints of quite a wide range of potential users and providers and policymakers.

When I say the trials may prove efficacy, I think it's reasonable to think about this as a potentially efficacious intervention for a number of reasons. Number one is there is biological plausibility. We know the mechanism by which this would potentially protect against HIV transmission. We know that these drugs have concentrated levels in the genital tract, which is where the majority of the world's transmission occur. We know that it works in animal models. We know that PrEP works for post-exposure prophylaxis, and we know that safety was demonstrated in the FHI Trial that has already been completed.

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In addition, despite imperfect adherence with other kinds of antimicrobial pre-exposure prophylaxis, we know it works for the prevention of mother-to-child transmission, for the prevention of malaria in travelers and for the prevention of OIs in a variety of AIDS-related infections. On the other hand, we are doing trials for a reason and that is that it may not, in fact, prove to be efficacious, but even if that's the case, the planning that we do now will come in handy when we have to plan for the next effective biomedical intervention whether that be microbicides or vaccines so it's not a wasted exercise even in that event.

Now the other thing to think about is that unlike vaccines and microbicides, the drugs being used for pre-exposure prophylaxis are already improved and available for the treatment of HIV infection around the world, so we are not talking about developing a new regulatory process or a new manufacturing and distribution process. These drugs are already available at reduced cost in many places and generic licensing is already in place around the world which would help greatly with the scale-up, not just for treatment, but if necessary for prevention.

In the U.S., we have a special case and that is that the way that regulation of drugs works in the United States, once a drug is licensed for a use it can be used for other uses at the discretion of physicians. And therefore, the day that a

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trial announces efficacy, any physician in the United States can begin prescribing it, and so it will stand us in good stead if we have guidance in place at that time so that it becomes implemented quickly, but in an appropriate manner.

The last thing, before I talk about some of the issues that we are talking about, is that in the early discussions at CDC, we found that we had to move from a process of identifying all the things that could possibly go wrong with PrEP implementation to more of a problem-solving framework. So instead of talking about whether PrEP would divert treatment funds, we began to talk about what existing or new funding streams will cover PrEP. Instead of talking about whether risk behavior will increase we began talking about, how would we include affordable risk reduction counseling in the package of services that would be available along with the medication? We also set up a process that would allow us to include multiple perspectives throughout the planning process and that includes potential users and providers, but also program officials at the state and national level, policymakers, communities themselves that would be heavily involved with this kind of implementation, the media, prevention advocates, researchers, and explicitly politicians.

We thought about using the framework of the Global Prevention Working Group in terms of planning for the rapid introduction to achieve what they called Sufficient Coverage

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Intensity and Duration to have optimal public health impact. We also wanted to build a program to take advantage of some of the features of PrEP that we can anticipate. This would be an intervention that is gender neutral, can be used by both men and women equally, but one in which covert use is feasible, taking a pill without letting other people know that that's what you are doing would be a fairly simple process, one that's coordinately independent and importantly may work for more than one type of exposure.

Right now, if you are an injection drug user, for example, you would have one intervention for your risk associated with your injection use and a second intervention for your risk associated with your sexual activity. PrEP has the possibility of interfering with transmission by both mechanisms through one intervention. It's also an intervention that can be stopped and started, so if you are going through a period of high-risk activity you might begin to take PrEP and a couple years later you may be in a more stable relationship or situation and feel that you don't need it and it would be very simple to stop taking it at that point.

The most important advantage of the PrEP Program that we want to be sure that we build in is that this would be the first time that we would have an opportunity to get high risk people in for periodic risk reduction counseling and HIV testing. We spend a lot of time to get people in for one-shot

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testing or for testing every year, but the opportunity to work with people every three months or every six months over a couple of years is a very important benefit of the way we would like to use PrEP. The other issue has to do with linking men as well as women to preventive care. In the United States, as in many other places, men access healthcare services much less frequently than women do, and so this would be one way to begin doing some prevention work with men.

So, for an example, in the U.S. when we thought about, how do we provide PrEP to high-incidence populations, we thought about, who is it that can provide each component? This is a biomedical intervention but physicians, for example, may not have the time and the structure to provide adequate counseling. On the other hand, the CBOs in the community may have the counseling expertise but won't be providing medication. Is there a way we can build the program to take advantage of those sets of experience? Where can we put the program so that people have acceptable access? We tend to put biomedical interventions first in major medical centers, and yet we know that many of the populations in the U.S. that are most in need of this kind of intervention don't have access to those services. So are there alternative delivery sites that we can think of? Who are the messengers who will talk to the people about this intervention and bring them to care?

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Another issue in the U.S. where we don't have government-sponsored health care for all citizens is, how do we reimburse for this package? We do have a system of reduced-cost pricing for medications which includes antiretrovirals, but that reduced-cost pricing is only available in a defined set of clinics and institutions. How do we make sure that those are included in the early implementation of PrEP? So again, this is just an example for each part of the planning process there develops a whole series of questions that require people with different expertise and background to work through and come up with appropriate alternatives.

The other thing we want to be sure is that throughout this process we have a systematic evaluation and that starts with the trials data, so we will learn quite a lot from the trials not just about efficacy but, for example, what's the frequency of safety monitoring that's needed and how would that be built into a program? We need to look at the existing data on our high incidence populations to know where we need to focus this implementation, and we need to do data collections specifically around missing pieces of information that we need for implementation planning. Then we will probably want to engage in some demonstration or pilot projects, and throughout this process we want to establish in advance what the evaluation criteria and mechanisms will be so that as we are

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rolling this out we get information on the costs, the various kinds of services, the process outcomes, the intermediate outcomes, and most importantly, the impact that it's having on HIV incidence.

So given all that, CDC has initiated conversations with a variety of stakeholders first of all to raise awareness about pre-exposure prophylaxis and the fact that we are only months to a year or two away from definitive data and decisions about implementation. We have assembled a multidisciplinary study group within CDC that includes people from the STD Program, the Reproductive Health Program, the HIV, Domestic Program, the Global Program to start working on implementation planning and the evaluation questions. We have put in place a process to do some surveys of national stakeholders, program managers, and potential participants so that we understand their perspectives on what it would take to implement PrEP effectively, and we are planning some focus groups with potential users about desired characteristics about a program where they would prefer to access this kind of service, for example. In addition, the U.S. Trial Community Advisory Boards have formed a joint committee to discuss community perspectives on possible implementation.

One specific problem that we have in the U.S. is that we have a very high level of racial and ethnic disparities that affect our epidemic, and it's very important that we not allow

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PrEP to be implemented in a way that aggravates or fails to deal with those disparities. So for example, the rate of HIV diagnosis in black adults and adolescents in the U.S. is 10 times the rate for whites. African Americans are 13-percent of the U.S. population, but they represent more than half the people diagnosed with HIV and AIDS, 61 percent of those under the age of 25 with HIV/AIDS diagnosis were black in 2005. And especially in young, black MSM we have very high incidence rates, rates that you would see in [inaudible] for example where in a seven-city study the incidence in this population was 14.7-percent per year, whereas in the white young men it was 2.5-percent. We also know that in the treatment arena, blacks are less likely to receive indicated HART, even when they are in care.

Now, if we fail to plan to deal with these disparities and the causes of these disparities, then we will have a much less impact on the epidemic than we might otherwise do.

Now, I have focused a lot on the U.S., but I want to say that in figuring out how to use PrEP around the world there are a lot of country-specific factors, so we have racial and ethnic disparities, but any country will have priority groups that they need to identify as the groups to be included early in a PrEP program if you want to maximize the reduction in the epidemic. Every country will need to decide what types of providers and what sites would be appropriate for the provision

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of PrEP. We need to think about what the barriers are to rolling out PrEP and design their implementation strategies to overcome those barriers. In many places, we have lessons to learn from what has gone on with the scale-up of prevention of mother-to-child transmission and antiretroviral therapy programs. There are a variety of reproductive health and pregnancy issues that will also be important to consider as we think about PrEP for sexually active women. And there are, of course, within each country funding and implementation partners that need to be identified and will be country-specific. At the CDC funded trial sites, we have begun discussion with local partners about how implementation might work.

You will note that on all of these slides, there is a little umbrella and that doesn't seem like an intuitive thing to do. I wanted to tell you just one brief story about that. There is a story of a community that was suffering a serious drought and the local elders gathered up all the villagers and they took them to the home of the religious leader who in the past had performed miracles, and they said to him, please, please, you must pray that we have rain. He looked at the crowd and he said, no, I will not pray, you have no faith. And they said, well, we do have faith and that's why we have come to you. That's why we are asking you to pray for us. He said, if you had faith, you would have come with umbrellas.

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And I think we need to think about implementation planning in a similar way as another kind of faith-based initiative. We need to have enough faith in the potential of PrEP to invest the time and energy in thinking about how we could use it effectively.

This is not a presentation of one person but a variety of people within CDC and in the wider community. If you want additional information about some of these PrEP implementation issues there are two good places to look. One is UCLA had a couple days of meeting about this and the transcripts of those meetings are online at this site, and Dr. Lynn Paxton at CDC who manages our trial portfolio has recently published in the *Lancet* about some of the implementation questions that need to be addressed for PrEP. Thank you. [Applause]

ELLY KATABIRA, M.B., Ch.B., M.Med: Thank you very much. We plan to have discussion and questions at the end of the first session, but if there is any burning issues for clarity that could be allowed, otherwise we will move on. Okay. Thank you very much.

The next speaker is Yasmine Halima, who has been the backbone of the industry leader for IAS. As I said at the beginning she is going to be presenting for professor Blume, and she is going to give the presentation on that. Before she does that, I just wanted you to know that in spite of being the backbone at ILF she is now a student getting her master's in

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the Program at Columbia University in New York, and demands that she be under the guidance of professor Blume. Yasmine?

YASMINE HALIMA: Thank you. Okay, every time I give a presentation no matter what the subject I always feel that I am not qualified that there should be someone else doing it who is much more qualified, but today I can honestly say that that sentiment is really truth. So I want to start by expressing professor Blume's regret on not being able to be here on short notice was unable to make it. I am not an expert I modeling, but I recently started an internship with Professor Blume at UCLA. My interest is understanding modeling techniques to assess the impact of PrEP on epidemiology, but also considering issues and equity and ethics. In particular, how can we define priority allocation criteria for PrEP should it be proven effective? So this is a presentation based on Professor Blume's work that we jointly put together, but I want to start with a disclaimer. I hope to do justice to her work, but I should stress that the expertise is all Sally's and the limitations are all mine.

Okay, so with that disclaimer in place, my presentation has three objectives to consider when and how models might be used, what kind of models can be used for what purpose, and finally to illustrate some examples from the microbicides in the treatment world drawing inferences for assessing the potential concerns on impact of PrEP.

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So why did we think a modeling talk to PrEP implementation might be useful? Well, the results of the first PrEP Trials are due as early as next year, and together with formative research and policy analysis modeling techniques can help determine what potential impact PrEP might have on a population of interest. More importantly, it can help inform policy decisions regarding distribution, allocation strategies, impact on local epidemics, and cost effectiveness. So when and how are models used? When we want to predict the unknown, different methods can provide different insight, statistical equations are used to predict and individual's risk of acquiring HIV, dynamic systems of ordinary differential equations can be used to predict the tentacle dynamics of incidence and prevalence, and operations research can be used to design drug allocation strategies.

I just want to make a point about the importance of assumptions. When Sally was teaching me modeling, one of the things that she said is every time you are presented with a model, you should ask the question what are the assumptions that have been made here and built into the model? The models are robust with assumptions built into it, the more assumptions the more complex and potentially less reliable the final outcome. The things that we don't know precisely will build in uncertainty analysis - so what's an uncertainty analysis? It allows us to pick a reasonable range of values. These have

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been sampled any number of times and simulated in a model or risk equation. These techniques translate parameter estimation uncertainly into prediction estimation uncertainly. And what that means is that these analyses enable us to one, predict the future with a degree of uncertainty and, two, to identify the key parameters that determine the future.

So how can models be used in infectious diseases? The models have a number of uses, for example models can be used to predict the epidemiological impact of interventions, to identify the most important variables that can drive an epidemic, and to design effect epidemic control strategies. Here's an example of a prediction. These are based on 1,000 simulations. The treatment rate was varied and the model used to calculate how many infections were averted. The blue data shows how many infections were prevented after one year of treatment, the yellow data after five years, and the red data after 10 years. I actually did have another slide, which I took out which is a very similar prediction in terms of the graph that is shows the impact of treatment in an African setting and so obviously the figures were very different because the background treatment rate is so different.

What are the potential issues that we can model with PrEP? We can look at risk reduction. We can look at the evolution of drug resistance. We can look at PrEP and behavior disinhibition, and we can look at PrEP and cost effectiveness.

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These issues are not new and they have all been addressed in the context of treatment, microbicides, and postexposure prophylaxis.

Here's an example of the first risk reduction. These are examples from published research. Sally's team, for example, have developed risk equations to calculate the risk of HIV infection of the female sex workers by calculating the risk before the introduction of microbicides and the risk after the introduction of microbicides.

These are some of the factors that we can build in a risk equation. What you put in depends on the result that you are looking for. Here are some factors that can be addressed in a risk equation to get meaningful results. First of all, transmissibility for an individual in various sex acts. The number of each type of sex act per [inaudible], number of partners, efficacy, protection used - whether that's condoms, microbicides, or PrEP - the proportion of each type of sex act and which protection is used, and the prevalence of HIV in a population. There are a lot of concerns about behavioral disinhibition. This slide shows the assumptions that were made in this particular model about behavior changes that could occur after microbicides are introduced. Condom users can remain condom users - that's the first box - or become condom users plus microbicides users, non-condom users would remain as non-condom users or as non-condom users but use microbicides.

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Different assumptions regarding behavior changes can also be included in the model.

Models can be used to answer many different questions. Here are the three questions that were addressed in this particular model. Can vaginal microbicides functionally reduce the risk of a female sex worker acquiring HIV infection? Which is more important to maximize microbicides use or microbicide efficacy? What plan of microbicide use and efficacy is needed to balance condom replacement? So in our model, to the first question they found yes, vaginal microbicides can substantially reduce the risk of a female sex worker acquiring HIV infection, and the figures that they calculated were 17-percent risk reduction for a low efficacy microbicide and 30-percent for the high efficacy microbicide. To the second question, which is more important use or efficacy, they found that microbicide use was most important. Intuitively this makes sense. Even if an intervenient is 100-percent safe, unless it is used, it can't provide protection. Changes in microbicide use have more of an impact for a highly efficacious microbicide. For highly efficacious microbicide, they calculated this at greater than 50 percent, poor adherence may not have as much impact and can still result in a high rate of this reduction. However, for low-efficacy microbicides, high use is need to obtain even moderate levels of reduction, so there are always tradeoffs.

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This slide is a schematic showing the tradeoff between microbicide use and efficacy and illustrates the answer to question two. I haven't showed you the tape, but there is a nice example of this by Blume, et al. in *Science*, showing the impact of risk behavior following the introduction of an imperfect vaccine.

Okay. So the question could microbicides make things worse? The model here identifies the conditions where microbicides could make things worse due to people replacing a very effective protection, i.e., a condom with a lesser effective protection method potentially microbicides. The answer isn't simple and depends on the initial condom usage, microbicide usage, and microbicide efficacy. And what you see of the benefits - and actually that says perverse but it means detrimental - and we do have a discussion about what words to use. This is a picture up on Sally's wall - I will say it's her office wall, and not at home - of condoms migrating. It's a point that she makes about semantics used in the field as she stresses that what we are talking about is condom replacement rather than condom migration.

Okay. So let's move on to some operational research type questions and look at the issue of resource allocation. How can we equitably, ethically, and efficiently allocate PrEP, especially in countries with limited resources to spend on prevention? So the problem faced here is that in a

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resource-limited setting there are not enough drugs for everyone who needs them, so what can or should we do specifically, how should you allocate the limited supply of PrEP among health care facilities? Professor Blume with her colleagues has addressed this problem in the context of treatment allocation in a South African setting.

This shows allocation of the epidemic and healthcare facilities in KwaZulu Natal, South Africa, and as you shall see, the importance of special heterogeneity becomes a very important issue in resource-constrained locations, so the next few slides shows an analysis on the impact of different numbers of healthcare facilities and different catchments sizes on treatment equity. Using these results, the authors were able to calculate how much drug should be given to each available clinic in the province in order to maximize treatment equity. So here's the equation, it shows the function of distance on access to treatment, so the slide shows treatment accessibility around each healthcare facility as a three-dimensional function that falls off steeply the further you go away from a healthcare facility. And we see as area of province that will receive drugs if the catchment area is 23 kilometers.

Okay, now see the same picture here, same healthcare facility, same population and notice what happens to the circles if you expand the catchment median to 60 kilometers. So what I have just shown you is explained in a very elegant

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model in the PNAS paper illustrates one approach to calculating the optimal allocation of drugs between urban and rural areas in KwaZulu Natal to maximize the impact of HIV.

This is how I got interested in modeling. Professor Blume had a paper - this paper - and I had spoken to her during the [inaudible] conference when she was putting this together, and she mentioned to me that they had noticed if you gave treatment to people in an urban setting as opposed to a rural setting you would get a differential rate of epidemiological efficiency. And her comment to me was, I don't know what you would make of the ethics of that, given that ethics was what I was studying at the time, and that's how we started our conversation and my study.

The paper discussed the epidemiological impact of different allocation strategies that allocated drugs differentially between urban and rural areas. The authors found that to have the greatest impact on the epidemic - that is, to maximize the epidemiological efficiency - it would be best to give all of the drugs to the urban centers. This, of course, does not deal with the issue of treatment equity. Okay, so she makes a point about ethics versus equity comparing two principles. They are showing that drugs are allocated where everyone has equal access, and the other principle was epidemiological efficiency in showing that drugs are allocated so that they have maximum impact on reducing the incidence

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rate. So it is by comparing the two studies they found that both goals are a treatment equity and epidemiological efficiency are both ethical but it's not possible to achieve both.

I want to finish with a couple of slides on calculating cost utility ratios. Basically, post-exposure prophylaxis costs utility ratio equation showing the cost of the PrEP Program, the number of HIV infections averted as a result of the use of PrEP, HIV-related medical care costs saved per averted case of infection, the number of quality adjusted life was saved per averted case of infection, and here's a graph that shows the results. So what is this? This is essentially cost benefit analysis to evaluate PrEP if it was used in 96 metropolitan areas in the U.S. The Y-axis is the cost utility ratio expressed in net cost in dollars per qualli saved, the lower the net cost per qualli saved the better the use of PrEP would be in that area. So what's plotted here is the cost utility ratio calculated for each of the 96 metropolitan areas were analyzed, therefore the 96,000 histogram along the X-axis. So one of the main messages of this slide was that we can extrapolate that the cost benefits of PrEP will also vary considerably both within a country and between countries.

So, to conclude, modeling techniques have been applied to assess impact on epidemiology, individual risk, address issues of access to interventions and cost effectiveness of HIV

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interventions. Models can help assess the impact of PrEP in specific country and target group settings. Models can help in forming policy development particularly in areas where resources are limited.

I want to finish by thanking Sally Blume and her team at UCLA for sharing their knowledge and their passion with me and their willingness and patience in teaching me the basics of modeling. I want to give a special thanks to Dawn Smith and Dave Paxton who have been wonderful in helping me find this program and put the meeting together. I want to thank Renee for her inspiration and support, and Rodney and Jacqueline my colleagues at the IAS for their support in my role at IAS, but most of all, I want to thank you for your attention. Thank you.

[Applause]

ELLY KATABIRA, M.B., Ch.B., M.Med: Thank you very much. Any quick questions for clarity? We will move on then and ask questions later. Before our discussion, the last speaker is Dr. Somyot, the Minister of Health of Thailand.

SOMYOT KITTIMUKONG, M.D.: Good morning. This morning, I will talk about the lessons learned from Thailand, especially on LB Program spending, that we have done it for many years, and also the last part of my slides, I will talk a little bit about the Entity Program in Thailand. I will start first with the issues in Thailand.

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About 20 years ago nowadays the number that have been infected [inaudible] a ministry problem, but the number of people still living with the virus is around 500,000 to 700,000 people still living with the virus, and then the rate of administration this year, from our estimation, is around 60,000 people. We know that even we are trying many things from the past up until now, I think in some good [inaudible] we don't have a perfect method and surely we are dependent especially in this light. You see that this is the issue of [inaudible] that one would try several things to lower the prevalence or even incidence.

Anyway, in some [inaudible] we can use condoms for example there is a trigger. We started a 100-percent condom program resolution. The government pays for the condoms and they will be providing condoms for [inaudible] female sex workers around 1989 or 1990. And you see on the slide after about 10 years we can lower the prevalence among direct and indirect sex workers and also the male clients who have sex with them and at the clinic. And also you see on the slide that there is an issue of prevalence among pregnant women and their consulate or even in [inaudible]. I want to remind you again that we started a [inaudible] Program 100-percent condom program in 1989/1990 at the beginning of the slide. About 10 years later, then you can see on the impact of the program.

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For access to the treatment and care, at the beginning we don't have - here we drop so we start treatment coming up to infection, for example like tuberculosis, PCP, critical [inaudible], and then we start giving the therapy in 1992, and then they seem to drop off in 1995, and up until nowadays we used a triple regimen in Thailand. For Thailand National Entity Program initiated in the year 2000, and we can say that we can cover the whole area of Thailand in the year 2004. It has been promised by the government that everyone who are Thai people to get access to the treatment and care.

So the package that we arrived at for the Thai people, we give retreatment three to four months, for example, and today I think we are spanning to try to give condoms reach out to the people who are receiving treatment. And the guidelines say that you start every treatment procedure for a level of less than 200 cells from [inaudible] if the people have [inaudible] especially the possibility for [inaudible] is quite higher than maybe if it was done [inaudible] they started therapy.

For this first line, I mentioned that we are using the 43 TC and tuberculin. It's a drug that is manufactured by the government pharmaceutical organization. So this was the guidelines that have been used in the past, and you can see that we used the drug called tipovir [misspelled?]. It contained three kinds of drugs, D-14, three [inaudible] and nuropene [misspelled?]. The cost in the past it was \$30 for

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one patient and now the cost is lower. In the year 2001, we started to try to give every treatment to the people. I want to give some details about the numbers of hospitals in Thailand around 1,000 hospitals is under the Ministry, so most of the hospitals in Thailand are under the Ministry, so at that time we started a program. We invited the hospitals to join the program, so at the beginning 109 hospitals joined the program. At that time we had limited batches so we can provide a treatment for just 3,000 people.

I can remember when I first walked into the a district hospital at the beginning of the program that we have a limited quota for the people, so I think a lot of people wanted to get into the program but we could not provide the drug for them at that time. But nowadays we have a budget and we can improve the program, and nowadays I can say that every district hospital in Thailand at the Ministry can provide treatment and care using LB treatment for the people. And last year we had transferred the program to the National Health Joint Office, so nowadays the Thai people, everyone can have the problem and want to get the treatment and care can get it.

So this is the number of people who are receiving the various LB treatment program, every treatment under the program. On the blue line is the intuitive number of the people and the pink line - the second line - you see the number who are receiving the drug, and the one program under the

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national insurance scheme. I want to tell you that the insurance scheme in Thailand we have three. The first one, National Health Joint for everyone for Thai people, and the second one Social Security if you are the worker, you have Social Security, and the third one, this is for a civil servant that can get treatment, and the doctors and the clinicians that are listed in the program.

So if you want know how many people are receiving the treatment in Thailand in the National Health Insurance I think it's more than 80,000 people are receiving, and for the Social Security more than 20,000, so if you add it up, I think it's more than 100,000 people are receiving LB treatment in Thailand. We also got the money from the Global Fund. We tried to integrate them and use the money to compliment. For example, we used the money from the Global Fund to buy drug or even to buy [inaudible] machine for example, and if the patient does not want to issue their status, they can pay and get a treatment in the private clinic or even in a private hospital.

In the past, we had the problem in distributing the drug to the hospital. We had 12 Regional Health Offices around the country, so we had to reorganize distributing the drug to the hospital by using something we call Window Managed Inventory or VMI, so you make a contract with a government pharmaceutical organization. Now we are working through the Internet. Now we have to distribute the drug directly from the

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government pharmaceutical organization to the district hospitals without - in the past we had to [inaudible] the drug and we had to [inaudible] regional staff, and from regional staff to the district. Nowadays, we have received and are able to distribute the drug literally from the GPO, the Government Pharmaceutical Organization to the hospital drug store by using computer to [inaudible] the staff.

And this is the picture that shows the front page of the Web site again CPO, you can look at it by visiting www.cpo.org if you want to, so this is something that we are showing on the website. And not just only it's a drug distribution mechanism that we had to address, we also had to address the company services, for example like the [inaudible], so we had to distribute the services to the whole country, so this is the cutoff distribution for centimeter or [inaudible] machine that we have distributed to 76 provinces. I think nowadays we can cover 74 provinces into which balances which cannot have the four-centimeter right now they can send a sample to a nearby province.

That's for every treatment program, but for our PMTCT I think we have used results from the study, for example like the results ATCT-3076 that shows that ATCT can decrease method resolution by two-thirds. And then nowadays, I think we have used the guidelines on 20-C to cover the whole country and the treatment from that. We also used the result of the study we

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called PMTCT a study in a paradigm, for example PCPT I that if you start PMTCT at 28 weeks we can decrease infection from 30 percent to 6-percent, and even add nurokene to existing regimen we can decrease infection to around 2-percent. So we are changing a regimen to a new regimen in the year 2004 - that current regimen that we used we have given ACT plus nurokene and also a new substitution [inaudible] free of charge to everyone, and we expect that we can decrease the infection rate to about 3-percent.

So this is the impact of the program. This is the number of pediatric cases from year 1984 to the year 2003 that when you try and cover the whole country in the year 2000, 2001 you can see the impact of the program on the global number of infections in infants. We have learned a lot from the two programs that we have to find a targeted population. We have to reborn our safe order in the program even in the pilot and managing the program. So in the both programs we started to use and test the pilot project and then we gradually stir up to cover the whole country, and also we have to admit a fact that if we follow the National Guideline we cannot accomplish this task. Now we are really trying to integrate every program in PMTCT to existing programs. And finally, I think we have to thank our government that nowadays they are the main source of the budget that we use in our program. That's all for my presentation. Thank you.

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[Applause]

ELLY KATABIRA, M.B., Ch.B., M.Med: Thank you very much. Are there any quick questions, clarifications? Yes, please. Kindly use the mic - I'm sorry.

MALE SPEAKER: Good morning. I just would like to understand the concept of the indirect sex worker.

SOMYOT KITTIMUKONG, M.D.: I think the definition of direct or indirect sex worker is very complex at best. For example, in Thailand, direct sex worker means that if the girl, the sex worker are working in the [inaudible], you shouldn't call them direct sex worker, but indirect sex worker is the people who are working outside for example on a street [inaudible] or are called to perform are called an indirect sex worker.

ELLY KATABIRA, M.B., Ch.B., M.Med: Thank you for that. now the session is open for discussion. Please use the microphone. Tell us who you are and your institution. Go ahead.

ROY CATES [misspelled?]: Hi, Roy Cates from MA Health Center in Nashville. It's really a great start to an exciting conference in this area, and it's fun to see right from the beginning a focus on PrEP. I loved Dawn's elements of planning that really take it from a positive spin right away, not in essence, diverting of resources but how do we add to resources, no disinhibition but rather, how do we design counseling? And

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I wonder if you have actually had experience - or any of us - have had experience in other areas where this positive spin, especially in times where we are going to have difficult study results that might not show effectiveness how that positive spin could maintain momentum.

And then for Yasmine, it seemed to me that the model that has been done that is almost directly applicable to PrEP is the microbicide model that was published because it really focuses on use as the essential component for any of these prevention measures, and I don't know if that would be at least where you would start a model for an oral pre-exposure antiviral compared to a topical pre-exposure antiviral.

ELLY KATABIRA, M.B., Ch.B., M.Med: Dawn?

DAWN SMITH, M.D., M.S., M.P.H.: That was a question to the audience, I think. He was asking whether people had experience with other interventions with this sort of positive thinking framework, so I would invite people to come forward if they have examples to give to Roy.

YASMINE HALIMA: Okay. Can I respond to your question about the, what have we learned about modeling and microbicides? We have had a lot of these discussions when you can't take a particular model and apply it exactly as it is with the equations built in and the assumptions built in to PrEP for microbicides given that one might be potentially dependent and the other is taken daily and the exposure rates

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might be different, and they might be available differently. One of the exciting things about PrEP is that actually if it works, we actually have a PrEP agent already available. It doesn't have to be developed, manufactured, and so on.

And so the answer, I guess, is both yes and no, but it depends also what we are looking at. We could be looking at operational research issues, which is about distribution, once we know that something works, how do we get it available to the people that need it. The other is, how do we use models to assess what the impact on their epidemiology might be? How do we change the epidemiological landscape? Shouldn't be giving it to those most risk for HIV, shouldn't we be giving it to those people we can most easily access, and so those are different kinds of questions maybe that we want to extrapolate from what we have learned from microbicides, but not to apply it literally as it is, and I think that's also one of the caveats that it's easy to do that and we should do that.

DAWN SMITH, M.D., M.S., M.P.H.: I would also add that there is actually already a model of PrEP implementation for those of you who were at FROY this year. We met Abbas from University of Pittsburgh along with the Imperial College has already developed a modeling exercise that is specifically tailored for looking at PrEP, and I think you'll see it in publications.

ELLY KATABIRA, M.B., Ch.B., M.Med: Go ahead.

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TOM COATS [misspelled?]: Hi, Tom Coats from UCLA, and thank you for a very, very interesting panel. Dawn, I am delighted by the activities you are leading at the CDC and look forward to the unfolding of those activities over the next several years, and I think it's just very farsighted that the CDC is planning this kind of activity. Every time that I see the compelling data that are presented on African Americans in the United States and particularly African American who have sex with men, it seems to me that this is a really, really, really strong argument for ensuring that the efficacy trials that are going on among men who have sex with men enroll sufficient numbers of African-American men who have sex with men in the United States, and I think it would do a couple of things for us. Number one, it might be an approach to reaching that population that we haven't tried yet, but number two, it will reach that population if it's done effectively, and I think enrollment in trials will be really quite crucial. Now I know the studies in San Francisco and Atlanta are attempting to do that, but I would really like to see those scaled up or other sites scaled up for efficacy trials really focus specifically on that population, and I think that would be a very strong contribution to the entire field, both of research but also of a practical way to reach that population.

The second point I would make, and now putting on a different hat, I sit on the board of the AIDS Project Los

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Angeles and, in fact, we have a planning meeting next Tuesday, and I think the dilemma faced by many AIDS service organization, at least in the United States, and non-governmental organization like AIDS Project Los Angeles is that it does not have a clinical arm. It does not do clinical service, and so we are trying to figure out how to strategically position ourselves to prepare for pre-exposure prophylaxis and even thoughts about male circumcision. As you know, we serve a very large Latino population where male circumcision is relatively low. While we don't have data on efficacy in that population, it seems it's something we really need to think about. So I think we are trying to think of a variety of strategies to position that organization to be able to incorporate biomedical prevention into it's full panoply and it may mean strategic alliances with clinical providers like the LA Gay and Lesbian Center or the AIDS Healthcare Foundation, it may actually mean mergers. I would encourage you to think of that as part of your planning.

The third point I would make, and this is a point that really came out in our forum at UCLA is the issue that the varied populations that are heavily burdened by HIV are these that have least access to care. I thought the modeling exercise, Yasmine, that you and Sally Blume did and particularly looking at KwaZulu Natal and thinking that the greatest benefit would be in Durbin where there is closest

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access to health care, and I have a project in rural KwaZulu Natal in [inaudible] and I know the difficulties of having people access clinic because of the burden of distance and hills and weather and so on and so forth. And again, I think that's going to be a very large and protracted discussion. It applies both in the United States and elsewhere. How do we get this to those folks that need it the most? Thank you.

DAWN SMITH, M.D., M.S., M.P.H.: I want to say a couple of things. Number one is, I know that the trial in the U.S., which also included a Boston site, has worked hard to recruit black MSMs into the safety study. And I think the approach that we are taking in terms of the survey of the user research that we are doing is we are really focusing very much on African American young people as the primary target for our planning. Not that we wouldn't provide it to other groups, but because of the access problems, the reimbursement problems, the many issues that affect that extremely high incidence population, our feeling is that if we can come up with strategies for delivering PrEP services to that population it will be easy to do it for the easier populations, but if we start with the easy populations then we'll recreate this disparity situation where we don't get around to the other things.

So I think outside of the trials, we are also trying to find ways to capture what the needs and the preferences are of

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those populations to incorporate into our planning early. In terms of the CVOs, I think I completely agree that we need to figure out in the strategies how to marry the different expertises that we have, to not make this a hospital center or a clinic based only intervention. So we have talked about things like, for example, whether you would come in initially to a medical center for screening, or you know, a clinic for screening and for prescription. But then when you have your periodic visits and your refill visits could those be done for example in a pharmacy with a counseling room that includes counselors from the community base organization and then the pharmacist is providing the refills. Could this be done in clinics that settings like, you know, K-Mart has now put in medical clinics throughout the country. K-Mart is a large department store chain. And again, could community-based organizations partner with nurse practitioners in those kinds of settings?

So I would encourage, again everybody to start thinking creatively about how we can put these things together rather than create a competition.

FEMALE SPEAKER: I also wanted to kind of add to the point to the issue that you raise about disparities in health and on equal access in some communities. I am a member of the U.S. Activist Coalition. And we recently did training in Louisiana, of all places on several issues concerning HIV and I

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was asked to give a talk on biomedical prevention technologies. So these, most of the people who turned up were very poor African American or poor Latino. And most of them were already affected with HIV. So I really wasn't sure what kind of feedback I would get, even I was going to a state of the art talk about science and about PrEP microcides. Then the level of interest was really remarkable and the reason for that was and we kind of engaged in discussion was because they could relate their disadvantages in terms of their experience and they were thinking about their children. And they described to me about their nephews and their nieces and real examples of stigma in the community. In fact, it's not recently for a long time. I haven't been to a meeting where people talk about HIV as their [inaudible]. That was a big surprise for me.

So we are talking about strategies that communities can use that work for them then I think you know PrEP could be a really powerful intervention both for men and for women and for MSN use.

MARK WEINBERG [misspelled?]: As some of you know, our lab has been involved in studies on drug resistance that involve different subtypes. From time to time I get wind of someone saying that Mark Weinberg [misspelled] is opposed to PrEP because of considerations of drug resistance and I just want to go on record that that is not true. I'm a very strong proponent of PrEP. I think all of us would agree that some

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level of drug resistance will be inevitable in regard to prevention strategies perhaps no matter which one we employ. And we need to be vigilant and we need to understand this virus but there is no doubt that PrEP is a major step forward and hopefully will provide meaningful results in preventing HIV disease before long thanks to you on this podium.

I do have a question in regard to modeling for Yasmine, who did a fantastic job and I think Sally would be proud, but it really relates to something that I think we don't have a lot of information on but is perhaps reflective of the fact that as we know certain viral subtypes seem to be responsible for a disproportionate number of new infections on a world wide basis. And it does suggest the possibility that there is a lot about the biology of transmission of HIV disease that we really don't understand. And perhaps certain viral subtypes do have greater agility in regard to transmissibility than others. And I just wonder if it's possible to use the modeling equations and experience to take some of these differences into account. Is that a direction that some of the modelers might think of going?

YASMINE HALIMA: Well, that's a great question. You know, Sally says whenever I ask her something about could this be model and she says anything can be modeled. So I guess modeling gives us a lot of potential. One of the exciting things about modeling is it can bring different kind of people

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together so Sally has one area of expertise. And when I was at her team, it was really interesting working some of her post hocs. You know you hear sarcastic [misspelled?] residence a lot but you don't hear case bi-bond mutations or K1 or 3N. So they have different expertise that they bring. And so the potential for modeling to bring experts like yourself in drug resistance, people who understand pharmacokinetics, people who understand ethics and equity, people you know, I think it's such a multidisciplinary, potentially it could be such a multidisciplinary approach that we could take. And the model is only as good as the information that you put in. So if people like yourself work with Sally and other modelers to build in those assumptions and define those as accurately as we possibly can in a given situation. And you can build in and Sally has already done this in terms of drug resistance but we could really put in Dawn's information and make the bonds much more precise but I really, as I said, rely on interface between different disciplines and different experts like yourself.

MALE SPEAKER: Yes, please.

HANS NEGEL [misspelled?]: Hi, I'm Hans Negel from Munich, Germany. I have a clinical question. How would you manage MSN, we did medical leukotomes in medical clinic these days on a Friday noon and he says he is going to Amsterdam for a large party there and we know from experience that these parties have 72 hours with almost as many sex partners. How you

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would manage, with the given information that you have now and I know it's limited, it's a medical question. It's an ethical question. It's lot of questions in one, but I would to hear the panel on that question.

[Laughter]

DAWN SMITH, M.D., M.S., M.P.H.: Now, we don't have the information on the amount of efficacy in PrEP. So I don't think we can say that you should or should not provide PrEP. I think it is a decision that you have to make as a clinician based on your best understanding of the literature and the needs of your patient. But from a public health point of view we don't yet have definitive proof that this is an effective approach.

So I don't think that we could give you specific advice.

YASMINE HALIMA: But you know, Hans, we do have interesting doctor, a maverick doctor in London, for example, and when some of his patients go to him and they put a certain scenario, he does talk about, I mean, what he does officially I don't know but I remember reading in *The L.A. Times* maybe a year or two ago about doctors who do prescribe PrEP.

HANS NEGEL: Now, hypothetically it would work and it may well. Does CDC have any plan for management of this situation? Do we have to test this man or don't we have to test him? How do we counsel about possible resistance or non-resistance? We don't know if he is infected. Still, he comes and he asks for something. So if CDC is

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planning something, I would be glad to hear that what would these management situations plans works?

DAWN SMITH, M.D., M.S., M.P.H.: Well, first of all, CDC will eventually have recommendations when the trial data is in and after we have had appropriate consultations and come to consensus about it but I think the important thing is that we are talking about PrEP programs now over the context of the trials and eventual implementation that are more than just giving out pills to people.

So we would always want to know somebody's HIV status before we would give them PrEP so if someone comes in you know five minutes before they are supposed encounter and you can't measure their HIV status, I don't think we would ever recommend that you give antiretrovirals to someone without knowing their HIV status. And therefore, knowing what's an appropriate regimen to put them on.

And the second thing is I don't think we would ever recommend giving PrEP without giving some level of counseling about reducing risk behavior, about adherence, about a lot of things. So I think that eventually, we will be talking about a whole package of things that goes together. I would think of it more like we think about hypertension treatment or diabetic treatment. You know you don't just give somebody an insulin kit and say go forth and manage your diabetes. There is a lot that goes with it that's built around that biomedical intervention.

I think in the case of PrEP, that's what we are planning or we are trying to develop.

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MALE SPEAKER: Lesley?

LESLEY UNKNOWN: A couple of comments, the first Yasmine please realize that you cannot believe everything that you read in *The LA Times*. [Laughter] That article that described off-label use of PrEP in fact was followed very closely by a study that was presented by Al LUE [misspelled?] at the Toronto meeting in which Al LUE of the San Francisco Department of Public Health did a very thorough series of surveys and inspections of circuit parties throughout the state of California including Los Angeles and San Francisco and he was unable to identify any substantial use of PrEP at this time.

I think it's important to distinguish between post exposure prophylaxis and pre-exposure prophylaxis. Post-exposure prophylaxis is recommended by the CDC. It is used in some urban centers but as nearly as we can tell PrEP is not used outside of a few boutique clinical practices in London and San Francisco and even in those settings it's very limited in its current use.

But the more important point is and I think that really serves to emphasize that the community has reasonable judgment in these affairs that people are waiting for the results of trials. They want to know whether this is really going to prove to be safe and effective and I think that there is a great deal more wisdom in our communities than sometimes you gives them credit for.

And following on that, I would like to emphasis that even though PrEP sounds like a clinical or biomedical intervention, its use is really going to be very dependent on engagement with community

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based organizations and it's for the following reason. Unlike a vaccine which might be reasonably be offered to the general public PrEP is only going to be cost effective if it can be targeted successfully to high-risk individuals and these are individuals who are HIV negative. They are not self-identifying as patients. They are self identifying as members of the community. And I think it's going to be our community based organizations who will have the best information, the most sophisticated information about where these people can be found, how they can be identified, and how best to counsel them.

There is a lot of talk and reasonable concern about the prospect of behavioral disinhibition. But remember the data. The data from post exposure prophylaxis is shown time and time again that risk behavior actually improves in the context of post-exposure prophylaxis. There appears to be a synergy between a pill a day and the efficacy of counseling but I think that synergy is one only if the PrEP is implemented in the setting of sophisticated counseling institutions. And these basically are our community based organizations who are out there on the front line finding creative ways to promote condoms, creative ways to promote counseling, and behavior changes and it's going to fit very nicely into the repertoire that add elad if it can be shown to be safe and effective.

ELLY KATABIRA, M.B., Ch.B., M. MED.: Thank you very much.

Let's move on. I think this is the right time to move on to some roles which related to implementation. We have with panel

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discussions, we have Kate Hankins, who is now the chief scientific advisor of UNAIDS. And she's coordinated the first UN work plan of male circumcision of HIV; co-chair the UNAIDS WHO expert panel, [inaudible] considerations by medical intervention.

We also have from the donor's prospective Rene Ridzon, the senior program design the HIV/TB program with the Bill and Melinda Gates Foundation. She is very responsible for the overseeing of long vaccine HIV prevention for your people in PrEP [inaudible].

We are supposed to have also [inaudible] from Nigeria but he is not here. And also we are supposed to have Gwen Paris from Tibotec. He is unable to be with us but we are very lucky to have Ben Plumley who is the vice president, microbiology, communication and public affairs from Tibotec. Ben is not new to this field. He was once the chief of staff at UNAIDS before going to Tibotec.

So, for this another give my co-chair and she is going to lead the questions and answers, so I hand over to Yasmine.

YASMINE HALIMA: Thank you very much. Before we kind of take questions, this is meant to be just an interactive session. To have experts up here for you to be able to put questions to them but I want to start the session by asking each of the panelists just to take two minutes and to consider from their agency prospective what are the critical issues and the contribution of their agency in PrEP implementation if it should be proven effective. Could we start with Renee?

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RENEE RIDZON: Thank you, Yasmine. I wanted to start off by saying that the Gates Foundation is exceedingly interested in support of trials looking at pre-exposure prophylaxis. It's a very promising intervention in something that we think is important to get a firm lance on us whether or not it's efficacious. The Foundation supported the trial in West Africa that showed that it was safe and is considering some additional funding for ongoing trials and planned trials of PrEP.

The implementation question is a very important one and something that a new foundation such as the Bill and Melinda Gates Foundation hasn't dealt with to date. And is something that we have been thinking about quite a bit. Actually, more sort of acutely with respect to male circumcision now that the trial results from male circumcision are available and show it to be a highly efficacious intervention. And so we've realized that the answer does not end at providing a relative risk and a P-value from a trial but it must be extend beyond that in order to think of proper ways for catalyzing implementation uptake and adoption of these methods.

The question of actually when you start to do this is a very hard one. And it's like in my experience as a physician when you do replace aorta valve that is insufficient. If you do it too early you have caused your patient some morbidity. If you do it too late you have caused your patient some morbidity and you have to read your crystal ball and decide exactly when is the right time to do it? And there is not a lot of indication as to exactly when that's going to

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be. So we you know, we have, we want to make sure we make efficient use of resource and time and put resources toward implementation when there is a good idea that we are going to be implementing something.

So we are going to learn some lessons from male circumcision that we are getting started with now. Hopefully we have a strategy in place. we will be thinking about that, funding some male circumcision projects and that will inform us about future interventions which we realize need to be implemented and will probably need Foundation support to implement.

Now ,that said, the Gates Foundation does not view itself as either the circumciser of all men in the world nor the provider for all PrEP in the world. So it's something that needs to be coordinated with ultimate partners and industries involved and international organizations. Thank you.

CATHERINE HANKINS: Yeah. I guess the question would be for the normative agencies. First of all, do you know what a normative agency is? I didn't until I joined one. And discovered that normative agencies such as UNAIDS and WHO require first of all that trials be completed in order to be able to come with recommendations on what should be done with the information. and in that process of coming to consensus as Dawn was speaking about at CDC, it's a question of validating the findings and then trying to look at what the situation to which they are applicable, the populations that they might be applicable to, and coming out with recommendations with

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respect to whether this is going to be applicable in a generalized epidemic, in a concentrated epidemic, et cetera.

Our experience in the last couple of years with male circumcision has prepared us, I think, somewhat from moving ahead with PrEP. Obviously there are a number of different trials of biomedical HIV prevention products going on in the field. And one of the things we think that is absolutely critical is that those that are going on now continue to their completion, that they have, they are not only scientifically vigorous but they have good community engagement and involvement.

We have come up with some guidelines for that called Good Participatory Practice Guidelines for Biomedical HIV Prevention Trials. And we have also updated the ethical consideration document from 2000, from the year 2000 that's used mainly for vaccines. And it's updated now for all biomedical HIV prevention trials.

So, this is the kind of role that a normative agency would play in the initial incidences of making sure that trials continue and that when results come in that there is an internationally recognized validation of the findings and recommendations for countries on how to move forward. Once those are out then our role moves into a technical support kind of role where we are looking at supporting countries to hold stakeholder consultations where they decide what the acceptability is, where this would sit, the population, the situational assessments. So, this is the kind of thing where you would look at service availability, mapping, where

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would this best provided by which providers and to whom, setting up an operations research framework so that as implementation moves forward there is iterative learning and improvement of programs, and trying to identify perhaps some lead countries that move forward with something like PrEP. There might be three or four countries that decide to move forward. We would give more intensive support to them and have them come together meeting regularly to share their experiences and become in a sense the peer community leaders but at a country level for the implementation of the new modality like PrEP stuff.

BEN PLUMLEY: Thanks, Yasmine. And good morning, everyone. As representing Tibotec, I suppose we can't speak on behalf of the industry as a whole but there might be some observations that might be quite useful to taking this debate forward.

Tibotec has had a long interest in preventive technologies. We made available the first compound on a relative free basis to IPM, the International Partnership for Microbicides, that's a non-nucleoside analog called TMC120. And it's now being looked at in the ring and as the gel.

We indeed have an interest in PrEP and have a compound in a very early development. It's a formulation of one of our other non-nucleoside analogs, TMC278.

Slightly more broadly we have an interest in RND for the global AIDS response, whether it be new compounds for TB, whether it

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be treatments for oral candidiases and of course access to our broader antiretroviral portfolio.

And in fact the parent company of Tibotec, Johnson and Johnson, provided the diaphragms for the recent USF Gates study looking at diaphragms in prevention.

So why would a company like Tibotec be interested in PrEP? I think it's both a responsibility and an opportunity but I think to be clear this will not be a business as usual model. It's not enough to expect the development of a compound for industrialized world markets, and then somehow expect that to be rolled out or handed over to global efforts. I think we have to look at a model of bringing RND much earlier on into the access agenda. Certainly, there will be compounds and there is research going on at the moment in existing compounds but we are going to have to be looking at this longer term.

And finally, I would just want to add that I think in terms of opportunities and concerns for PrEP, I think somewhat has Robert Grant observed there really does need to be an emphasis in incorporating PrEP into the broader prevention efforts. It's something that Kate and I have worked on for many years in UNAIDS and the previous places, but this would not and could not replace existing comprehensive prevention efforts, rather it might be a tool to help us maximize the utility of those. Thank you.

YASMINE HALIMA: Okay, so I would like encourage you to come to the microphone with questions for all these lovely people here.

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But while you do that, I want to start with a couple of questions.

One to industry representative and one to Kate.

So Ben given that we may not, there may not be strong commercial incentive for a PrEP agent, given what it is that we want to use it, could you describe what might be the incentives and importantly the disincentives for industry to get involved in PrEP research and implementation.

And my question to Kate would be I'm intrigued at your, that the concept of lead countries and the meetings that I have been in on PrEP research, we have talked about country preparedness for PrEP research. Could you say a little bit more about what your criteria for country preparedness for PrEP delivery program might be?

Could we start with Ben?

BEN PLUMLEY: Okay, well, I refer the need for a different business model here. I have to say I'm probably, I'm going a bit beyond perhaps what some other colleagues would do but I think that current business model for developing compounds for the industrialized world is actually probably coming to the end of it's time. I think we are going to have to be looking at models of contributing to global health initiative ways and I think that's going to be through low price, high volume models. I think it's going to involve collaborations with funders like the Global Fund, like the curative agencies like UNAID once we have compounds that have come through the full regulatory process. and I think increasingly companies like ours if one is going to play in the global health

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arena has to recognize the role that meeting the needs of all people at risk or living with HIV face.

CATHERINE HANKINS: I think this is a very interesting question. Thanks, Yasmine. The country preparedness is probably going to depend on a number of different things but what happened with male circumcision was because we had one trial reporting and it was agreed and understood that we would not come out with recommendations based on the results of one trial, it meant there was lead time to work on country preparedness while we were waiting and anticipating the results of other trials.

I think we would have to look at the timeline to see how much, Dawn is talking about when the first one is going to report, to see how much lead time there is going to be or are they going to come so quickly and in such an avalanche that it will not be that kind of preparation time.

I would in terms of potential lead countries and I'm just inventing this on the spot in a sense. One of the things that could be looked at would be, and I would be very interested to hear what Elly has to say about this, to take a country such as Uganda that's already instituted in at least two districts now and beginning to roll out other districts, community based home HIV testing where we meet that criteria that Dawn wanted where we know the HIV status of a person and where counseling can be associated and where 60-percent of the households that have a HIV-positive person in them are discordant couples, that this would be a prime population in which to try to

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move the initial integration of PrEP into a developing country setting.

And that is just one example I can think of where we might do also the, I would call it a pilot program, not a project but a pilot program to see how that rolls out and obviously because that's district focused then you could fold the kind of community consultations to find out about the acceptability of this and understanding about it, etc. I mean those would be the kind of things that.

ELLY KATABIRA, M.B., Ch.B., M. Med.: Yeah, of course, Uganda will always be very interested in the outcomes of this study. And bear in mind the magnitude of our program.

Yes, I was going to say to the moving to getting the communities involved in that statistic is a way of preventive measures, [inaudible] definitely approaches to implementations of Uganda, as you all may know, the second set of studies have been done for a while and already talking about the issue. So, the situation, suppose slightly different compared to other examples.

One other thing which I had wanted to make a comment later on. When someone from the audience talked about specific targets of whomever populations, which might be cost effective, in some countries particularly in sub-Saharan Africa it is no longer easy to identify communities which are [inaudible]. There is an instance with the high cell perverts, perverts with HIV, what is the high risk of being sexually active. Many people now of course for example South

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Africa [inaudible] runs rampant. You may be a nun and on your way to the church and suddenly become risk group though you are not initially classified that so it's actually the issue mainly be sexually active but I think PrEP has to be seen in that way as you try to implement t findings.

YASMINE HALIMA: So Renee, if I could ask you, you mentioned about the limited data of the agency in terms of actual infrastructure, capacity building, and delivery of interventions that work. I wonder if you could comment a little bit how you see the future of PrEP research.

RENEE RIDZON: Well, firstly, I do want to say just with respect to microbicides, The Gates Foundation has put well over, at this point, probably in the range of \$200 million into microbicides and things for. That's not quite limited role but it's, but again it's not going to be providing microbicides, the issue of microbicides for the world supply if the candidate is found not be effective.

I also actually wanted to emphasize the need and Dawn talked about this but the need once implementation starts very good monitoring and evaluation because they are going to be very important lessons that need to be learned. So we need to be wary of that and make sure that we have the mechanisms in place to best be informed of what we are working on, that does work better and what doesn't work so well.

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So then you asked me about future PrEP research. There was a very good meeting that was held by NIH and Ward Gates put it together in January of this year. And I really enjoyed it. I attended this meeting and this brought the importance, of many of the important research stakeholders with regard to PrEP into a room and talked about where we need to go with PrEP research. And it was a very good exercise for some fairly good consensus building about where PrEP research needs to go. And the following three or the following few important points came out of that meeting.

Firstly, that the ongoing trials do not have the ability to rule out less than 30-percent effectiveness because of the size, of the power of the trials. Then as future trials go forward they should be able to determine whether or not the intervention is 30-percent or more effective because cost effectiveness modeling has shown that for this to be effective on a public health intervention, from a public health intervention point of view that that effectiveness to be seen. And so there was a call to make the trials have enough power to actually answer those different questions.

Also, there was a realization that the current trials are, when the results are put together, there is going to be an over representation of men in those trials, and therefore more information is needing to be available for women. Also, it recognized discordant couples as being a risk group for HIV infection, as Elly pointed out, in areas where the epidemic is well established and that there needs to be interventions for discordant couples, especially since condoms

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cannot be used in the case of discordant couples who are looking to conceive. So that PrEP might be a very ideal intervention for established discordant couples, all age of the infection captions in discordant couples but by discordant couple, I mean established long-term discordant couples.

And so the field has responded nicely in designing trials that are sort of arranged or looking at those needs and are designed around those needs. So there is a – oh, and the other element that was discussed was the need for an intervention to look at MSNs more closely because the only trial that was on going to date is a safety trial in MSN and would have the ability to talk about efficacious.

I think that there has been a move to try, for the trials to meet those parameters with power and to include groups that were highlighted as high risk groups.

ELLY KATABIRA, M.B., Ch.B., M.Med.: Yes? Tell us who you are and your institution.

RUTH BERTON [misspelled?]: Yes, My name is Ruth Berton from [inaudible] Nairobi. My question, maybe to Kate, the largest number of people in discordant relationships are discordant couples. Now [inaudible] we know that women do not disclose their HIV status to their partners. [Inaudible] less than 15-percent would disclose to their partners. Is there any one group [inaudible] this PrEP studies to look at models of the disclosure or informing people that they exposed to HIV so that they find out [inaudible] in that discordant relationship so that it would benefit from PrEP.

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My second question is there a group of people that's cause to have babies [inaudible] and these new products being looked at in the context of PrEP is there [inaudible] to look at them in the context of this making a difference?

CATHERINE HANKINS: Maybe Dawn could answer that question, that second question? Even the first one.

DAWN SMITH, M.D., M.S., M.P.H: Yeah, there is a trial ongoing now, a safety study, looking at - I believe there's a zidovudine alone arm, a TDF and zidovudine arm and a Truvada and zidovudine arm, looking at dosing and safety for prevention of perinatal transmission. So that - yeah, that is being looked at. In terms of discordant couples, I'm not aware of any work that's done in association with PrEP that's looking specifically around disclosure issues. I think in the trials, we certainly ask questions about whether people tell their partners they're in the trials, but I don't think we've looked specifically at what she's asking about.

FEMALE SPEAKER: I can address the trial, but I also want to just follow up because I've become an advocate on a certain point and it's about the perinatal transmission. It's important to take a look at drugs that are going to prevent transmission to breastfeeding babies from infected moms, but of course we all need to bear in mind that the most effective way of preventing perinatal transmission is to provide good contraception to HIV infected women who do not want to be

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pregnant in the first place. As far as the trials that are ongoing and perhaps [inaudible] can also address this, in the microbicide trials, there has been discussion as to whether there should be partner testing, and in what place this partner testing is taking place.

And I think in the trials certainly where there's a sera converter, partner testing is offered, because you know, probably you're going to find another positive person if the person who's converted has a regular partner. But there's been talk about whether or not partner testing should be offered to just the participants who are uninfected, and I don't know what the status of that is with regard to happening, if that's been resolved or how that's happening in trials. And do you have any information on that? Do you want to? No. So I think it's not happening, but it's certainly something that has been discussed as well. And Lynn will comment on that, I think.

LYNN PAXTON: Hi, I'm Lynn Paxton from CDC. I just wanted to make a comment that in our - for example in our Botswana trial, we actually encourage our participants to bring in their partners for testing. So it is offered to them. So that's not -

FEMALE SPEAKER: Not just to sera converters but all participants.

LYNN PAXTON: Not just the sera converters. It's a service we make available to everyone.

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FEMALE SPEAKER: What about the people that screen out negative?

LYNN PAXTON: Well, once they screen out negative, you know, they're really just no longer part of the study, but we always encourage people to know their status on their own. But it's not actually formally offered to their partners.

FEMALE SPEAKER: With microbicide trials in [inaudible] we offer that they can bring in their partners [inaudible]. So that's a totally different aspect of the partner [inaudible].

FEMALE SPEAKER: And I would just say the experience from the home-based testing program is quite interesting, because it is conducted under the conditions of the three Cs, meaning that there's confidentiality, counseling and consent. People decide when the people are in their home whether they want to receive their results together or receive them separately. The testing is done right then and there once you agree. And we know from around the world that when couples get their results together, there's less domestic violence, there's more understanding of the situation, there's more support of the situation.

So I think all of our efforts to try to reach out to get partners to come in, I mean they're laudable, but they're not anywhere near as successful as when we actually reach out to people in their homes and ask them to take HIV testing and they counsel and together.

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FEMALE SPEAKER: I do want to add, though, with regard to one trial that is ongoing and that is a trial that is where Connie Callum is the principal investigator and it's a trial that is being done to look at suppression - it's in discordant couples, and the HIV infected partner who also has HSV infection is given suppression of HSV in order to decrease infectiousness of HIV, based on data that has shown that HSV and HIV have a co-pathogenesis. Anyway, in that trial, there needs to be couples counseling and testing because discordant couples are recruited into the trial. And one of the legacies of that trial will be establishment of couples counseling and testing programs in the sites with the trials ongoing. And it isn't a no-brainer in that if you know how to counsel an individual, you know how to counsel a couple. There's additional training and expertise and things that need to be in place for couples counseling. But a move toward increased amount of couples counseling that is done is also probably important, and it is well accepted in the context of the trial where it's being used currently.

MALE SPEAKER: Kate MacQueen is going to kill me, but as part of the Gates-funded West Africa trial, there actually was a series of protocol driven formative data collected, part of which was planned to find out what was going to be the best approach to implementing that type of intervention, if successful, and for a whole variety of reasons, the trial

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didn't provide an answer to the if successful part, although as you pointed out it was safety. Kate, I don't know if you want to describe at all the plans for how you are going to be gathering data in order to guide the implementation in those countries where the trial had occurred.

KATE MacQUEEN: Yeah, it was obviously an inspirational goal at that time. And basically, we wanted to be able to interview participants to find out their experiences in the trial. What could be done to help encourage use? What were the factors that encouraged compliance or became barriers to compliance and what that would mean for rolling out a program? We planned to interview all of the clinical staff working on the trial to find out what they were seeing as the barriers and facilitators. We planned discussions with providers in the community, NGOs, others who were providing services and care, which, we also had interviewed quite a number of them before the trial even began as well. We wanted to basically look at a range of issues, collect a variety of data, that would help us to understand how we might do a translation to a program. What needed to be in place, what the recommendations were going to be locally for making it happen in a constructive manner?

We ended up actually doing that kind of follow-up, a set of follow-up activities after the trial in each of the three countries where we conducted the research, but it took a bit of a different focus. We ended up actually looking more at

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what was the experience with the trial, especially in those places where controversy arose, and the implications for conducting research in the future rather than focusing so much on how the outcome might be applicable to the possibility of an actual program. So at this point, as we're looking at the possibility of research, Truvada in Africa, we are basically looking at a similar model. Also, I know that with Lute's CS study, there are also some opportunities to again look at issues around well what would be the possibilities following a trial, how you follow up with information to the communities and making sure that ultimately, the outcome becomes a positive one and that we have lessons learned that can be applied, whether to a particular trial outcome or to the development program later, how we can begin to consolidate that information.

I guess the last thing I would want to say related to that is one of the struggles I think we all face is that there's a lot of experience that we're all gaining from implementing these trials, whether it is how to work with discordant couples and improve our ability to improve communication between the couples, to bring more people in for testing and reduce the stigma associated with infection status. One of the things we struggle with is getting all of that information to a place and in a form where we can all learn from it. It often becomes trial-specific lessons learned, and

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it requires actually a fair amount of energy and resources to bring a group of people together and come up with a way to consolidate that knowledge.

And so one of the things that I think is really important is that we have more opportunities to do that in a targeted, focused way, so that that information and that learning from experience doesn't disappear. It's not often written up. It's not often put in any form that we can use in subsequent trials. And over the course of five years, ten years, that knowledge gets lost. So just a plea for finding a way to build that knowledge.

BOB BAILEY [misspelled?]: Bob Bailey from the University of Illinois in Chicago. Several people have said that we can learn a lot of lessons from circumcision, and one of the things that we did learn is that there's a certain amount of evidence that has to amass before the international public health community is willing to start even thinking about surgical intervention. So I would just put in a plea in the case of PrEP that the normative agencies and others try to decide now what level of evidence are you going to need before you actually endorse PrEP? And what kinds of evidence from what populations? Is one trial going to be enough, or do you need several trials?

One of the things from the modeling, I think, that comes out is that models are sensitive to cost of the

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intervention relative to risk of the intervention. And then the HIV PrEP [inaudible]. So in some, as our colleague from Uganda suggested, in some populations where prevalence is high, PrEP may be appropriate for a broad spectrum of the population. So what's going to happen when there's a generalized epidemic? Is PrEP going to be advised for everyone? And is it going to have to be clinic based in that case? So I haven't heard much discussion about specific expectations [inaudible].

And then one other thing is we had a trial on circumcision and there was a lot of lead time. So we had one trial that showed efficacy. Now we have three trials that have shown efficacy where seven months after the time when all three trials had shown efficacy and still circumcision interventions have not started. So we'd like to not be in that kind of situation with PrEP. So it's great that this panel is meeting, but there's still a lot of work to be done, and I would just encourage everyone to keep working at it, so that when and if an effective, efficacious treatment comes along, we're in a better position than we were with circumcision.

FEMALE SPEAKER: I guess representing the normative agencies, I should reply to Bob. I think one of the things about the role of the normative agencies as sort of the international public health's representatives, we act as kind of a gatekeeper, not so much on domestic resources. I mean a country could decide to go ahead, but they'd prefer to wait

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until the World Health Organization or UNAIDS come out with recommendations. But certainly a gatekeeper on international funding through the Global Fund, through PEPFAR, through World Bank [inaudible]. And if the example of male circumcision is to be followed or similar, none of those agencies will move unless a country has decided and made an explicit request for funding in order to be able to implement. And I think male circumcision is a little different from PrEP in the sense that there are so many cultural overlays in terms of the way in which people think about it and their willingness to move on it. And sometimes, this is not reflective of what the population thinks. There are some higher order gatekeepers that take some time to convince about things.

But I think with PrEP, the question would be that you asked how many trials, which populations and so on and so forth. I think that's something that we have to see. It is, you know, in a sense like a regulatory thing where FDA and other regulatory agencies will not move on results from one phase III trial, never. So there has to be more than one trial. There has to be some confirmation and validation from other trials before there would be a recommendation made. But at this point, I can't say how many trials and which populations are going to move with what. I see Dawn's getting up to the microphone, so she can maybe speak to perhaps some discussions that have occurred in the U.S.

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DAWN SMITH, M.D., M.S., M.P.H.: I would say a couple of things. First of all, for the U.S., CDC is the normative agency, and so that's why we have started to engage in planning for the US and not addressed issues about Africa and other things yet. In terms of the number of trials, it's interesting if you look at the other example, at the other pole, is prevention of mother-to-child transmission. That was a single trial. And the trial stopped early, and within three months, the American College of Obstetrics and Gynecology, CDC and the whole public health system in the U.S. had issued guidelines for how to use it. The reason that that happened that way was that a lot of thought and planning had gone in before the trial result came out, anticipating that it might, in fact, work.

So I think there's a range of things. Sometimes if it's a new mechanism, it's a vaccine for example, it is going to require more than one trial, there's no doubt about it. Okay? It may be one large efficacy trial, but it's probably going to be multiple sites and cover lots of populations and you're going to have a broad look at it. But it's not always the case that we need multiple trials before we decide to act. And so I think the important issue is that we do need to specify in advance. We do need to start having conversations. You know it may depend on the result of that first trial. Let's say that the first trial shows 90-percent efficacy. It's going to be treated very differently than if it shows 40-

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percent efficacy. So I think it's the process of discussing it and coming to some preset conclusions is really important.

ELLY KATABIRA, M.B.CH.B., M.MED.: We're running behind time, so Tom, can you be quick and the next one? Brief, as brief as possible.

TOM: I'll be extremely quick. I'll speak as a social scientist, and usually we speak for a long time, but I won't. It's really quite an interesting observation that the brilliance of the International AIDS Conference in Durbin was the world standing up and saying it's really unconscionable that where you live determines whether or not you have access to ARVs. And people have talked about for example male circumcision from a human rights perspective. But it seems to me, it's quite surprising, and this may happen with PrEP, and it certainly should be happening with prevention of mother to child transmission - it's quite surprising to me that the world isn't standing up and saying we should have access to this as a fundamental human right. This is a life-saving, life-extending technique. And why is it that we don't have that level of people yelling in the streets and saying, this is just patently unfair that this is not accessible now?

So I think one the best things that we could probably do in order to generate that kind of activity, and I come from an era, I was in Berkeley in 1968 rioting in the streets, is to perhaps figure out ways of building civil society that would

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activate and energize countries to not do business as usual. I find this an extremely frustrating event that we have these conversations when in fact one would hope that the countries would demand this as a right to save their populations. Thank you.

PETER [INAUDIBLE]: I'm Peter [inaudible] from the Ministry of Health in Kenya. I just want to echo Bob's comments here that for circumcision, yes, there's been a lot of time lag between the time the results came out and the time that we were starting to see the implementation. I believe that we have an opportunity to do it different with this, and I guess a lot of guidance from WHO, looking at already sensitizing governments to be able to have some basic information to start beginning the process of engaging what we call the gatekeepers, and I can ensure you that there's a lot of gatekeeping that would be seen with PrEP, probably more than with male circumcision, and we need to start that process even when we don't know there the results are going to go.

So we have the two scenarios of if the trial shows some evidence, if not, then what do we need to do, and what level of engagement do we require? And that process should definitely start now.

ELLY KATABIRA, M.B., CH.B., M.MED.: Thank you very much. I would like to take this opportunity to thank the panelists and

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all those who have contributed from the audience, and also all
of you who have dared to come out on a Sunday to -

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