The Search for an HIV Vaccine: Where Are We, Where Are We Going, and How Can We Get There Faster
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MITCHELL WARREN: Not too early morning session for the first day of the 18th international AIDS conference here in Vienna. My name is Mitchell Warren and I direct AVAC, an advocacy organization dedicated to AIDS vaccines and the development of other new prevention tools. And it's my great pleasure to welcome you here.

For those of you that have been in Vienna for the last couple of days, this may be the coolest room you have been in and we hope that it will stay that way. We're doing our best, I'm told, to keep it cool. It's really an honor to be here with you and particularly with the 11 people you're going to hear from over the course of the next couple of hours. Now, I know saying 11 people and two hours might send shivers down your spine. We aren't here to provide a full array of lectures of 11 people. We really want this, as best we can in this environment, to have it be a conversation.

There are two presentations and the rest of the people involved are going to engage in various panel discussions and the great hope is that the panel discussion is both a chance for them to engage with each other, but also for all of you to be part of the conversation. So during the course of the morning, you'll hopefully get some cards or pieces of paper or make up your own. If you do have questions, if you want to pass them to the outside of your rows to the outside, we will

collect them and as I go through the morning we'll try to moderate the discussion so that your questions that are on your minds will most arise to the top to get addressed. And at the same time, I'm going to do my best to try to open up the moderations to all of you in the audience so that we can really have conversation as best we can.

It's really a great pleasure to introduce our first speaker who has a bio that many of you have heard many, many times. Peter Piot has been in each of these conferences in varying capacities. In this conference here in Vienna, he may be getting the award for the most relaxed individual in an AIDS conference. As many of you know, for over a decade he ran the joint United Nations program on HIV/AIDS and therefore was a very active participant in these conferences and he stepped down from that position last year. What some of you may not know is his long-standing commitment both before UNAIDS, during UNAIDS and since UNAIDS to the development of a safe and effective HIV vaccine.

Currently, in addition to many other hats that he wears, Peter is the president of The Global HIV vaccine Enterprise under whose this session sits today. So you'll hear a lot about the Enterprise at different points. But we wanted to start with Peter helping to frame the whole conversation so I'm going to turn it over to Peter Piot.

PETER PIOT: Thanks Mitchell, and good morning everybody. Indeed, I've been at every single AIDS conferences and at the, throughout times we've heard incredible promises that the vaccine would be close and this is probably a field that has suffered more from over-promising than any other one. But I could say that I believe that today we are— is this okay? That there has been more progress over the last couple of years in terms of our understanding of what may lead to a vaccine than perhaps in the previous 10 years.

There's been huge progress in terms of less people infected, less people dying, and we'll hear about that at this conference. This year also, is the year that universal access to treatment should have been a reality according to resolution of the UN General Assembly. I heard Michel Sidibé from UNAIDS on the meeting that we had on prep, pre-exposure prophylaxis on Friday making an important statement and that is let's not dream. We're not going to get there.

We're not going to get there considering also that in many countries there are now, there's no money for enrolling new patients for antiretroviral therapy, that somebody has to die before someone new can be enrolled. That's also part of the reality.

And yet the old myth, the old obsession of that we see in AIDS has come up again and this conference is a test and treat, which will stop the epidemic. And it seems as if we

haven't learned that there is not one single solution to stop this epidemic. If it were, we would have done it and found it a long time ago.

Last year around this time, a bit later in the year, we had the very exciting results coming out of Thailand. First time, we had, let's say a proof of concept that it can work and this is given not only an enormous boost to the field but also, I would say, has put HIV vaccine development back on the world stage. It's clear to me that we have been working on an H2031 project that, if we intensify currently available methods for behavior change and male circumcision and so on and hopefully soon also pre-exposure prophylaxis, that we can do a much better job in bringing down new infections.

But in order to really, I would say, not say eliminate but bring this epidemic under control, we need a big game changer and that game changer can only be an HIV vaccine and that's what we are all working about.

The invitation for this meeting asked a few questions. How close are we to developing an HIV vaccines? Where are we? Where are we going? And how can we get there faster? Some of these sound like very existential questions but they're real and I think that again, as you will hear, we have made progress definitely since the last conference [inaudible] in Mexico.

Today's panelists are going to share a lot of information. Much of it will be new and that will answer

partly some of these questions. We unusually hear a lot about obstacles in the search for a vaccine and they're, of course, they're real. But we're hearing mostly about progress. I think that's what we should focus on. Each of our speakers represents an organization that is part of the Global HIV vaccine Enterprise and all organizations; all members are committed to sharing information and working together to set scientific research priorities. And I think, here also, we've come a long way.

From a field that traditionally has been suffering from balkanization, from non-sharing of information, for going for the home run and hoping that, to win the big lottery with a vaccine development, I think we are now in a far more mature environment. Although one can wonder, what is the right balance between a more mission-driven research to develop a vaccine and the absolutely need for innovation and entrepreneurship even for the craziest ideas.

So, if one day we will have a vaccine, or when we will have a vaccine, it will not be to the credit of a single person, a single lab, a single company, a single initiative and that we'll be able to come to the stage and say look, this is it and I can take all the credit. It will be, and it should be, a stage where all of us and all of you here and many others will have to share that credit because it is through the incremental progress that we're seeing in each of the

components of the Enterprise that we're going to make it. So let me thank each of the organizations making up the Enterprise and many contributors that made this program possible.

Let me know turn to the first speaker and back to you Mitch, or is it? Yes, then it's my great pleasure to introduce my friend, Jose Esparza, who has been of all battles when it comes to HIV vaccine research and is currently in charge of HIV vaccines at the Bill and Melinda Gates Foundation which is one of the founding organizations of the Global HIV vaccine Enterprise. Jose? [Applause]

JOSE ESPARZA: Thank you. I'll need [inaudible] slides. [Interposing]. So many thanks Peter and good morning to everyone. As Peter say, my name is Jose Esparza and I am the senior advisor on HIV vaccines at the Bill and Melinda Gates Foundation in Seattle. And I'd like to thank Mitchell and the organizer for this invitation.

However, I must confess that when, that I was a bit intimidated with a topic I was asked to discuss, because it's a subject with many points of view and also with many interpretations. Nevertheless, I will use the next few minutes to share with you my very personal and high-level perspective on this question. And I hope that the distinguished panel that will follow my presentation will add additional insights to this important question.

Although, I was asked to discuss what have we accomplished in 25 years, I wanted to start with what we have not yet accomplished. And some of you may remember that back in 1997 President Clinton announced the national commitment of developing an HIV vaccine in 10 years. And you may also remember that he compared that challenge with President Kennedy's goal of putting a man on the moon before the end of the 1960s.

Well, President Clinton was almost right. Because 12 years after his statement, not 10 but 12, we have the first signal of a human efficacy of any HIV vaccine and, of course, I'm referring to the RV144 trial in Thailand. And I guess that when President Clinton made the commitment he actually did not specify the level of efficacy of the vaccine.

More seriously, the reality is that today we are not close to have a practical HIV vaccine that can be used in public health programs around the world. And I, I would like to challenge ourselves to achieve that goal within the next 10 or 15 years or even less. And I know that many of you in this room may think that waiting 10 or 15 years is too much. But we know that that is what it takes to move a Candida vaccine through the complex series of clinical trials to demonstrate efficacy.

So, to achieve that goal, it is very important not only to produce new and exciting science, but it's also important to

harness that science to develop new Candida vaccines for clinical trials. Now, this figure comes from the modeling paper that John Stover and colleagues published three years ago. And John modeled three-year scenarios based on different vaccine efficacy and population coverage. In this model, the highest scenario at the bottom of the slide, if a vaccine with 70-percent efficacy and eventual 40-percent coverage begins to introduce in 2015, that vaccine will result in more than 80-percent deduction in the rate of HIV transmission by 2030, 15 years after the introduction of the vaccine.

And modeling work with other preventive interventions does not predict same impact and a vaccine remains the best hope to control the epidemic. But what his model is telling us is very exciting but it's also telling us that we need to work hard to have an effective vaccine deploy within the next 10 years or so and this is why we need to have a sense of urgency. We are doing science not only for the sake of science but mostly for the sake of people who need the vaccine.

This slide is a bit busy but shows a simplified chronology of HIV vaccine research that can be particularly interesting for the younger members of this audience. Not for John Cohen, for instance, who knows all of this. AIDS was identified in 1981 as a new disease and in three or four years the etiological agent, HIV, was found. And once we had the virus, the expectation at that time was that we would have a

vaccine very soon and in fact, the first phase one trial of a GP160-based vaccine was initiated in 1987, three years after the virus was discovered.

But that was just the beginning of a long road, a road that is filled with scientific obstacles. Some of these obstacles that we didn't know at the time, but some of these obstacles are related to a variability of the virus and also to the ability of the virus to escape natural immune responses that failed to limit virus replication leading to chronic infection and eventually to AIDS.

Now, some of you may remember that in the late 1980s there was a period of optimism because experimental HIV vaccines protected nonhuman primates. But soon, we realized such protection was mediated by antibodies' responses to whole cell proteins and not mediated by viral antigens that could be developed as practical vaccines. And that was a major disappointment in the field at that time.

During the 1990s, the field engaged in a very intense effort to develop vaccines that induce protective antibodies, neutralizing antibodies. And there was also a global modernization that included the NIH and WHO and later on UNAIDS to initiate the preparation of vaccine trial sites in developing countries. This in part, motivated by the discovery of multiple HIV [inaudible] that could impose the need for different vaccine formulation for different parts of the world.

But in the late 1980s, we experienced a second major disappointment when it was found that antibodies induced by the envelope Candida [misspelled?] vaccines neutralized laboratory-adapted strains of the virus but not the [inaudible] clinical isolates that mediate natural infection. And today we refer to those viruses as, as you know, as X4 or R5 viruses.

So in the early 2000, we witnessed a shift in vaccine development for antibodies to cell-mediated immunity. These leading to the development of a series of Candida vaccines based on viral vectors of DNA. The antibody people continued their work in parallel, and this period of paradigm shift was responsible of many controversies in the field; controversies that are too many and too complex to be summarized here. Sufficient to say that during this controversial period took place the first two phase 3 trials, efficacy trials of an HIV vaccine and I refer to the GP120 [inaudible] trials conducted in Thailand and North America.

As you know, negative results from those trials were reported in 2008 with many people saying I told you so. But the second vaccine tested in efficacy trials was a lentiviral 5 vector vaccine. I'm referring to the step trial conducted in the Americas and primarily in South Africa with the Merck vaccine.

In 2007, these two trials were prematurely terminated because lack of efficacy and a hint that a vaccine may have, in

fact, increased acquisition of HIV. And that was, in my recollection, a third and most disappointing moment in the long road to an HIV vaccine. So, the [inaudible] trial in 2003, by the way.

So finally, results from the latest efficacy trial, as Peter say, were announced 10 months ago and I refer to the RV144 trial conducted in Thailand using a canarypox prime and a GP120 boost. and this is a trial that was conducted against the best opinion of many experts in the field. But the one that actually gave us a modest efficacy signal. So now we can start building an RV144 to improve the efficacy of HIV vaccines and we finally have good reasons to be more optimistic.

Now, this is my top-of-the-head list of accomplishments and it's a very personal list. As mentioned before, an important advance was the recognition of the genetic immunological and biological variability of HIV, information that is essential for vaccine development. We have learned much about the complex structure of the HIV envelope and that is helping us in the rational design of emergence that can induce Broadly neutralizing antibodies.

Structural studies of the envelopes are now being strengthened by a series of Broadly neutralizing monoclonal antibodies that can help identifying epitopes to be used in reverse vaccinology approaches. We have also learned much about pathogenesis and potential mechanisms of protection in

humans. Although my personal appreciation is that we need to learn much more in this front.

During the last couple of years, seminal work has been done to categorize the early events of HIV infection both from the virological and immunological perspectives. We know that in most cases the infection is initiated by just one virus party, one virus, and that within days or weeks that initial infection has disseminated systemically leaving us a very reduced window of opportunity for a vaccine and a nasty response to control the infection at the portal of entry.

Nonhuman primate models for vaccines have also been optimized and we hope that these new models will serve us better in advancing to clinical development of novel Candida vaccines. And vaccine regimes have also been optimized to induce balanced CD4 and CD8 immune responses. And another generation of inserts for cell-mediated — CMI vaccines have been developed using conserve or consensus sequences and more recently computer-generated mosaic inserts that may be able to deal with the challenge of the HIV genetic variability. In fact, vaccines based on mosaic inserts are now moving to the clinic.

For many years, we were fixed on the idea that the only protective antibodies were dosed and mediated in vitro, virus neutralization. But recent data is suggesting that there are other antibody functions, such as antibody-dependent cell

cytotoxicity that could be potentially relevant for protection and this is opening new avenues for vaccine design.

And, as I mentioned before, recognizing this small window of opportunity between local infection and systemic dissemination, new efforts are focusing on vaccines that can induce protection at the mucosal portal of entry of HIV. But, in addition to progress in laboratory science, there has also been progress in the clinical trial front.

A large number of vaccine clinical trials from phase one to phase three have been conducted in many countries around the world, including developing countries. And those trials have been conducted to the highest ethical and scientific standards. Some criticism is that we have been too slow and conservative in conducting large-scale efficacy trials with only three vaccines tested in efficacy in 25 years of HIV vaccine research and this may need to change.

We have also learned that every time that we get the results from an efficacy trial, those results come as a surprise to us. Vaccines that the scientific community thought would work didn't and vice versa. And of course, RV144, the trial in Thailand, was a pleasant surprise and is a light at the end of the tunnel but we are not there yet.

So this is my last slide. When I was preparing for this presentation, we also came to, as a surprise to me when Alan asked me to do it, I went back to some of my old papers

and I found one that I co-authored with Bill Hayward and [inaudible] 16 years ago and I see [inaudible] is in the audience. This was probably 16 years ago.

What he said is that most of what we say in the paper is still relevant today. At the end of the paper, we tried to make a case to move more expeditiously to larger scale efficacy trials because, we argued, these trials offered unique opportunities to establish efficacy of different vaccine concepts, to validate animal models, to obtain information on immune-correlated protection— I'm quoting from the paper— "to explore the significance of viral genetic variability in relation to vaccine-induced protection, to evaluate different endpoints for vaccine efficacy and to generate additional date on vaccine safety."

In summary, I believe that today we are closer than ever to having an effective vaccine that can be used in public health programs to stop the AIDS pandemic. But that will require that existing and new science is efficiently harnessed to develop novel products that are rapidly introduced in human clinical trials. And I thank you very much for your attention. [Applause]

MITCHELL WARREN: Thanks so much, Jose. It was fantastic overview and really I think a excellent but somewhat sobering last slide in terms of all that's left to be done and how history sometimes moves slower than we would like. With

that in mind, we're going to move straight to our first panel discussion to really pick up on where Jose ended the presentation. So I'm going to call the panelists up, Robin Shattock, Linda-Gail Bekker, Seth Berkley and Merlin Robb and as you take your seats there what we'd like to do for the next 30 minutes or so is to really build on what Jose described and really talk about some of the ways forward for accelerating the search for an AIDS vaccine. And a lot of the conversation around how do we prevent a presentation in AIDS 2014 or 2016 at the conference from concluding with the same slide and to really try to figure out how we, we take things forward.

This panel then is going to focus very much on what needs to be done in the coming years. Our second panel is going to look at a lot of the issues about how we might go about doing that. But we'd like to start with– I'm going to ask each of the panelists to just very briefly, in two or three minutes, give their perspective on what are some of the priorities that need to be done. Again, if you have questions that you want to ask, I'm going to open up the floor later on for that but also if you have cards or pieces of paper you can pass them to the outside and we'll collect them.

We have an incredible panel with different perspectives here. Robin Shattock is based in London and has been a leading researcher both in vaccines but in the larger HIV prevention world and looking at a range of issues at a basic science

level. Merlin Robb is at the U.S. Military HIV Research program. They were the implementers of RV144 and has been running their clinical trial operations. Linda-Gail Bekker, fondly known to all, or most, at least, as LGB is based in Cape town at the Desmond Tutu Foundation at the University of Cape town and has been a clinical trialist and leader of efforts in Cape town and in South Africa not only involved in the Phambili trial but in, again, a range of HIV prevention trials. And Seth Berkeley needs no introduction to this audience as the president and CEO of the International AIDS Vaccine Initiative and a dear friend and a former boss.

So, I'm going to, I think, start with Robin then and if each of you just want to take a couple of minutes to describe some of your thoughts on the priorities, I don't want to have to be interrupting, so two to three minutes each and then we'll take some questions.

ROBIN SHATTOCK: Thank you, Mitchell. I was hoping I was going to be the last person on the panel to speak because then I could just agree with the others. I think Jose really put a very good summary in terms of the priorities for HIV vaccine research and I think there has definitely been a shift in the last perhaps two years to really focusing on trying to develop vaccines that can focus an immune response at the mucosal surface. And this really links into two things. One, that we know in 80-percent of individuals a single virus is

transmitted. That means in terms of the potential challenge it may be that there's a relatively small balance between infection and immunity.

And the other aspect is the RV144 trial which has given this first glimmer of hope that there may be potential for protection with a vaccine delivered with a non-neutralizing antibody. So, I think that we need to focus more effort on generating both systemic and mucosal responses and it's interesting that in all the clinical trials to date there has been very little mucosal immunology so we do not know where the vaccine's successes or failures relate to whether there were appropriate mucosal responses.

The other aspect is that we need to generate new adjuvants, new vectors, new immunization approaches to get the immune response to the right place at the right time. That may be critically important for mucosal responses which by and large are short in duration and so we do not necessarily have the technology to maintain mucosal responses at a sufficiently high effect of concentration to block immunity without relying on a recall antigen response. And a memory response may be too slow for protection.

There will be lots of talk about the interesting new Broadly neutralizing antibodies and they open up a real hope for identification of novel immunogens. But one thing we've also noticed from the elite controls from which these

antibodies have been derived, they are only induced after many years post in the infection event. If this actually equates to requiring a particular type of antibody maturation, again we need to come up with practical vaccine approaches that can mimic that maturation process without the requirement for multiple injections or immunizations over a prolonged period.

And then, finally, something that I think the vaccine community needs to engage with, needs to engage with very actively and is something which the Europrise network which I'm associated with is focused on, that is how do vaccines fit with a wider prevention portfolio. If we have a partially effective vaccine that can be delivered, how can that be tested at an arena where there may be effective microbicides or pre-exposure prophylaxis and is there potential synergy between a partially effective vaccine and other prevention technologies that mean that we can start to have an end-road, a significant end-road, on the number of new infections quicker than we can develop a fully protective vaccine. And I will leave it there, thank you.

MITCHELL WARREN: Great, thanks Robin. That's great. [Applause.] And you got a big applause from the other room when you said Europrise which is great. Merlin?

MERLIN ROBB: Thank you. I'd like to thank the organizers the opportunity on behalf of the Thai collaborative team that conducted RV144 to be represented in this impressive

panel and I'll focus on our perspectives on the meaning of the trial very briefly and what we're doing to follow up on the study. Beyond the hook that this signal event that protection can be afforded by a vaccine provides to all of us, in terms of vaccine research and development and Robin just touched on this, the observation that this vaccine had in effect in the absence of neutralizing antibody against primary isolates as well as in the absence of robust CD8 mediated T-cell immunity informs us that there are other immunofactors that may be able to afford protective effects and broadens the possibilities for what vaccines might perform in the future based on novel designs.

This isn't to say that those responses are not important. If we can achieve a primary neutralizing antibody or we can broaden the magnitude and breadth of T-cell mediated immunity, those would undoubtedly add to the efficacy that we've observed. So, what are we doing to follow up on 144?

First and foremost, we are actively engaged both internally with our scientific team in Thailand and the United States in evaluating the samples from RV144 to identify a correlate of immunity. Further, we've engaged some of the best and brightest minds in the HIV vaccine research world, over 30 investigators internationally, including Robin and his colleagues, to evaluate samples that are available from RV144 in the search for a correlate.

Second, we are actively planning and hope to start the first of these studies in the spring, follow-up studies in Thailand using the RV144 regimen with extended boosting first in individuals who received the vaccine in the original study to look at the responses and in terms of very late boosting five and a half years after their last vaccine and in a new low-risk population to, in both case, define for the first time the mucosal immunity associated with this vaccine product as well as use state-of-the-art assays to better define the immune profile of this successful regimen.

Beyond that, we're engaged in stakeholders in Thailand and elsewhere in southeast Asia. As you know, the RV144 population was very low incidence; a magnitude 10 less incidence than in other vaccine efficacy trials conducted heretofore that might be important and critically any effective vaccine is going to have to be effective in much higher-risk populations and so we are seeking partnerships and developing plans to do such a study predominantly in MSM but in other high-risk populations potentially as well in Thailand. So this is our look to the future and I look forward to your questions.

MITCHELL WARREN: LGB.

LINDA-GAIL BEKKER: Well, thank you Mitch and thank you also to the organizers. I represent, I guess, the continent hardest hit by HIV. I come from Africa and particularly southern Africa and I also bring, I hope, to this panel, the

sort of impression looking to the future from a clinical trialist's point of view on the ground where HIV is still very much, you know, part of our daily lives.

And so I thought, and this is the challenge in fact, Robin, is that by the time you're getting to this end of the panel, you're looking for something you can add to what has already been said and so I thought I would pick up on the how will we do the clinical trials going forward and there is no doubt that I believe that the need to put whatever the scientists deem useful into human studies is a very useful exercise. I think what we have learned in the last three or four years is the enormous wealth of information that we can gain from human studies even when they're considered flat or of no efficacious benefit.

The enormous amount of information that comes from human studies makes them absolutely imperative. But there is no doubt also that the last three to four years has set the safety bar much higher. So, the job has really just got a lot harder. My answer to that is well, that just means we have to get a lot smarter about how we do this. It should not be something that stops us doing what has to be done.

Robin has hinted that we are also in a very exciting phase at the moment where we're going to see the outcomes of some other prevention modality trials that are in the field at the moment. So what will prick microbicides, increase

treatment do in terms of our ability to run good vaccine studies in the future. And my answer to that is again we have to just get smarter about how we do it. And I would agree that we have to, I like the Europrise's sort of concept, we have to get out of our silos as prevention experts and start to put all of the prevention modalities into the room, as it were, to discuss how trials could be designed that will answer a number of questions going forward.

I would also be a strong protagonist at the moment for the need for a very multi-faceted team when protocols are designed. There is no doubt we need behaviorists on the team. We need social scientists on the team. We need to really understand how we estimate incidents before we go into clinical trials. Maybe the modelers can help us to understand what the impact if we also believe, which I think is a principle that cannot be undermined, the principle that the highest standard of prevention needs to be offered to a clinical trial participant. Then it means we need modelers in the room to help us understand what the impact on incidence may be going forward and then we need to design these studies so that we can still answer the questions in the most effective way.

Other challenges we meet at the moment is that communities are kind of tired to a certain extent of hearing, you know, we're going at it again and I think some of our social marketing around the prevention field needs to be

revitalized. We need to get that excitement. When I sit here today I'm really excited that on Tuesday we'll be hearing about a new prevention modality. We need to transmit that to our communities, that they see that there are incremental steps, in the vaccine field there have been marvelous incremental steps.

The Thai study was that glimpse that Mitchell talks about at the end of the tunnel. We need to transmit that to our community so that they catch the excitement. Mitch's other famous saying is you know, the vaccine field is not for anybody who requires certainty and I guess that's the whole of the prevention field to a certain extent. But we need to bring a certain amount of assurance to our communities that we've got the situation in hand. There is uncertainty but we're moving forward in incremental steps.

The other piece that is around this that I feel compelled to say: I live in a country where 5 million people are infected. I mean, that's an awesome amount. We've got 120,000 people on treatment. Yet we know that as universal access to treatment is the theme of this conference, 5.5 million people in low-end income countries are not accessing treatment. For every five people, however, that we put, every two people that we put onto treatment, five get infected. So we've got to moderate somehow, and again that comes around social marketing to our policy-makers of how, and to the funders, how do we balance this?

On the one hand, we've got to carry on getting treatment out there but it's something that is bigger and almost an impossible task. It means we are also looking to turn the tap off on incidents. And so what's happening in the vaccine field, in the prep field, in the microbicide and in other circumcision et cetera. needs to also be moving with as much emphasis and force in order to make sure that the finances do not flat line as we go forward. So that really is from the heart and from southern Africa. Thank you.

MITCHELL WARREN: Thank you so much. [Applause] The view from New York, Seth. [Laughter]

SETH BERKLEY: I hope more than New York.

MITCHELL WARREN: And the world.

SETH BERKLEY: I just want to pick up where Jose left off and say from our prospective it is a really exciting time. As Merlin had said, we have to build on the RV144. We believe that certainly one is going to need neutralizing antibody and cell mediator responses.

Before I talk, which I was asked to talk about where we are in neutralizing antibodies; I just want to say that on the CMI side there are six products at least in the pest to the animal models that look better than the Merck Ad5 did. Those are moving into humans now. Some of these approaches have greater than 50-percent control of infection in the animal

model. We are going to see a lot more and improved products and I think that is going to be exciting.

In the antibody field, we have had kind of a burst of energy going on recently. Obviously, at the end if we can figure out that non-neutralizing antibodies work, that will be a great thing. It sets the bar lower. We still think that neutralizing antibodies would be better than non-neutralizing antibodies.

What we have found now is, as people had seen neutralizing antibodies before in human. They were rather unusual structures. They weren't incredibly potent. Some of them were pretty broad.

Over the last period of time, there has been a real renaissance in looking at these antibodies. First a discovery of PG9 and PG16. Why are these special, extremely potent, and a new epitope on the surface of the virus, which seems more accessible. That really helps us in terms of thinking about moving forward.

What is also interesting is PG16 primarily looks at the native trimer. We are beginning to get glimpses into the structure of what we would like to have for natural immunity. You heard last week that the vaccine research center published new potent antibodies on CD4. We had CD4 antibodies before that protected around 30-percent of strains. This was a much more potent and broad antibody. In fact, there are more

antibodies to the CD4 that are going to be discussed in the near future.

In a sense, it is going to be a very exciting time. I can tell you that there are more than a dozen more neutralizing antibodies that are in the process of discovery. In those, there are some new targets as well. We do not know exactly how many, we do not know exactly the sites. What we are going to have is gone from very poor targets to now a whole series of exciting new targets.

Of course, the challenge in all of this is to turn these into immunogens. In that area, there is a lot of excitement going on now.

The first one would be with these new antibodies can we understand the native configuration of trimer. What we know is that the previous immunogens we have used have not been like native trimer. Recently more and more data has been coming out on what the differences are and how we might improve upon that. We still do not know what the structure is. If we did, it would be very helpful.

We can use these new antibodies as tools to look at potential immunogens. We can ask the question, if you have 100 immunogens then they bind better to the neutralizing antibodies than others. That suggests that they may be closer to native configuration. We can use these as tools to help us when we are looking at empiric antigens.

You have heard already about the concept of reverse vaccinology. We are quite excited about that. Just to say that of course in the drug sector people do this all of the time. They have a receptor and they go backwards and make drugs from it. For the first time the Merck Corporation has successfully done some reverse vaccinology. They have taken an antibody D5 to the prehairpin region. They have been able to turn that into an immunogen and produce antibodies that work. It is not a particularly potent set of antibodies, but the proof of concept is there. There is other work we know about that is also showing proof of concept. I think it is exciting.

At the end, what we have though is an opportunity. If you put for example the VRC antibody together with PG16, it neutralizes more than 99-percent of the strain. We could think now about doing passive immunity as a way to move forward. This of course would not be a public health approach. We also can think about gene transfer as taking the genes, putting those into people, having people make those antibodies. That is likely to provide protection.

Both of these approaches are being discussed now. Of course, at the end of the day though, the goal as Jose laid out in his talk is for us to have a vaccine that is going to be available to everybody. That is going to require creating immunogens that will produce perhaps not these exact

antibodies, but antibodies with this level of potency. A very exciting time from our point of view.

MITCHELL WARREN: Great. Thanks very much Seth. [Applause] It is clear from all four that there is an enthusiasm in this field that is quite palpable I think depending on where one goes and where the conversations are.

I want to ask, and I guess all four are welcome to respond. One of Jose's points in one of his slides, and it has come up a great deal in the last couple of years is how few things have made it into efficacy trials, three products basically tested, and this desire to test more. Linda-Gail, you described quite rightly how important human clinical trials are.

I guess I would love to hear what each of you think is what might the next couple of years look like in terms of what does come next. Merlin, you described follow onto RV144, but above and beyond understanding that vaccine combination, put you speculative hats on. Over the next couple of years, what else might get into a later stage efficacy trial and how do we decide what to take into a later stage efficacy trial. Anyone want to start with that?

MERLIN ROBB: I would be glad to. I am sure Seth has many thoughts on this as well. We view the field as perhaps collectively and certainly MHRP viewing the vaccine development as a two-pronged approach. A regional approach of which RV144

and some of the efficacy trials planned in the next few years will use vaccines with inserts representing the single clade in monophyletic epidemics so that variable of genetic variability is minimized.

For many years, in fact for decades, our program has emphasized development of vaccines that can be tested globally and then would move more rapidly into if they are successful into a global public health domain.

I think Seth was referring some of these vaccine constructs that use mosaic inserts, multiclade inserts or consensus inserts that then might be tested in sites that have multiple circulating strains, lots of recombinant. At the end of the day, such vaccines are going to be critical as we move forward to control the epidemic.

If we are lucky enough to find a correlate, which is a difficult task in general, the statistically robust definition of a correlate is actually only been defined to my knowledge in the case of influenza in a paper by Quinidol just a few years ago. That disease, that vaccine was for influenza. They used data from the 50s.

Vaccinology is driven by the notion of correlates, which are perhaps not always statistically robust, but never the less meaningful. We certainly hope out of 144 that we might or in other studies might achieve that. That is a game

changer. That would guide the rational development of vaccines for all of us.

The timing though of these next generation global vaccines relative to those that are either going to be repeated in monophyletic, relatively monophyletic epidemics in Thailand or in South Africa for example is an issue. We also believe very much with Jose's concept that the way forward is going to be best described by the number of efficacy trials we are able to mount and launch of rational concepts.

How do we distinguish these? Although this is not very satisfying in terms of precision, notionally we would group concepts and if a concept is a variant, a nuanced variant of one that is already in an efficacy trial, it should not probably go forward.

What we are interested in is looking at disparate concepts that distinguish mechanisms of efficacy. Even in the absence of correlates, will provide us some sort of guide as to what is potentially useful. If we develop something that is highly efficacious, then critical.

MITCHELL WARREN: Great. Seth?

SETH BERKLEY: Let me just add where Merlin left off and say first of all that we have to be smarter about our clinical trials. We need to do them faster. We need to do smaller numbers if we can. We need to move towards adaptive trials.

The reason is that we started off at the beginning of this with efficacy trials where the goal was to try to have a trial that would not only produce efficacy but ultimately, the traditional phase three. We need to see a lot of our clinical work now as part of the discovery, development continuum and move things in to get a signal. If they have a signal then to extend the size of those trials. Working through exactly what that looks like is going to be really important. As we heard, we often get surprises from clinical trials.

With that said, I agree completely with Merlin and I would add one other point which is we do not have a validated animal model. That would help. Even if we did not have a correlate, if we had an animal model we really knew was right, I think we are better on our animal models. They should not be gateways.

Obviously, if you have something that looks really promising in the animal model, you are going to be more excited about that then something that doesn't, although again until it is validated we do not know what that means.

Lastly, I just want to mention that of course there is one other vaccine in efficacy trials that was not discussed so far and that is the DNA Ad5 that is moving forward. It has been a little slow in recruitment. That recruitment has picked up and so we will have an answer from that.

My hope is that one of these new vaccines that look better in the animal models will be in trial about the same time that the follow up trials will be going on for RV144. That is obviously going to depend on how things go.

MITCHELL WARREN: Great. Robin, did you want to–?

ROBIN SHATTOCK: I just wanted to add one extra quick thing to that which is really, we also need to move away from this paradigm of going from small animals to primates to humans. It has not been predicted. I am a great believer in the primate model could be informative. I think it should be done in parallel with human studies.

Even at the stage before efficacy trials, there is a very great need to do many more human immunology studies. Phase one studies, understanding more about human biology, mucosal responses, many more adjuvants and approaches and the type of sort of grunt work which is not necessarily high profile science, but it is critical to product development.

MITCHELL WARREN: That is great.

LINDA-GAIL BEKKER: Maybe just one other word and that is I would fully endorse that. Then also, sort of added research around what are the predictors in these human studies that were really informed of the clinical trials. Endorse what Seth said. I think this notion of the gold standard randomized control trial in our efficacy studies.

I really think it is very exciting that we are bringing trial design experts into the room, epidemiologists to say that maybe isn't that usual placebo versus setting out and getting an answer with an efficacious end point at the end. Maybe that is not the way to do it in the future. We have to get a lot smarter about it.

MITCHELL WARREN: Great. I realized I cannot really see much out there. If people have questions, we do want them. Jennifer, are there cards and pieces of paper being passed around? If you have questions, also, there is a microphone on the side there I see and maybe one over there. If people do want to go up to either one of those two microphones, we will happily take questions.

While we are waiting for people to come, I do want to – Both Robin and Linda-Gail, you both provocatively talked about combination prevention. I wonder if one of you might want to pick up on that. What does that look like? Again, give me the next two to three years. Are you talking about a prep vaccine prime boost as opposed to a DNA Ad5 prime boost? What might that look like?

ROBIN SHATTOCK: So on an experimental level, there are many ways how the different technologies could fit together. On a practical level, if one of those other prevention technologies are shown to be efficacious before we have vaccines in the field, then it is likely that vaccine

candidates will be trialed in an environment where either prep or microbicides are being used.

From an experimental point of view, microbicides and prep could definitely reduce the challenges that a vaccine has to respond to. It could make it more easy for a vaccine to be efficacious, particularly if it is not fully protective in its own right. If developing a vaccine-based immunity requires some sort of mucosal activation, it may be important to have prep or microbicide that can reduce the chances of increased susceptibility during an immunization regime.

Then finally, if you look at it from the other side. If you look at new prevention technologies, prep and microbicide were the biggest hurdle would probably be compliance. If there is patchy compliance or intermittent use in the background of a partially effective vaccine, it may be that the vaccine can bridge perhaps a less than optimal use of a microbicide.

The final issue, which really has not been explored is if you are vaccinated and you don't have a broad response or a response to a virus in a geographic region. It may be that protected exposure may actually allow your immune system with a vaccine on place to see a virus and broaden the immune response to be more effective against a predominant virus in a local region or in your local parts.

MITCHELL WARREN: That is great. Linda, are you going to join in here?

LINDA-GAIL BEKKER: I think that says it beautifully. I also just want to put in that I think the prevention of the future is a combination. It is a method mix. So we either design the studies now taking that into consideration from the get go.

The sort of passive approach is as Robin says where we design the vaccine studies anywhere, but we at least collect authentic data about what people are using in addition so that can be added into the analysis at the end which clearly again means the study needs to be designed carefully taking that into consideration.

But I say to the former, where we from the get go say whatever comes, until we get the smallpox equivalent of our magic bullet vaccine it is going to be a combo. Let's take that head-on and design the studies appropriately.

MITCHELL WARREN: That is great. Just so everyone is aware, just a bit of a plug for a session this afternoon in this very same room at 3:45 looking at antiretroviral-based prevention. Both what it might mean if those trials shall benefit, but also I think some of the conversations picking up on this are going to be really important.

I think there is a question there. If you want to introduce yourself and also, if we can keep the questions kind of brief so we can get as many in as possible.

MICHAEL MUNYWOKI: Thank you very much. My name is Michael. I am the HIV/AIDS Policy Adviser for the UN Mission in Sudan. Thank you for the good presentation and for the good job you are doing.

I would wish to hear much more when it comes to the generic preventative vaccine development, focusing on the different clades or the strains of HIV. When it comes to generic vaccine development, what kind of generalities are we looking for linked to this one?

MITCHELL WARREN: That's great.

MICHAEL: Thank you.

MITCHELL WARREN: Thanks very much. Seth, do you want to talk a little bit about that?

SETH BERKLEY: I didn't quite hear it– [Interposing]

MITCHELL WARREN: If I can, I believe the question was looking at the diversity of HIV clades and subtypes, was that correct and how vaccinology might have to deal with that?

MICHAEL: Exactly. How the clades would impact on the progress of development of the vaccine.

SETH BERKLEY: So first, of all one of the interesting things, of course, is clades are defined genetically and not phenotypically. What do I mean by that is what we are really

interested in is how they present and what type of immunity is required for the different ones. What is changed over the last decade, and Jose put this, I think, as point number one is that in the past there was a lot of push to look just at the clades, the circulating viruses in the West. N

Now I think, as far as I know almost no studies looks just at the west. They may decide to choose the clade, but they are always thinking about the different circulating viruses. We have in both our trials, our clinical trials that are being trialed look at this, but also in the antibody work that is going on now. For the first time we are collecting samples from around the world and getting neutralizing antibodies from Africa, from Asia, from the west and so we can understand about getting broad based protection.

The critical thing I think that has also changed in the last 15 years is a recognition that no longer can we talk about a region or a location. People move, viruses move, and we really have to have a global response. It may be that we can look at local immunity but at the end, we have to have broad based immunity.

Even in the west, a lot of the new infections that are occurring are occurring from types of virus that are not from those areas because of immigration, because of people travel and bring it back etc. I think it has really changed.

MITCHELL WARREN: I think there is a question at the microphone back there.

PROFESSOR HEISIME: Thank you very much for enlightening us and bringing us up to date. I am Professor Heisime [misspelled?], member of the Scioto Parliament Sodaveria[misspelled?]. There are two points I would like you to comment on about. This was not part of the discussion is the ethical aspects of the clinical trials. Obviously different, the component of [inaudible] varies from one country or from one region to the other.

Also, the ethnic variation. Obviously the enterprise has to be a global sort of collaborative efforts; otherwise it definitely will be limited to certain regions.

These two points, the ethical aspects and the degree of globalization of the effort of the enterprise. I would like to hear from you about that. Thank you.

MITCHELL WARREN: Great. Thank you. Linda-Gail, did you want to respond on the ethics part of this?

LINDA-GAIL BEKKER: I am happy to pick up on the ethics piece. Obviously, particularly in this era, we now consider human clinical trials with what we consider the highest ethical standards. Every single one of our clinical trials, products are only put in the field if they are considered that there isn't some safety issue related. That clearly is based on what we know at the time.

Knowing everything we know in animal studies, in primate studies a product is carefully done phase ones where participants are very carefully scrutinized throughout the study. Safety is gathered in phase twos where smaller numbers. By the time you get to phase three, as far as we know, a lot of the safety issues have already been put out of the door.

The STEP study clearly puts some anxiety in the field around the notion of this increased susceptibility to HIV. It only came apparent in the phase 3 or 2B phase when people were at risk for sera converting to HIV.

That is perhaps the unpredictability of the field that is always out there. What I think it has taught us is that the safety bar has to be really high. I think clinical trials of the future will even in the 2Bs will require lots of safety looks, DSMBs that are safety monitoring boards that are looking as the study rolls out to make sure that our participants are not being put at any kind of risk.

I think the ethics has to be paramount. It has to be foremost in our thinking. We need to design the studies around those kinds of ethical safeguards.

MITCHELL WARREN: Great. Seth, did you want to add something?

SETH BERKLEY: I just want to add two quick points on the global nature. Again, that has changed a lot. Vaccine trials now have been done in 25-odd countries. That is very

different from where it was a decade ago. That is important not only to get diversity of genetics, looking at different viruses, different people but also prepare communities for understanding how these vaccines work and ultimately for access and to use the best science that exists around the world.

On the ethics issue I agree completely with what Linda-Gail said. I think one of the things that are also important though is the increase in capacity of regulatory agencies in the developing world. That is important because of course ethics stay the same everywhere in the world. The risk benefit ratio varies by the magnitude of the problem and available interventions. We have to be able to have that conversation.

One might want a vaccine that was a hotter vaccine, but was more efficacious in a place that has a very high incident you might want a vaccine that is a little less hot that requires many more doses. For example, in a place that has a very low incidence. Those discussions can only be done by having local groups engage in that risk benefit discussion. It is a very important part of what we need to do.

MITCHELL WARREN: Great. Well, thank you.

We are going to be moving on in just a minute because we still have many other exciting things to come. I do want to conclude with each of you. There is a sense, an amazing sense of enthusiasm coming from all of you. The list of things to do gets longer and longer. Our resources are constrained. We

have seen relative flat funding, even declines in the past this year flat funding for aids vaccine research. New trials, new products, new adjuvants, translating neutralizing antibody discoveries into vaccine concepts, doing it all over the world, building a clinical trial capacity. How are we going to do it all?

In about 30 seconds or so each, I would love to get a quick snapshot. What is the top priority or priorities and what are some things that you may want to do differently either not doing because we do not have the resources nor doing things in a different more efficient way? Maybe we will start the other direction. Seth, I am having you start and we will work down to Robin.

SETH BERKLEY: Well, the interesting thing, and Mitchell certainly know that is that the look at the funding for this year is relatively flat. That is good news. The reason it is relatively flat is that Obama had a stimulus push that kicked it up. In fact, we have seen a decline again.

We have seen particularly a decline in Europe. We have seen a decline along the pharmaceutical manufacturers and I think the challenge is that we need to expand the groups that engage in this. That is going to be very important going forward. As we have heard from Peter at the beginning, even if we use all of our existing interventions as best as possible, we are still going to have a gap. We need better tools and

better tools have been a relative orphan compared to what we have spent on existing interventions.

We have to be smarter. We have to be better. I think we do need more resources.

MITCHELL WARREN: Linda-Gail?

LINDA-GAIL BEKKER: Yes, I mean aside from the more resources which I think is inevitable I think about being consensus of the cost while we sort out the next steps.

It is something again in countries where I come from, we are not always good about sorting out our priorities. I think in this field, in the prevention field as a whole, we really do need to have a very serious talk about priorities and try to reach consensus around priorities and not necessarily go for the gold standard. Perhaps with some compromises which will get us as close to the answer as we can in a more cost conscious way.

MITCHELL WARREN: Great. Merlin?

MERLIN ROBB: Well, I think that Seth had articulated this. We need to get more out of the studies that we have done. We did not collect mucosal samples in RV144. In fact, we did not collect a whole lot of blood from Corlet's [misspelled?] research because there was a strong scientific consensus that the product was not going to work. So, I think that in general we also have to plan for success. We need to look at the current VTN study and begin to think now of how it

is going to impact on the field if it's successful. It's a very different vaccine then 144.

We need to put in place to the extent that we can afford to do so, some of the materials that we will need to exploit that kind of success. Adaptive designs and designs of trials that maximize our opportunity to discover correlates and our interleaved with nonhuman primate studies are very important as well so that we get the maximum scientific insight for the next generation of vaccines with every human trial we mount. They are going to be expensive and difficult.

MITCHELL WARREN: Robin.

ROBIN SHATTOCK: So from a European perspective I think we need to see more funding, new funding particularly from national governments. It would be nice to see more philanthropic donations in the European Union rather than funding of football clubs. [Laughter] We need to see –

MITCHELL WARREN: Although they did win the World Cup. [Laughter]

ROBIN SHATTOCK: We need to see some more sustainability of the European efforts and continuity there.

On a global basis, I think we need to see more collaboration. There have been some very good examples of the ways to do big science. I think people are working more collaborative fashions. There needs to be the right balance between that type of big science and small science. I think

critically we need to look to enhancing the promotion of young people, young training and vaccine science across the world.

Finally, really I think we need as we plan the clinical trials also to start discussing the single vaccine approach may not work for all modes of transmission. It may be that a vaccine to prevent women may look very different from a vaccine to prevent men and three different routes of transmission.

MITCHELL WARREN: Great. Well thank you all so much. [Applause] We are going to come back to many of these issues in the second panel with new panelists as well as this is the perfect segway into the next presentation.

What you heard Seth, Linda-Gail, Merlin and Robin describe all relate very much to how the world gets on and does what it does, needs to do in the search for an aids vaccine.

We are going to now have a presentation on the development of a road map really for the way forward. Much of this work is done under the umbrella of the Global HIV vaccine Enterprise that was first conceived in 2003, was established in 2004, and has had as its executive director for the last almost two years. Now Alan Bernstein who hails from I was going to say the great state of Canada, I meant the great country of Canada, sovereign country of Canada and now based in New York running the Global HIV vaccine Enterprise. So over to you, Alan.

ALAN BERNSTEIN: Thank you very much, Mitchell. It's really my great pleasure to thank all of you, for attending, I think, this very important and very timely discussion. I think we've had a very early interesting discussion already this morning, about the search for a safe and effective HIV vaccine. I think the word obstacle was used several times already today. This field has been fraught with very many scientific as well as organizational challenges.

However, the past five years, especially the last 18 months, has been the richest period of HIV vaccine research since the epidemic began, marked by three very important advances.

In HIV vaccine research itself, and other areas of scientific research with important implications, for HIV vaccine development, and in the field-wide collaboration catalyzed by the global HIV vaccine enterprise.

Together, these advances herald exciting beginnings of a new chapter in HIV vaccine research that is bringing us closer to the development of a safe and effective vaccine. Our challenge now is to build on those advances as quickly and as effectively as possible.

This is a new chapter in HIV vaccine research. I think a vaccine is within our sights. But, reaching that goal will need the commitment and it will need the resources, it will

need great science and it will need the collective vision of the enterprise.

To transform HIV vaccine research efforts we must focus on four areas. First, we need to do a better job of unifying basic, preclinical and clinical research, into a single research agenda. Second, we need to develop a global data infrastructure and culture that will enable rapid data sharing. Third, we must expand our efforts to attract new minds and new ideas. Forth, it's absolutely critical that we broaden funding sources, and increase funding levels, while at the same time ensure that we're using existing resources, maximally, efficiently and effectively.

The issues I'm going to talk about today and it will cover a lot of what we've already heard in one package, all of these will fall into these four categories.

Transforming the global research effort is not going to be easy, many challenges lay ahead. Let's just take a look at some of those challenges. And let's not forget, while I've listed these as challenges or as obstacles as you've heard, I think they are also great opportunities.

So, first, we have to transform our view of clinical trials. We need more trials, and we need to view clinical trials, especially clinical efficacy trials, as an integral part of the discovery process, not as the culmination of discovery. One great lesson that we've already learned from

RV144, the time trial, is how important and how influential clinical efficacy trials are in driving the research agenda.

Second, data. Data is fundamental, should say data are fundamental, to biomedical research. Our current approach to data does not take full advantage of the powerful Internet and communications and computational technologies. Nor do we have in place the agreements neither to allow for the rapid sharing of data across the entire global research community. To succeed we need to assure we can analyze fully and rapidly the huge amounts of data that is likely to be generated over the next few years.

Young people. Young people and investigators from other fields find it challenging to enter and to succeed in this field. However, a robust HIV vaccine research enterprise depends critically on our ability to attract and to nurture, and to retain talented new investigators, especially from the developing world. We need to pay special attention to this issue.

Fourth, to move forward with the greatest speed and impact, especially at this moment in time, we must both maintain and expand current levels of commitment from existing donors, and funding institutions, while attracting new funders to the endeavor, and continue to look for ways to use existing funds more efficiently.

Current funding primarily comes from a very, very limited number of donors. Many countries with significant human, scientific and financial resources could more effectively and actively support HIV vaccine research.

As Jose Esparza said in his remarks at this symposium already, we have been too slow and too conservative in our approach to clinical efficacy trials. How do we ensure that prevention trials that we do are as smart and as rapid as they possibly can be. That we're not simply testing, for example, vaccine candidates that are no longer showing promise. How do we best take advantage of rapid advances in other areas of biomedical research?

The advances that we've just heard about and the panel discussion and many, many more hold great promise, for driving the future design and testing, of novel HIV vaccine concepts.

How do we develop a sustainable, clinical trials agenda especially in those countries where the incidents of HIV Aids is the highest? We need to maximize and make the most efficient use of clinical trials sites.

Seventh. HIV vaccine trials will not and cannot succeed without significant community engagements. I think I learned that from Linda-Gail. This will be an increasing challenge as we initiate more and more complex trials. We must build on existing community engagement efforts and reaffirm our

commitment to the centrality of communities that are involved in both local and national and international research efforts.

As both Robin Shattock and Linda-Gail said in their comments in the panel, vaccine development is only one component of a much broader HIV prevention landscape. The results of other prevention trials, some of which we'll be hearing at this meeting, will undoubtedly impact on the future of HIV vaccine research. So we must continue to explore how vaccine research best fits into this changing landscape of prevention.

Ninth. Nonhuman primate research holds an extraordinary promise for the field; but its contributions to advancing HIV vaccine development have not yet been fully realized. To move forward it's critical that we encourage researchers in that field to focus, and to collaborate on those key areas, where nonhuman primate research will have the greatest impact.

Finally, we will not develop a vaccine without industry involvement. And yet the pharmaceutical and biotechnology industries find it hard to justify the long term, risky investments in HIV vaccine research. If we are going to develop a vaccine, we need to enter into discussions with industry and together develop a strategy, a strategic approach and long-term approach to partnership.

Here at this meeting the enterprise is releasing a new overview of the top ten challenges and opportunities facing the field of HIV vaccine research. The road to prevention, contains clear recommendations, to accelerate HIV vaccine research, and identifies opportunities to make the field more dynamic, more collaborative and more efficient, moving forward.

It is being released in advance of the launch of the scientific, strategic plan of the global HIV vaccine enterprise. A plan of the enterprise council, and a consultative effort involving more than 400 researchers world-wide. The plan will be released at Aids Vaccine 2010 Conference, in Atlanta, Georgia, in September.

I encourage you to read the "*Road to Prevention.*" The strategic approaches outlined in this document provide the key framework, to help guide the priorities and activities for HIV vaccine research and funders moving forward.

Let me tell you a little bit about what the enterprise is doing, to address the major challenges in the field. We gathered more than 100 scientists from every field of HIV vaccine research, and from nearly every part of the world, to address the challenges and opportunities in HIV vaccine research over the next five years, and to guide the future of the field.

The working groups that were formed were ask to address the following five topics. Immunogens and antigen processing,

post-genetics and the great challenge of HIV sequence diversity, novel approaches including systems biology, bridging the gaps, which in fundamental and preclinical and clinical research and finally young and early career investigators.

Let me share with you just three of their recommendations. First, clinical efficacy trials are the cornerstone of new approaches to vaccine design and development. Despite their fundamental importance, to HIV vaccine development, as you've already heard this morning, only three vaccine concepts, and four clinical efficacy trials in humans, have been completed in the 27 years since the virus was first identified.

The working group calls for an increase in the number of the clinical efficacy trials, to test the diversity of vaccine concepts. A unity of basic, preclinical and clinical research, and the formation of multidisciplinary clinical trials programs an agenda, to ensure that clinical efficacy trials are part of both of the discovery and product licensure process and that these trials fit into a broader HIV prevention landscape.

Second, we will see a marked increase in the amount of data produced by clinical trials and other areas of vaccine research over the next five years. It's critical therefore, that we develop new approaches that will enable the field to share and make this information globally accessible.

If analyzed properly and rapidly data can yield important insights into vaccine immunogenicity and efficacy. The working group of novel approaches calls for global data sharing agreements among investigators and the creation of a coordinated, integrated, harmonized quality controlled data bases.

And third, there's an urgent need to continue to fuel the engine of discovery and innovation needed to develop a successful HIV vaccine. We are not there yet. True innovation will be achieved most effectively if new investigators, both from other areas of science and young scientists are actively encouraged to both enter the field and are mentored ensure their success.

However, young and early career investigators face greater obstacles today then their advisors and mentors once encountered. The working group on young and early career investigators calls for a multifaceted initiative that stress mentorship, career development, the importance of strong host institutions and rapid data sharing.

The Enterprise 2010 scientific, strategic plan will present a shared vision and a new strategy to build on these recent advances we've heard this morning, and harness the current momentum and optimism in the field, to develop a vaccine as quickly as possible.

Originally developed in 2005, and now updated for 2010, the plan is not the plan for any single organization, but rather a statement by the Enterprise council, of their shared vision, of how best to move forward. It is a shared accountability, to collectively align independent strategies and activities, to address the critical roadblocks as well as the emerging opportunities and to maximize both global cooperation required in the quest for a safe and effective vaccine.

Throughout the talk I've been stressing the importance of collaboration. And recognizing this, two dozen leading scientists and funders in 2003, proposed the creation of a completely new type of scientific undertaking. A unique alliance of independent organizations committed to working together, to speed the development of a safe and effective vaccine.

Today, that bold vision is the Global Vaccine Enterprise. The Enterprise is comprised of over 30 stakeholder organizations worldwide, as shown on this map. [Map view]. The Enterprise brings together stakeholders, promotes collaboration, catalyzes fresh thinking, and supports new approaches to overcome the most pressing scientific and organizational challenges in HIV vaccine research and development.

The creation of the Enterprise and its emphasis on a shared scientific strategic plan represents an unprecedented response by the International scientific community, to the scientific public health and humanitarian challenges posed by HIV Aids.

Global participation is key, if the field is to secure the rich diversity of science, and the support that is so urgently and so greatly needed. We now have the opportunity to truly transform this field. To build on the progress of the last five years and to begin this new chapter of HIV vaccine research.

A strategic plan, however, is just a plan. It needs to be implemented. I believe that working together, and that includes all of us in the room, and everyone here at this conference. We can implement the plan and we will develop an HIV vaccine. Thank you very much. [Applause]

MITCHELL WARREN: Thank you, that's great. Thanks so much Alan. I'm now going to call up the second panel, to really pick up on exactly where Alan is leading us with the road map. So, Gabriella Reiner [misspelled?] Mark Thumbi. Oh, there's Thumbi. Great. Let me get back to here.

So, we're very much in the first panel, we looked at some of what needs to happen. This panel is going to begin to explore how we might make some of that happen; how we might transform some of the ideas we heard at the outset. Some of

the issues raised in the scientific plan and how do we make it come alive.

We have four very distinguished panelists and I'm going to do the same thing, asking each of them to briefly describe the view from where they sit, on this table looking out at you. And then we'll engage in some conversation.

We have Gabriella Calazans [misspelled?] from Brazil, who works in the HIV vaccine trial unit, in San Palo, Brazil, the HBTU, affiliated with the NIH funded HIV vaccine trial network.

Rainer Engelhardt is in the Public Health Agency of Canada, and is the Assistant Deputy Minister there.

Mark Fienberg is currently at Merck and has been the head of public policy in the vaccine program at Merck for a number of years. Before that was a researcher and himself in academia as well as previously at NIH at the office of Aids research. So he brings a multi-compartmental experience to the conversation.

Thumbi Ndung'u is based in the University of Quazi Enital [misspelled?] in Durbin [misspelled?] and leading scientist there and also was one of the co-chairs of the young and early career of investigator committee, of the enterprise that Alan describes.

So four different perspectives of how we indeed accelerate the search. I think, Thumbi, we want to start maybe

with you, for just a quick sense of where things are from where you sit. I think we're going to start in the middle.

THUMBI NDUNG'U: Thank you very much the organizers for the opportunity to participate in this important session. I thought that Jose Esparza gave a very good overview of the progress that has been made in HIV vaccine field since the 1980s and onto where we are currently. And as he presented some of the scientific challenges and how they've been addressed over the last decades, I thought that one of the most important differences that I could see that other than the science and the development in the science that has been achieved in the field is actually increased collaboration, in terms of bringing [inaudible] to address the complex issue of HIV vaccine development.

And I think it is true that in the last couple of years, with all the advances that we are seeing, one of things that aligns the advances we have seen over the last couple of years, or the last five or so years in the field is actually increased collaboration between researchers, academia industry and [inaudible] the communities I'm involved in and have a role and a stake in the development of an HIV vaccine.

Actually, just before the session, perused through some of the key publications that have come out in the HIV vaccine field, showing the development of novel antibodies that might have implications for HIV vaccine. And if one looks at these

publications one sees that actually the development of or the identification of these antibodies has come from collaboration people in the industry, people in the developing world, researchers in the developing world, actually contributing important regions have led to these regions. And these antibodies have been identified in the developed world countries.

And I think the same can be said of progress in terms of addressing the issue of why certain people are able to control the HIV virus, at least control it.

And again what one sees is the global collaboration of people; people in different areas. This also applies to looking at acute infections, looking at efficacy trials., the RV144, again, you see collaboration between industry, between government agencies, between people in the developed world, and in the developing world. And I think that that underlines the progress that we're seeing in the last couple of years. I think that ought to continue.

In terms of moving forward, to address the issues that Alan Bernstein presented, I think that innovation is going to be still very key. We don't have a vaccine, the science is not quite there to give us a safe, effective and affordable vaccine and I think that the innovation is going to be key.

How do you get to innovation? I think that as Alan very eloquently presented, there are very key advances in the

whole scientific field that you can take advantage of the vaccine field, and we'll need to take advantage of and we'll need funding from stakeholder funding, increased cooperation, from developing and developed countries. We need to attract new minds, and new ideas into the field and it think if one looks for example, of the innovative findings in the field, what one sees is actually a lack of involvement of the investigators, particular in developing countries. And I think that that needs to change as we move to the next phase of HIV vaccine field.

I was thinking actually of an issue of developing antibodies. I'm thinking that although the antibodies that have been recently discovered to be very effective, have been isolated or described from a developed country [inaudible] and while that is very good, I think one can imagine how much we could shorten that, and discover a process in this, could be done in developing country laboratories; with developing country, investigators involved at the fundamental of research in order to try to speed up the process of HIV vaccine research. And I think we need to involve [inaudible] orders. I'll stop there with my initial comments.

MITCHELL WARREN: That's great. Thank you. Mark?

MARK FIENBERG: It's a pleasure to be able to participate in this important discussion. I assume as a representative of a company that's been involved in HIV vaccine

research and development for over 20 years, I was invited to speak to the industry perspectives on that rather than engage on a broader discussion of some of the other issues. I'll focus my comments on that aspect and in particular I just wanted to quote a couple of statements that were made in the Road to Prevention documented by that Alan Bernstein just introduced to you, with respect to engagement of industry.

There are a couple of comments that are made in this document that I completely agree with. It says industry expertise is critical to quickly and effectively advance vaccine candidates to product licensure. Today we face a compelling public health imperative for industry and academia to explore new and innovative approaches of collaboration.

Subsequently makes a statement that the challenge for the field today on systematic, strategic approaches that maximize the scientific values of such partnerships, minimize the risk for industry and allow for more open, non-exclusive arrangements, especially for precompetitive areas of research and I completely agree with all the statements.

The a challenge I think for all of us is to not just have those be good sounding statements in a strategic plan, but really translate that into something concrete and meaningful that's going to drive progress. And a couple of thoughts about how that might happen early, some of the issues that need to be addressed.

First off, I think it's very important for people to be specific and realistic about the definition where industry engagement could provide the most value. It's not like you can ask companies individually, or companies collectively to engage across the entire spectrum because that's not where their contributions are going to be greatest. And if you ask non-specific questions, you're going to get non-specific commitments.

If you ask specific questions around things that are really key, then you can provide a rational for that. I think your chances of success in industry engagement are going to be a lot greater.

I think for industry a meaningful engagement in this area would be essential for the field overall to have a much better sense about priorities, both with respect to their research. Questions are as well are what are the potentially most promising candidates to develop because the field itself doesn't have priorities. It's a lot more difficult for any individual companies or companies more broadly to figure out how to engage.

I also think it's important for the field overall to have a better sense about the real nature of product development. Namely how vaccines are normally developed and the way the field has been approaching it is totally the opposite of the way vaccines are normally developed. The way

companies develop vaccines is they have a very good and specific articulation of the what products you want to develop are. What are the specific attributes of the product that you want to implement so they could have the greatest public health impact, and that's your starting point.

You go back to the early stages of development to have what we call an end 10 view, from early development to implementation, about how you get to the product you want and typically, the field is really sort of driving things, from the product end, without a clear idea of what you really want in the end.

Another important attribute of successful industry programs is companies are very willing, in fact they need to kill programs early that are less likely to be successful to be successful, and that hasn't really been the track record in HIV vaccine field.

So, if we're thinking about how to engage, I think are a number of potential ways. One I think, industry can provide advice either about specific technologies or the realities of product development to the field more broadly, and I think there are a number of or for that could be imagined of how to make that happen.

I think there are opportunities for companies to work together in this arena, I think that's probably the most realistic way for companies to think about doing that. And I

think, figuring out how to share and mitigate risk for companies in a realistic way is going to be important; but there are a number of new models out there, and I'll just mention one, because really, this is an area where we're talking about doing vaccine development for which the chances of getting a return on investment are very unlikely, at best. And, we faced a similar situation in that regard in terms of how Merck could contribute to developing vaccines for low income countries, where there is no commercial market for them; and we engaged in a very positive partnership with the Wellcome Trust. It's called the MSE Wellcome Trust Hilliam [misspelled?] and Laboratories.

And it's an external joint venture that is really focused specifically developing vaccines for diseases of the developing world. And there's no commercial return that's going to be coming out of that.

And I think similar, it's intended to be a platform for engagement of diverse [inaudible], including other companies, academic researchers and the like. And I think if one were to think about what kind of model akin to that or perhaps optimize for the HIV vaccine field, might be relevant for that. That would be a very good and concrete discussion we could have.

MITCHELL WARREN: Great. Thanks so much and we'll come back to a number of those points. Rainer, I think we have a microphone there.

RAINER ENGELHARDT: Thank you.

MITCHELL WARREN: Is it on? I'm not sure if that's on or not. Alright, great. [Interposing]

RAINER ENGELHARDT: So, it's my pleasure to be here. Thank you for the invitation, and we're representing the Government of Canada on this panel. And in particular the Canadian HIV vaccine initiatives that we're engaged in and have been engaged in for some time. That initiative is lead by the Public Health Agency of Canada, and the agency together with the Canadian institute for health research, we account for the majority of the HIV funding of Canada.

The vaccine initiative itself was engaged, was established several years ago now, to implement the partnership between the Government of Canada and Bill and Melinda Gates Foundation, and that is very closely aligned with the enterprise of scientific strategic plan, that Alan identified.

That vaccine initiative altogether is really a key component of Canada's comprehensive and long-term approach in that global fight against HIV Aids. And it touches on many of the primary elements of the enterprise's strategic plan.

The contribution that Canada has been long-standing in HIV research and we think that has a lot to offer in the global fight against HIV and that goes from experience and expertise, early discovery research and social sciences and epidemiological research and so forth.

To strong community and nowadays, more and more community and public health infrastructures engaging also political leadership, you'll see our minister is here; should be here now, on HIV Aids and vaccine development in particular.

So over the past few years, Canada has been actively working to fill gaps identified in 2005 Enterprise's SSP while still trying to keep up with the rapidly changing HIV vaccine landscape, and also the community landscape that is changing very rapidly in Canada, and throughout the world. In short, we certainly agree that the search for an effective HIV vaccine requires new ideas, novel approaches, and sustainable funding. Here in the government of Canada we have been a strong supporter of that and look to continuing that strongly in future years.

We see a series of key gaps and just to be, I suppose, effective in where the money goes, identification of those gaps is really important, and the majority of these gaps are really in the low and middle income countries. That is why I am pleased to be on that panel here with Dr. Ndung'u, a presence from South Africa who has spoken and will be able to speak certainly on those issues right worth most important. Another gap is the introduction of early career investigators into the field of HIV research that Alan has identified.

I can say that Canada's funding programs in HIV are increasingly focusing on or making it an important component of

that funding that young researchers are brought, early career researchers, are brought into that fold one to really get new and innovative ideas out, but also to assure some sort of continuity over the years to come and we see is a gap, in particular, there is a need to improve the capacity of national regulatory authorization particularly in low and middle income countries where the clinical trials are planned, or are ongoing and strengthening that capacity is critical.

So in support of all this amongst other activities, government of Canada has for instance provided $2 million to the World Health Organization in efforts of this sort, and in addition, we are providing through Health Canada's expertise in regulatory authorities and regulatory development, providing that to the low and middle income countries in years to come.

There remains significant gaps in supporting researchers in moving these HIV vaccine candidates from pre-clinical research into clinical trials in humans and central to this is a need for a sustained human and physical capacity to conduct clinical trials, and again, in support of this, the government of Canada is providing support to Canadian and LMIC or low-middle income country researchers to build sustainable African capacity and leadership to conduct these prevention trials and vaccine trials in particular.

The teams being funded for this will be meeting later this week here in Vienna at this conference for their inaugural

meeting. In their various programs represent support for a large number of African countries. One critical area which governments, governments overall, not just Canada, can take leadership as ensuring that the sectors involved in HIV vaccine development are fully engaged. The multiple sectors and particularly involvement of the affected communities, and communities not in a municipality sense, but communities of stakeholders are critical in that work. In support of this, funding has been provided to support community projects to increase that knowledge, that engagement of Canadian communities as well as other communities outside of Canada, on issues related to HIV vaccines. We will be continuing to support that work in coming years.

Me personally, as a former head of the Biotechnology Association, the national one in Canada and having been involved and led a number of biotechnology companies over many years, I certainly recognize the critical need for committed engagement on the part of the private sector in this work, and I am very pleased to see Mark here on this panel for that.

So just in closing, I do not want to make this too long, I would like to reiterate that the government of Canada at least is very committed to supporting global efforts to engage in the development of safe and effective and affordable and effectively accessible HIV vaccines. So I am optimistic and remain optimistic that by working together collegially that

we can make really positive gains in confronting and curbing the need, the disease and the need for an effective vaccine.

MITCHELL WARREN: Great, thank you. Gabriela?

GABRIELLA CALAZANS: Thank you. I would like to thank the organizers for the invitation, and I believe that we are facing a greater recognition that HIV vaccine trials do not happen in a gap. It happens in a context within which we made social and programmatic drivers of the HIV epidemics and AIDS, and this recognition helps us understand that although the struggle for an AIDS vaccine, as well as other HIV biomedical prevention strategies, relies on the better intentions to promote and achieve the good.

The implementation of clinical trials, sometimes reinforce those social and programmatic drivers of the HIV pandemic. They are sometimes imposed to communities, they sometimes disrespect communities or economies, and do not answer relevant questions to the communities in which they happen. To deal with this greater recognition, in 2007 AVAC and UNAIDS has launched the Good Participatory Practice guidelines in order set standards on how to ensure community and other stakeholders participation in the trials.

From 2008 to now, AVAC has funded 12 small projects around the world to promote consultations on these guidelines and this process has led us to the launching of a new version of the GPP guidelines today, and this new revision proceeded

has increasingly incorporated the community's perspective on the GPP guidelines and has tried to ensure a human right's perspective on that.

However, the implementation of the Good Participatory Practice guidelines requires funding, requires prepared staff, and growing partnership on the ground between the clinical trial teams and communities in which the trials happen. I believe that I am here representing a group of community partners that are here with us and what are trying to say, and ask, and propose in this panel is that we need much more community perspective on the HIV vaccine agenda.

We need to be prioritized. The Good Participatory Practices requires site maintenance and the maintenance of these partnerships on the grounds, and we believe that all of this, although this is considered as a priority on the new enterprise strategic plan, we believe that we need to have a much more implemented agenda of doing GPP guidelines. GPP guidelines in our expectations should be a requirement and a standard to the realization of clinical trials and that is what we expect from the future on how to do vaccine research.

MITCHELL WARREN: Great. Thanks so much Gabriela and thank all four of you. [Applause]

If you do have questions, there are microphones toward the front here and I think toward the mid-section back there.

Please make your way there because we do want to make sure we have a conversation.

What is very striking, I think, about what all four of you described are, it seems clear, I think Mark you kind of said specifically the words are there, we know in some ways what needs to do, now we need get very specific whether it is about industry, or about government integration, or about community, or about young investigators.

And I am wondering then, and maybe Mark since you kind of kicked that off, what might be even a more concrete example, what as someone sitting in industry, what might you be looking for as a way to engage and around what specific issue and again, I don't think no one is going to hold you to it specifically unless you would like us to, give us an example of how that would work.

MARK FEINBERG: A kind of broad but important question. I think the vision of the HIV vaccine Enterprise was to really have a common vision of what AIDS vaccine development needs to accomplish, how it would need to work, how different partners would work together. I mean because to be perfectly honest, and I have probably contributed to this as much as anybody over the years, is the field has been kind of chaotic. There are a lot of different things happening in different places.

People addressing or focusing on different issues, and there really has not been a way to integrate across the

different areas and prioritize what are the key questions. How do we work together to resolve them as effectively as possible to the extent to which the HIV vaccine and Enterprise in the field more broadly can help make that happen and I think it really then, from that vision would derive a series of specific action items for different stakeholders.

Whether it is the community, whether it is governments, whether it is industry, and I think to the extent of what might happen for industry, a clear articulation of what is the specific part of the process where industry expertise could contribute the most to overcome existing barriers that are now very frustrating to the field overall, and I think that is something that is doable and based on the characteristics of that.

I think you can rightly ask companies either individually or probably better collectively, how do you come together to solve this. I think if there is clarity around what the need is, and how people could contribute, and what the boundaries of your expected responsibility and contribution would be, I think the chances of getting a concrete positive sustainable engagement will be much better.

MITCHELL WARREN: Great, thanks. To me, similarly, I think every document for a number of years has described the importance of engaging young investigators, really creating the next generation, particularly in the developing world. So it

is not an entirely new issue and I would like to think it is not just about money. What is our problem? We keep identifying it. So what is not happening that is not about money that would change the way in which we are creating careers for investigators?

THUMBI NDUNG'U: Again, it is a difficult question. It is something that we as part of the young and new career investigators that Global HIV vaccine Enterprise put together that we went over a lot trying to discuss what are the bottle necks, well the difficulties particularly for young and new investigators from the developing world. I think while the difficulties are multifaceted, they are not so big so that they cannot be overcome.

I think one of the ideas that we talked about is coordination of efforts in terms of trying to develop capacity and trying to increase the presentation of investigators from developing world because obviously the resources are limited and there are many needs. There needs to be some kind of coordinated effort.

One of the ideas specifically that we discussed is a committee if I could just mention here, was the issue of developing centers of excellence in the developing world that would then act as a way to attract gifted and seistic [misspelled?] young investigators from the developing world and

then making sure that they have the resources within those centers of excellence.

Again, I know that it is not a very novel idea. This is something that has been discussed over and over again. I think there needs to be sustained effort to equip centers of excellence in certain areas of the developing world and to support this with sustainable funding, and with local leadership, and participation of local, state [inaudible] particularly people in industry and universities.

One of the things that actually strikes me is that when you have a meeting like this to discuss about vaccine development, you actually do not see a lot of local developing world state quarters are important in driving that process like government representatives, like university, senior university representatives in meetings like this.

But if it was a meeting, for example, about implementation, if for example, we had a HIV vaccine today and we were talking about how do now implement it, you would see a lot more participation from local developing country state quarters.

I think there needs to be a concerted effort and a bit of seriousness both in terms of the state quarters from the developing world, but also from people who are able to drive process of the developed countries like key funders, organizations like the HIV vaccine Enterprise, and others to

try and support and make sure there is a coordinated effort that makes sure that we develop the next generation of investigators in the developing world.

MITCHELL WARREN: Great, thanks so much. I think, Mark do you want to add something?

MARK FEINBERG: Yeah, I just wanted to add, I mean there is obviously the sort of the logistical aspects of engaging young investigators, but I think there is also the emotional aspect of engaging young investigators.

I started working in AIDS in the early '80s about the time that HIV was first discovered, and shown to me, the cause of the disease. At that time it was a very exciting thing and we had no idea how long the epidemic would last or when the solution would come, but I think it is fair to say that no one at the time would think that it has taken so long, but I think quite now, quite clearly now, it is clear that AIDS is going to be around for far longer than anyone in this room is going to be alive, and you need figure out how you motivate people to get in engaged, to devote their careers to something where the goal is unclear as to when it is going to be realized and a vaccine is a pretty specific deliverable. You either have it or you don't and to figure how to engage people so they feel that it is valuable to devote their careers to something that could well be a long term thing, I think we have to be realistic about and find ways of doing that.

MITCHELL WARREN: It is a really great point. I think what we will do real quickly because I know we are going to be short on time, why don't we take three very quick questions or four questions, quickly in succession. Could we get a microphone in the front please? There it goes, go ahead.

ASAN JAY: My name is Asan Jay [misspelled?] from the Medical Research Council with Uganda and I am immunologist, and I coordinate the West African network for HIV intervention research.

My question actually touch upon the last question and answer by Thumbi, but I think what I want to know is in my mind there is a gap in south. You talked about collaboration really when you started to speak, but there is a gap by south-south collaboration and south-south networking. And I am wondering what has AAP or the AIDS vaccine program, African AIDS Vaccine Program, whether they have designed or devised a strategy plan to really enhance the south-south collaboration?

Because it seems as it is not African driven. It is more coming from, and I thank the Global Health Research Initiative of Canada that is actually trying to bring about networking, and also recently The Wellcome Trust funding agencies that allow the formation of the initiative for strengthening health research capacity in Africa, bringing in African scientist and their funders together.

But then through that then we encouraging networking. I am not seeing African driven initiatives to really bring in the south-south because that is key and essential even if you want to enhance the capacity development that we want to impact on more HIV collaborative HIV vaccine research within the region. I am wondering what is the AAP doing?

MITCHELL WARREN: We are going to get there in just a minute because I see someone in the queue who might be able to quickly answer that too. Why don't we take Catherine and Leslie and Gus real quickly.

CATHERINE COOK KEY: Hi, Catherine Cook Key [misspelled?], I am from the U.S. National Institutes of Health, AIDS Vaccine Research Program, and my question is for Dr. Feinberg. I would just like to hear a little bit more about the model you spoke of with the Wellcome Trust and what is the structure and how does it work. Thanks.

MITCHELL WARREN: Great, thanks.

LASHLA BEMECU: Hi, my name is Lashla Bemecu. [misspelled?] I am the coach here for the African AIDS Vaccine Program. I actually had a comment to add to the some of the discussions and I might touch on what my colleague just mentioned earlier. I think, in fact, the challenge we have had in getting, in finding an effective vaccine has humbled a number of us, and I think in the last two or three years we have started doing things differently that would probably

impact our ability to do exactly what Alan presented in his presentation.

One of those things that I want to point out is what the African AIDS Vaccine Program has done within the continent, and that is just like Robin mentioned earlier, of engaging Europe is to engage the leaders within the African continent to ensure that things that Thumbi talked about earlier about sustainability and building the infrastructure is actually there and that there is ownership. We cannot have ownership without putting something in there.

One of the things that I want to bring out is really the progress that we have done along those lines using the higher representative of the African AIDS program. Madam Kagame, the First Lady of Rwanda who made a whole session of the African Ministers of Health world meeting to be solely on what the African leaders are doing in terms of putting an effort, and providing infrastructure, and some funding to ensure that we get an effective vaccine and that young scientists like Thumbi actually have laboratories that can do the kind of work that he is capable of doing.

Of course, we saw a first HIV vaccine candidate come out of Africa so it is not unusual that that is going to happen. The other thing that the field has taught us also is in the importance of providing a very concerted similar message across especially when we made various leaders, and I think we

have done a fairly good job of really not confusing the public or the policy makers or the leaders ensuring that we give one global enterprise kind of message.

And final comment to just address what my colleague mentioned is, in fact, that is exactly what the African AIDS Vaccine Program is about because we have learned within the vaccine field that it is very important to set up networks and currently the African AIDS Vaccine Program is doing that within the African continent. Thank you.

MITCHELL WARREN: Real quickly, Gus and then you will give it back to the panel.

GUS GANSADES: Gus Gansades [misspelled?]. It's primarily for Mark Feinberg although Robin touched on this in the previous panel. It is the business about wanting to ensure that we have a sort of more unified approach to what we want to develop and more a sense of which products we think are going to work. The trouble is we sort of say this in the context of a trial which involved a product which nobody thought was going work and which might have been stopped if we had that approach. So it is a question about how practically do you square this circle, about how you combine a logical approach to development while at the same time allowing room for serendipitous discovery.

MITCHELL WARREN: Great thanks, Gus. Mark, why don't we go with that, a quick thing about the MSD Wellcome Trust partnership and then answering Gus' question in either order.

MARK FEINBERG: I can just speak mostly about Hilliman Labs which is the name of the Merck and Wellcome collaboration. There was in recognition of fact that there is a lot of attention on global health funders like the Gates Foundation, and The Wellcome Trust, and the NIH are fostering a lot of basic discovery research in trying to develop vaccines that go after diseases of the developing world yet all of those investigators have a very difficult time translating those discoveries into real vaccine candidates that can be demonstrated and have proof of concept.

And then be configured in a way to be manufactured and that space, that bridge between concept and proof of concept is really the area where industry's contributions are most unique, and we felt that we could help address those by bridging that gap in partnership with an organization like The Wellcome Trust where we would work with academic or government scientists to take their ideas from concept to proof of concept, doing the product optimization, product development efforts.

And then partnering with low cost manufacturers to ensure that the optimal vaccines developed specifically to meet the needs of the developing were developed and available as affordably as possible.

So Merck and The Wellcome Trust both devoted significant financial resources to it, but to be sustainable it is going to need to attract other resources and it is intended to engage other companies as well. It is going to be located in New Delhi in India and it is now getting up and running. And really it is a very exciting enterprise, and I just put it out there as a model because one can imagine that a major gap in the HIV vaccine field is exactly the same, one taking a promising idea and turning into a real vaccine candidate, and that is where industry involvement could be very valuable and I think it that is the specific ask of the industry.

Companies could have a meaningful discussion about how they could engage in a collaborative way to address that more broadly and I think there are lots of ways that would, that I think could be imagined that would be very valuable.

MITCHELL WARREN: Great. Did you or anyone want to talk a bit about your own experience in the biotech industry about Gus's question in terms of how do you make that determination about killing projects but at the same time leaving room for serendipity.

RAINER ENGELHARDT: Well, I guess that is basically a business decision that is made depending on what the state your development of a particular project. I am not sure that that question is so relevant to where we are right now which with respect to an effective vaccine development.

If you don't mind, I would like to address a slightly different point which is that the absolute essentially of collaboration amongst the different sectors including industry to move this forward because the paradigm for collaboration here is very different from the paradigm that one would normally find amongst government agencies or industry to industry as little as that happens or does happen.

I think we all need to step back and view the collaboration as really as an opportunity essentially, an essential opportunity to get to the end goal and the paradigm is to how one gets to the end goal here is different as well. We are not likely to end up with a product is a conventionally marketed and sold product. It is not the typically cardiovascular disease treating product.

This is a public health product which has to be developed and delivered with interventions by governments, by international organizations where it is needed most and delivered in a fashion which in a way ignores which company is the marketer and so the whole paradigm for, and we need that, as to how we establish that to move this agenda forward especially since we have set ourselves, and had to set ourselves, very short time frames.

So collaboration in the broadest and most horizontally broad and in depth sense is essential to move this forward in

that it has to involve not just the developers but actually and I am touching on several points here.

MITCHELL WARREN: No, these are great points.

MARK FEINBERG: It is really the effectiveness of that collaboration. The effectiveness of implementation will critically depend on uptake and the uptake is going to be in those countries, those communities where the HIV is needed, essentially needed and without having that whole panoply of players together, it will never work.

MITCHELL WARREN: Yeah, Rainer that is a fabulous series of points and I want to just quickly turn toward the end to Gabriela.

On that, when I look out at the last few years we have had ups, downs, surprises all around. Engaging communities is as important I would argue is, and you have argued so beautifully, as industry or investigators and I am curious from your perspective engaging communities in what are going to be more complicated trials, complicated trial designs, complicated concepts on the back of very complicated research results and I am curious how it looks to you sitting in a trial unit in Sao Paulo, Brazil.

GABRIELLA CALAZANS: Well, I think that to really do engage communities first we have to have the certainty that our side is going to continue working. It is not just our side but the sides are continuing working, but the things that if you

have insecurity on the maintenance of your work it is very difficult to keep the relationship with the communities. This is when first point.

The other thing is that much times our work is very dedicated to recruitment and when we are not recruiting we don't have enough funding to keep the relationships with the communities so it is difficult to keep them informed on what is happened, and what needs to be done, and so I think this is a challenge and that is why we do believe that if good participator practices could be considered a standard to the realization of the implementation of clinical trials maybe we would have from funders, sponsors, and researchers, and much more continuous relationship with communities and this is what we are expecting to have.

I do believe that we have in this room not all the people that are responsible for doing this, but we have people that really can do a difference on making this became a standard and I think this is a challenge for us to have this commitment.

MITCHELL WARREN: Great, well thank you. The list of challenges never gets shorter unfortunately, they get longer. These are conversations that need to continue. There is a session actually beginning in a few minutes. I am not sure if it is in this room or nearby about some of the broader networks

for vaccine research. Again, the anti-retroviral basic prevention session in this room at 3:45 might be helpful.

All of the participants you saw in this session are around and I think would happily take questions from people. There is also a prevention research roadmap for the conference to give a sense of where some of these sessions are including a session on Tuesday Afternoon at 2:30 that I believe Jose may, I think you chairing and with Seth around where we are with AIDS vaccines to get in more depth here.

I would draw your attention to Tuesday at 1:00 with the results of a trial referred to by a number of people, the Caprica004 trial and most of all I want to thank you all for coming and really, from Peter Piot's introduction all the way through Gabriela's final point, saw a recurring theme of how do we not only build the networks in the capacity, but how do we sustain them for the long term, and how do we make very difficult prioritization, and decision making.

And how do we do it all in a collaborative way that still leaves room for competition and serendipity and that is the wonder of science and I am delighted to work with all of you and look forward to many more conversations as we get further down this road. Thanks very much, and thank you all.

[Applause]

[END RECORDING]