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**XVII International AIDS Conference
AIDS Vaccines – 2010 and Beyond:
Charting a Course for the Future of AIDS Vaccine Research
August 6, 2008**

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ALEXANDRO: -Vaccine Initiative. I will ask every that is sitting towards the back to come towards the front because it is a very large room and it is easier for us to have a warmer session with people down here. We hope this session will also be an interaction session, which will be really hard if you are sitting in the back of the room. So, if people can move forward, that would be great.

So, welcome to AIDS Vaccines - 2010 and Beyond:
Charting a Course for the Future of AIDS Vaccine Research. We have a panel of distinguished experts and a lot of experience here. I would like to first introduce our chairs for this session.

Dr. Salim Abdel Karim [misspelled?] from Capreza from the University of Quazulu Natal who is a very experienced researcher in HIV prevention, including AIDS vaccines, and has had a very long career of contributions to HIV and AIDS research. We are keeping the introductions very informal, just to set the tone.

I would also like to introduce Dr. Alan Bernstein, who is the Executive Director of the Global HIV Vaccine Enterprise. Dr. Alan Bernstein used to be based in Canada at the Canadian Institute of Health Research where he was the Founding President of that organization. He did a remarkable job there until he was recruited to the Global HIV Vaccine Enterprise.

Dr. Bernstein is also a co-sponsor. On behalf of IAVI, thank you very much for co-sponsoring this session with us.

I will hand it over to our co-chairs to introduce the speakers.

ALAN BERNSTEIN, PH.D.: Thank you, Alexandro. Now, those of you who are in the back, there is food in the front, so if you want to move forward—it is my deep pleasure to introduce Craig McClure, who will say a few words to open this session. The most important thing you have to know about Craig is that he is Canadian. The second most important thing is he is the Executive Director of the International AIDS Society. So, with that, Craig McClure [applause].

CRAIG MCCLURE: Thank you, Alan, fellow Canadian. Good evening and thank you for inviting me to give opening remarks. Since the last International AIDS Conference in Toronto two years ago, the field of HIV vaccine research has had a tough time. In the last 12 months, I understand that meetings of vaccine researchers and advocates alike have been about as much fun as eating crushed glass. Media reports have not helped. Headlines like "Will We Ever Have an AIDS Vaccine?" or "HIV Vaccine Hopes Dashed" do not exactly inspire, well, hope. We are still with the ludicrous and nonsensical calls from some within our own AIDS troops to divert all funding for vaccine research to antiretroviral therapy.

I say this is a time for optimism. Why is this a time for optimism in the field of vaccine research? First and

foremost, we have a range of excellent, proven prevention and treatment tools in the kit bag, and we finally have substantial resources and political will to implement them. Condoms, clean needles and syringes, opioids substitution therapy, information, counseling, circumcision, STI treatment, and antiretroviral drugs themselves are all excellent prevention interventions. And on the treatment side, we have well over 20 antiretroviral drugs in 5 separate classes, allowing people at least three different shots at undetectablizing their viral load and living productive and healthy lives. We have generic competition driving down prices, and we have fairly well coordinated financing mechanisms to fund the response. And that, without belittling the urgent need to develop and HIV vaccine, quite frankly, gives us some time to reflect, to go back from the drawing board, and to learn from what we have achieved to date.

Secondly, this is a time when the field is opening up to new ideas. As we move towards the fourth decade of AIDS, we find ourselves in exciting scientific times. Gene therapy and stem cell research are coming into their own, and young and brilliant minds are emerging from universities with bold new ideas. And the setbacks we have faced have led to new discoveries that, while they perplex us, also challenge us to go forward. What is it about this virus that so totally dysregulates our immunes systems, almost from the moment of infection? Why are the elusive neutralizing antibodies so

elusive? What exactly happens during primary infection and what about those long-term non-progressers?

Thirdly, there are growing international calls for research to be expanded in conjunction with the scale up of current prevention and treatment intervention. Last year the International AIDS Society issues the Sydney Declaration, calling for 10-percent of all resources devoted to HIV to go towards research. Since then, WHO, the World Bank, the Global Fund to Fight AIDS, TB and Malaria, and the IAS have all joined in the call for expanded research capacity in resource-limited settings, both for operations research, to learn from what we are doing as we scale up, as well as to expand basically clinical, epidemiological, socioeconomic and behavioral research.

Good research drives good policy and programing. The future of the AIDS response will depend on the future of research, including vaccine research. The push for more research, part of a comprehensive response to HIV, comes at the same time as a clarion call for health system strengthening. While in some circles there are foolish cries that AIDS is getting too much money, most people in the field of global health realize that recent unprecedented resources for HIV and global health are beginning to result in success, and that the AIDS movement can be mobilized for global health for all.

The rollout of HIV services means not only increased access to ART for those who need it. It also mean improved

laboratory capacity, trained and retained human resources, improvement infrastructure, improve commodities management, and improved monitoring and evaluation programs. All of these can be leveraged to improve overall health systems, including research capacity.

Vaccine research is an essential part of a comprehensive response to HIV. Our response to HIV is as extraordinarily unique as the virus itself. HIV vaccine research in the past 25 years has altered and expanded dramatically our understanding of the human immune system. What will be learned in the next 25 years will radically expand that understanding. Whether we have an effective preventive HIV vaccine in 10 years, 20 years or 50 years, the search must go on. Along the way there will be more setbacks and hopefully a few eureka moments. We need to remember that old mantra of Seth Berkeley's, the race for an AIDS vaccine is a marathon, not a sprint. What we now know is that marathon is a relay that may need to pass from generation to generation. There will be no greater tool to ultimately end this epidemic than a preventive HIV vaccine. Thank you for listening and I hope you enjoy your deliberations this evening [applause].

DR. SALIM ABDEL KARIM: Thank you very much, Craig. It is my pleasure to welcome and introduce to the podium Dr. Seth Berkley, who I am sure needs no introduction, but I thought I was just touch on one or two points about Seth. So, most of you might not be aware that Seth's first exposure and

interaction and coming face to face with the HIV epidemic was in Uganda. That was soon after he had been at the CDC. So, he knows the face of the epidemic where it hit worst, and he has that perspective of the way in which communities have risen to the challenge of the HIV epidemic.

Since then, he has moved back to the U.S. and was at the Rockefeller Foundation when he created IAVI and currently, besides being the IAVI, he also holds academic faculty positions and professorships at both Columbia University and at Brown University. I know of no one who shares this passion for vaccines and who has been able to stand up and shout louder from the rooftops for a vaccine. He is going to tell us today the state of the vaccine field and share with us some of the prospects that lie ahead. Thank you [applause].

SETH BERKLEY: Thank you very much, Salim. Let me just start by saying something about Salim which people may not know, which is that he was chair of the 2000 critical Durban meeting. And at that meeting, it was not only a very important time for antiretroviral therapy, but it was a very important time for vaccines. Vaccines were on the agenda virtually every day, through every time slot and it was unbelievably supportive of that.

The second point I want to make—I guess Craig has had to leave, but I did want to say that one of Craig's first loves was as an AIDS vaccine activist. He was very active in Canada

in working on AIDS vaccines, so it was wonderful to have him come and give remarks.

Alex has given me an impossible task. He has asked me to in 10 or 15 minutes give you a state of the field. I am going to try my best to do that. Given that we have an audience of people working on everything from science, to the activism, to community, I am going to try and make it relevant for everybody.

In summary, I am going to start off talking about why an AIDS vaccine, where we are now, good and bad news and what this means, and then how we prepare for the next couple of years and beyond.

Now, I do not think I need to say this for this audience, but I do want to remind everybody that the reason we need a vaccine is because AIDS and HIV is still continuing to devastate communities. You know the numbers, but particularly women bear the brunt of the epidemic, representing almost half of all HIV-infected adults worldwide and certainly the vast majority in Africa. This is critical because women need tools that are friendly to women and that they can control. Ultimately, obviously, we need microbicides and better barrier methods, but a vaccine is the best tool to do that.

Without a vaccine, we are going to see the epidemic continuing. I think the in data that came out of the U.S. people focused on the fact that there were more cases. Yes, that is an important issue. It is important for planning and

because of the sheer magnitude of the disease, but I think that hidden in there was the fact that it is now 15 years that despite scale up of treatment, despite scale up of prevention, we are still seeing 60,000 cases a year over this time period, suggesting we need better tools.

Craig has already said that AIDS vaccines should be part of a sustainable comprehensive response to use the tools we have today to prevent the further spread of the virus, treat those who are infected and mitigate the societal impact, but we must invest in better tools. It is not just vaccines, but is better drugs, better diagnostics, better barriers methods and microbicides and ultimately a vaccine. We also have to remember that if we look at the current demands to try to get to access for all by 2010, the costs are enormous. In lower and middle-income countries, it is estimated that access for all by 2015 will be \$54 billion a year going on from there, and so better prevention and better prevention tools are critical to being able to financially support that.

What could a vaccine do? Well, it could have a very dramatic effect. What is important is that even if a vaccine did not have unbelievably high efficacy or coverage, you still could avert a lot of infections. Obviously, the better it is, the more the coverage and the better the response. These are some models that were done, pretty sophisticated models looking at the effects of vaccines. So, we have to remember that

although we want a perfect vaccine, even an imperfect vaccine can have a dramatic effect.

Lastly, people say, well, that is all fine and good, but is an AIDS vaccine possible? You heard Craig say that people have been saying that it is not. What I would say to that is that we know that immune control of HIV is possible. We know that most people who get HIV infected control the infection and suppress viral load for a period of time before they have slow destruction of their immune system. We know there are people that are highly resistant, highly exposed and uninfected, children of infected mothers, and then these long-term non-progressors who are nature's kind of experiments, in essence, of people who control infection for many, many years, some to undetectable levels.

We also know that there are experimental candidate vaccines and ways of looking at this that have shown effect. The live attenuated vaccine works well against homologous challenge in macaques, at least the best model we have now. And neutralizing antibodies from humans and put into macaques can give you sterilizing immunity. So, we have lots of information in humans and in monkeys that it is possible. The question is how to make it practical.

So, where are we now? I am going to go back because I think it is important to ask where we were a little bit more than a decade ago. In that period, there were very few things in the pipeline. There were very few vaccines and little

investments by the public or private sectors. In those years, about \$150 million worldwide was invested. No vaccine had ever been tested for efficacy. There was little interest in vaccines. There was very little interest in vaccines for high-incidence countries. Nobody had designed vaccines for those regions. There were no trials occurring in the developing world. There was limited capacity for trials and there was no political leadership for vaccines in the north or south.

We have come a really long way since then, so that is some of the good news. There has been a big growth in funding. We have gone from this \$150 million to today's total which I believe is \$961 million. A working group on this funding released a report here at this conference on that, and this summarizes that growth. One thing that is important about seeing this is that the pharmaceutical sector has been relatively flat and is minority of it. Most of the funding now is coming from the public sector and most from the U.S. government. This is something that, as activists, we have to try to make sure to do, that we get broad-based support AIDS vaccines.

There are now efforts in place to inform and engage effective communities across the world. This is really exciting and we have seen community advisory boards work south-to-south cooperation across the world, not only within Africa, but across Asia, from Asia to Africa to Latin America and back. So, it has really become a truly global effort.

There is a lot more capacity for research in developing countries. This happens to be an IAVI site. This is what was started before. We built a beautiful facility, but more importantly this laboratory has not only done a bunch of trials, but has good clinical practice, good laboratory practice, has gone on to be accredited as a laboratory, and then went on to become a reference laboratory for the Bill & Melinda Gates Foundation in collaboration for AIDS vaccine development. So, this shows the quality of work that is going on in these places that were not part of the AIDS vaccine effort more than a decade ago.

Now there are 26 countries that have done trials, many in the developing world, which again brings a global perspective to this. This is critical because we know there are different strains of virus circulating in the world and also the genetics are different, so making this a global effort is absolutely critical.

Finally, there has been a lot more political leadership over the last decade. Leaders from India just declared this a national goal. You can see pictures here of Bill and Melinda Gates who have made this into their highest priority of the foundation, almost a campaign. Here is Gordon Brown who has made this a priority. I can go on and on. It is a truly global effort.

Perhaps most importantly, there has been an extraordinary growth in scientific knowledge. It is

brehtaking what we know about the virus and what we know about the immune system. So, you can look and say the glass is half empty and we do not know everything or understand everything. That is true, but we know an enormous amount. This cover of *Nature* looks at the structure of one of the broadly neutralizing antibodies and where it binds to. These give clues to science to make better products.

The bad news is that finding a vaccine is extraordinarily complicated. Why is that? Well, the virus itself integrates, so you have to get to it very quickly. It has hyper-variability. There are different strains circulating around the world. We do not understand the immune correlates of protection. We know that HIV suppresses and kills cells of the immune system. It targets the immune system itself, which is what we need to rally to protect against. We do not have perfect animal models, and clinical trials are long and costly.

But what that means is that although we are attacking an aggressive and fast-moving target, we have to test in people. This is a human disease HIV, so we can use monkeys and we can use laboratory animals to give us clues, but at the end of the day we have to test in humans. Success is going to take a lot of time. There is a whole series of other issues around policy and political will to be able to do this, given that it is a marathon, as you have heard. We have to have high-level global commitment leading to action. We have to have incentives for industry to engage in this. They are not

spending and using shareholder's resources, so we have to help because they are critical. There are ethical, regulatory and IP challenges and health system challenges. So, to do that, we have to build this global support and optimize the environment for safety and ethical trials.

Other bad news is that the current pipeline is inadequate. The focus has been on cellular immunity almost exclusively. We need to move into neutralizing antibodies, mucosal immunities, a combination of these and other areas that are not even listed here.

So, where is the world? As of August 2008, there have been two efficacy trials completed, the Vaxgen gp120 showed no efficacy. That was an antibody-based vaccine that focused on lab-adapted strains. Although it gave good antibodies against lab-adapted strains, it did not provide protection against wild-type. And the Merck candidate I will talk about because I think it is important for everybody here to know about. There is an efficacy trial ongoing Sanofi and Vaxgen that is an all-vac candidate. We are expecting data next year. This is being done in Thailand on 16,000 people.

There are a whole bunch of other candidates in clinical trials. Jorge Beloki [misspelled?] reminded me to make sure this is said because the plenary that went on about vaccines was looking forward and did not talk about the important work that is going on. There is a whole range of other products that are moving forward, including a decision soon from the NIH

on whether they are going to move forward with a DNA Ad5 and that discussion is ongoing. As you know, there was a decision made not to move it forward in the design it was in, but there was also a sense that if a smaller trial went forward that that would move forward.

There is also a whole range of other products in phase 1. Our assessment is that ultimately the best of these—and what do I mean by the best disease? I mean ones that look better than the Merck product—will then move into a screening test of concept trials and we will see if these approaches provide advances over the candidates that are above.

This is a list, which I will not go through, of candidates that are in clinical trials. You can see that the pipeline is far from empty, but, again, we need more diversity in the pipeline. What that means is that it is likely there is going to be a dip in the pipeline and not that many things as have been tested in the past, but there is going to be a rise again as all the new work that is going on leads to new candidates.

Let me just mention what happened with Merck. This was a phase 2b trial of an Ad5 gag/pol/nef. It was an excellently designed trial, a multicenter, randomized, double-blind, placebo-controlled phase 2 test-of-concept. It started with the STEP trial which was 3,000 people, 1,500 with low preexisting anti-Ad5 antibodies and 1,500 with higher levels.

And then there was another trial in South Africa, the Phambili

trial, which was started later. The Data Safety and Monitoring Board at their first meeting stopped the trial for futility. Again, this was an excellently designed trial, really excellently designed. The data at that time showed that, in fact, there was no different in viral load between the two groups and there was no difference in infection rates between the two groups, although there was a trend towards a higher infection rate in those who received vaccine. That was concerning. This was not statistically significant, which is important. If you looked at the people who had low Ad5 titers, there was no difference between the two groups, but people later found out that, in fact, there was a higher infection rate in the group who received vaccine than in placebo. What is interesting, if you go back and look at the HIV rates in the vaccine versus placebo, in the low Ad5 titers you can see a slightly higher rate than is seen in placebo, a little bit higher in the high Ad5, but also the placebo rate went down, the infection rate, which confounded the effect.

And so one of the issues—as I said, this was an excellently done trial—is when we look at the randomization that occurred, it was excellently randomized, but one of the issues is that there are differences between those who have low Ad5 titers and those who have high Ad5 titers. One of the questions is whether there are potential confounders that we have not identified yet. There is a fabulous program now to go back and look at the data, try to do studies to figure out if

there are other factors such as HSV or other exposures that might explain this, but at the moment, of course, for safety reasons people are worried about this and that is what delayed the VRC trial.

So, the upside of the bad news is that the failure from this trial has challenged the field to be more efficient. It prioritizes future candidates. The scientific agenda is changing to reflect these science findings. That is the normal process of product development. You have a failure of a candidate, you learn from that, you take those learnings and put them into the next candidate.

So, for today's priorities, we need better assays to predict efficacy. That is an important issue. Up until this point, we looked at gamma interferon LE spots [misspelled?] and Merck gave pretty high levels of those. That is not the best thing. We need T-cell functional assays. We need candidates that can elicit broadly neutralizing antibodies and more potent targeted cellular immunity. We probably need to better understand what is in the vaccine. Most of the focus in the vectored approach has just been on the vectors and not necessarily what is in it. So, there is a lot that can be done there.

So, in preparing for the next couple of years and beyond, what is going to happen post the Merck vaccine, what is the impact? Well, first of all, there has been a shift, as Tony Vauchey [misspelled?] said, a twisting of the knob towards

discovery. He did not say we are abandoning clinical research. Clinical research is critical to the field and to the discovery effect. So, it is a tweak of the knob towards discovery. NIH has said that they are going to be redirecting funds there. The Enterprise has been reviewing this and looking at suggestions. There is a greater focus on neutralizing antibodies and validating the SIV model because we now have a negative validation of the SHIV model. We do not yet have a positive, obviously, validation of the SIV. That will be critical.

For the clinical research agenda, we are going to adapt to the capacity to answer today's question, a lot more clinical research rather than licensure trials. So, it will be small trials trying to answer critical questions. Obviously, if you have positive results you will roll them into larger trials, but will not go with very large trials to start with. In the absence of these intermediate efficacy trials, right now there is maybe some excess capacity and we are going to have to use that smartly and sustain it. That is important. It takes years to build this capacity and we cannot let that capacity disappear. We obviously have to develop better assays, as we have mentioned. The funding landscape is changing. Large pharma, which was not investing very heavily, even up to this point now, is cutting back further, so it is even more on the shoulders of the public sector. There is going to be more investment in upstream research. And then we do believe that

as a result of the STEP trial there are probably going to be greater regulatory hurdles, which may slow down clinical development. The STEP results may also change the way we think about doing trials. One of the important things about this is that there is a lot of very interesting work on innovative trial design that can help prioritize promising candidates swiftly. I think more of that will be seen.

If you think about it, what this cartoon does—and this from our blueprint—is we are going to be looking at a set of immunogens and a set of different candidates and we are going to be looking at issues of technical feasibility, small animal models, then looking at non-human primates, then early clinical trials, and then that is going to lead to a prioritization of candidates going into these small efficacy-type trials to look for some proof of efficacy in humans. And then ultimately that will lead to larger efficacy trials.

Lastly, let me just say that scientists alone cannot solve this problem. The research does not happen in a vacuum. We have often said that bad science will kill the effort, but so will bad political will, community involvement, or advocacy engagement. And so with a reduced clinical pipeline, how can we engage the clinical trial centers in the developing world that have done such a superb job to make sure that they continue to actively engage in the effort? We have to sustain the capacity that was built and use it effectively, but we also, where possible, have to get these research centers

engaged in some of the upstream research. Obviously, that has to be done appropriately and make sure that there is adequate capacity in countries to do the research that people are trained for and exchanges, but that is an important priority.

How do we keep the communities informed and engaged over the course of many years and in the face of multiple priorities? We will discuss that on the panel, but this is a critical issue because if the communities lose desire, do not want to volunteer and do not want to have trials in their areas, it is a huge problem.

How do we keep the advocacy? What effect is it going to have on the volunteers, activists, donors, political leaders and young scientists? So, it is critical to redouble our efforts on advocacy.

And finally, what can the broader AIDS response that Craig talked about contribute to accelerating research, and how we do integrate our research into other prevention research, other research that is going on, to support today's goals as well as tomorrow's needs?

We released our AIDS Vaccine Blueprint. We do that every two years. There are copies of it for everybody. We released here the presis [misspelled?] and there is a full-length blueprint, which is, for those working in the field, much more interesting. The big deal we tried to put in this year, in addition to our normal covering of this data and the field and giving recommendations, is a set of interim

milestones. We do not necessarily know that these are the right interim milestones, but we believe that the field ought to be broken up into interim milestones now. We all ought to agree what those are and then we ought to go after them, because that will allow us to tick off critical things that have to be solved for us to get to where we need to go. And so that was the main thing.

We talked about three waves of vaccine development in the blueprint. The first wave, like hepatitis B in the early years, ended when the VaxGen approach looked like it was not promising. The second wave, the cellular immunity moving forward, in a sense ended with Merck. The third wave we called harnessing innovation throughout the field. This is across the entire field with the preclinical side really being bold and strategic, engaging industry and seeking ideas from other fields. In clinical trials, adaptive enrolling trial designs, smaller trials. In partnerships, find new ways and better models to keep us going. In advocacy we need to develop the next generation of advocates, working with women's groups and advocates for other diseases. And in developing country engagement, how do we engage the work that they can do strategically and get them even more involved?

We have to persevere. Vaccines are very powerful tools, but they take decades to develop. There is a lot of experience, a lot of years for a lot of vaccines, and HIV

vaccines are probably the toughest vaccines that the world has ever worked on.

I would like to end by, of course, thanking our donors which we could not do our work without. We have a fabulous set of donors that support us and allow us to be flexible in what we do and move with the science as necessary. At the end of the day, I think all of us here want to imagine a world without AIDS, and that is what we are really working towards. Thank you very much [applause].

ALAN BERNSTEIN, PH.D.: Thank you very much, Seth, for that very comprehensive overview of the field with where it is and where it is going. When Seth first asked me to co-chair this with Salim Karim, I immediately said yes because it gives me the opportunity to work with Salim, somebody who I knew, when I first met him back in May of this year, would be a friend and colleague for life. So, it is a real pleasure and honor for me to be working with you, Salim, on this.

The title of this session is "AIDS Vaccines - 2010 and Beyond: Charting a Course for the Future," so there are at least three words that talk about the future here. That reminds me that Marshall McLuhan, who was a well-known futurist, really did not like that term. Every time he was asked about predicting the future, he had a quip that he would come back with. One of them was that predicting the future is passe.

With that in mind, I want to urge our panelists to remember two things. This is about the future and you do not necessarily have to have a crystal ball, but I think we are interested in hearing each of your views separately and in a conversation about where you think the field is going and needs to go. And secondly, please remember to keep to five minutes so that we have time for a dialogue.

It is my pleasure to introduce and call to the podium our first speaker, Dr. David Apuuli. Again, as with Salim, I first met David in May of this year. I was immediately struck by a lot of things, his warm personality, his humor, his passion for the battle against HIV, and the combination of that personality with being a superb administrator, a politician, and one of the strongest supporters for HIV vaccine research anyway, and certainly in Africa. He is the Director General of the Uganda AIDS Commission and has been for almost a decade. He is an MD. He is on IAVI's Policy Advisory Committee. I think he chairs it. He is a board member of the Infectious Disease Institute in Kampala, Uganda and a member of PEPFAR Board. David [applause]?

DAVID KIHUMURO APUULI, M.D.: Thank you, Alan. I thank all those who invited me. I traveled very far to come here. It is a long way. It is a pleasure to be able to say a few words. Really what I am going to say is what the perspective is from [inaudible], especially people like ourselves who are involved in coordinating the response at the country level and

playing a role in terms of advocacy at various levels around the globe.

I will keep mine very simple. They told me to take less than five minutes, which is not much. After the last few days that we all have had, we come out with a definitive feeling that we cannot treat ourselves out of this epidemic. The figures speak for themselves. Craig showed you some of the figures. The number of people who were put on treatment in 2007 is a small fraction of the new infections that occurred. In fact, I believe that some of the success that we are talking about in this conference is transient. I speak from the perspective of my own country and my neighboring country, Kenya, where there was success, but in the last few years, after careful analyses of data, we see the number of new infections is rising. So, I think the success we are talking about in this conference is transient. That compels us to think outside the box.

The second thing that I have gotten out of this conference is that, in fact, provision of ARVs, in terms of sustainability and resources, is going to be very difficult. I speak from a policy perspective because when we are talking at the country level, we have told our people this is what will happen. We have convinced them.

There are competing demands and the resource envelope is limited. Only 41-percent of the people in the world who need ARVs are getting them. In my country, it is only 42-

percent. In fact, when you calculate the amount of resources that would be required over the next five years in Uganda for ARVs to make sure that 80-percent of people who need them get them, it would require an excess of \$1 billion. Now, that is one country. If the PEPFAR organization gives \$48 billion for everything, that is just a small fraction of all the countries. How much would we need for the whole world?

This compels us to think that in fact we must target what we do. The facts are glaring in front of us that, in fact, a vaccine is the only way out. That is what I say and that is why I am a very big advocate of an AIDS vaccine. But it is important that these facts are presented at various levels, from the highest level of government and civil society to the lowest level. I think that is important. Sometimes that is the missing link because I find in a conference like this there is activism about many other things, including treatment. There is no activism about an AIDS vaccine. As somebody said, there is not activism about prevention. I did not see and have not seen it.

Now, The STEP trial and the [inaudible] study indeed dampened our hope, but I think our resolve must remain resolute because the information earned through these research efforts compels us to believe that an AIDS vaccine is possible. I think it has been said, but I am going to repeat it. We have phenomena that we know, [inaudible] and we know that these things happen, so therefore we know we can find a vaccine. But

we must remain resolute and determined to find the final blow that will finish off this virus.

As I said on Sunday when we had the forum, I said that slipping is not falling. I am quoting a politician from our neighboring country, Kenya. "If you are walking in a slippery area and you just slip, that is not falling. You stand up and you continue." And I think that is what we must do. And history, of course, reminds us that the road to vaccine research and development is long, rough and full of potholes, but we must go on all the way and eventually to trial.

I come to a very important point as somebody involved in policy. In explaining the above scenario to our political, religious, technical and community leaders, we need to simplify the language. My personal experience with Yoweri Museveni, who is the President of Uganda, at night in a hotel room in Bangkok in 2004 is still valid in my mind. Saith [misspelled?] came. He was trying to explain to the president the importance of an AIDS vaccine. The president, as I said, oh, this virus, is it like an enemy that comes and wipe out the whole armed forces of our country, the army, the air force, the navy, the intelligence? And he said, yes. Is it like an armored enemy that you cannot shoot at, even with all the missiles? And he said, yes. Anyway, it was an animated discussion. At the end of the day, Saith got one of the best advocates for vaccines on the African Continent. Saith is very clever. The president said so, what do you want me to do? He said, Mr. President, I

want you to write to the G8 and tell them that we need more resources for AIDS vaccine research. And he said, please go and draft this letter and I will sign it. He did and the rest is history and you know what happened in Scotland.

But all this I say, we must be able to explain to our other people who are not in this room, not in this conference. Today, as they said, there is only one pipeline and the blueprint gives us reasons why we must now think again looking at all arms of the human immune system or response. What he was talking about really are the different arms of our body and how we respond. We did not waste time, as he said. We have learned a lot. We have built capacity. You have seen pictures of those beautiful labs in Uganda. We have very good scientists. And really, we have gained.

The only thing I think I want to put simply is this—for those of you who attended the prevention series yesterday, we talked about combination prevention. I think we need to talk about a combination research approach, to look at the human immune system in parallel and in combination, as you said.

Finally, I want to say that my voice is from the south. Sub-Saharan Africa is bearing the brunt of this epidemic. It would be foolhardy and illogical to exclude developing countries from participating in AIDS vaccine research. The strains are different all over Africa and an AIDS vaccine would be such that it would be of use in all parts of the world, especially in Africa. We have demonstrated our capacity to

participate, and Uganda takes pride in the contributions of our scientists and research volunteers have made. We thank our site partners for supporting the scientific capacity building in Uganda, and we wish to see this continue. We ask for the voices of support from the developing world to join with the voices from Africa to tell the doubting Thomas's that Africa must have an AIDS vaccine. I thank you for listening to me [applause].

DR. SALIM ABDEL KARIM: Thank you very much, David. So, I think Alan gave you a perspective that the purpose of this session is really to give a sense of how we are moving forward, but if I can for just a few seconds take you back to 1996, which Seth had a slide on. In 1996, vaccine research was really completely undeveloped in South Africa, so I invited two people to come there and help stimulate and get us galvanized to think about HIV vaccines. The two people I invited were Seth Berkeley and Peggy Johnston. It was in this meeting of about 100 people that Peggy gave a presentation which changed my life. In those days, I used to have a lot of hair, so I did not look anything like this. But I sat there, mouth agape, listening to the science and it was inspirational. They say that in your lifetime you are very fortunate if you have three or four people who have served to inspire you. Well, I am now presented to you somebody who has inspired me with her depth of understanding and her knowledge of HIV and the way she is able to put it all together so you get the big picture. Ladies and

gentlemen, please welcome Peggy Johnston, Director of Vaccine Research and AIDS in the NIH. Peggy [applause]?

MARGARET JOHNSTON, PH.D.: Thank you, Salim. Are you trying to say that it is my fault that you have lost the hair on your head? I apologize for that, but if it converted you to a vaccine advocate, it was worth every hair on your head.

What I am going to do in five minutes is talk a little bit about the scientific priorities and what the U.S. NIH has been doing to help contribute to those priorities. I have the advantage, in that we held a scientific summit not too long ago and got the input of several hundred researchers in person at the summit, as well as over 700 individuals that watched the summit on a webcast. So, I am going to give you the output of what we heard.

The bottom line of this was that we needed to torque our investment in AIDS vaccine research more toward discovery and discovery-related research and a little less around the empiric, classical approaches of trying to find an AIDS vaccine. What that means is many things. First, it means understanding why people who are infected do not typically induce broadly neutralizing antibodies. And it also means translating the information that we now have about the structures on the HIV envelope that are the targets of broadly neutralizing antibodies and translating that information into an immunogen that can induce those broadly neutralizing antibodies in vaccinated individuals.

Another key priority for us is to understand the earliest steps of infection, including the role of innate and mucosal immunity in natural infection. Now, as we heard this morning with Bob Siliciano, that window of opportunity that we have from the virus enters to the time when it firmly establishes itself in latency is a matter of days. Now, with other vaccines, we never had to worry about understanding whether innate or mucosal immunity played a role because a more empiric, classic approach of making a vaccine worked. Well, we are now at a point in the HIV field where we have to figure out what these things mean and see if there are ways that we can manipulate that, extend that window of opportunity and give the immune response more of an opportunity to get going and control, if not eliminate, the virus.

So, there are also cues that we can get from studying exposed, uninfected individuals, such as macaques that have high retroviral levels in SIV infection and do not get disease. Another message from our summit was to more closely link the non-human primate and the human studies so that we can better understand the significance of various non-human primate models and be able to more directly compare the data that we get from those two systems.

And also, most importantly on the clinical side, we need to understand more thoroughly the results of the STEP trial. I personally believe that the STEP trial was one of the best accomplishments of the last year, even though the vaccine

failed. There is nothing like human data, a human experiment, to reset one's priorities. We learned an awful lot from that trial, even though the vaccine did not work. We learned, first of all, that natural immunity to the viral vector is something that we are going to have to pay attention to because it may play a detrimental role to outcome. We learned that a smaller trial design can give a result efficiently and effectively, not only about the efficacy, but also about the safety of the vaccine. And we also re-calibrated, as a result of the STEP trial, how we view non-human primate models and which ones we wish to pursue and utilize more thoroughly.

So, as we move forward, understanding the results of the STEP trial are going to be very important. For example, knowing the sequences of the viruses that vaccinees became infected with will tell us whether the immune responses in those vaccinees provided any immune pressure on the virus that infected those people. If that turns out to be the case, then we can build on that to get broader responses and hopefully broader pressure on the virus and broader control.

I think it is also important for us to learn what happened at the tissue level, at the mucosal level. So far, we do not have any hints from what circulates in the blood that help explain the increased risks of acquisition that occurred in men who entered the trial with prior immunity to the Ad5 virus, natural immunity to the Ad5 virus, and who were uncircumcised. We need to understand that.

So, what have we started to do to tackle these scientific priorities? Well, first of all, on the clinical end, our HIV Vaccine Trials Network has revised its scientific agenda to follow up on the STEP results, first and foremost, both to use existing specimens in collaboration with researchers outside the network to learn as much as we can about what happened, and also to potentially do some additional trials that will be more invasive in nature so that we can find out what is going on at the local sites of exposure when one is exposed to a viral vector such as Ad5.

In addition and importantly, we look forward to working with partners to develop more assays, potentially better assays that will hopefully more accurately predict the outcome in a clinical trial than the assays we have been using.

So, in addition to the clinical research that we hope will inform discovery, we are also going to focus on non-human primate research. That is starting by having the HIV vaccine trials soon to elicit a request for proposals to work with them to more closely link the non-human primate and clinical studies. We are also going to be working with partners to expand capacity to provide non-human primates to researchers because as more research has been funded in AIDS vaccine development, the demand for non-human primates has now far exceeded the supply and we need to address that as quickly as possible.

We are planning a couple of workshops, one in conjunction with the Non-Human Primate Symposium in Puerto Rico to encourage the application of genomics research to non-human primate research, and then one a little later in year which will help inform us as to what specific initiatives in the non-human primate arena we should consider for the coming year or two.

So, in addition to clinical and non-human primate, other areas of discovery are high on our research agenda. We will be pouring money into discovery research and having new initiatives to solicit investigator-initiated research. One of these is currently on the street and actually goes a little beyond vaccine research because even though we are confident that a vaccine can be obtained, we definitely want to hedge our bet and look for other approaches that we might be able to institute that can protect from transmission. This initiative is called HITIT, Highly Innovative Tactics to Interrupt Transmission. We are hoping to bring in some research that will look at novel ways of exploiting what we know about the interaction of HIV with the host to kind of block that system.

In summary, we are at a turning point scientifically in the field. We are getting lots of input. We are continuing to get lots of input, and we are trying to implement actions based on input as quickly as we possibly can. Thank you for your attention [applause].

ALAN BERNSTEIN, PH.D.: Thank you, Peggy. Being relatively new to the field, I have turned to a lot of people for advice about who I should get to know and who is a key scientist and opinion leader. One of the people I have relied on a lot is Jose Esparza, who is a Senior Policy Advisor for HIV/AIDS at the Bill & Melinda Gates Foundation. He oversees the very significant investments that the Gates Foundation is making in vaccine research. When I asked Jose, who is a key person, a key scientist in Latin America, the first and only person he told me was Mauro Schechter. And so it is a real pleasure for me to introduce Mauro Schechter to you. Mauro is the Professor of Infectious Diseases at the Federal University of Rio de Janeiro in Brazil. He works on the HIV pathogenesis, the natural history of the disease and, according to *Science* magazine, is the most cited author in Latin America working HIV/AIDS research. Mauro [applause]?

MAURO SCHECTER, M.D., PH.D.: Thank you, so now I know who to thank or blame or both for being here. What I was asked to do is talk briefly from the perspective of a clinical researcher working in Latin America.

I have been involved with HIV vaccine-related studies for almost 15 years, initially with what was then called PAVE, but became [inaudible] and is now known as HVTM. Over this decade and a half, we and others in Rio de Janeiro built a site capable of conducting good quality research, a site that is capable of going through an FDA audit with zero findings. And

anyone who has been through an FDA audit knows it is not a fun experience and having no findings at all is also quite a testimony to the quality of the clinical research being done by the team.

So, what we learned in a very schematic way is that what seems obvious, but is not that obvious, is that to conduct a clinical trial one needs a product, a population, and investigators capable of conducting the trial. Having a population means building trust. Having a team of investigators means investing in training, particularly in settings like ours in developing countries in which there are no research careers—when you go to medical school or to nursing school, whatever you do, no one tells you that there exists a career in research. So, we need to motivate, find these people, train them and keep them. So both the trust and training of healthcare workers take very long to build, but both of them take very, very little to destroy. In one moment they are here, the next moment they are gone.

So, I think the present dilemma, after the news we heard about the trials that did not succeed in terms of efficacy—although, as Seth reminded us, the STEP trial was an extremely well-designed trial and was a very successful trial because it gave an answer and quickly—is what do we do in order not to destroy what took us so long to build. What can we do to make sure that the infrastructure we built is there when the next vaccine comes? There will be a vaccine to be tested and

we will need the infrastructure to be there when that happens. And we need also to be prepared when that happens to not only keep the trust we built within the communities that we have been working with the last few years, but also communities that we never managed to reach. Again, Seth brought up the point of women. In every single trial one of the main problems has been how to recruit high-risk women. That is a thing we have been failing with and that we need to tackle.

Very briefly—in other words, straight to the point—what are the bridging activity one needs to do, in our setting in Latin America and in other developing countries, while we are waiting for the next vaccine that will come? So, I think we need two things, very broadly. One is to find ways to maintain our teams. What we have been doing at my site is we have been trying to get more involved with trials of drugs from big pharma. We have been involved now with the PREP studies, those are prevention trials that are dealing in a way with similar populations. And we are trying to advocate, as we are doing now, for our centers, our sites, to participate in early-phase trials. On the population side, what we are trying to do, because the PREP trial keeps our contacts in the gay community, is we are trying to get small grants to run small studies that can allow us to establish relationships with commercial sex workers in Rio de Janeiro. Thank you very much [applause].

DR. SALIM ABDEL KARIM: Thank you very much, Mauro.

So, the final member of our panel this evening to give a short

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input is Dr. Suniti Solomon. Suniti, for those of you who are not aware, is one of the pioneers in India on HIV and AIDS treatment. In fact, I went to visit her in Chennai where she runs an amazing program called YRG Care. But not only is she a pioneer in the treatment area, she is also a leading figure in the HIV vaccine field and, in fact, she is doing a vaccine trial in Chennai. So, it is our pleasure and honor to have with us this evening Suniti Solomon. Thank you.

SUNITI SOLOMON, MD: Thank you. My task is to talk about clinical trials and community engagement. We all know that without the community, there are no clinical trials—no volunteers, no trials. We need to recruit and retain them. When YRG Care got its first clinical trial funded by the NIH, we did not know how to go about it. The first thing we did was to build rapport with the community. We went to maybe 40 or 50 different communities in Chennai where we built a rapport and found out what their needs were so that there was a true partnership between the scientists and the community and there was mutual trust. And then we built what is known as a community advisory board, about which I had never heard anything before. We included in this community advisory board people from different communities. They were sex workers and drugs users, MSM, HIV-positive people, the police, the advocates and doctors. They would not sit next to each other, but we had to build them up over a period of years. Today, they are of such great help to recruit volunteers for whichever

clinical trial we do. That was the first beginning of the rapport.

Then there was a vaccine trial, a phase 1 vaccine trial, an MVA vaccine trial. The trial went to the ICMR center and they needed to recruit volunteers. They struggled with it. Finally, YRG Care was called in to recruit volunteers. It is very important to start talking to the community right at the time we are thinking of a vaccine trial because it takes roughly six months to build up that mutual trust and recruit volunteers. It took us some time, but we were able to get the 32 volunteers within the next 4 months and the vaccine trial went into being. So, that is about the rapport we build with a community.

The second-most important thing is that we need to also build a rapport with the media because media involvement is very, very important in any trial. The media can write whatever they want and your trial is gone. We needed to make sure that the media came out with the right things, so we had a media workshop where we explained about the vaccine trial. People were worried. An HIV vaccine, will I become positive? That was the first question. And so it is very important to give in simple language the details to the media and to the political people so that the right information comes out.

I am just giving five bullet points. The next point I would like to talk about is the dissemination at the end of the trial. We always forget the community. We always forget the

volunteers. It is so important that they not get the message from media or from a third party. It is our duty to tell them what the results are. For example, we had a phase 3 trial of the microbicide, cellulose sulphate, where we had enrolled in our center 500 sex workers. So, the minute the results came out—and the results were not good, as I am sure you all know—we had to go to the sex workers that we had recruited and give them the results. Luckily for us, there was not a single incidence.

That brings me to the next point. How do you choose a community? Now, in the state I come from in India, the sero incidence is almost nil. In most of the clinical trials, the endpoint is seroconversion, so if there is no seroconversion, we cannot get that community to be part of the trial, so that is another important thing we need to talk about.

Most of the community people ask us, okay, we will join your trial. If I seroconvert, what is the standard of care you will give me? Who is funding this trial? Will we get the same standard as the people who are funding? So, if I become positive, will I get treatment for the rest of my life? These are points we need to talk about. Also, we need to talk about the cultural acceptability. Everybody is talking about the success of circumcision. Let me tell you that it would never work in India because the Hindus object to it. It is a religious problem. So, we have to be very culturally appropriate when we plan a trial.

Lastly, I would like to talk about distributive justice. In most of the clinical trials, it is the low socioeconomic people that get recruited, then when the vaccine or the drug comes out, it are so expensive these poor people cannot afford to get them. So, the risks and benefits have to be across every strata of the society, gender-wise and economics-wise, so that the whole community will benefit from it. Thank you very much [applause].

ALAN BERNSTEIN, PH.D.: Thank you, Dr. Solomon. I am going to kick off this panel discussion with a question and then if Salim has one, he will jump in. I would invite the audience to start thinking about questions or points you would like to make because the panel discussion will go on for about 15 minutes or so, and then I would like to open it up to all of you.

This is a satellite about the future and the future, of course, is about young people and young people make the future. Craig McClure in his opening remarks talked about a relay race. This is a marathon relay race where we have to pass the baton on to the next generation of researchers.

The Enterprise, with a lot of partners, held a satellite on Sunday—which seems about 10 years ago now—where we discussed some of the issues around young people and the barriers and the opportunities that they face in getting engaged and involved in HIV research generally and vaccine research in particular. I thought it was an outstanding

session. I guess my question to all the panel members, from their very different perspective, is what in your view should and could and is being done to make sure that we do have somebody to pass the baton to? Not to put anybody too much on the spot, I will ask Dr. Apuuli about the perspective of Africa. You made the comment that Africa needs to be engaged in HIV vaccine research. What are your thoughts about how to engage young African scientists in this effort?

DAVID KIHUMURO APUULI, M.D.: Thank you very much, Alan. We were discussing one afternoon about how we can tap the young scientists in African universities who have innovative ideas, but may not necessarily have any funds. I think we need to be able to establish linkages with our various universities and [inaudible]. I am sure if there were more grants for doctoral or postgraduate work in these areas, we would be able to attract scientists who would join the pool that would provide what is needed for the future. I think this is possible. This is possible and can be explored. We talked about it. The networks can be established.

ALAN BERNSTEIN, PH.D.: It is interesting that you made that suggestion, because that suggestion also came out in the satellite from a young researcher at Salim's institution, actually. It is interesting that it has come up twice. Does anybody else want to jump in on this one? Mauro?

MAURO SCHECTER, M.D., PH.D.: I would make a comment. That is a point that I failed to mention. About two or three

years ago there was sort of a mantra that kept going on and on about what we were doing wrong in HIV research in general in developing countries, because you do not see new researchers. Everywhere you go it is the same faces, just all of us in our mid-50s. You will see me, James and others—the same guys. Where is the next generation? I think in the vaccine field we will fail again as a relay marathon when every time we have a problem we just shut down the sites and tell them, look, next time. We are not giving the right message if we do not tell all the researches that this is a relay race, a long race, but if you join now you will be able to have a career and work for a period of time. It is not that you will work for two years and then it will be gone.

MARGARET JOHNSTON, PH.D.: I think as we put more emphasis on discovery research, it will make it somewhat easier to attract younger people into the field. I think what we will be looking for is the application of new technologies to HIV vaccines, so young researchers who have learned those new technologies in other areas, whether it is genomics, proteomics, whole genome analysis and so forth, they will have opportunities to bring those tools into the HIV field.

I think the other point I would like to make is that, in my mind, there is a misconception that large consortia impede young investigators from joining the field. My own experience has been quite the opposite, with organizations like CHAVI, in particular, that are more focused on the research

rather than the trial side. There is an opportunity for young investigators to get funding for their projects without having to go through arduous first-time application to get a grant. They can help develop a field and develop their career with basically free money from the consortia. So, I think there are several opportunities there.

The third thing I would say is that for applications that come in to us, we pay special attention to new and young investigators and give them special consideration in the funding considerations.

MAURO SCHECTER, M.D., PH.D.: I hate to disagree with Peggy, but I have to. Basically, this is very well for U.S. investigators, but there is no career in genomics in Rio and Chennai.

MARGARET JOHNSTON, PH.D.: I do not think we disagree on that.

DR. SALIM ABDEL KARIM: If I can just touch on the issues that Mauro and Peggy and David have initiated, on the one hand, the south has been very heavily involved in undertaking the trials, but the question I have is how do we go beyond that? How do we go beyond that to the stage where we are able to get more of the discovery research also being done in the south? How do we build these relationships between north and south, given the lack of research labs and so on in the south? What are the ways and mechanisms that we might want to think about for the future to help develop this new cadre of

researchers in the south as well? Perhaps, Mauro, you might want to kick us off and then I will ask Peggy to comment.

MAURO SCHECTER, M.D., PH.D.: That is a very good question. I think that is something particular to Brazil and to my setting, in which it is very difficult to attract people to academic careers. So even though we have had the Fogerty Grant for 10 years now, I always find it difficult to recruit people to go and PhDs in other countries, in the U.S. I think that is particular to Brazil, or maybe even to Rio, because I think people do not have that difficulty in South Africa, for instance. But I think one of the things that you rightly pointed out, which is that you need to find ways to also have genomics in Rio one day.

DR. SALIM ABDEL KARIM: Seth, you wanted to comment?

SETH BERKLEY: I just think it is a critical priority. One of the priorities is to make sure you balance the research capabilities with what you can do at the sites. That is the important balance. In the past, a lot of training has gone on. People who have gotten advanced training go on home and there has been no equipment or ability to do that research. Today we have these fabulous laboratory facilities that are around the world. We have an opportunity to begin to build those into discovery as well, and we have to do it through a partnership. I think that is going to be our challenge over the next 5 to 10 years.

DR. SALIM ABDEL KARIM: Just to pick up on that, if you look at the Ugandan labs that you have built, has that become the kind of center that has now attracted younger researchers to focus more on lab science in Uganda?

Okay, so let me just take on the next issue, which is related to this. On the one hand, we want to get more of the discovery research done. We want to engage across the globe. It is amazing when you look at the panel. We are talking about a truly global effort. We have people from four continents. We have Africa, South America, the U.S., and Asia. What are the ingredients that we need in order to encourage more communication and more collaboration across the globe, so that we are working in one joint effort in dealing with this problem? Let me start off by asking Suniti to comment.

SUNITI SOLOMON, MD: I think people in the south, in the developing countries, go abroad. They go to the western world and get trained. What they need when they come back is the infrastructure. So, if you just train researchers in the north and they come back home and there is nothing to take, why will they come back? And so we lose a number of our scientists to the western world. But if we could have a true collaboration between the north and the south and build the infrastructure, the laboratory, the things we need—maybe not as good as in the west, but at least that which we can work in—taking into consideration many things. For example, natural disasters are so common in the developing world. There is a

tsunami and then everything is gone. There is a cyclone and it is gone. So we need to have all that back up.

I am speaking from my own experience. I started my lab in an old little kitchen, which was 4 feet by 6 feet and I just did two or three tests there. Today our lab is quality-assured by the College of American Pathologists. I would say it is one of the best laboratories in the country for HIV. It is not a gourmet setup. It is an ongoing mental organization. So, it is possible through hard work and collaboration. We collaborate with Brown University, with Hopkins and with many other universities with the U.S. I think it is true collaboration when they can build up the lab for you. They can build up the training, your capacity, and then give you what is necessary to complete the research. That is true collaboration between the west and the developing world [applause].

ALAN BERNSTEIN, PH.D.: I am going to throw this open now to the audience, or maybe to the people sitting in the chairs. I will not call you audience. I encourage you to come to the microphone and state who you are. I see Jose going to the microphone. Then state your question.

JOSE ESPARZA, MD, PHD: I am Jose Esparza. You know, a significant absence in the panel is somebody from biotech or the pharmaceutical industry. There is a lot of innovation in the biotech sector. At the end of the day, the industry has the expertise for the development. We need to harness both the creativity of biotech and the expertise of the industry. My

question to the panel is what are we doing wrong? What should we do in the next two years, by 2010, to remove disincentives or to create incentives that would bring those two important sectors to the field?

ALAN BERNSTEIN, PH.D.: Seth, I know IAVI has a number of partnerships with the private sector. Why do you not have a stab at this one?

SETH BERKLEY: Let me answer if I can in three ways, Jose, for that very important question. At the end of the day, innovation is concentrated in biotech. First of all, trying to create incentives to get them engaged at the beginning—no biotech company—I should not say none, but very few are going to say that HIV vaccines are where they are going with the company because that is not seen a very profitable area. So, one of the challenges is whether you can take existing biotech companies working in other areas and have them do some experimentation to see if their technologies are relevant. As you know, we have created an innovation fund just to do that with you, to try to see if we can get those companies to engage. I think if they do have products that are useful, then I think they will engage because you have given them some proof-of-concept and we have to work it out. But there are also financial incentives like the advanced-market concept that has now been used for other vaccines that may create an artificial market. And also, if the whole field is moving and

big pharma starts getting interested again, they could potentially provide a pull.

But the other thing I would like to mention for the future that is important is biotech in the developing world. Although it is somewhat nascent, there is really interesting technology. We are now working with two biotech companies in India, one which we are working with on trying to do medicinal chemistry because they are very good at it and they are willing to put a lot of FTEs on the problem, but also one that does in silica modeling and they just happen to be some of the best in the world at doing that. And so I think figuring out how to get the Chinese biotech and Brazilian biotech and South African biotech and Indian biotech engaged in this is one of the challenges that I think we have as a field.

DR. SALIM ABDEL KARIM: I am wondering something. Jose, does the foundation have programs that could serve as an incentive, or has the foundation been thinking about how to incentivize biotech in the developing world to get involved in vaccines, or is that being done through ARV?

JOSE ESPARZA, MD, PHD: I want to suggest it for you, but we can fund the private sector. That is within our possibilities. Of course, we impose some conditions and those conditions are defined by us as global access or global access strategy. When we fund an academic researcher or a biotech in the future, we will make sure that the results from the research are available, or at least there are not impediments

to make that research or those products available in developing countries. But we do have that possibility.

ALAN BERNSTEIN, PH.D.: Does anybody else from the audience want to pose a question or make a comment?

ZACHARY ZIMANA: Thank you. My name is Zachary Zimana [misspelled?] from Burund. I am working the [inaudible] AIDS, the original initiative set up by the six countries of the Great Lakes Region. As some may expect, after this conference when we go back in our countries, the situation will be just to ask, how far are you with the vaccine or what are the new developments about the AIDS vaccine? It is not really easy for people who are not researchers like us to give a simple and concrete response. That was really a very interesting PowerPoint presentation from Dr. Seth, but it was not really to capture one message giving, on one hand, optimistic aspects assuring that really we are near good results, but on the other hand we have some bad news. To weigh which message we will be giving to the Burundians or Congolese or others will not be really easy, for me for example. So I would just simply ask whether I can have a simple message to give to my communities when I am back saying about the AIDS vaccine, what is now being done the next few years and what can we hope? At the end of the day, the hope is to say there is something really interesting to share with you. That was my first question.

My last question is this. In some different programs, we face issues of budget allocation about research. Is there

any information about maybe challenges you may have or you may face in terms of budget allocation about research or about AIDS vaccines? Thank you very much.

ALAN BERNSTEIN, PH.D.: Alright, two interesting questions. I see Seth grabbing the microphone. Let me phrase the first one like this, Seth. You are in an elevator with a political leader. You are going between floors one and eight. What do you say to him or her?

SETH BERKLEY: I will answer that directly, but I want to give you a background statement first, which is that 10 years ago the first vaccine blueprint was written by the lady sitting to my right. At that point, we really laid out timelines because we had a bunch of products that had not been tested and so what we knew is that we could test these products and if they worked, you kind of knew what the timeline was. Now I think we are in a different situation because we have a lot more science, yet we do not have a particular product we are putting our money on. Therefore it is much harder to predict the timeline. I just wanted to give that background because we were probably too optimistic. I know I felt I was when we were doing timelines in those days. Obviously, we were. I think we have learned from that. But to answer Alan's and your question, I think the answer is that an AIDS vaccine is possible. Huge progress in science is being made. And you have to trust science. We will get there. I think that that is the answer.

ALAN BERNSTEIN, PH.D.: Peggy?

MARGARET JOHNSTON, PH.D.: Well, I would not answer the question, but what I would say is combination prevention. We have tools that we can use and implement and scale up today, and we need to do that. We need to do it quickly and we need to do it now. And when we have a vaccine someday, whenever that is, we can add that as a new tool to the prevention toolbox, but let us not wait for that. Let us do what we can today, as much as we can [applause].

ALAN BERNSTEIN, PH.D.: I cannot remember your second question.

SETH BERKLEY: The second question was about budget allocation. The answer is that we are doing much better than we were 10 years ago. The world is spending a much more significant amount of money. I think the critical thing is going to be sustaining this over a period of time. So, making sure that the money is available reliably over that period of time and that there is flexibility is critical to making sure that it can keep up with the science advances that occur.

ALAN BERNSTEIN, PH.D.: There is a question over there? Go to the microphone.

FEMALE SPEAKER: Good evening. It is a very simple question which is related to what the guy asked before. I have been working on AIDS for about 15 years. Every world conference is almost the same, then there are another 10 years and another 10 years and there will be 5 years. This time it

is growing. Every year it is growing and there is no vaccine. But on the other side, I see there are very specific drugs for the fusion, for the nucleus, very specific—medicines are growing so far from every part of the virus specific for attacking this part, but the vaccines just stop there. It is very difficult because the virus is changing, the tropism and all the kind of reasons that are very difficult for me to understand because on the other side, there are very specific, very direct to every part of the virus that is going to be healing the patient, but the vaccine is like staying here and the drugs are going there. It is like unbalanced. I cannot understand it. Humbly I ask why. I understand it because every year is the same. There is no answer for that. Thank you very much.

ALAN BERNSTEIN, PH.D.: Excellent question. Peggy, do you want to answer?

MARGARET JOHNSTON, PH.D.: Peggy, that is a very good question and there is a level of answers to that. I guess what comes to my mind are several things. First is really a human nature issue. That is, in general, people have valued treatment more than they have valued prevention. There is a value one can see when one gets treated and the person gets better. It is difficult to see when something does not happen. And so in general, regardless of what field you are talking about, AIDS or cancer or whatever, treatment is a value to society monetarily more than prevention. That has driven the

innovation from the private sector to make drugs and to sell them, whereas we do not have that same incentive for prevention because look how much vaccines cost. They are generally very cheap. They are given once or a few times and they last a lifetime, as opposed to a drug that you have to take once a day for the rest of your life. And so the market incentive for companies to be involved in treatment is much more than vaccines.

I would also say that because of the special characteristics of HIV and the way it hides itself from the immune system, in many ways it has made it much more difficult scientifically to make a vaccine than to make a drug. So the analogy I would make is that we cannot cure HIV and we do not have a vaccine either, because I think that curing HIV and getting rid of that latent virus is the same order of magnitude of difficulty as making a vaccine is. The drugs are more of a temporary measure of keeping people alive.

ALAN BERNSTEIN, PH.D.: Okay, I was about to say that in a session I was at the moderator asked the following question: What keeps you awake at night? So, I am going to ask each of the panelists to ask the following question in 25 words or less and then I think we will wrap up. This is about the future, so the question I will pose for you is this—and this is actually a paraphrase of the question that Richard Horton asked at the session this morning. What surprise would you wish for? That was not my question. But answer that one.

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ALIZA PEDROZA: Hi, I am Aliza Pedroza from Mianarez [misspelled?]. I am an old researcher. I was working on HIV variability to start with, so I was very pessimistic about vaccine. In the early '90s I become optimistic again, but I think it is a very difficult problem and what keeps me awake at night is whether we should do efficacy trials. That is what keeps me awake at night. High-risk population—I still do not know if it is ethical to go to high-risk populations and put them in vaccine trials when we do not know at the time if it is necessary between vaccine and challenge in an animal model. That might be a very important question, so that keeps me awake at night—should we do efficacy trials.

ALAN BERNSTEIN, PH.D.: That is a very good issue and I will ask the panel. Seth?

SETH BERKLEY: A lot of people who criticize vaccine research criticized the VaxGen trial. As you know, there was a huge controversy about whether it should be done or not. A number of people have said that it led to some really important lessons. I know a lot of people do not believe that because they only focus on the science, but prior to the VaxGen trial people said, well, you cannot do vaccine trials because one of two things will happen—either you will give the information and there will be no infections, or people will think they are vaccinated and they will go out and do wild, high-risk activities and it will not be ethical. What is interesting is that we now have data from that experience. What happened is

when you went ahead and counseled people, their risks dropped, the infection rate dropped over time. It started going back up, but it did not cross the baseline. To me, that answers that question because what you have is obviously a group of people who volunteered and understood the risks. They did not have increased risks. In fact, they had decreased risks, but their risk did not go to zero, which explains ultimately why you need a vaccine. So, in essence, that does not keep up at night. Maybe I should start.

What keeps me up at night is the issue of people losing interesting HIV and vaccines and therefore having us continue to make these breakthroughs, be close to having candidates that are really exciting, but not having the finances to be able to keep them moving forward.

DR. SALIM ABDEL KARIM: Perhaps let me add just one additional perspective. If we did not do the STEP trial, how would we know that circumcision has some impact on risk of infection? How would we know that preexisting immunity has some impact? So, in a way, those questions could only have been answered by the fact that the human studies were done. And I think what we have learned—certainly in the microbicide field and now in the vaccine field—is that HIV infection is really the most critical and most central safety endpoint as well as efficacy endpoint. And so we do these studies with HIV as the endpoint because it is the ultimate endpoint and the

only one we have right now to be able to answer the question of whether the vaccine is safe or efficacious.

Going back to Alan's question—

ALAN BERNSTEIN, PH.D.: What surprise would you wish for over the next 5 to 10 years? Tell us in one sentence so we can cover it, and then we will close this session.

MARGARET JOHNSTON, PH.D.: Well, I have to explain before I give the one sentence. There is some in vitro evidence that suggests that binding antibodies will block the interaction of HIV and dendritic cells. So, if infection begins in some people with the interaction of the HIV virus with the dendritic cell and if binding antibodies can inhibit that, than maybe we will see a positive signal at some level from the Thai trial next year and then we can build on that.

ALAN BERNSTEIN, PH.D.: Okay and I am going to start at my right and go right across after that. The question was what surprise would you wish for in the near future? You wanted to know the question, David.

DAVID KIHUMURO APUULI, M.D.: I understand and hear. I think I wish we could decipher what it is in the few people who are able to keep the virus at bay for a long time. What do they actually have that can help science?

ALAN BERNSTEIN, PH.D.: Suniti?

SUNITI SOLOMON, MD: Okay, in very short, a world without AIDS, but I know that is not going to happen. I would like people to find out what it is that prevents acquiring the

infection in some people in this world. Is it mucosal immunity or cell-mediated? We do not know, but some of them never get infected, in spite of repeated exposures. How is it that we have these exposed seronegative people?

SETH BERKLEY: There are a lot of surprises I would like to see. Recently we have been looking for more neutralizing antibodies and we found some serum that is super neutralizing. I would love to find a really new binding site where it turned out that you could neutralize pretty easily all the viruses from it.

ALAN BERNSTEIN, PH.D.: Mauro?

MAURO SCHECTER, M.D., PH.D.: I think what Peggy said, a positive signal in the Thai trial next year and something that leads us, through the Thai trial, to understand or find correlates of protection.

DR. SALIM ABDEL KARIM: On a personal level, I would like a medical drug that makes instant hair. But on the HIV front, it has been amazing what we have seen in terms of the neutralizing capacity of monoclonals like 4E10. The surprise I would like to see that we are able to find an antigen that is able to stimulate in the human body such a broadly neutralizing antibody.

ALAN BERNSTEIN, PH.D.: I posed the question, so I do not have to answer it. I think what I will do is just make a couple of closing remarks and then Salim can feel free to jump in.

This has been, to me at least, a very stimulating and interesting conversation that is rooted, given who has been talking, in a very strong reality of what all of our panelists actually do on a day-to-day basis. So, it has not been a crystal ball session, which I think would have been a waste of time, but rather a very informed projection as to where the world is going in HIV vaccine research.

I think I take from this that the overall view is very positive, but that there are significant scientific challenges. My own view of that is that that is a very realistic view. Unless we have a realistic view, we really will not make progress as quickly as possible. And so starting with the STEP trial, which has been my entry into this field, I think the discussion and debate and naval gauging that has gone on has been outstanding in terms of trying to decide where the field needs to go, rejigging what the priorities are and should be going forward and recognizing what the needs are in the field. So I personally feel very optimistic about the future, and I think it is reflected in the conversations that we have had here this evening. Salim?

DR. SALIM ABDEL KARIM: Just by way of concluding, I think we have had some amazing discussions and input today. We have looked at the whole range of events. We know what a vaccine is capable of because we saw it in smallpox. We would really like to have that, but we know that there are many challenges in getting there. On the one hand, we heard from

panel members how the setbacks in the STEP trial and Phambili trial are actually opportunities to learn. Those were exceptional trials and they are going to teach us an amazing amount about what are some of the key things that will enable us to move forward.

I think what we have also gotten a sense of is that we are not going to solve this problem as isolated groups. This is a global problem. We have to solve it at a global level. We have to find the partnerships and the mechanisms for us to work together south to south and north to south. We have to build the next generation of researchers. We have to develop them and create the opportunities and the infrastructure for them to thrive. But ultimately, all of us up here at the table and all of you in the audience—all of us are contributing to an HIV vaccine. We are all doing so in our own little way, whether it is participating in trials, conducting trials, doing research or advocacy. What makes it all come together is the fact that we share this vision that a vaccine is doable, a vaccine is possible, and that one day we will have a vaccine. Thank you very much [applause].

ALAN BERNSTEIN, PH.D.: I want to make one more surprise and then one comment. The surprise would be that when we gather two years from now in Vienna that this room is filled with activists and people who are demanding that the world focus on a vaccine, make the resources available, and that this is a critical priority. This conference is particularly

important because, as you know, vaccines have not been given a lot of priority, so that would be a big surprise to me, but one we can aim for.

I want to extend a special thanks to Alex, who many of you, who really put this session together and did an incredible job. There was a job of work behind it. He has been fighting this battle for a very long time. I would like to give him a real round of applause [applause].

DR. SALIM ABDEL KARIM: Thank you very much. You have been a wonderful audience. Travel safety back to your hotels.

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