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HOPE FOR THE FUTURE: DEVELOPING AN HIV/AIDS VACCINE

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BEFORE THE

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ONE HUNDRED NINTH CONGRESS

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HOPE FOR THE FUTURE: DEVELOPING AN HIV/AIDS VACCINE

Thursday, June 23, 2005

U.S. SENATE,
COMMITTEE ON FOREIGN RELATIONS,
Washington, DC.

The committee met, pursuant to notice, at 10:00 a.m. in Room SD–419, Dirksen Senate Office Building, Honorable Richard G. Lugar, chairman of the committee, presiding.

Present: Senators Lugar, Kerry, Feingold, Boxer.

OPENING STATEMENT OF HON. RICHARD G. LUGAR, U.S. SENATOR FROM INDIANA

The CHAIRMAN. This hearing of the Senate Committee on Foreign Relations is called to order.

During the past two and a half years, the Committee on Foreign Relations, on multiple occasions, has addressed the horrific consequences of the HIV/AIDS pandemic. We've examined many subjects related to HIV/AIDS, including the intersection of AIDS and hunger, the AIDS orphan crisis, the impact of the disease on women and girls in the developing world, and the implementation of the President's Emergency Plan for AIDS Relief, commonly referred to as PEPFAR.

This five year, $15 billion initiative is unprecedented in its scope and importance. According to Ambassador Randall Tobias, the global AIDS coordinator, the United States is currently treating 235,000 men, women and children with antiretroviral medications, in 15 of the most afflicted countries in Africa, Asia and the Caribbean. American agencies are also heavily engaged in prevention efforts and caring for some of the millions of orphans this disease has created.

Despite this work to treat those living with HIV/AIDS and to prevent new infections and corresponding efforts by organizations such as the Global Fund, the Bill and Melinda Gates Foundation, and the World Bank, the disease is outpacing us. According to the latest figures from the U.N., there are approximately 40 million people living with HIV/AIDS around the world today. An estimated 4.9 million people were newly infected last year. This means that every day around the globe, some 14,000 people contract HIV/AIDS.

Of the 40 million people living with the disease, U.N. AIDS estimates that five to six million people, mostly in low and middle income countries, need antiretroviral treatment immediately. Accord-

ing to the latest statistics in U.N. AIDS, only one person in ten who needs the drugs currently is receiving them.

The social, political and economic consequences of this pandemic are enormous. HIV/AIDS does far more than weaken the immune systems of individuals, it destabilizes families and the social and economic infrastructure of communities and nations.

The AIDS crisis in sub-Saharan Africa has profound implications for political stability, development, and human welfare that extend far beyond the region. In addition to the crises in Africa, public health workers warn of a second wave of countries on the verge of a potential AIDS crisis, such as China, India, Russia, Nigeria, and Ethiopia. In fact, just two days ago, during a hearing on Russia, this committee heard testimony about the threat that AIDS poses to that country.

Getting ahead of this pandemic through prevention and treatment programs alone will continue to be a very difficult challenge. That's why today we'll be looking toward the future to see what hope scientific research can offer for the prevention of the spread of the disease, and specifically, we will examine the progress in developing an effective HIV vaccine.

Historically, vaccines have led to some of the greatest achievements in public health, and are among the most cost effective interventions. During the 20th century, global immunization efforts have eradicated smallpox, virtually eliminated polio from the Western Hemisphere, Europe, and much of Asia. Vaccines for diseases such as measles and tetanus have dramatically reduced childhood mortality worldwide, and the vaccines for diseases such as influenza, pneumonia, and hepatitis help prevent sickness and death among young adults.

An effective HIV vaccine is the world's best chance to stop this pandemic, but the search for an HIV vaccine must not come at the expense of our immediate life-saving response. Let me stress that we are not limited to an either/or choice between vaccine research and HIV/AIDS treatment. Rather, we should pursue an all-of-the-above approach that includes vaccine research, education and prevention programs, and treatment efforts as a part of a truly comprehensive response to the crisis. It's also important to note that funding is only part of the challenge for vaccine researchers. At this stage, we must also improve scientific coordination, government cooperation and public awareness.

Because of the promise that an HIV vaccine holds, I've introduced a resolution, Senate Resolution 42, supporting initiatives to accelerate research on this effort. I've called this hearing to raise understanding of the scientific and administrative hurdles that must be overcome to make the vaccine a reality.

Last summer, at a meeting of the G-8 at Sea Island, the member states endorsed the Global HIV Vaccine Enterprise, which is a virtual consortium of the world's leading scientists and independent organizations dedicated to an HIV vaccine. Modeled after the human genome project, the Enterprise seeks to accelerate efforts to develop an effective HIV vaccine by enhancing coordination, information sharing, and collaboration globally.

In support of the Enterprise, President Bush established a new HIV vaccine research center, known as the Center for HIV/AIDS Vaccine Immunology. My resolution commends the G-8's and the President's actions, and urges the President to work with the G-8 countries to support the Enterprise efforts. We want to know more about what the scientific community is doing, and we welcome input on how Congress can support these efforts. I view Senate Resolution 42 and this hearing as just a start. We're continuing to work to identify legislative options that might help advance vaccine research.

Today we are honored to be joined by a number of witnesses who have brought their estimable talents to bear on addressing the global HIV/AIDS crisis. First of all, I would like to welcome my special friend, Representative Peter Visclosky of Indiana to the Senate Committee on Foreign Relations. The Congressman is the author of the companion resolution to Senate Resolution 42, which he has introduced in the House of Representatives. He's taking a lead in promoting legislative awareness of HIV vaccine issues in the House.

I've had the pleasure of working with Pete on many initiatives over the years, I'm excited to have him as a partner in advancing the Lugar-Visclosky Resolution. I also want to thank Representative Peter Kind, the lead House Republican co-sponsor, who could not be with us today.

Next, we will welcome actress Ashley Judd, who joins us in her capacity as Global Ambassador for YouthAIDS, an organization dedicated to educating and protecting young people from HIV/AIDS. Ms. Judd has traveled extensively in Africa and Asia, where she has raised awareness of HIV prevention, and has been a source of comfort and strength to individuals stricken with the disease. She also has been a committed advocated in this country for AIDS education and philanthropy. We look forward to her presentation, and thank her for sharing her important work with us today, which will underscore the urgency of achieving an AIDS vaccine.

We will also hear from three distinguished experts in the field of HIV vaccine research. Dr. Anthony Fauci, is Director of the National Institute of Allergy and Infectious Diseases at the National Institute of Health. Dr. Helene Gayle is Director of HIV/AIDS/Tuberculosis and Reproductive Health with the Bill and Melinda Gates Foundation. Dr. Seth Berkley is President and CEO of the International AIDS Vaccine Initiative. The enterprise of these three individuals is extraordinary, and we're grateful for the benefit of their counsel today. I look forward to hearing from our witnesses about the progress of the enterprise, and other efforts in developing an effective HIV vaccine.

May 18th is HIV Vaccine Awareness Day, and this year's theme was "Hope for the Future." Given the potential lifesaving benefits of an HIV vaccine, this was an appropriate theme, and one we have adopted for today's hearing. I am confident that this hearing will help us better understand what the public and private sectors can do to accelerate efforts in developing an HIV vaccine. I note the presence of two of my distinguished colleagues, Senator Kerry and Senator Boxer, and I ask their permission to proceed with the wit-

nesses, unless you have an opening statement, Senator Boxer. I thank the Senator.

It's a pleasure to call now upon Pete Visclosky of Indiana.

STATEMENT OF THE HONORABLE PETE VISCLOSKY, UNITED STATES HOUSE OF REPRESENTATIVES, WASHINGTON, D.C.

Representative VISCLOSKY. I want to thank Senator Boxer for allowing me to testify today, to highlight the need for a coordinated effort in developing an HIV vaccine. Mr. Chairman, in particular, your leadership on this issue throughout the years is laudable, and it is an honor to work with you now on this initiative.

This is a time of great opportunity in the fight against HIV, and the United States has a chance to assume a leadership role in developing an HIV vaccine. I'm proud to work with you by introducing the Lugar Resolution in the House, as House Resolution 286. This resolution is significant because it represents a bicameral, bipartisan effort to combat HIV.

I'm particularly happy to represent Representative King, as well—he could not be here today, he is chairing a hearing—my fellow Notre Dame alumnus who has joined with me in introducing this important legislation reaching across the aisle to do what is right.

Working between the parties and between the chambers of Congress, we can make considerable progress on the issue. Your initiative to coordinate research is important if we are ever going to get ahead of the disease. The magnitude of the crisis is unfathomable.

Most disturbing, last year alone roughly 600,000 of the cases worldwide afflicted children. In fact, 50 percent of the new HIV cases reported in 2003 were in young people between the ages of 15 to 24. The worse area of the world, of course, is Africa. Sub-Saharan Africa has only 10 percent of the world's population, yet it has 60 percent of the world's HIV/AIDS cases. Over 7 percent of the adult population is living with the disease, orphaning a whole generation of children. HIV is ravaging the continent. But this is a disease that knows no boundaries, political or cultural. Eastern Europe and the former Soviet Union have experienced a nine-fold increase in the number of HIV cases over the last decade alone.

HIV is affecting every facet of life in the hardest hit areas of the world. In addition to the human toll of the AIDS pandemic, this disease threatens the political and economic stability of those countries and regions. AIDS cases in key government officials have gone undisclosed for years in some countries. AIDS threatens to destabilize governments in Africa, Southeast Asia, and Eastern European nations, and could have serious repercussions for global stability.

The country of Zambia offers a good example. Between 1984 and 2003, there were 102 special elections, due to vacant public offices. Of this number, 29 elections were due to the deaths of the incumbent. Similar figures can be cited in numerous sub-Saharan African nations. Often times these deaths or resignations are reported as due to prolonged illness, instead of AIDS, masking the true extent of the problem.

While this epidemic is worse in other parts of the world than it is here at home, we cannot ignore the ravaging effect of HIV and what it is doing to our nation. Today, AIDS is one of the top three causes of death for African American men and women, for example. There are close to 1 million people living with HIV in the United States today. This is an epidemic that is affecting the security and public health of our nation, and we should act.

In order to fight this epidemic, we must have a coordinated global effort, and the tools of the public health community must be expanded to include more prevention technology, such as the vaccine. Given the scientific complexity of developing an HIV vaccine, only a large-scale coordinated effort can effectively accomplish this goal.

Yet, in 2004, only 1 percent of the spending on HIV-related programs worldwide went toward vaccine research. We cannot sacrifice current efforts to combat HIV and AIDS, instead, we need to expand the scope of the fight against it. The global community must come together and share research, resources, and technology if the goal of creating an HIV vaccine is to be achieved.

Without increased resources and coordination, the development of the vaccine remains unlikely. Senate Resolution 42 and House Resolution 286 are important first steps in coordinating the efforts on vaccine research. Last year at the G-8 summit at Sea Island, the United States took the lead on this issue, and encouraged the G-8 members to endorse the Global HIV Vaccine Enterprise. This virtual consortium, if you will, of scientists, researchers, and other stakeholders committed to developing an effective vaccine will be critical to accelerating efforts to develop it. We must continue to build on the G-8's efforts to develop an HIV vaccine through global cooperation and coordination.

Senate Resolution 42 and House Resolution 286 will show the world that the United States is committed to the Global HIV Vaccine Enterprise, and that we are committed to the development of the vaccine. Mr. King and I will continue to work hard in the House for the passage of H.R. 286. Mr. Chairman, I know you and others in the Senate will be similarly occupied, and I do urge the committee to support Senate Resolution 42.

The CHAIRMAN. Thank you very much, Congressman; we really appreciate your personal witness and your leadership on this effort.

Let me ask my colleagues if they have questions or comments for the Congressman?

Senator KERRY. Mr. Chairman, I do not have a question for the Congressman. I want to thank the Congressman for taking time to come over here and for his concern and involvement in this issue.

I would like to make just a couple of comments, and I ask the indulgence of the Chair because the Iraqi Prime Minister is here, and I have to go over and meet with him quickly, but Mr. Chairman, I really commend you for holding today's hearing. As we both know, there's a lot of attention that's been given to treating victims of HIV/AIDS, as it ought to be, and we've done a fair amount of good work on this committee, but I really want to express a very deep frustration. And I think the Congress itself ought to be—I don't know, I mean, the words just sort of leave you gasping for

where the reality is, because we've been at this for five years, six years in the committee—Senator Frist and I co-chaired in 2001, a national effort, and we passed legislation right here in this committee, and we put together the Vaccines for the New Millennium Act of 2001. We put in incentives for pharmaceutical companies to develop vaccines. It passed this committee, passed the Senate, and it was stripped out in conference by the Finance Committee.

So, the Congress of the United States is culpable. It stripped it out. We had an opportunity to do something on this in 2001, we talked a lot about it; we have big hearings, you know, big moments, but I think it's critical that we really get this right this time, Mr. Chairman. Now, it wasn't in committee that we did it—the tax credits were done on the floor—so I want to make that clear. But, Mr. Chairman, you've been committed to this; you're deeply committed to it; this committee has been deeply committed to it; we've tried to do what's right; we even got Senator Helms on board, and we had a unanimous effort out of this committee; and yet, a few people are able to strip something, and the result is, you know, millions more people get infected, and millions more people are going to die. And we are looking at something that we know is a national security issue, as well as a moral and compelling human condition issue, because countries that have this kind of devastation with respect to their human infrastructure, are countries that are going to wind up as failed states, and we all understand the consequences of that.

So, Mr. Chairman, I hope that you and I and others can really work together and convince our colleagues of the importance of getting it right this time, and I really look forward to doing that with you. I hope you'll join again in supporting that effort within the Millennium Act Bill for those credits.

The CHAIRMAN. Senator Kerry, I deeply appreciate your recitation of the history. I think it's very appropriate that the committee, and all who are witnessing, hear and understand the struggle. This is a situation in which resiliency by the committee, as well as those who are involved, is of the essence because there has been disagreement about the priority, about the money, about the program. But, here we are again, and this is an important initiative, and I welcome your enthusiasm, as always, and your resiliency.

Senator Boxer, do you have a comment?

Senator BOXER. Just one question, I wanted to thank you, Mr. Chairman, very much for holding this hearing, and thank Senator Kerry for his strong leadership on this. I do have a question. When President Bush announced his plan, the President's Emergency Plan for AIDS Relief, it was very well received by, I think, everyone in the Congress and in the country and around the world, and he announced plans to spend $15 billion to combat HIV/AIDS. He announced that in his State of the Union speech, that was January of 2002, and as of March '05, only a very small percentage of the program's funds have been spent, now my understanding is it's just a couple billion—I'm asking, Congressman, if you're aware of that—but the other issue that concerns me is that China, India and Russia are not on that list of countries. And my good staff tells me that if India, China and Russia were to reach even half the preva-

lence rate of sub-Saharan Africa, or 3.7 percent, more than 92 million people would fall ill. Ninety two million people. So, I guess my question of the Congressman is, what's your sense about how the spend out is going, and does it concern you that these countries are left out? Is it realistic to just shut our eyes to the potential catastrophe here?

Representative VISCLOSKY. Well, we shouldn't close our eyes. The trend is very disturbing, and I think the position you have enumerated here, really suggests why we should make sure that the Senate and House resolutions are passed, and that we do everything possible on a daily basis, and continue to focus attention on this problem. Because the situation, from my perspective, continues to deteriorate, and again, you state the problem very well.

Senator BOXER. Thank you.

The CHAIRMAN. Thank you very much, Senator Boxer. Clearly the spending issues have been before the committee, as well as the issue of Russia, specifically, which you have commented on. In our hearing just two days ago, we had testimony that as many as 100 cases of HIV/AIDS are actually in Russia now, although the status of denial exists on the part of the government, but that won't cure the realities. So, I appreciate your illuminating that. Thank you very much, Representative Visclosky; thank you for coming over today.

The Chair would like to call now our second panel of the morning, a very distinguished guest, Ms. Ashley Judd, Global Ambassador of YouthAIDS. Would you please come forward, Ms. Judd? We welcome you to the committee, and we look forward to your testimony.

Let me mention to you and to all of our other witnesses, that the written testimony that you have submitted to the committee will be included in the record in full. So, you need not ask permission, that will occur, and then we will ask that you make your presentation or summaries in ways that you find most acceptable, and then we will proceed with questions. Please proceed.

STATEMENT OF MS. ASHLEY JUDD, GLOBAL AMBASSADOR, YOUTHAIDS, WASHINGTON, D.C.

Ms. JUDD. Good morning, honorable members of the committee, it's a genuine honor, thrill, and pleasure to be here before you today, and I'm most grateful to have been invited.

As you have stated, my name is Ashley Judd. I am the Global Ambassador for YouthAIDS and a member of the Board of Directors of Population Services International (PSI), which is the parent company of YouthAIDS.

YouthAIDS, a global initiative, is working in more than 60 countries to educate and protect young people from HIV/AIDS. YouthAIDS generates funding to develop worldwide education and awareness programs to prevent the spread of HIV amongst the most at-risk population: youth.

Before I begin my testimony, I'm actually going to give you a sneak preview of a VH1 program—I doubt VH1 has ever been played in this chamber before.

It is a documentary that was made of my trip to Madagascar to see our programs which are funded by the global fund. The documentary is entitled, "Tracking the Monster," and will air August 23rd, it also features India Arie, the unabashedly spiritual singer of terrific integrity. The contrast will be of the decimation in Kenya and the hope in Madagascar. This clip highlights the way we reach out to youth.

AV stuff is always so tricky, is that department feeling a little pressure right about now?

[The transcript of the video clip played for the committee follows:]

TRANSCRIPT OF MS. ASHLEY JUDD'S FILM PRESENTATION

[A portion of the presented video is spoken in French. The translated French is indicated by italic text.]

TEXT: Roughly 60 percent of teenagers in Madagascar are sexually active.

MAN: We are going to be going to a school today, and the youth are an important target of our HIV activities because in Madagascar they actually have a greater rate of HIV than any other group.

MS. JUDD: Is there very limited understanding of how the virus is spread?

WOMAN: Oh yes.

MS. JUDD: Sweet.

MAN: These are all your friends from the [name of school not translated].

MS. JUDD: One of the things I really love about the YouthAIDS Global Ambassadors is that I'm always working with kids. We educate them about risky behavior before they have a chance to engage in it. And so many kids here in Madagascar, and so little time, we needed to get the word out in a big way.

MS. JUDD: So I'm scheduled to shoot a TV spot with some students. *Do you know what we're going to do together?* It will play on Madagascar television. *Has someone already explained it? No? You're going to shoot a commercial with me! We have 30 seconds to present information that can save lives.* The topic: abstinence.

MAN: *For the moment you must abstain yourselves. You can prove your love without having sex.*

MS. JUDD: So roses, *chocolates, love letters, my personal favorite.*

TEACHER: *Have you ever written a love letter?*

STUDENT: *No, not yet.*

MS. JUDD: *Maybe you can practice on me. I can be your first. And I can tell you, I was too young, and I still have my regrets. Now, I wish I would have had a conversation like this, adults and young people talking with me—encouraging me to wait.*

MS. JUDD: Tim's co-worker, Lantu, wrote the script for the spot. *A.J. that's me.* I speak to the camera. *Ok, so it's like this. The basketball is between the couple. I throw the ball and I say: Over 150,000 people are already infected with HIV in Madagascar. Sex can wait. Play like a winner. Sex isn't the only proof of love. The ball is in your court. What do you think of the dialogue?*

STUDENT: *It's cool.*

MS. JUDD: They do think it's important to get the word "cool" in there, somehow.

TEACHER: *So, I'm cool because I practice abstinence.*

MS. JUDD: That would be good?

STUDENT: *But one must not say that. Slang isn't allowed in school.*

MS. JUDD: *Especially because it is slang and is forbidden in school; it gives the feeling that it's between young people, and not an adult telling you all this. Cool.*

Ms. JUDD. So, in addition to showing how we dialogue with youth to hear what it is they would like to see in their education and dialogue about abstinence, I get to show off my fancy education from the University of Kentucky.

As an actor, I know the importance of setting the stage, but never in my career have I had to set the stage for a drama as devastating, and of such historic proportion and consequence, as the HIV/AIDS emergency that we now battle.

There are currently 39 million people living with HIV, the virus that causes AIDS. Twenty million have already died. Roughly half of the infected adults are women, and tragically, 2 million children carry the virus—all preventable. In 2004 alone, the last year for which we have reliable statistics, there were 3 million deaths related to AIDS-related cases and nearly 5 million new infections.

To what in recent memory can we compare this new catastrophe? Approximately 50 million lives were lost during the infamous darkness of World War II. That number will be surpassed by deaths due to AIDS when those now infected inevitably, and most in shameful fashion, are laid to rest. Stalin's totalitarian regime in the Soviet Union took a toll of 20 million lives, roughly equal to the number that have already died of AIDS-related causes globally. These numbers are staggering. They are truly without precedent, and our words and actions in the face of this crisis will certainly be studied for generations to come. How will history judge us?

With the hope of doing more to save lives, this committee has convened to hear testimony, principally about AIDS vaccine, an eagerly awaited strategy for prevention. Dr. Fauci, Dr. Gayle, and Dr. Berkley, all of whom are leaders in the public health community, will address this important topic. I would like to focus my testimony on another critical aspect of AIDS prevention, and that is the imperative need to do more for girls and women around the world.

In Africa young women are up to six times more likely to become infected with HIV than their male peers. And little, if anything, is being done to address the problems that put young women at such high risk, and more must be done if we honestly hope to stop the HIV/AIDS emergency.

To give you an idea of how bad things are, let me tell you about a group of young women in Zambia. These young girls, aged 15 to 19, met with PSI staff last year, to talk about abstinence, and their experiences growing up, generally. I was going to give you more detail to try to conjure them right in this room, but then I remembered that all of our conversations are confidential and anonymous. So I'm going to call one of them by the name of a friend I made in Madagascar, Sahule.

Sahule lived with her sister and brother-in-law, and Sahule's sister and her husband had a fight one night, and her sister left the house in a fit. At about 1:30 in the morning, Sahule awoke in pain, and discovered her brother-in-law on top of her, raping her. Family elders, after learning of the incident, decided this was something

the family should take care of on its own. It was never reported to the police, and ultimately nothing was done.

Immediately after Sahule told this story, another young girl told how she was locked in a room and raped by her boyfriend. She kept the matter a secret for fear of being mocked. After hearing these two stories, two other girls in the group of 10 described how they had also been raped, one by an uncle who pushed a cloth in her mouth and tied her hands, and the other by the 19-year-old friend of her brother. One of the girls reported the case to the police, but the other did not because she was ashamed of herself.

Five others in this small group also reported how they were accosted, or barely managed to escape or avoid sexual violence. All of this had happened before these young women were 19 years of age. And in this testimony, I am not even touching on the outrage of sexualization and sexual violence toward pre-pubescent girls, which is shockingly pervasive.

What can we conclude from this group of young women who shared their stories of abuse? I think we can conclude that most of us in this room really have no idea of how difficult life is for women in Africa, and elsewhere in the developing world. Even though sexual violence happens everywhere on our planet, women in developing countries are at extremely high risk of abuse; social norms and economic pressure are often at the root of the problem.

Recent research confirms that these young women's stories are not isolated cases. A report published in 2002 concluded that nearly one out of three women surveyed in South Africa, a country I have visited, had their sexual initiation through rape. Is there a more sordid and cynical rite of passage to adulthood?

The abuse of girls and women stretches beyond sexual violence. I will now tell you about a degrading and utterly common phenomenon known as "cross-generational sex." The social norms in many developing countries that determine what is tolerable, or at least not punishable, for a man to do to a girl or woman, have also created an environment in which girls as young as 15 are encouraged to seek financial or material gain by entering into empty sexual relationships with men a generation, or more, older than they. These cross-generational relationships are common across the continent of Africa, and result in young women exchanging their bodies for modest financial support—lunch, perhaps a cell phone, a pair of plastic shoes, or maybe half a liter of fuel to heat the shack in which she is raising her younger siblings.

And while these relationships are fundamentally transactional, this is not commercial sex. These are young women in both urban and rural settings who have been persuaded by both peers and adults that have an older sexual partner, a "sponsor," as they're called—quite a perversion on a relatively happy word—is an acceptable and common way to acquire fashionable items, or meet basic needs that they need for their very survival. Rarely do these young women consider the possibility of becoming infected with HIV. But the risks are very real.

Already at an increased biological risk because of our anatomy, such cross-generational relationships are fueling the HIV/AIDS epidemic among young women. Two recent academic journal articles

document how a young girl's risk of HIV infection increases significantly as a result of having an older partner. Both papers were clear that this practice of cross-generational sex was an important factor which explained why young women are six times more likely to be HIV positive then young men in Africa.

And here I pause to ask you, honorable members of this distinguished committee, are we really doing everything that we can to protect young girls and women from HIV/AIDS?

We want them to abstain, or at the bare minimum, delay their sexual debut, but it will be difficult, if not impossible, for them to do so if they are not protected from sexual abuse, exploitation, economic disempowerment, poverty—the norms that encourage sex with older men for support and survival.

I am confident that this problem of cross-generational sex slices across the politics that color the current, and highly polarized, debate on how best to combat HIV/AIDS in Africa. People of all political and spiritual persuasions are deeply distressed and disturbed by the abuse of girls and young women.

But if that is, in fact, the case, why is so little being done to address these problems? With all the research that has been conducted, it's certainly not because we don't know that it's happening. I would like to think it's not because we don't care. I believe it is because the problem is so pervasive, so deeply rooted and so long standing, that we simply don't know where or how to start. The journey to decrease the vulnerability of girls and women in the developing world must begin, like all journeys, with the first steps. I'm getting a little "George Washington crossing the river," very moved by all of our beautiful monuments in Washington, D.C.

Here's how we can start: First we must acknowledge that preventing HIV/AIDS amongst young women will entail reversing social norms and practices which support their abuse. Societies must reject violence against girls and women, as well as social norms which encourage young women to exchange sex for financial and material support. The Global Fund, thanks to its unique country-level structures, could play an important role in coordinating local partners, and I've seen personally what their good work in Madagascar can do, and for further detail and information about the programs they have there, and the vulnerable population it serves, I refer you to my diaries at www.youthAIDS.org.

Second, acknowledge that the transformation of these unhealthy social norms must come from within. This does not mean that we stand by idly waiting for something to happen; it means that international organizations and donors must work hand in hand with indigenous groups that are prepared to fight for change in their own communities. The African Union will be a key partner in this struggle, and they are eager to begin their work. I have a lot of hope.

Third, honorable committee members, you could insist on legislation that would tie future foreign aid to a country's demonstrated commitment to enforcing laws that protect women from all forms of sexual violence, genital mutilation, including statutory rape, and reaching all the way to strengthening our anti-human trafficking laws.

And fourth, national campaigns promoting healthier gender norms and role models for men should be launched throughout Africa and in many, many other places in the developing world.

Having an HIV/AIDS vaccine would be of great benefit to women of all ages because it could reduce their chances of becoming infected. As there is no vaccine to prevent the abuse of girls and women, however, there is nothing more important in this struggle against this virus and its diseases, than reversing destructive social norms, cultural practices, traditions, myths, beliefs, superstitions, religious ideas, and the flat out ignorance that perpetuates our economic disempowerment, lack of status in society, and general gender inequality.

I thank you so much for letting me be here today, and my last remark is that we're a very special, unique country, and we have accomplished unprecedented things in our history. I do believe that our greatest export is our ideas, gender equality being the most important one. Thank you so much for your time today.

[The prepared statement of Ms. Ashley Judd follows:]

PREPARED STATEMENT OF ASHLEY JUDD

My name is Ashley Judd. I am YouthAIDS' Global Ambassador, and a member of the Board of Directors of Population Services International (PSI). YouthAIDS, a global initiative of PSI, is working in more than 60 countries to educate and protect young people from HIV/AIDS. YouthAIDS generates funding to develop worldwide education and awareness programs to prevent the spread of HIV among the most at-risk population—youth. Distinguished members of the Senate Foreign Relations Committee, thank you for giving me the honor of testifying here today.

As an actress, I know the importance of setting the stage. Never in my career, however, have I had to set the stage for a drama as devastating and of such historic proportions as the AIDS epidemic that we now battle. There are currently 39 million people living with HIV, the virus that causes AIDS. Twenty million have already died. Roughly half of the infected adults are women, and over two million children carry the virus. In 2004 alone, the last year for which we have reliable statistics, there were three million deaths due to AIDS, and nearly five million new infections.

To what in recent memory can we compare this catastrophe? Approximately 50 million lives were lost during the darkness of World War II; that number will be surpassed by deaths due to AIDS when those now infected are laid to rest. Stalin's totalitarian regime in the Soviet Union took a toll of 20 million lives—roughly equal to the number that have already died of AIDS globally. The numbers are staggering. They are truly without precedent, and our words and actions in the face of this crisis will certainly be studied for generations to come.

With the hope of doing more to save lives, this committee has convened to hear testimony principally about AIDS vaccines as a strategy for prevention. Dr. Fauci, Dr. Gayle, and Dr. Berkley, all of whom are leaders in the public health community, will address this important topic. I would like to focus my testimony on another critical aspect of AIDS prevention, and that is the urgent need to do more for young women around the world.

In Africa, young women are up to six times more likely to become infected with HIV than their male peers. Little, if anything, is being done to address the problems that put young women at such high risk, and more must be done now if we honestly hope to stop the AIDS epidemic.

To give you an idea how bad things are, let me tell you about a group of young women in Zambia. These young girls, age 15–19, met with PSI staff last year to talk about abstinence and their experiences growing up generally. I'll start with someone who I'll call Jane.

Jane lived with her sister and brother-in-law. Jane's sister and her husband had a fight one night, and her sister left the house for the evening. At about 1:30 in the morning, Jane awoke in pain, and found her brother-in-law on top of her. Rap-

ing her. Family elders, after learning of the incident, decided this was something the family should take care of on its own. It was never reported to the police.

Immediately after Jane finished telling this story, another young girl told how she was locked in a room and raped by her boyfriend. She kept the matter a secret for "fear of being mocked."

After hearing these two stories, two other girls in the group of ten described how they had also been raped—one by her uncle, who pushed a cloth in her mouth and tied her hands; and the other by the 19 year old friend of her brother. One of the girls reported the case to the police, but the other did not because she was "ashamed" of herself.

Five others in this small group reported how they were accosted, or barely managed to escape sexual violence. All this had happened well before any of the girls had reached the age of 19.

What can we conclude from this group of young women who shared their stories of abuse? We can conclude that most of us in this room have no idea how difficult life is for young women in Africa and elsewhere in the developing world. Even though sexual violence happens in all corners of our planet, women in developing countries are at extremely high risk of abuse. Social norms and economic pressure are often at the root of the problem.

Recent research confirms that these young women's stories are not isolated cases. A report published in 2002 concluded that nearly one out of three young women surveyed in South Africa had their initial sexual experience through rape.[1] What more sordid and cynical rite of passage to adulthood could we imagine for a young woman?

The abuse of women stretches beyond the sexual violence that I just described; I will now tell you about a degrading and common phenomenon called "cross generational sex."[2] The social norms in many developing countries that determine what is "tolerable" (or at least not punishable) for a man to do to a woman have also created an environment in which girls as young as 15 are encouraged to seek financial or material gain by entering empty sexual relationships with men a generation or more older than them. These "cross generational" relationships are common across the continent of Africa, and result in young women exchanging their bodies for modest financial support—such as lunch, a cell phone, plastic shoes, or half a liter of fuel.

And while these relationships are fundamentally transactional, this is not commercial sex. These are young women—in both urban and rural settings—who have been persuaded by both peers and adults that having an older "sponsor," and sexual partner, is an acceptable and common way to acquire fashionable items or meet basic needs. Rarely do these young women seriously consider the possibility of becoming infected with HIV.[3]

But the risks are very real. Already at increased biological risk, such "cross generational relationships" are fueling the AIDS epidemic among young women. Two recent academic journal articles document how a young girl's risk of HIV infection increases significantly as a result of having an older partner. Both papers were clear that this practice of cross generational sex was an important factor which explained why young women are six times more likely to be HIV positive than young men in Africa.[4] [5]

And here I pause and ask you, honorable members of this distinguished committee, if we are really doing everything we can to protect these young girls from AIDS? We want them to abstain, or delay their sexual debut, but it will be difficult for them to do so if they are not protected from both sexual abuse, and from social norms that encourage sex with older men in return for financial support.

I am sure this problem of cross-generational sex cuts across the politics that color the current and highly polarized debate on how best to combat AIDS in Africa. Peo-

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[1] Jewkes R, Abrams N; The Epidemiology of Rape and Sexual Coercion in South Africa: An Overview. *Social Science and Medicine.* October, 2002; 55 (7): 123 1–44.

[2] Luke N, Kurz K; Cross Generational and Transactional Sexual Relations in Sub-Saharan Africa: Prevalence of Behavior and Implications for Negotiating Safer Sexual Practices. AIDSMark. 2002.

[3] Longfield K, Glick A, Waithaka M, Berman J; Relationships Between Older Men and Younger Women: Implications for STIs/HIV in Kenya. *Studies in Family Planning.* Volume 35, no. 2, June 2004. pp. 125–134.

[4] Gregson S; Sexual Mixing Patterns and Sex Differentials in Teenage Exposure to HIV Infection in Rural Zimbabwe. *The Lancet.* June, 2002. Volume 359. pp 1896–903.

[5] Kelly, R; Age Differences in Sexual Partners and Risk of HIV-1 Infection in Rural Uganda. *Journal of Acquired Immune Deficiency Syndromes.* Volume 32, no. 4. April, 2003. pp. 446–451.

ple of all political and religious persuasions are deeply disturbed by the abuse of young women.

But if that is the case, why is so little being done to address these problems? With all the research that has been conducted, it is certainly not because we don't know this is happening. And I would like to think it is not because we don't care that these young women are being violated or contracting AIDS. I believe it is because the problem is so pervasive, so deeply rooted, and so long standing that we simply don't know where or how to start. The long journey to decrease the vulnerability of women in the developing world to AIDS and sexual violence must begin, like all journeys, with first steps. Here is how we can start.

First, we must acknowledge that preventing AIDS among young women will entail reversing the social norms which support their abuse. Societies must reject violence against women, as well as social norms which encourage young women to exchange sex for financial or material support. The Global Fund, thanks to its unique country level structures, could play an important role coordinating local partners.

Second, acknowledge that the transformation of these unhealthy social norms must come from within. This does not mean that we should stand by idly waiting for something to happen. It means that international organizations and donors must work hand in hand with indigenous groups that are prepared to fight for change in their own communities. The African Union will be a key partner in this struggle, and they are eager to begin work.

Third, honorable committee members, you could insist on legislation that would tie future foreign aid to a country's demonstrated commitment to enforcing laws that protect women from all forms of sexual violence, including statutory rape.

And fourth, national campaigns promoting healthier gender norms and role models for men should be launched throughout Africa and in many other places in the developing world.

Having an AIDS vaccine would be of great benefit to women of all ages because it could reduce their chances of becoming infected. As there can be no vaccine to prevent the abuse of women, however, there is nothing more important in the struggle against this disease than reversing destructive social norms that endanger women across Africa and in other developing countries.

I thank you again, honorable members, for allowing me to contribute today.

The CHAIRMAN. Thank you very much, Ms. Judd. Let me just pursue for a moment the very important point you made about cross-generational sex and its impact on girls in Africa. What type of interventions does your organization, YouthAIDS have? What sort of programs? Are they effective? At how broad a scale have you been able to approach the situation?

Ms. JUDD. So that I don't waste your time, may I consult with my colleague?

In general, I can say that peer education is a very powerful tool, I've seen it around the world, and that entails like talking to like, so you get a young woman, one who is a little more empowered and a little more educated about medically accurate sex education and her reproductive health, talking to a vulnerable at-risk girl about the different ways she can protect herself.

In Kenya, we have a fantastic mass media campaign that's called "NEmA Chill," it's a combination of Swahili and English slang as you saw from our campaign from Madagascar, slang being extremely popular with young people. The NEmA Chill Campaign is on televisions, radios, billboards, it's painted on the sides of buildings, so it's able to transcend literacy issues, and what it encourages kids to do is "chill" which is a euphemism for being abstinent, and I can tell you that kids are embracing this message heartily. I was in the bathroom at the Nairobi airport talking with the janitor, she wanted my necklace, which I was reluctant to give her because it was special—my husband had given it to me. When I

asked her if she'd been tested for HIV (HIV status is a whole other very important issue), she said, "Oh, I've been tested, and I chill." Which is the slogan, so I gave her my earrings. It was obviously saturating the population.

The role model campaign we have in Uganda is fantastic for girls who already have a little bit of a leg up; they're in University, and the exact name of the program is "Go Getters." We get older women to come in and talk to the girls about the importance of setting long-term goals and getting past instant gratification. The older women mentor them, and we use faith-based organizations and businesses to help provide internships for the girls who enroll in the Go-Getters Club.

The CHAIRMAN. Let me just proceed to the Madagascar situation which was illustrated so well on the film. I congratulate you on your linguistic ability as you communicate with those in the film. What is your general view of abstinence programs? You responded to that a bit, but obviously you've addressed that in Madagascar, is this effective?

Ms. JUDD. I will be completely blunt with you—I was not a fan of abstinence programs until I saw, first hand, that there are kids that are really hungry for an abstinence message. I was doing a peer education session in a classroom where we were talking about the ABC's—abstaining, delaying sexual debut, being faithful to one partner, correct and consistent condom use. We reach out to dynamic, poised, compelling young people to be the peer educators. I was assisting in this. And when the peer educator was finished, this one kid raised his hand, he wanted to go back and talk about abstinence again. So that was a one-on-one experience that I had that made me say, "You know what? This is really valuable, and valid." And then, of course, our "Chill" campaign as I mentioned in Kenya, is wildly popular.

We actually have been doing abstinence in Kenya since 1988, and in fact have just launched one that is considered to be the largest abstinence campaign in the world. However, I would like to say that one is not effective without the other, and there must be a balanced and targeted approach. Married women need condoms. Married women are at risk for HIV, married women in Cambodia are the highest new infection group—it is common around the world for men to have extra-marital sexual relations, and they bring HIV home to their wives, who then pass it on to their children. Married women need to know how to successfully insist upon and negotiate a condom with their husbands.

The CHAIRMAN. Let me just follow through with one more question because you mentioned the African Union in your comments. Describe more extensively what role the African Union might play in the things that you have talked about today?

Ms. JUDD. The African Union has such an excellent mandate to look after its population across Africa, not just in sub-Saharan Africa, and their leadership has the potential to be extremely dynamic. And again, it's that "like helping like," so it's not a bunch of us blowing in there saying, "This is really how you should do it." And again, with your permission, I'll get a little more detail from my colleague.

We need a continent-wide advocacy campaign—getting heads of state to all agree on the same principles of education. An example is that we work with Muslims in Eastern Africa, and we have helped to develop standardized information about medically accurate sex education and HIV prevention, and the Imams can use these standardized texts in mosques. They don't have to second guess themselves, or wonder if they're getting it right. It's very factual, this is the information, and people don't have to be nervous or editorialize. Also, of course, I had the great privilege of working with the All-Africa Conference of Churches in Nairobi, they sang "We Shall Overcome." I felt very at home. In this way we will collaborate to challenge the African governments to implement laws against female genital mutilation, statutory rape—there's tremendous potential there.

The CHAIRMAN. I think the point you make about the heads of state of the governments, plus the religious leadership, is very important. As you have found in some countries, without describing any one scene, the official leadership has been in denial that there's a national problem. That has made it very difficult for others within the government, or NGO's, or other persons, really, to take an active part.

Ms. JUDD. There's a lot of superstition; there's a lot of ignorance, and there are a lot of myths. In Kibera, which is the second largest slum in the world, in Nairobi, I saw peer educators have a fantastic impact on a very poor, an extremely poor and disempowered population. And during the question and answer periods, a lot of those myths come to the surface: Can you get HIV from a mosquito bite? Can you get HIV from shaking hands? You know, if someone is HIV-positive, many people believe they should be ostracized and outcast—and the leadership, when they break the silence and start breaking down the cultural taboos, are going to have a massive positive impact on their population's health and well-being.

The CHAIRMAN. I thank you. Senator Boxer, do you have questions of our witness?

Senator BOXER. Thank you again, Mr. Chairman. Ashley Judd, I just want to thank you so much. We have discussed your work before, and I'm just so proud of you and seeing you actually bring such an important message as an American leader in this area, it's just, it's tremendous. I just don't want to lose this opportunity to publicly thank you, as I did privately. If everyone did just a fraction of what you've done, it would just change the world.

I'm very proud that Chairman Lugar and I have been working together on providing assistance for orphans and other vulnerable children in the developing world. We had a bill last year, we're working on a new version of it this year, and among other things, our bill would authorize the President to provide assistance to orphans by eliminating school fees, increasing pediatric health care, increasing psychological support for orphans and victims of the disease. And what we're learning is that you also have to protect the inheritance of these orphans, widows and sick children when something happens to the father, when the father dies of AIDS, and they're just left, and they're so vulnerable, and people will take

away their inheritance, and they find themselves in desperate straits.

So, I was just wondering, and I know this—I didn't tell you about this question, so you may want to consult with your colleagues—but you've got a golden opportunity, with both of us here—is there anything we're missing in our approach to this bill that you think we could do to make part of this bill? And if you don't have the answer today, we'll be happy to take it in writing over the next few days because I think on the heels of this hearing, maybe we will have some momentum to get our bill through. Anything come to mind, when the breadwinner dies of AIDS?

Ms. JUDD. The situation of orphans is so utterly devastating. An specific example I can give you is that of an exquisitely beautiful young Kenyan woman named Scola whom I met in a brothel, she's 19 and was actually nursing her second child while she was forced to work in commercial sex. Her parents died of HIV/AIDS-related causes, her older brother vanished and she did not have any inheritance rights to the small bit of land that her parents had owned. Her boyfriend left her when she became pregnant with their second child. She'd had no sex education whatsoever. She didn't know anything about abstaining, or how to delay her debut, or how to protect herself from both pregnancy and STD and HIV. This has forced her to feed herself and her two children, as her first baby—a 10-month old—had increased dietary needs, and she literally couldn't satisfy him on a daily basis, she ended up on the streets, and this isn't always the right answer universally, but we just stuffed money in her pockets and sent her home. There was no way that we could tolerate this woman finishing her work in the brothel that night, she had to go home and breastfeed her second child. It was disgusting what had happened to her.

What I've learned from both YouthAIDS and Equality Now—which does such fine work—is that we have to press the local leaders in the African countries to lobby their governments to put that legislation into place to legally empower mothers and their children.

We would love to take more time to consider what you said, and appreciate your inviting our input. Education, of course, is the most critical and fundamental tool, and that can be done through schools as well as peer education.

Senator BOXER. One last question I have, Mr. Chairman.

You suggest that future U.S. foreign aid be tied to a country's demonstrated effort to reduce statutory rape. What is your assessment and the assessment of your colleagues on African countries willing to prosecute individuals for the crime of rape?

Ms. JUDD. It's sketchy, it's sketchy. You will get a judge who is all for it, and then somebody from his tribe comes in, and he's like, "No," he wants to revert and do it the traditional way with his people, and it just takes education, ongoing education. And how do you say that word? Sensitization, of the issue.

Senator BOXER. Well, thank you very much, and Mr. Chairman, I do hope that we can work with YouthAIDS as we put this together. It's a perfect opportunity for us, and I think with the bipar-

tisanship you bring to this issue, maybe we can actually make a difference in the lives of some of these young people, which would be a contribution.

The CHAIRMAN. The Senator makes an excellent point, and this hearing may be able to spur that legislation. And we do invite the testimony, as the Senator has indicated, the record will remain open so that further comments by your organization, YouthAIDS or others are welcome.

Well, Ashley Judd, we thank you very much for appearing today and for your very compelling testimony, and being forthcoming in your responses to our questions. We wish you every good fortune in your good work. Thank you.

Ms. JUDD. Yes, sir, thank you, Mr. Chairman.

The CHAIRMAN. The Chair would like to call now in our next panel, Dr. Anthony Fauci, Director of the National Institute of Allergy and Infectious Diseases at the National Institutes of Health in Bethesda, Maryland.

Dr. Fauci, we welcome you again to the committee. We appreciate especially your testimony on this occasion this morning, and ask you to proceed.

STATEMENT OF DR. ANTHONY S. FAUCI, DIRECTOR, NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES, NATIONAL INSTITUTE OF HEALTH, BETHESDA, MARYLAND

Dr. FAUCI. Thank you very much, Mr. Chairman, and thank you for giving me the opportunity this morning to discuss with you the role of the National Institutes of Health in the research endeavor to develop a safe and effective HIV vaccine.

You've just heard in the statements, as well as from Ms. Judd, about the compelling reason why we do need an HIV vaccine, and that is the extraordinary problem that does not have an end in sight, with approximately 40 million people worldwide living with HIV, the vast majority of them living in developing countries, two-thirds of whom are in sub-Saharan Africa.

There are, as you know, 5 million new infections each year, with 3 million deaths this past year. One of the things we need to do is as important as anything else—the prevention of HIV infection. As is shown on this poster, there are multifaceted ways that we can prevent HIV infection, ranging from interruption of transmission from mother to child, to topical microbicides, which are a woman-based way to take into her own power the ability to protect herself, just like the use of condoms, as Ms. Judd has mentioned.

But importantly, there's the issue of a vaccine, without which most of us feel we will not have a totally effective prevention campaign. But there are particular issues related to vaccines that provide a very unique and rather compelling challenge, very unique when you compare it to the other successful vaccines that you mentioned in your opening statement.

And these relate to the fact that the natural immune response to HIV is inadequate—I'll get back to that in just a moment. HIV hides itself from the immune system, it actually targets and destroys the very immune system that's programmed to protect the

body against an infection. And then, finally, it replicates rapidly, and mutates, so it's constantly evading and eluding our ability to control it.

With regard to the first one—namely that the immune response is inadequate—this is really quite unique. If you look at all the killers that we've had to face—smallpox, polio, measles and others—although there's considerable morbidity and mortality, the vast majority of people who get infected with those infections ultimately completely eradicate the microbe, in these cases, viruses from the body. So, when we develop a vaccine, we try to mimic the natural infection itself with our vaccine. The problem with HIV is that HIV doesn't do that—the body is not able to completely eradicate the virus by itself, so we in the field of developing vaccines have to do even better than the natural infection itself, and that is a formidable scientific problem that we're all putting our efforts toward.

If you look at the vaccine research resources, this is the NIH HIV vaccine research funding. Dr. Berkley will shortly give you an idea of what the global effort is, but as you can see, this is actually very dramatically increased over the past several years, to the point now—we at the NIH are scheduled to spend in fiscal 2006 over $600 million for research alone on HIV vaccine.

Now, importantly, the vaccine endeavor does not include only the development of products. There is a list of products that are in clinical trial, those that are in different phases, and those that are in the pipeline. But what we've done over the years is develop an international network of clinical trial sites. I know it's difficult to see from that distance, but this is a map of the world with a number of our sites, including the NIH's vaccine trial network, as well as the Department of Defense and the CDC. This is an interdigitated network that is ready and already functioning in a manner of being able to do the kinds of vaccine trials internationally, in which information will be readily shared.

You mentioned in your own statement, and in Resolution 42, the issue of the Global HIV Vaccine Enterprise. Just a word about that—this is a concept that was developed a couple of years ago, and in fact myself and others including Dr. Berkley, Dr. Gayle and others, were involved in putting together a piece in the scientific journal, *Science,* in which we called for, and spoke of, the need for an enterprise. As you correctly said, it's a virtual consortium of stakeholders, of funders, of scientists, who are dedicated to the common goal of developing an HIV vaccine. The reason why it's important is because it has become clear to us that the scientific obstacles were so imposing that we needed to have a commonality and a coordination in our effort. The basis and the fundamental infrastructure of this is a strategic plan which we've worked on for well over a year, and is now publicly available on a website for all to see. For any countries or other funders who want to get involved in HIV vaccine research, there is an agreed upon, strategic plan.

One of the things that was in that plan was the question of developing centers that could do vaccine research. This was modeled after the highly successful NIH Vaccine Research Center on our campus in Bethesda, which goes from the fundamental basic research, up through and including the conduct of clinical trials. And

when the President gave the endorsement of the G-8 in Sea Island in the spring of 2004, one of the things he put on the table is that we would get the ball rolling by initiating yet another extramural center that was mentioned in Resolution 42, and that is the Center for HIV/AIDS Vaccine Immunology, which we refer to as CHAVI. The review of the applications for these have been finished, and the winner of the award, which is a seven year award, will be announced within a reasonable amount of time this summer. We do hope that this will serve as an example for other nations and other funders to abide by that spirit of the Enterprise and of the strategic plan.

Finally, let me just close with a comment that when one looks at how we might successfully confront AIDS in the 21st century, it is based very heavily on basic and clinical research that would call for treatment, care and importantly, the concept of prevention. And integral to the concept of prevention is the development of a safe and effective vaccine.

Thank you, Mr. Chairman, and I'd be happy to answer any questions you have.

[The prepared statement of Dr. Fauci follows:]

PREPARED STATEMENT OF ANTHONY S. FAUCI, M.D.

Mr. Chairman and members of the committee, thank you for giving me the opportunity to discuss the ongoing efforts of the National Institutes of Health (NIH) to develop a safe and effective vaccine for the prevention of human immunodeficiency virus (HIV) transmission. Today I will first briefly outline the daunting scientific barriers that must be overcome to develop such a vaccine, and then describe some of our domestic and global HIV vaccine research and development programs, including a major new international initiative to foster global collaboration and cooperation in research leading to the development of an HIV vaccine.

Approximately 40 million people worldwide are now living with HIV/AIDS. Sub-Saharan Africa is the hardest hit, with more than 25.4 million people infected. South and South-East Asia together account for more than 7.1 million infected people, with 1.4 million more in Eastern Europe and Central Asia, 2.1 million in Latin America and the Caribbean, 1.1 million in East Asia, 1 million in North America, 610,000 in Western and Central Europe, and 35,000 in Oceania. Approximately 14,000 people worldwide are newly infected with HIV every day.

The first line of defense against any disease, and particularly an infectious disease pandemic, is prevention. Fortunately, we have proven ways to prevent HIV transmission. For example, in addition to the role that certain antiretroviral drugs play in the treatment of HIV-infected individuals, drug regimens have also been shown to dramatically reduce the risk of HIV transmission from mother to child in both developed and developing countries. Moreover, the risk factors associated with HIV transmission have been well defined, and prevention programs are operating to some extent in most nations of the world. In virtually all developed nations and in certain developing countries such as Uganda, Brazil, and Thailand, these prevention programs have proven effective in slowing the spread of the virus. Interventions that have been employed successfully include mass media campaigns; voluntary HIV testing and counseling; screening of donated blood; education and outreach to at-risk populations; behavioral modification programs, such as the promotion of abstinence and fidelity; abbreviated courses of antiretroviral drugs to prevent mother-to-child transmission of HIV; treatment for drug abuse, which could include measures to reduce the sharing of contaminated injecting equipment by injection drug users; and condom distribution. Missing from this arsenal of preventive tools, however, is an effective vaccine.

Historically, vaccines have led to some of our greatest successes in the fight against infectious diseases, including the eradication of smallpox, the near eradication of polio, and enormous reductions in the disease burden imposed by measles, mumps, hepatitis, influenza, diphtheria, and many other infections. For virtually all

infections, particularly viral infections, if the patient does not die, the immune system ultimately clears the infection and the person is immune to subsequent exposure to the infectious agent, sometimes for life. An effective vaccine preparation only needs to mimic the effect of natural infection on the immune system to prevent infection and/or disease upon exposure to the infectious agent in question.

Smallpox, for example, was a terrible disease, but most patients survived and were protected thereafter by lifelong immunity. In 1796, Edward Jenner demonstrated in England that smallpox could be prevented by inoculation of a person with material from a cowpox lesion. This finding led to the development of a modern smallpox vaccine which was deployed globally in a massive campaign in the 1960s to eradicate smallpox from the human population, a goal that was achieved in 1979. Jenner's smallpox vaccine, like the modern equivalent, was based on a live virus that was closely related to the virus that causes smallpox but that did not cause illness. Vaccination primed the immune system to fend off infection if the person subsequently was exposed to the virulent smallpox virus. The Salk vaccine against polio, which became available in 1955, was based on a killed polio virus. Injection of the inactivated virus alone was sufficient to provoke an immune response that mimicked natural immunity and was capable of blocking infection upon exposure to the live, virulent virus.

The scientific challenges that must be solved to develop an effective vaccine against HIV have proven more daunting than those challenges that scientists had faced previously. Perhaps the biggest obstacle is that immune-mediated eradication of HIV from the body, with subsequent naturally induced immunity, simply does not occur. Even after more than 60 million cumulative HIV infections since the beginning of the pandemic, there never has been a documented case in which a person with established HIV infection has completely eliminated the virus from his or her body. The fact that the immune system is apparently never able to defeat HIV on its own makes it more difficult for scientists to develop a way to induce a protective immune response. In other words, a vaccine that mimics natural infection will likely not be good enough. It must do better than natural infection in inducing what should ultimately be a protective immune response.

We have gained a solid, if incomplete, understanding of how HIV evades and ultimately defeats the immune response. First, because the primary target of its devastation is the immune system itself, HIV disables the very cells that are responsible for fighting it. Second, HIV is a retrovirus, which means that it can integrate its viral sequence into the chromosomes of infected cells. Thus, the virus can shield itself from immune attack for many years, only to emerge when the infected cell is activated by the immune system to fight another infection. Third, HIV conceals the protein components that can induce a protective immune response, and therefore presents itself to the body in a way that makes it difficult for the immune system to respond effectively. Fourth, HIV is genetically diverse and rapidly changing, especially in its outer coat proteins; its mutability allows HIV to evade the modest protective responses the immune system is naturally able to make.

All of these factors combine to create a scientific challenge as difficult as any we have ever confronted in infectious disease research. I do not believe it is an insurmountable problem, however, and we are doing everything in our power to meet this daunting challenge. Our activities include a strong program of basic research on HIV and the immune system, multiple initiatives to create and test new vaccine candidates, and development of a large, international network of clinical research sites through which vaccine candidates are evaluated. NIH leads the Federal effort for the development and evaluation of HIV vaccine candidates; the U.S. Centers for Disease Control and Prevention, the Department of Defense, and other Federal agencies collaborate in this effort. In budgetary terms, the President's Budget request for fiscal year (FY) 2006 for HIV/AIDS research at NIH is $2.9 billion. Of this, $607 million is for vaccine research and development; this figure represents a nearly six-fold funding increase for vaccine research over the past ten years and accounts for the majority of global HIV vaccine development spending worldwide. In fact, the NIH HIV vaccine program represents the largest public investment in HIV vaccines in the world.

Development of a successful HIV vaccine candidate rests upon a foundation of basic research on the virus itself, including how it attacks the human immune system, and how the immune system responds to HIV infection. Since the earliest days of the pandemic, researchers have applied what they had learned about the virus to create vaccine candidates, which then were tested in both animals and human volunteers. In the 21 years since HIV was first identified as the cause of AIDS, we have made considerable progress not only on these basic HIV research questions,

but also in our overall understanding of the structure and function of the immune system.

These advances are now allowing us to pursue new vaccine strategies, and create new vaccine candidates that would have been impossible even a few years ago. In the early years of the pandemic, vaccine development efforts focused primarily on humoral immunity, that is, on the induction of specific antibodies that could neutralize the virus. From these studies, scientists discovered that it is extraordinarily difficult to raise antibodies that neutralize the many strains of the virus that circulate in the world. Because of this difficulty, development efforts have focused more recently on cell-mediated immunity, which, in general, does not protect against initial infection but can stop progression of disease in animal models. The leading candidates that induce primarily cell-mediated immunity are now or will soon be in clinical trials that will determine whether this approach may have an impact on infection or disease progression. Researchers are now turning their attention to the identification of new vaccine candidates based on strategies that induce both humoral and cell-mediated immunity.

Clinical testing of candidate vaccines is a key component of vaccine development. Once a candidate vaccine has been developed in a pre-clinical setting, the process by which the vaccine is tested in humans requires three distinct phases of evaluation. Phase I trials are the first human tests of a candidate vaccine, generally conducted on small numbers (10–30) of healthy adult volunteers. The main goal of a Phase I trial is to evaluate safety and, to a lesser extent, to evaluate the immune responses evoked by the vaccine. In addition, different vaccine doses and immunization schedules are compared. Phase II testing involves a larger number of volunteers (50–500) and is designed to generate additional safety data as well as information to refine the dosage and immunization schedule. Occasionally, preliminary efficacy data are gathered from Phase II studies. Phase III trials are the definitive test of whether a vaccine is safe and effective in preventing disease; these trials involve thousands of volunteers. Successful demonstration of efficacy in a Phase III trial can lead to an application for licensure of the vaccine. These three phases take several years to complete.

Because most HIV infections occur in developing nations, HIV vaccine testing must in large part be carried out internationally. Many of the countries most affected by the HIV pandemic, however, have few resources and, in many cases, have virtually no public health or medical care delivery infrastructure. NIH has therefore developed an extensive network of clinical research sites in partnership with thirteen countries worldwide that are capable of conducting rigorous and ethically sound clinical trials of candidate vaccines. Since the 1980s, NIH has conducted a total of 85 clinical trials of candidate HIV vaccines in the United States and worldwide, involving more than 18,000 human volunteers. The majority of these trials have been Phase I immunogenicity and safety trials; nine such trials are currently underway. Others are larger Phase II studies designed to gather further safety data while beginning to shed light on possible efficacy. One large Phase III trial currently underway is testing a two-pronged "prime-boost" strategy of two candidate vaccines that in combination induce immune responses quantitatively and qualitatively different from those induced by either component alone. Only one other candidate HIV vaccine, AIDSVAX, has undergone a Phase III trial, and it unfortunately did not prevent HIV infection.

A few years ago, it became apparent that although the scientific research base was expanding rapidly and substantial resources were being devoted to HIV vaccine research by the U.S. government, international coordination of and support for HIV vaccine development efforts could be improved. In 2003, a group of scientists, of which I was a member, proposed the creation of a "Global HIV Vaccine Enterprise" to foster collaboration, cooperation and transparency in the conduct of HIV vaccine research on a global scale. The proposal, published in the journal Science, called for the creation of a "virtual consortium" of independent government and non-government organizations committed to accelerating the development of a preventive HIV vaccine. President Bush proposed this concept of a Global HIV Vaccine Enterprise to the G-8 meeting of industrialized countries in June 2004, which endorsed it unanimously.

Since then, the Global HIV Vaccine Enterprise has continued to grow and mature. It is important to note that the Enterprise is not a distinct organization with a hierarchical structure and formal leadership, nor is it a multi-national fund that centrally administers pooled resources. Instead, Enterprise partners will advance HIV vaccine research and development through the shared implementation of a globally developed strategic plan, mobilization of increased resources for vaccine development, and greater collaboration among researchers from participating organizations.

The overarching purpose is to efficiently bring resources to bear on the gaps in HIV vaccine research, while at the same time allowing for flexibility in how research is carried out by the various participants.

The strategic plan that will guide the Enterprise was published online in January 2005 in the journal Public Library of Science Medicine. Importantly, the plan concludes that the major difficulties encountered in the development of an HIV vaccine are scientific. The plan proposes five major activities to address the scientific priorities: (1) creation of HIV vaccine development centers or consortia to address the key scientific obstacles; (2) creation of a network of individuals and companies with vaccine manufacturing expertise to facilitate advancement of improved candidates; (3) development of a global system of laboratories that will standardize laboratory evaluation parameters; (4) sharing of common reagents; and (5) development of a network of clinical research training centers, all with the full engagement of scientists from developing countries.

At the same time the President sought and obtained G–8 endorsement of the Enterprise, he announced that NIH would fund a major new research initiative, called the Center for HIV/AIDS Vaccine Immunology, or CHAVI. This initiative builds on existing Federal HIV vaccine research efforts, such as the Dale and Betty Bumpers Vaccine Research Center (VRC) located on the NIH campus in Bethesda, MD. Five years ago, NIH inaugurated the VRC, a single state-of-the-art facility that brings together scientists with different areas of expertise critical for rapid development of vaccines against HIV and other infectious diseases. The research scope of the VRC encompasses all stages of vaccine development, including basic research; design and development of vaccine candidates; preclinical testing; production of vaccine candidates; and conduct of human clinical trials to determine vaccine safety and efficacy. To date, the VRC has conducted or supported twelve Phase I HIV vaccine clinical trials. A VRC vaccine candidate designed to protect against the three major classes of the virus in the world will advance to Phase II clinical testing in the United States, Africa, South America, and the Caribbean in the coming year.

CHAVI is based on the VRC model, but with two key differences: CHAVI will be dedicated entirely to HIV vaccine research, and unlike the "bricks and mortar" VRC, CHAVI will be a "virtual center" that will link scientists at multiple sites into a single functional unit. The mission of CHAVI will be to support intensive, coordinated, and multi-faceted approaches to address key immunological roadblocks to the discovery and development of a safe and effective HIV vaccine, as defined by NIH and as identified by the strategic plan of the Global HIV Vaccine Enterprise. We are now evaluating several very strong applications from groups of leading HIV researchers, and we expect to make an award this fiscal year. Funding for CHAVI will be provided for seven years; the award will be approximately $14 million in FY 2005 for start-up costs; funding for FY 2006 is estimated to be as much as $49 million.

In closing, Mr. Chairman, I look to the future of the HIV pandemic with both deep concern and great hope. Concern, because as bad as the situation is now, unless we can change the trajectory of the pandemic it will certainly become much worse. Hope, because I am optimistic that a successful vaccine candidate will eventually emerge, even though the scientific barriers to success are such that I cannot say when that day will come. In fact, success is likely to be only incomplete at first, and a partially effective vaccine will have to be studied and refined. Meanwhile, we at NIH will do everything in our power to successfully address as rapidly as possible the complex scientific obstacles to the development of an HIV vaccine.

Thank you for this opportunity to testify before you today, and I would be happy to answer any questions that you may have.

The CHAIRMAN. Well, thank you very much, Dr. Fauci. Let me just ask, how well can we anticipate the global community will keep up with providing treatments for HIV/AIDS? As we discussed broadly today—and we really can not get it down to a country by country analysis, but I made the assumption in my initial statement that treatment is occurring, but at the same time, the numbers of cases are outstripping the treatments, very rapidly—if this were thought of, some think about a war, maybe that's not the appropriate terminology, but it's like the war is not being won, the numbers are overwhelming us. How does treatment fit in to the process, including as you say, prevention, we have care and then hopefully, the vaccine, and why is a vaccine important? I think it

is, and you do, too, but explain in the course of this tripartite approach, where all this fits?

Dr. FAUCI. Well, in fact, you just said it yourself, it's a tripartite approach, you can't do one without the other. We cannot abandon people who are already infected, so it's our responsibility to get treatment to them as well as care, and that includes care for orphans of the epidemic, children whose parents have passed away because of HIV.

Prevention is paramount, because if you just look at the numbers, simple math will tell you that we have 5 million new infections each year, and we aren't even beginning to see the end of it, because we still haven't emphasized the potential new epicenters in Asian countries, such as China and India and other countries where you have over a billion people, and just a small percentage increase in infections spells out in tens and tens of millions of new infections.

Now, just to answer specifically the question of treatment, over the past couple of years, there have been considerable strides made with the President's Emergency Plan for AIDS Relief, the $15 billion program over five years, the Global Fund, as well as bilateral agreements. The difficulty is that even though we're going in the right direction, the gap between people who need treatment, predominantly in developing nations, and those who are getting them, is still enormous. It's much, much better today then it was two years ago, but we can't be complacent and say, because we're making progress we don't have an awful lot to do. With regard to vaccine—as in any disease that's a communicable disease—it's an integral part of the prevention process.

The CHAIRMAN. I appreciate that explanation. You will recall, I suspect, as we became involved as a Congress in this area, and began to think about appropriating money, there were divisions in our body, as well as at the White House, and what have you—when it came to prevention and treatment, there were some persons who devoutly felt that abstinence was the only course, and that prevention included that, but was a little bit broader, but the President, I can recall, in a very dramatic meeting in the East Room, when he asked me to be on the platform with him as a sponsor of this legislation, talked to the faith-based community and to others, about the fact that we needed to do both.

We're extending that today to say both, plus vaccine. This has been perceived then, hopefully not now, as really a bridge too far. Something that's not a pie in the sky, but on the other hand, sort of off the charts in terms of reality. People say, get real, we have to deal with people here and now, which we're saying today, we do. It's not one or the other of these, but all three of the above.

The importance of understanding that is tremendously valuable in the political context. Senator Boxer has asked, Senator Kerry, likewise, about various bills and initiatives we've offered, and some do better than others, some have had more enthusiasm and some find appropriations after we've authorized money, as you have found in your institution, but this is one of the purposes of our hearing today, to try to give more of a global approach, really, to our own legislative efforts.

Now, let me just ask your own view about what has been called being a popular wave, a second wave of potential crises in various countries are often mentioned or omitted from that, but the thought is that quite apart from our concentration of attention on African states—Russia, China, various other very large, and India is mentioned from time to time—are turning into potential crises which may or may not being acknowledged completely by their governments, but the reality is in a world as small as ours, it's going to have enormous impact, whether people recognize it or not, but what is your own view about the second wave business?

Dr. FAUCI. Well, history has proven that that is indeed what is going to happen when people deny the realities of what HIV is and how it spreads in their societies, and I would even go beyond that, Mr. Chairman, and say not second wave, it's probably third or fourth wave. Because when the reality and the awareness in this country—mainly because of our health care delivery system and our ability to recognize infections—when it occurred in the early 80's there was this big wave in the developed world, and in the developing world, it was felt, "Well, there's not much of a problem there," when in fact it was smoldering and getting ready to explode, which is what happened in sub-Saharan Africa and the Caribbean. Absolutely, you can predict, as surely as we're talking to each other now, that the explosions are going to occur in countries, and we already have the indications, if you look in Eastern Europe, in Russia over the past year and a half, that has been the fastest growing caseload of HIV in the world. If you look at the slope of the increase in the number of cases. If you look at China and India, that's a disaster waiting to happen, particularly because of what we've seen in some quarters of people of those countries, they don't really admit that they have a problem. And if you don't admit you have a problem, you're not going to do the appropriate things to prevent that problem from exploding. So, I'm very concerned about the fact that there are people, and even leaders throughout the world who think as people have thought a decade or two decades ago, "That's somebody else's problem, it's not going to happen to us." It is going to happen.

The CHAIRMAN. I had an experience, just anecdotally, at the ultra pure laboratory in St. Petersburg, Russia, I was visiting the laboratory under a different set of circumstances, the Non-legal Cooperative Threat Reduction Program during the few years that chemical or biological substances were involved in research there and were trying to persuade the employees to take up other courses, which they have been doing, with half of the employees doing some pharmaceuticals used in St. Petersburg hospitals. But, during the course of that visit, members came from Moscow to talk about AIDS in Russia. They said, essentially, what we heard in testimony here in this room a couple of days ago, that they felt that the cases were approaching a million in Russia, which was a sizable number of cases, largely unacknowledged by many parts of their government. They have administrative/legislative situations in Russia as we do here—people having different views.

But we heard, disturbingly, two days ago from experts on Russia, that the population of the country might decline very, very sub-

stantially in the course of the next quarter century due to HIV/AIDS. We've already heard that due to the birth rate being lower, great problems of alcoholism and tuberculosis, that already there was an unusual demographic feature of Russia—a declining population of a major European state. But the suggestion was the decline might be all the way from the range of a 140 million persons, more or less, to something in the hundred tens, or a hundred twenty millions in the course of a quarter century of time, which is astonishing and has, of course, an enormous impact on a major country in the world today.

So, this is a situation that could be compounded if China or India were not to take preventative measures as has been suggested by Ms. Judd earlier. The United States cannot intrude into the affairs of all of the countries, we can't surround their leadership, and say "Do this and that," and so forth. The question is how, through our diplomacy, how people in your business, as you deal with professionals, can have an influence? In the same way as a local sailor has influence with these DUMA members, all of us in our various ways, perhaps, may have this kind of interest, and I appreciate your own specific leadership.

Let me ask one more question and then I'm going to be recognizing my colleague—you've commented in testimony before other committees about the NIH budget and the problems that you have in conducting the vaccine research in the years ahead. You mentioned a little bit today about the new Center for HIV/AIDS and Immunology at NIH. Describe as best you can, what the budgetary problems are as you perceive that institution that you have founded, and its growth, give some dimensions, maybe, for the intermediate future.

Dr. FAUCI. Well, first, thank you for that question, Mr. Chairman. The budget for the NIH is a substantial budget, as you know, it's $28.6 billion. We have devoted greater than 10 percent of our budget to HIV/AIDS, which is a substantial amount, it's about 11 plus percent of the budget, $2.93 billion for HIV, of which $607 million will be for vaccines.

The issue that we're facing at the NIH is no secret, as you know, due to generosity of the Congress, we've been able—from 1999 to 2003—to have a doubling of the NIH budget. But what we have now, this year and in previous years is a situation where the increase is, because of the constraints of budget throughout the government, is about a .5 percent increase. When you're dealing with a .5 percent increase in budget, a lot of the momentum that you may have built up during the doubling period, you have to re-look at it, and re-prioritize, so if we have opportunities, for example, for vaccine trials, we have to take a very careful look. We'll do it as best as we can, we'll spend the money we have, which is substantial, as best as we can, but when you have that kind of constraint, it may, in fact, cause a delay in certain projects that you would like to complete.

The CHAIRMAN. I understand.

I welcome now Senator Feingold to the hearing. Let me just mention to the witnesses and those who are in our audience, even as we are involved in this important hearing, the Senate is in the

final stretches of debate on the energy legislation, which is important to the country, and likewise in the last hour we've had a visit from the Prime Minister of Iraq, with some of his Cabinet officials, which has occupied the Committee on Foreign Relations, understandably, some of our members. But we appreciate the appearances of members, it's duly noted, and we appreciate, especially, Senator Feingold coming over to raise some questions now.

Senator FEINGOLD. I thank you, Mr. Chairman, for that and for holding the hearing, and I thank you, Doctor, and all of the witnesses for your testimony and for your dedication to this issue that we all feel so properly compelled to focus on as often as we can, and the Chairman has been very helpful in that regard.

Let me ask you just a few questions. My understanding is that the coordinating committee of the Global HIV Vaccine Enterprise has noted that the acute shortage of qualified personnel is a major bottleneck to conducting clinical trials in the developing world, and this seems to echo serious concerns about the overall state of health care infrastructure in many AIDS-affected countries, especially the problem of training and retaining qualified personnel. Doctor, what steps are being taken by the United States to improve the human resource capacity in the developing world, both in terms of clinical researchers, and more broadly in terms of health care professionals?

Dr. FAUCI. Well, with regard to what we at the NIH do, which is part of the broader issue that you mentioned, Senator, is that in our programs in our vaccine trial networks, our prevention trial networks and our AIDS clinical trial groups for therapy, we have a substantial training component to train people in-country. We've learned from our own experiences, from the experiences of the European countries, that when you go into a developing nation and just do your thing—noble as it may be—and get out, without leaving an intellectual capital infrastructure, as well as some physical infrastructure, then after a relatively short period of time what you've done, essentially, goes to attrition. So, we've made it an important part of the networks that we've created internationally, to train people who, in fact, would maintain and continue that intellectual capital in those countries, specifically in the area that we're responsible for. There are other areas, and namely the delivery of health care, of trying to train physicians, that in fact we need to do much better on. People—not just physicians—physicians, health care providers, nurses and technicians.

Senator FEINGOLD. How do you keep people there under this technique that you've talked about, because I've heard this complaint in African countries from the Presidents of countries, concerning personnel, health care personnel, and health care workers. It's basically a complaint about donors and developed countries poaching some of the key health care people. Are there incentives being used to keep them there? How do you do that?

Dr. FAUCI. Not good enough, Senator, in that what we often see is that we will train people who will become really quite qualified, and within their own native country, after a while if they don't get the firm, long-term, committed support from their own nation, then

they either move to something else or leave the country, because since they are trained, they know they can get a job someplace else.

Senator FEINGOLD. That's what I'm getting at, the concern about people going to Europe or the U.S. or elsewhere after they become quite proficient and enormously helpful in their own country.

Dr. FAUCI. So what we really do need, and we've not been successful, we need to put pressure on the nations that are the host countries to provide for the sustained support of those individuals, and that is not an easy thing to do, because you're essentially requesting another country to do something that they may not have the resources to do, or might not want to do. But it certainly is an appropriate thing to do, or we'll lose the people that we've trained.

Senator Feingold: Maybe that's a targeted thing we could help with. To the best of your knowledge, does the U.S. intend to make any new proposals on the health care infrastructure issue of the G-8 meeting in Gleneagles?

Dr. FAUCI. To my knowledge, no, but I don't have the full knowledge of exactly what's going to be put—I know there are certain initiatives that will go on, but I do not know if that is one of them.

Senator FEINGOLD. Maybe we'll try to follow on that. Let me ask you another question—where does the effort to find microbicides that can halt the spread of HIV stand, and how much is being spent on this effort internationally? How soon might we expect to find something that can make a substantial prevention difference in this regard, and how much of the international funding is the United States providing for this effort?

Dr. FAUCI. Good question, and thank you for that question. In fact, microbicides, particularly over the past several years, has become one of the major initiatives that we have been pushing. We started off with something like $25 million, we now total up to about $70 million. Of particular note is a trial that was just started recently, an international trial testing two candidate microbicides in the United States and in sub-Saharan Africa—the site in the United States is in Philadelphia, there are three or four sites in sub-Saharan Africa to test two products, as you know, because the rationale, the need for a topical microbicide is quite important, particularly if you're dealing with societies or a societal infrastructure or philosophy where women really don't have any option to be able to protect themselves. You heard Ms. Judd mention the idea about allowing, for example, married women to use condoms, sometimes they can't negotiate the use of a condom, even within their own marriage, and end up being a battered wife. But if you had a good, successful microbicide, you could use it without even the knowledge of your sexual partner. So we are moving on this, I feel cautiously optimistic and confident that within a reasonable period of time, we will have a safe and effective topical microbicide. We certainly have made strides over the last year that are much better than they have been in the previous several years.

Senator FEINGOLD. What portion did you say was the American funding of the overall budget?

Dr. FAUCI. Our institute, it's about forty something; for the total NIH, it's about $70 million.

Senator FEINGOLD. Thank you, Doctor.

Efforts to address public health crises in the developing world from polio to AIDS, as you know, are often hampered by some suspicions regarding the donor intentions. And there have been instances of improperly conducted research in the developing world that have sometimes lent some credence to these suspicions.

What can you tell the committee about the ethics of vaccine trials and clinical research in the developing world?

Dr. FAUCI. That is something that we have paid considerable amount of attention to, because years ago, there wasn't that much attention. There may not have been flagrant violations, but there wasn't explicit attention paid to the ethics of a clinical trial, particularly of a vaccine.

One of the things that we've initiated is that you don't go into a trial unless you have a clear cut plan that if the vaccine is successful that that vaccine will be made available to the country in which you have done the testing. So you can't use a country as a testing vehicle, without providing the benefit that if you're successful, you in fact would make that vaccine available to them. That's also very important.

Also, we have a considerable number of training exercises now, particularly in the arena of informed consent, so that you get informed consent and education of the parties involved in a language and a venue that relates to them, not in a Washington, D.C., Boston, New York, discussion, but in a Kampala, Nairobi discussion. That's also something that I think has not been fully appreciated in the past, but is fully appreciated now.

Senator FEINGOLD. Finally, to what degree are governments in developing countries and local officials consulted about ethical standards and briefed on the procedures in place?

Dr. FAUCI. Intensively, in fact, you really can not, and should not, but you can not get a trial going in—for example—the rural area of sub-Saharan Africa without the elders and the leaders, the cultural leaders of the tribes involved and of the populous involved to buy in fully to a trial. In fact, that's an important dilemma that we sometimes face, because when you're trying to get informed consent, not infrequently if you go into a community, the elders make informed consent for everybody—we've got to do both—we've got to get the buy in of the leaders, but you've got to make sure that individuals who participate are not swayed because their elders have consented for them, so you have to have both a broader, generic consent, as well as individual consent.

Senator FEINGOLD. Thank you, Doctor, for all the answers, thank you, Mr. Chairman.

The CHAIRMAN. Thank you very much, Senator Feingold. I join the Senator in our thanks to you, Dr. Fauci, for your remarkable leadership every day at the Institute, and for your specific testimony which is most helpful this morning. Thank you very much, sir, we appreciate it.

The Chair would like to call now a panel composed of Dr. Helene Gayle, Director, HIV/AIDS, Tuberculosis and Reproductive Health at the Bill and Melinda Gates Foundation, Seattle, Washington,

and Dr. Seth Berkley, President and Chief Executive Officer of the International AIDS Vaccine Initiative in New York. We welcome the panelists, Dr. Gayle, I appreciate your coming this morning from a remarkable philanthropy effort by Bill and Melinda Gates and the foundation they have founded, and for your remarkable advocacy. I would like to thank also Patty Stonesifer, co-chair and President of the foundation with whom I had the privilege of collaborating on an article in the Washington Post this year, on January the 19th, entitled, "Speeding an AIDS Vaccine," at that time our office collaborated, I know with you, personally, to make certain that we had the facts straight, and that we knew what a remarkable initiative you have given.

And Dr. Berkley, we appreciate especially your coming today and the remarkable work of you, personally, and your organization. We look forward to hearing from both of you, and I'll call first, I'll call upon you, Dr. Gayle, for your testimony.

STATEMENT OF DR. HELENE GAYLE, DIRECTOR, HIV/AIDS, TUBERCULOSIS AND REPRODUCTIVE HEALTH, BILL AND MELINDA GATES FOUNDATION, SEATTLE, WASHINGTON

Dr. GAYLE. Thank you, I really want to thank you, as others have, for your committee and the leadership particularly as Chair to learn about the progress for developing a safe and effective HIV vaccine, and we really very much appreciated the Op Ed that you mentioned working along with our President, who is an Indiana native, as you know.

We also know that in addition to your tremendous leadership in this area, all of the members, virtually all of the members of your committee have traveled and have taken on the issue of HIV/AIDS seriously, and have traveled to Africa and other parts of the world where HIV has really had a toll, and I think they all—as yourself—have returned even more committed to this issue. So, we really thank not only you, Chair, but also the committee for its leadership.

As you mentioned, I direct the Gates Foundation efforts in HIV, TB and reproductive health, but I also am the co-Chair of the Global HIV Vaccine Enterprise. In the time that I have I want to briefly touch on our Foundation's work, but also highlight some of the issues related to the HIV vaccine Enterprise, and we have submitted a more detailed version of my testimony to be included in the record.

I'm not going to reiterate the statistics that many people have already gone into here, I think we know them well, but suffice it to say, that HIV/AIDS represents the greatest global health challenge of our era. The epidemic has not, in fact, peaked as we talked about before, but instead, is relentlessly expanding throughout the world. And we talked about the issue of next wave countries that are going to have a huge impact on the global epidemic.

Ultimately, we do need a preventive vaccine to end the spread of HIV worldwide, and the work in this area must be seen as one of our highest priorities. However, as several people have also mentioned, it's important that at the same time we recognize that this cannot be allowed to compete with the equally important need to

expand existing HIV prevention and treatment services, so they must go hand in hand.

Important progress has been made in the search for a vaccine, and developing an HIV vaccine is one of our Foundation's highest health priorities. To date, our Foundation has granted more than $126 million for HIV vaccine research, much of it, in fact, to the International AIDS Vaccine Initiative, NIAVI, and you're going to hear more from Dr. Berkley in a few moments.

Thanks to the effort of institutions like the NIH, and NIAVI, and many, many others, we really do know a lot about HIV, much more than we did at the beginning of this epidemic, but despite all of this tremendous work, progress in finding a vaccine has been far too slow.

So, let me just describe for a moment, Dr. Fauci alluded to it in some of his comments, the Global HIV Vaccine Enterprise. As he mentioned in 2003, the Foundation joined with more than 20 leading international researchers in vaccine efforts, including Drs. Fauci and Berkley, called for a new global effort to address the roadblocks to accelerating the progress to vaccine research, and the Enterprise was launched and the Enterprise was born.

This Enterprise is premised on the belief that finding a preventative HIV vaccine could be accelerated by a different kind of approach than the traditional research paradigm that has been used for much of the biomedical research in this country. That paradigm generally relies on more individual and a more independent approach, and it's been critical for stimulating new ideas, advancing our understanding of HIV and our body's response to HIV, but it's also created research silos, and a much less coordinated effort than we need for this, for developing this vaccine. This way of doing business is still going to be important, but by itself is not sufficiently targeted to most efficiently reach our target of an effective and safe HIV vaccine.

The Global HIV Vaccine Enterprise is an international alliance of researchers as has been mentioned, and it also includes advocates, donor organizations, and others who are united in their commitment to work together to accelerate HIV vaccine research.

Let me emphasize that the HIV vaccine Enterprise is not a new bureaucratic organization, and the Enterprise itself is not going to conduct biomedical research. Instead it is an alliance dedicated to increased focus, resources, and importantly, the collaboration and coordination of HIV vaccine research. It's guided by the strategic—the scientific strategic plan that Dr. Fauci mentioned in his comments, and I think importantly it included more then 120 people from 15 countries around the world to put that plan together and really look at what were the major scientific roadblocks, and propose a series of large-scale, collaborative HIV vaccine research centers to address them and focus on accelerating progress in these areas. The plan also calls for increasing the capacity to conduct clinical trials, something that Senator Feingold alluded to in developing countries and also addressing some of the key challenges like intellectual property, manufacturing and regulatory issues in order to expedite vaccine research and eventually to expedite the delivery and the access of a safe and effective vaccine.

One of the examples, the first example of support to the Enterprise was the vaccine center, the Center for HIV/AIDS Vaccine Immunology, which Dr. Fauci talked about. Another example in support of the Enterprise is the meeting of interested donors that the Welcome Trust, one of our major partners in the Enterprise will host on behalf of the Enterprise in October—as an effort to educate donors and help mobilize additional resources needed to implement the scientific plan. We hope that others will continue to follow the lead of NIH and Wellcome Trust and others in really focusing efforts around the strategic plan of the Enterprise.

Several have already mentioned the U.S. Government's role in launching the Enterprise, and the birth of the Enterprise, you yourself mentioned that last year's Sea Island summit of G-8 nations was really important in giving the political endorsement and also announcing the first financial contribution to support the Enterprise strategic plan, the Center that Dr. Fauci talked about. In two weeks G-8 leaders will again gather in the United Kingdom, and we hope that the upcoming summit meeting will generate a further and more specific affirmation of the G-8's commitment to the Enterprise, and we would appreciate and assistance that the members of this committee could provide in encouraging the Administration to advocate strongly for continued G-8 support for a robust, global HIV vaccine research effort.

The challenge of creating this HIV vaccine will be a marathon, it's not a sprint. In working to strengthen the vaccine research effort, it's going to be important to understand that while a vaccine may not be achieved overnight, staying the course over the long haul is really what's key.

Now let me suggest a few other ways that you and the committee could help. First of all, to arrive more quickly to the day when we will have an HIV vaccine, substantially more funding is needed for HIV vaccine research, and I think Dr. Berkley is going to discuss some of the funding issues, but we know that there's a tremendous unmet need.

When our foundation recently announced the availability of up to $360 million new dollars to begin certain aspects of the Enterprise scientific plan, we received proposals equal to three times that amount. So clearly there is good science waiting to be funded. So that's first, more resources.

Second, to engage—to increase the engagement of private industry in the search for an HIV vaccine, we recommend that the U.S. government significantly increase it's support for programs that provide incentives for private companies to conduct research on HIV vaccines and other global health technologies. With incentives, industry is in fact a willing partner. A good example of this is the Bio-ventures for Global Health, an initiative of biotechnology industries and foundations including ours to help small biotech firms conduct critical research into solutions like an HIV vaccine, we're very proud of this bio-venture, we just announced funding in support for this, and we think those kind of public/private partnerships are going to be the key in working on developing an HIV vaccine, and giving incentives for this is important.

And third, as has already been mentioned by several people today, the need to support a comprehensive approach for HIV. This means making maximal use of all the prevention tools we have available. You yourself mentioned, Mr. Chair, we need a comprehensive approach that includes all the strategies that we know—to encourage abstinence, faithfulness, condom use, treatment of other sexually transmitted diseases, providing antiretroviral treatment to HIV infected pregnant women, encouraging people to get tested—all of these things are going to be necessary to make a difference, if we really use these to reach the people who need them most. We know that we can reduce what is a preventable infection in large measure, just by using the things we already know exist and work if we use those fully.

But we know that existing methods of prevention don't serve the needs of all populations and all life circumstances, and I think Ashley Judd talked about that in great detail. This is especially true for women who are now roughly represent one half of all new infections worldwide, and about 30 percent of new infections even here in this country. It is critical to invest in research on microbicides and other potential methods for women to protect themselves from HIV while we continue our search for a new vaccine.

So, let me conclude with just a few words about the overall importance of prevention. Others have also hit on this issue, but prevention—reducing the spread of HIV is not only vital in its own right, but is also critical to the success of HIV treatment initiatives. Last year while the world scaled up treatment programs to deliver antiretrovirals to an estimated 700,000 people, there were five million new infections. Unless the number of new infections is sharply reduced through prevention, treatment programs will quickly become unsustainable. In short, prevention helps preserve the promise of treatment for those who need it.

Although the quest for a vaccine and other new prevention tools is daunting, I have no doubt that we can succeed. To do that, we need not only the world's best scientific talent, but also sustained political support, significant new funding and stronger collaboration within the field between developed, and developing countries.

I'll close, but again, thank you for hosting this hearing and for your continued efforts to expand U.S. leadership in the fight to bring an end to AIDS, and I look forward to your questions.

The CHAIRMAN. Well, thank you very much to Dr. Gayle for your very comprehensive and compelling testimony.

[The prepared statement of Dr. Gayle follows:]

PREPARED STATEMENT OF DR. HELENE GAYLE

Let me express my thanks to the Chair and this committee for holding this hearing to learn more about progress in HIV vaccine research. It is an honor to appear before you and with Dr. Anthony Fauci of the National Institutes of Health (NIH) and Dr. Seth Berkley of the International AIDS Vaccine Initiative (IAVI). Thank you also to Ashley Judd for your very informative remarks.

I am Dr. Helene Gayle and serve as the director of HIV, Tuberculosis, and Reproductive Health at the Bill & Melinda Gates Foundation. I am also co-chair of the Global HIV Vaccine Enterprise, serving with Dr. Michel Kazatchkine, who is France's Ambassador on HIV/AIDS and Transmissible Diseases. In addition, I serve

as president of the International AIDS Society and co-chair of the Global HIV Prevention Working Group.

In my testimony today, I will discuss the importance of an HIV vaccine in the fight against AIDS, the work of our foundation in supporting HIV vaccine research, the establishment of the Global HIV Vaccine Enterprise, and finally a few thoughts on the role of an HIV vaccine within the broader picture of HIV prevention and treatment.

Last year, more people were infected with HIV than in any previous year. The nearly 5 million children, women, and men who were newly infected in 2004 brought the total number of people living with HIV worldwide to nearly 40 million. A few weeks ago, the Centers for Disease Control and Prevention (CDC) announced that here in the United States the number of people living with HIV topped 1 million. You are all aware of the human and financial cost that lies behind these numbers so I won't elaborate further, other than to say that the epidemic continues to outpace our efforts to contain it, and the road ahead is indeed long. More, much more, must be done now if we are to have a chance of beating this deadly virus.

Ultimately, a safe and effective preventive vaccine offers the best long-term hope for stopping the spread of HIV. Put another way, there is no conceivable way to end this epidemic without a vaccine. Thus, global efforts in the vaccine field must be seen as of the highest priority, but should not have to compete with the equally important need to expand current HIV prevention and treatment services, or with other aspects of our efforts to fight poverty and eradicate disease.

Much good research has been done, and important progress has been made toward a vaccine. Scientists across the globe have been working on finding a vaccine for about as long as we have known about HIV. The United States has been a leader in the global search for a vaccine, largely through the efforts of NIH, and also through the Army Medical Research program, the CDC, and countless laboratories in academic research institutions and pharmaceutical and biotechnology companies throughout the country. Our nation leads the world in biomedical research capacity, and so we have led the world in HIV vaccine research.

These efforts have taught us a great deal about the virus: how it enters the body, establishes itself, multiplies, and evades and undermines the immune system. Though far from a cure, drugs have been developed that can, for many, substantially slow the impact of the virus. These antiretrovirals—ARVs—give hope to millions who are living with HIV infection.

Yet despite all of this tremendous work, progress in finding an HIV vaccine has been too slow. If we measure the end of the pipeline for vaccine candidates, we see only a few drips. While a number of candidate vaccines have been tested in human trials over the last 18 years, only one approach has completed the Phase III trials that ultimately are needed to establish whether something that worked in a test tube is effective in humans. Sadly, no candidate vaccine has yet emerged with demonstrated capacity to prevent HIV infection. Additional research progress is urgently needed to develop a new generation of candidate vaccines with a better chance of success than those currently being evaluated.

All of us are disappointed that we currently lack a safe and effective preventive vaccine. Those of us who are participating in this hearing are united in our desire to make the search for an HIV vaccine as short as possible. An understanding of the history of vaccine research, though, helps us put into proper context the global effort that is currently underway. This year we commemorate the 50th anniversary of the vaccine against polio—the one developed by Jonas Salk. Few people remember that it took many years for Dr. Salk and his colleagues to travel from concept to an approved product. Indeed, the first two trials for the Salk vaccine occurred in the mid 1930s. Moreover, the vaccine that was successfully tested 50 years ago was subsequently improved by additional research.

In the case of HIV, certain basic scientific questions remain unanswered, and critical areas of research merit substantially greater attention. In 2003, the Bill & Melinda Gates Foundation joined with a group of international researchers and vaccine experts, including Dr. Fauci from the NIH and other U.S. government officials, and Dr. Berkley from IAVI, to author an article in Science magazine that described these challenges in more detail and proposed a new global effort to address them. (I have attached a copy of this article and ask that it be incorporated into the record.) We called for creation of a global alliance, modeled in many ways on the Human Genome Project, to concentrate and accelerate the world's HIV vaccine research efforts.

[The documents to which Dr. Gayle refers throughout her prepared statement can be found in the appendix to this hearing.]

This was the start of the Global HIV Vaccine Enterprise, which is an alliance of researchers, advocates, donor agencies, and others united in their commitment to work together to accelerate HIV vaccine research. Soon thereafter, six working groups were established, bringing together some of the best scientists and advocates, to design a blueprint for action. Early this year, the results of their work were presented with the publication of the Enterprise's Scientific Strategic Plan. It identified six areas for concentrated work and collaboration:

Vaccine Discovery: While vaccines for some other diseases have succeeded by triggering an antibody response, there is now a strong consensus that an effective vaccine for HIV will need both to generate a broad-based antibody response that can neutralize the virus and recruit and influence the immune cells that suppress the virus's ability to replicate and evade the immune system.

The Strategic Plan proposes a two-pronged approach to broaden the candidate pipeline. First, we should expedite rigorous testing and comparative evaluation of candidates currently in the pipeline, although none of these is believed to induce the full range of immune responses that scientists believe will be required. Second, new and better candidates must be developed to widen the product pipeline. Simply put, we must speed up clinical research on what we have, and push more vaccine candidates into the pipeline.

Laboratory Standardization: Improving collaboration and strategic prioritization in the vaccine field requires that we have a common way of understanding trial results and comparing different candidates. We need to build tools and systems that enable scientists working across the globe to compare their work from one laboratory to another, and from one clinical trial to another.

Product Development and Manufacturing: Processes will be needed for producing consistent, active vaccine batches on a sufficient scale to meet the needs of large clinical trials and eventually worldwide demand. Typically, manufacturing processes are built slowly over time, as each vaccine candidate advances from early clinical testing to late-stage evaluation and licensure. Worldwide capacity for manufacturing new products is limited and exists almost exclusively in the private sector, which usually gears its capacity in the early years of a product to address demand in high-income countries.

The historic reliance on private industry for manufacturing capacity may not meet the world's needs in the case of an HIV vaccine. Few private companies are presently engaged in any form of vaccine research, and many fewer still are involved in HIV vaccine research. To address the manufacturing needs associated with vaccine research, the number of private sector organizations working on HIV vaccines should significantly increase, and product development and manufacturing capacity should be built in the non-profit and governmental sectors.

Building Clinical Trial Capacity: Demonstrating that a candidate vaccine works in humans is difficult, time consuming, and expensive. Global capacity to conduct this research is limited, especially the large Phase III studies that involve tens of thousands of healthy human volunteers. Research on vaccines and other new prevention technologies is best conducted in parts of the world where HIV is hitting hardest because this is where we most urgently need to know if a vaccine is safe and effective. Yet these areas are already reeling from the effects of the epidemic, and as we have seen in the struggle to expand access to current prevention and treatment services, there are simply not enough trained people and adequate facilities to do this work at an accelerated pace.

Building Regulatory Capacity: In this country, we all benefit from the oversight provided by the Food and Drug Administration, which helps ensure that medical products on the market are safe and effective. This capacity does not exist or is very weak in many of the countries hit hardest by AIDS, so their ability to regulate HIV vaccine clinical research and to ensure that clinical research is conducted safely and ethically is quite limited. Weak national regulatory structures can significantly delay the initiation of clinical trials and the approval of new products.

Intellectual Property Issues: Intellectual property issues often inhibit the flow of information and dialogue among researchers. To permit and encourage the active, real-time collaboration needed to accelerate HIV vaccine research, a framework is needed that allows organizations working on novel vaccine candidates to share information openly without compromising protection of their intellectual property. (I have attached a copy of the full Strategic Scientific Plan and ask that it be incorporated into the record.)

Having identified these six core focus areas, the Enterprise aims to create new groups and mechanisms to the monitor the Plan and to make appropriate revisions as necessary.

The Enterprise is not a new institution that will make grants or conduct biomedical research on its own, and the Enterprise's Scientific Strategic Plan is not intended to describe the entirety of HIV vaccine research. Rather, the Enterprise is an alliance for strategic planning, collaboration and information-sharing, and its Plan focuses on the key challenges that will most benefit from global collaboration. The Enterprise is premised on the belief that finding a preventive HIV vaccine could be accelerated by an approach that augments the traditional paradigm for biomedical research. The usual research approach relies principally on individual research teams, working independently from others, generating incremental progress. This way of doing business is still important but by itself may not be sufficiently targeted to most efficiently reach the goal of an effective HIV vaccine.

To have a meaningful impact on the global search for a vaccine, the Scientific Strategic Plan must be shared with, and embraced by, others that have important roles to play. We hope that funders of HIV vaccine research will use the Plan to guide their allocation of new resources—both to direct resources toward key challenges and to ensure that recipients of such funds adhere to the spirit of collaboration and transparency represented by the Enterprise. This doesn't mean that we want to stifle innovation. Just the opposite. We strongly believe that greater communication and collaboration are essential to speeding up our progress. One example of support for the priorities identified in the Enterprise Strategic Plan is the resources that NIH will make available for a new Center for HIV/AIDS Vaccine Immunology.

In October, the Enterprise will convene a Funders Forum, hosted by the Wellcome Trust in London, to bring together those currently funding HIV vaccine research with those that could potentially provide additional resources. The Funders Forum will help current and future donors better understand the Enterprise and its Scientific Strategic Plan, and our hope is that it will also persuade them to use the Plan as a guiding tool in their funding processes. We are also hopeful that other donor countries and private foundations and businesses will soon be in a position to commit new resources towards the Enterprise plan.

The Enterprise also intends to engage policy makers, advocates, clinical trial hosts and volunteers, regulatory and host government officials, and others. The first meeting of stakeholders was held in May of this year, also in London, and was co-hosted by the Enterprise and the United Kingdom's Department for International Development (DfID). We are also working to establish a permanent secretariat for the Enterprise and have launched an international search for its first executive director.

The U.S. government has played a very important role in the birth and development of the Enterprise. At last year's Sea Island summit of G-8 nations, the U.S. shepherded through a strong statement of political support for the Enterprise and announced the first financial contribution to implement the Enterprise's strategic vision. (I have attached a copy of the G-8's endorsement to this statement and ask that it be incorporated into the record.)

I was also very pleased that the goals of the Enterprise were highlighted in an op-ed in January, 2005 in The *Washington Post* by Chairman Lugar and by Patty Stonesifer, President and Co-chair of the Gates Foundation. (The op-ed is attached, and I ask that it be incorporated into the record.)

Let me now briefly describe the work of our foundation in supporting HIV vaccine research. It is a critical part of our broader global health agenda, which focuses on a fundamental commitment by Bill and Melinda Gates to global health equity. It is both a philosophical premise that people shouldn't suffer from illness and disease simply because they were born into poverty, and an understanding that improving health is fundamental to fighting poverty and giving every child an equal chance at a safe and productive life.

Our commitment to HIV vaccine research has been longstanding, initially reflected through our support for the International AIDS Vaccine Initiative, to which

we have made grants totaling $126.5 million. IAVI, which is based in New York City, is a not-for-profit organization that conducts HIV vaccine research through partnerships with private industry and developing world scientists and also advocates for a greater global response in this area. IAVI is a partner in developing the HIV Vaccine Enterprise. We also support the work of the AIDS Vaccine Advocacy Coalition, also based in New York and an Enterprise partner, which is a small organization with a big, informed voice that helps to monitor global progress on HIV vaccine research.

More recently, we have helped to launch the Enterprise and are currently serving as its interim secretariat. The foundation announced in February a commitment of up to $360 million over five years to fund work on scientific priorities identified by the Enterprise Plan, including development of novel candidate vaccines and laboratory standardization. I should tell you that the response was overwhelming. We received more than $1.4 billion in requests for support, many of which were for serious, innovative research. We are now in the process of identifying those that best match the goals of our request for proposals, but there clearly is great, unmet demand by researchers.

We are also committed to doing more over time. We work closely with our colleagues at the NIH, the Wellcome Trust, and other government and research agencies across the world to leverage our resources with those from others. We hope that more resources are forthcoming, because a significant gap exists between resources currently available for vaccine research and amounts needed to finance a robust research effort. IAVI has estimated that $700 million was spent worldwide on HIV vaccine research last year, including in the public and private sectors, and that as much as $1.2 billion per year may be needed to develop a more robust and comprehensive approach. That gap of $500 million is about equal to what the NIH is currently investing in this area, so we need others to step up to the plate.

Finally, let me describe how HIV vaccines fit into the broader context of the global effort on HIV/AIDS. Vaccines are part of the long-term strategy to prevent expansion of the epidemic. In all probability, we will not have a safe, effective preventive HIV vaccine for more than a decade. I would be delighted were my projection to prove too pessimistic, but this timeframe represents the best estimate among leaders in the field. Moreover, developing the kind of preventive vaccine that can halt the epidemic will likely happen in stages, with the first generation of vaccines protecting only some people some of the time, and then improving over time to protect more people all of the time. Because an estimated 95% of all new HIV infections occur in developing countries, we would also hope to see vaccines that require one shot instead of three, that would not need refrigeration, and that could be easily administered. This will take time.

Even a very good vaccine will not be a silver bullet. It will take time to get the vaccine to those at risk. We see even today that vaccines that are cheap and effective sit on shelves while millions of children suffer and die needlessly. Our track record for getting vaccines to those who need them is poor. Even after a safe and effective vaccine emerges, we will also need to continue and possibly even expand our other prevention efforts.

For the medium term, we see the importance of developing other new tools to expand options for slowing the spread of HIV. We know that our current strategies aimed at abstinence, faithfulness, condom use, treatment of other sexually transmitted disease, and encouraging people to be tested for HIV can make a difference if they reach the people who need these the most. HIV infection remains 100% preventable, but today fewer than one in five adults at high risk for HIV have access to existing prevention information or services. We also know that existing methods of prevention don't serve the needs of all populations and all life circumstances. This is especially true for women, who now represent roughly one-half of all new HIV infections worldwide and about 30% of new infections in this country. Many women are at risk for HIV not because of their own behaviors but because of the behavior of their male partners. It is critical to invest in research on microbicides, vaginal ointments or gels, female barriers like diaphragms or female condoms, and use of anti-HIV medications for prevention—these are all potential methods for women to protect themselves from HIV without requiring their partner's knowledge or permission. These will be our best hope for reducing the spread of HIV in the short to medium term.

Providing life-preserving therapies, such as antiretroviral drugs, is a pressing global priority. At the current rate, however, another 50–60 million people will have contracted HIV during the 10 years it might take to find an HIV vaccine. Unless the rate of new infections is sharply reduced through prevention, demand for

antiretrovirals will rapidly outstrip the world's financial and technical means to deliver them. Effective prevention helps preserve the promise of HIV treatment.

Let me conclude by suggesting what you can do to help:

1. More funding is needed. We know that this is a familiar refrain, and the American people have been extremely generous in the global fight against AIDS. We need to continue to expand our efforts and to do so at a faster pace. We will find an HIV vaccine to help bring an end to this global nightmare, and that day will come much sooner if researchers have the funding to do their work.

I mentioned earlier that the G-8 endorsed the Enterprise at its summit last year. In two weeks, G-8 leaders will gather again in the United Kingdom. We hope that the upcoming summit meeting will generate a reaffirmation of the G-8's commitment to the Enterprise, and we would appreciate any assistance that members of this committee could provide in encouraging the Administration to advocate for continued G-8 support for a robust global vaccine research effort.

2. We need to engage the private sector. There is a wealth of talent and knowledge and experience in the private sector that we must have to be successful, although too few companies have joined this effort. The reasons aren't complicated: vaccine research is risky, expensive, and the financial payouts are small in comparison to more lucrative pharmaceuticals. Moreover, we don't yet have enough candidate vaccines with demonstrated efficacy in the test tube to excite private sector investments. You can help by supporting the purchase and use of vaccines that are currently available—there's no better inducement to private investment than knowing that there's a market ready, willing, and able to purchase their products. If they see the vaccines we have now gathering dust on the shelf, why should they believe that an HIV vaccine will be treated any differently?

We also need to increase support for programs that provide incentives for private companies to conduct global health research. With incentives, industry is a willing partner. A good example is BIO Ventures for Global Health (BVGH), an initiative of the biotechnology industry and charitable foundations to overcome the market barriers, funding barriers, and information barriers that have long restricted biotech firms from conducting research into diseases that primarily affect developing countries. BVGH is working with companies and foundations to build new partnerships and is preparing a series of business cases that describe market and funding opportunities for biotech firms to increase their involvement in global health research. In addition, BVGH has represented the biotech industry in negotiations with finance ministers over the role that advance purchase agreements can play in spurring research into critical solutions like HIV and malaria vaccines.

3. We need to support a comprehensive approach to HIV. All that you are doing now to support the expansion of prevention and treatment services for HIV is extremely helpful in our HIV vaccine research work. As an example, in the course of clinical research on vaccine candidates, thousands of volunteers are screened and tested. For this research to be ethical, they need to be provided access to the best prevention and treatment services available regardless of whether they are enrolled in the trial. If the responsibility for providing these prevention and treatment services falls onto the research project itself, the financial burden is so substantial that the research itself is inhibited. On the other hand, if other programs like the Global Fund to Fight AIDS, Tuberculosis, and Malaria or the President's Emergency Plan for AIDS Relief (PEPFAR) are able to step in to fund those services, the research can move forward without carrying the load for an entire community.

4. We need your patience. This will be a long, tough road, and there will be more failures than successes. That is the nature of scientific research, and we need to know that you will persevere with political commitment and resources until we've accomplished our goal.

I thank all of you, and particularly Chairman Lugar, for your interest in this area, your commitment to U.S. leadership in the fight against this terrible epidemic, and your special interest in supporting the global effort to find a safe and effective preventive HIV vaccine.

Let me also acknowledge the tremendous leader we all have in Dr. Fauci. He has been a stalwart supporter of the Global HIV Vaccine Enterprise, and a real partner to our foundation in this and so many other areas of biomedical research.

Thank you again for allowing me to share my thoughts with you. I look forward to your questions.

The CHAIRMAN. I call now upon Dr. Berkley to continue this panel's discussion. Dr. Berkley?

STATEMENT OF DR. SETH BERKLEY, PRESIDENT AND CHIEF EXECUTIVE OFFICER, INTERNATIONAL AIDS VACCINE INITIATIVE, NEW YORK, NEW YORK

Dr. BERKLEY. Thank you very much, Mr. Chairman, for the opportunity to appear before you to discuss the state of vaccines and also to talk about IAVI. We appreciate your interest in this critical matter because obviously we need to continue to work on this over the future and we'd also like to commend what the United States has done in responding to this terrible epidemic. The U.S. really has been the leader, we applaud what President Bush and the Congress has done to try to get out these treatments and push prevention and the important research that Dr. Fauci talks about.

The focus on the short-term emergency, which is what most of it is about, is critical and appropriate, but without these better tools, we're not going to be able to end the epidemic, as you've heard from the other speakers. Just to emphasize, and I think you brought this up in your question, the goal must be to the end this terrible epidemic, and if we lose sight of that goal we can get caught up in the day to day needs of both the existing prevention technologies today, as well as treatment as a critical issue. As a result, we were really happy with the U.S. leadership at the G-8, and hopefully, as Dr. Gayle has said, that that will continue for this year, your resolution that just has been submitted is quite important, as is the other work of the members of the committee.

On behalf of my organization, IAVI, I also would like to express appreciation for the financial and political support that this country has provided to our organization. Our mission is to ensure the development of a safe and effective, accessible, preventive HIV vaccine for use throughout the world, and our particular focus is developing countries. We represent true collaborations in our science and policy programs, and I think what's important is that we bring with us, not only the U.S. government, but seven other governments who support the important work going on, the European Union, which has been slow to support these activities, is an active supporter now, the World Bank, a range of corporations, a range of private foundations, Dr. Gayle has already talked about the Bill and Melinda Gates Foundation, but also Rockefeller, Sloan, Starr, AIDS charities, *et cetera*.

Your funding has really created a unique model of an efficient and global non-profit public/private partnership, and we're committed to work with the best in the world, not in any one country. So, whether that be in London, whether it be in Nairobi, or New Delhi, whether it be in Ohio, or Washington State, whether it's a small company, privately traded, a larger bio-tech, publicly traded, or frankly, a large vaccine manufacturer, individual researchers, or the outstanding team of scientists that Dr. Fauci has working at

the NIH, we can demonstrate partnership and efficiency. In fact, we're very happy that the NIH has recently decided to test one of their candidates at two of the sites IAVI has developed in Africa. This is a tribute to the types of partnerships we've created on the ground in the developing world with the key stakeholders and the political support that's associated with this. And this is really the type of collaborative work that IAVI and other groups represented today recognize as important in creating the Global HIV Vaccine Enterprise. We're a founding member of this, and we really welcome the opportunity to share our global experience, expertise and model of innovation with many others.

You've already heard today, without a vaccine, we are not going to be able to get rid of this epidemic, and the virus is always on the move, we didn't talk about that, but drug resistance is spreading and the virus is constantly changing. As a physician, I believe that every life is sacred and providing treatment is absolutely critical, and of course we must do everything to prevent every new infection we can, for the reasons Dr. Gayle has said, however, the current prevention and treatment strategies, which is the question on the table, are only partially effective. So therefore, we absolutely have to go ahead and push forward on a vaccine, and one of the important points is that lifetime treatment is the only option for those infected. And the drug toxicity and viral resistance spreading—this does not bode well for a global, sustainable response. And as this committee was responsible for thinking about overseas development aid, this is something that is going to continue to expand unless we do something to stop it.

So, we need to think of the work on vaccines, not only as pushing the science forward, but really as a way to avert these future treatment costs, which are going to be an enormous cost for public treasuries around the world, and not only developed countries, but in developing countries. These costs will bankrupt their ability to do the broad range of issues, whether it be women's education, other vaccine work, water and sanitation, because the focus on AIDS is taking up so much money. So we really have to go ahead and get a vaccine.

Why don't we have one after 20 years? Science does remain the greatest challenge, but we really have good reason to think the science is solvable. From the effort today, we know that monkeys can be protected by certain types of vaccines, but that people get immune responses and hold the virus in check for a long time and suppress it. We also have now found individuals who make the right type of antibody response. So, building on these, we have to take the best in academic science, and we have to connect that to the best in industry. This is a critical important point.

This epidemic, the worst infectious disease epidemic since the 14th century, compels us to work as quickly and efficiently as possible, and our paradigm as an organization is premised on a focused business model to enable us to do that.

Ten years ago, and people asked about this, the total global spending on AIDS vaccine research and development was less than $160 million—that's public, private sector, philanthropic, all of it. And obviously that was clearly inadequate, particularly given how

complex it is to make a vaccine, as Dr. Fauci explained. At that time a lot of basic research was done, but with little emphasis on product development, and whatever product development work was being done was focused on countries where the markets were best, and not where the epidemic was spreading quickly.

The private sector where most of the expertise resides, stayed on the sidelines because of the scientific challenge, because of the political controversies, because of the unclear market and resultant financial risks. As a result, we were established in 1996 to fill that gap between the public and private sectors, and to establish a new model.

IAVI is now working in 23 countries, and has raised almost $400 million in new funds, and I'm very proud of the work that the team has done on the ground, not only here in the U.S., but in Africa, in India we've talked about a number of times, and in Europe in such a short time. In nine years since we've been founded, we've brought six different candidates from the laboratory to the clinic for testing on human volunteers in nine countries. And those countries now have a high quality infrastructure to conduct clinical trials and analyze results, and obviously this quality is critical, Senator Feingold asked, because safety of participants is absolutely critical to being able to do this.

We are now the largest funder of vaccine research in Europe. That's a disgrace, and one of the things we need to do is figure out how to increase European investments. We also brought the first vaccines forward in India, and in many of the African countries that are now engaged.

So, we're now working on new ways to take this innovative model, using industry-like paradigms to bear on trying to solve some of these scientific questions that Dr. Gayle has talked about, and then to design immediately new candidates and test these—that fast process is critical. We have an example of this in the Neutralizing Antibody Consortium, which brings together the government, academia and researchers, and together they are trying to solve this problem.

The other critical point is that developing countries are critical to being involved in here, because the incidence of HIV infections is highest. They need to be full partners, because they can not only ensure that the trials go well, but that they have manufacturing systems, they have scientific groups that can help, and that communities are ultimately prepared for the distribution and use of vaccines, which is a critical issue we're going to have to do at the end.

Countries like India have a science and technology field, they've got vaccine manufacturers, in fact, most of the vaccines for UNICEF now are made in India, so getting them engaged is critical. And this is not only important for the vaccine effort, but also provides a meaningful, sustained development effort that will build on their scientific capability, and that's going to have long-term benefits for the communities, including for the distribution of the other preventions and the treatments we've talked about. We also have to make sure that we do think about accessibility now, because that has been the way other vaccines have not been able to

be used, and we need to work with religious leaders, political leaders, community leaders, in doing that.

The private sector is something that hasn't been mentioned enough here, because we need their expertise. They are the only people who have made vaccines in the last 50 years, and yesterday we announced a new partnership with Glaxo-Smith Kline, one of the world's largest manufacturers, to move forward a vaccine for Africa, and this is really important because they are committed to bringing all of their technologies to bear, along with our technologies, and to try to accelerate them forward. And, of course, like all our partnerships, there exists an agreement that this will be made available at a low price in adequate quantities for the poor living in the developing world, so a new paradigm working, that's important.

So, my asks for this committee are obviously to sustain and continue the leadership and commitment that's here. This does need more funding, you've heard that from Dr. Gayle and Dr. Fauci. The world is now spending a little less than $700 million, this is hundreds of millions short of what we believe is needed, and what does that mean? We believe that there ought to be a program that is absolutely optimized for success in the shortest period of time. The cost of the epidemic now is $25–$30 billion a year, so optimizing that program and getting every single vaccine that's out there tested and all the ideas jumped on is absolutely critical. Ninety percent of the expenses are coming out of the United States, most of this is from the public sector, so these are things we need to change. We think the world ought to be spending about $1.2 billion globally to do this.

The other issue is that new incentives for industries Dr. Gayle has talked about are critical, an advanced purchase commitment, a legally binding agreement to pay a decent price to companies that successfully make an AIDS vaccine for use in the developing world, would help overcome the substantial scientific and commercial risk that industry currently faces, and industry has really come out for this, and as you know, this is on the G-8 agenda in Gleneagles, and we hope that the U.S. government will support the leadership of the U.K. Treasury in this, and we were with Chancellor Brown two days ago discussing this.

Other important incentives include liability protection and tax credits as Senator Kerry talked about, and we're also delighted the new bio-defense legislation, under consideration by the Senate will also include now major diseases of poverty, AIDS, malaria and TB, and so we're very optimistic that Congress will continue to set this example for all countries, rich and poor, to make sure that these technologies are included.

The other issue that the Committee on Foreign Relations could do is to encourage the PEPFAR, Global Fund and the World Bank to ensure that communities where critical prevention research is being conducted are prioritized for voluntary counseling and testing services and antiviral treatment. This collaboration of synergy would appropriately reward those communities engaged in this absolutely critical research, and make U.S. efforts more successful in building capacity for research in these countries. So, I thank you

for very much for the opportunity to speak to you and tell you what IAVI is doing.

[The prepared statement of Dr. Berkley follows:]

PREPARED STATEMENT OF DR. SETH BERKLEY

Mr. Chairman, thank you for this opportunity to appear before you and other members of this Committee to discuss the state of vaccine development globally and to describe the work of the International AIDS Vaccine Initiative, IAVI. We appreciate your interest in this critical matter and we look forward to working with you and other Senators in the future. Your role is crucial to ensuring adequate resources and incentives to accelerate vaccine development.

The United States has been a leader in the global response to this terrible epidemic, and it must continue to lead. We applaud President Bush and the Congress's work to significantly expand AIDS treatment and prevention in the countries hit hardest by this disease. This focus on the short term emergency is critical and appropriate, but without better tools, we will not be able to end this terrible epidemic. And that must be our goal; to have an effective end game strategy. As a result, we were also gratified by the outcome of last year's Group of Eight summit, chaired by the United States, which called for increased resources and coordination to accelerate the development of a preventive vaccine. Senator Lugar, we welcomed your leadership in introducing a resolution on AIDS vaccines in the wake of last year's G-8. We hope that this year's G-8 summit will agree to fulfill its earlier commitments and undertake creative and concrete new incentives to spur research and development. We also applaud the important work on global AIDS undertaken by other members of this Committee.

On behalf of the International AIDS Vaccine Initiative, I want to express appreciation for the financial and political support provided by the United States to our organization, whose mission is to ensure the development and delivery of safe, effective, accessible vaccines to prevent HIV infection around the world, with a particular focus on developing countries hit the hardest by HIV/AIDS. IAVI's scientific and policy programs represent true collaboration and have also attracted funding from seven other governments, the European Union, the World Bank, corporations, and private foundations such as the Bill and Melinda Gates Foundation and the Rockefeller, Sloan, and Starr Foundations. Your funding has helped create a unique model of an efficient and global non-profit public-private partnership, committed to collaborating with the best scientists around the world, whether in London, Nairobi or New Delhi; in Ohio and Washington State; whether with a small biotech company, a large vaccine manufacturer, a leading academic researcher, or the outstanding scientists of our own government, including Dr. Fauci's team. Indeed, we are delighted that NIH has decided to conduct a test of one of their AIDS vaccine candidates at two of the sites IAVI developed in Africa—a tribute to the partnership we have fostered with developing country researchers and other key stakeholders in the field. This is exactly the type of collaboration that IAVI and other groups represented today recognize as critical, and the basis for our joint establishment of the Global Vaccine Enterprise. IAVI, as a founding member of that Enterprise, has welcomed the opportunity to share our global experience, expertise and model of innovation.

As you know, Mr. Chairman, the devastation caused by HIV/AIDS is almost unprecedented in modern times. The facts are staggering: five million people worldwide are infected with HIV each year, including over 40,000 Americans. More than 20 million people have died of AIDS and it is likely that more than 100 million will have been infected or died of this disease before we have a vaccine. For the first time since the height of the epidemic in the US in the 1980s, more than 1 million Americans are infected and living with the virus that causes AIDS.

As you have already heard today, without a vaccine, the infection will always be with us and always on the move. As a physician, I believe that every life is sacred, and so providing treatment is vitally important. We must also focus on doing our best to prevent each and every new infection. However, current prevention strategies are only partially effective, and with lifetime treatment as today's only option for those infected, and with drug toxicity and viral resistance spreading, this does not bode well for a sustainable global solution. A preventive vaccine is the best long-term solution to blunting and ultimately ending the epidemic. Without one, the epidemic will continue to spread personal tragedy and economic hardship as well as political instability. Funding vaccine research is also an important investment in

averting future treatment costs—an enormous future burden for public treasuries around the world. Like all other viral infectious diseases, ultimately the most medically and economically effective prevention will be through a vaccine.

So why don't we have an AIDS vaccine after 20 years? Science remains the greatest challenge, but we have good reasons to believe that we can solve the scientific challenges that currently stand in our way. From our efforts to date, we have learned many useful things. Monkeys can be protected by certain types of vaccines; most people develop immune system responses that suppress the viral infection for years; and we are beginning to uncover individuals who make some promising antibody responses. We can build on these, but to do so, we need to match the best in academic scientific research to the best in industry. The magnitude of this epidemic, the worst infectious disease epidemic since the 14th century, compels us to work as quickly and as efficiently as possible. The IAVI paradigm is premised on this focused business model and has enabled us to do exactly that.

Ten years ago, total global spending on AIDS vaccine research and development was less than $160 million. That may sound like a lot of money, but given the high cost of biomedical research and product development, especially against a foe as dreadful and complex as HIV, it was woefully inadequate. Basic scientific research was conducted, but very little emphasis was placed on actually developing a product, and what little product work was being done, was not designed to ensure its applicability for use in the countries that have the worst epidemics. The private sector, where most vaccine product development expertise resides, generally stayed on the sidelines, because of the scientific challenges, political controversies, unclear market and resultant financial risks. To address this situation, IAVI was founded in 1996 to fill the gap between the public and private sectors and to establish an innovative new way of tackling global health crises.

Mr. Chairman, IAVI is now working in 23 countries and has raised almost $400 million in new funds. I am very proud of the progress my team in the U.S., Africa, India and Europe has made in so short a time. In the nine years since we were founded, IAVI and its international partners have brought six vaccine candidates from the laboratory to the clinic, for testing in human volunteers in nine countries—countries that now have high quality infrastructure to conduct clinical trials and analyze results. Quality is critical, as the safety of all our participants is of paramount importance to us and to the global effort we are attempting to create. We are also now working in innovative ways to bring the industrial model to bear by harnessing recent scientific advancements to answer critical scientific questions, and to use that information to design and test new candidates. New models of applied research and collaboration—such as the neutralizing antibody consortium of government, academic and industrial researchers—are critical if we are to solve these enormously difficult scientific challenges.

It is critical that developing countries conduct AIDS vaccine trials because the incidence of new HIV infections is among the highest in these areas. We welcome them as full partners in these efforts so that they ensure that trials go well, their manufacturing systems are available to help with product development, and that communities are prepared for the ultimate distribution and use of vaccines. Some of the emerging technological innovators such as India have enormous scientific talent to bring to the effort. Our activities in these countries will not only advance vaccine development, but provide very meaningful and sustainable development assistance that will provide long-lasting benefit these communities, including for current prevention and treatment efforts. We will also continue to engage with political, religious and community leaders in developing countries to ensure that once a vaccine is available, the vaccination effort succeeds at the grassroots level. We have been pleased by the enormous level of political will that many countries have now demonstrated in support of vaccine development.

We are also committed to engaging the private sector, because we need their unique expertise to accelerate the development of a vaccine. To that end, IAVI recently entered into our first product development agreement with a major global vaccine manufacturer to focus on vaccines designed to elicit immune responses against variants of HIV that circulate predominantly in Africa, although of course the ultimate goal of the collaboration is to develop vaccines that would be applicable worldwide. Like all of our partnerships, our agreement contains provisions to ensure that any AIDS vaccine that emerges will be made in adequate quantities and will be accessible to the poor living in developing countries.

I ask for your sustained and increased leadership and commitment. Research into designing and testing AIDS vaccines needs more funding. Today, total global spending including basic research, product development and clinical trials to develop a

vaccine still is less than $700 million, hundreds of million short of what we believe is needed and a very small percentage of total spending on AIDS. IAVI and its partners in the Global Vaccine Enterprise estimate that approximately $1.2 billion needs to be spent annually in the coming years to speed the discovery and licensing of an AIDS vaccine. More incentives are needed to harness the expertise of the biopharmaceutical sector. An advance purchase commitment—a legally binding agreement to pay a decent price to companies that successfully make an AIDS vaccine for use in the developing world—would help overcome the substantial scientific and commercial risks they currently face. Other important incentives include liability protection and tax credits. We are delighted that new biodefense legislation under consideration by the Senate will also include the major diseases of poverty—AIDS, malaria and tuberculosis. We are optimistic that the United States Congress will continue to set an example for other all countries—rich and poor—in making vaccine development a priority and ensuring that it is included as part of the comprehensive HIV/AIDS agenda.

The Foreign Relations Committee could also encourage the PEPFAR, the Global Fund, and the World Bank to ensure that communities where critical prevention research is being conducted are prioritized for voluntary counseling and testing services and antiretroviral treatment. This collaboration and synergy would advance prevention, treatment and research, would appropriately reward communities engaged in important global research, and make U.S.-funded efforts more successful and sustainable by building long term research capacity in these developing countries.

I thank you for this opportunity to highlight the need for a preventive AIDS vaccine and IAVI's efforts to develop a vaccine, and I look forward to answering any questions you may have.

The CHAIRMAN. Well thank you very much, Dr. Berkley. I want to ask both of you to comment further because you have already highlighted some specific ways in which the pubic/private partnership is operating, and by that I am include foundations with governments and with private enterprise—is the Enterprise idea one that's, since this coordination, how does it fit? I'm trying to get some scope of who's in charge of this? And no one can be completely, we're dealing with several different nation states, we've got the G-8 meeting to try to coordinate at least eight of those states successfully, foundations that are prominent in this country, hopefully some are elsewhere likewise, and of course, you have mentioned, Dr. Berkley, ideally that private firms obtain an order or a commitment for a substantial amount of business in the event that they make commitments up front now, they're helpful. And so you might want to elaborate further, because that would be an important incentive, perhaps, but discuss if you can again, more broadly, given this invitation, first of all Dr. Gayle, this partnership among these various classifications of entities in the large world, so that we are the most effective in coordinating what we are doing, have some metrics to determine how much progress is occurring.

Dr. GAYLE. Right, thank you for that question, because I think sometimes this concept of the Enterprise, because it's not directly funding, or conducting research, is sometimes difficult to get a grasp of, but I think in some ways it's the most analogous to the human genome project, it was not an entity, but really a collaboration between the major partners that united around a blueprint, so that's the same as our scientific strategic plan, united around the highest priority areas that we think can make the biggest difference towards developing an HIV vaccine. So we have a plan that we hope that additional funders will fund against, and that's a critical part of it. But we also have an international steering com-

mittee, the coordinating committee, that is 19 people from multiple different countries including India, two countries in Africa, several European countries as well as the United States, and that coordinating committee is the body that convenes to make sure that the Enterprise is moving forward.

The CHAIRMAN. How often do they meet so I have an idea of the governance situation?

Dr. GAYLE. Well, so far we have met three times over the last 15 months. Since this is still in the launch phase in many ways, I think we still have to see how often we'll meet, but at least twice a year, and then there's sub-committees of this coordinating committee that have met to look at development, overall development, to look at something as straight forward as the selection of the executive director, because we still are in the search for an executive director. The interim secretariat of the Enterprise is right now with the Gates Foundation, so we have agreed to provide the initial support to get this launched, but we don't want it or don't think that it should stay within the Gates Foundation, and it will become its own entity with an executive director, a steering committee, forums where donors can meet, forums where other stakeholders can meet, and importantly, forums that bring together the scientific community that is collaborating around the scientific plan.

The CHAIRMAN. So, you have Enterprise as sort of the overall plan?

Dr. GAYLE. Right, exactly.

The CHAIRMAN. And then the coordinating committee, the 19 members as you've mentioned, plus sub-committees undergirding their activity, and a search for an executive director, but meanwhile, the Gates Foundation's serving that purpose, although as you've indicated, you would prefer to pass that along to someone who's identified by the 19, but I think that gives a good idea, at least to the general public, as well as the members of this committee that there is some plan there. So all of these efforts that we're mentioning may be parts of that plan, people may come into this in some way, but the coordinating committee hopefully is overlooking the whole thing to make sure there are not some elements of the plan that are forgotten all together, or are not addressed, is that correct?

Dr. GAYLE. Exactly, and part of the role of the coordinating committee is to be the guardians, if you will, of the strategic plan, and to make sure that all elements are fully developed and that they are kept up to date as our science advances, and as we keep evolving the search for an HIV vaccine.

The CHAIRMAN. Dr. Berkley, you mentioned this company, Glaxo Smith Kline collaboration the last day or two they were involved, but let me ask you from your perspective—clearly there's been an ongoing dialogue as to why companies that gifted in pharmaceutical products and not simply tackling this head-on and sort of solve the problem, and the spirit of enterprise that we often get with this. Now, granted it's a very difficult problem, or set of problems that are involved, and the scope of the capital, and the risk that is involved in this is very substantial, and so you double back by pointing out one way that you offer some incentives, is that at

the end of this there are orders for pharmaceutical products, or whatever the product is that's going to work in this thing, with the idea that it needs to be at least relatively inexpensive, given the numbers of cases all over the world that need to be treated.

And, sort of give some idea, sort of at the end of the rainbow of this. How is, whatever is going to be produced, physically, who may do that? In this country or around the world, how much it may cost, how are we likely to have something that has the expense elements that lead to high distribution, as well as a distribution channel that often is a part of marketing in this situation.

This has always been the delicate part of this, because you say, this is not exactly a commercial enterprise, this is a real live search for a humanitarian concern, but so, at the end of the day we know that somebody somewhere has to produce whatever it is, and manufacture, continue on, distribute, sell, handle the money—so give some idea how what you are doing fits into this and what we can anticipate?

Dr. BERKLEY. Thank you very much, and let me add on to Dr. Helene's comment about how this works.

So, if you think about the Enterprise as the coordinator, we're about 10 percent of the vaccine effort, and Dr. Fauci is about another 80 percent, so together we're now most of the world's effort. What's interesting about the way we're working, is we are a partnership that sits outside of government, but working with governments, and for the governments that give us money, they do not target that money to their own national programs, that's very important, because the tension now is between national research and global research, and we want the best products in the world to rise up, and that's what we see our job to be.

The CHAIRMAN. We kind of have a trade war here.

Dr. BERKLEY. Absolutely.

The CHAIRMAN. The need for a WTO adjudication, or someone needs to rise above this, hopefully.

Dr. BERKLEY. So each of the governments is supporting its own work, but then, what we do is take a small amount of money, and try to do it globally. Now, what's important about trying to get industry engaged, why are they not engaged? Well, to the big companies, it is the scientific difficulty, but also the market is mostly in the developing world, and it is politically controversial. You know, the day a vaccine comes out, it might not be a required vaccine because of all of the social controversies, religious controversies and others, and lastly, because of that, their own business has been under attack in terms of patents and other issues, so they're quite nervous in this area, and it's not a good place for them to invest capital.

Small companies which are critical, you know, the bio-tech is where innovation occurs, their lead comes from the big companies, because that's who buys the products in the end and that's who their venture capitals look at for direction, so there really has been almost a failure of the ability to do that. And the role we're playing in that is by both directly financing those groups where it makes sense, but that the important part of that is that we're fast, effi-

cient. Seventy-five percent of the people in IAVI are out of industry, we speak their language, we operate like a business, we hold them to milestones, and they understand that and trust that, and so, the more we can get these groups engaged. The other thing that would help, though, are these long-term incentives—why? Well, because when they sit there and they compare this to other products, the opportunity costs—even if we pay for the research—the opportunity costs are huge, and so if we can say, "Look, there is going to be a market, look, you'll be able to sell it," and most importantly, it will get to the poor, so that we will not be dragged across the PR of the world and say, "Why didn't you provide it?" You know, because they'll now believe it really will get to the poor people, then we can tip those companies into bringing their expertise.

Another big issue, though, not to forget is distribution, because for current vaccines, the six of them costs a dollar, the distribution system costs $35. And an AIDS vaccine would be going to adolescents, commercial sex workers, IV drug users, and other groups that we don't know how to reach, and so there's going to need to be a real global effort to do that, but obviously, given the cost-effectiveness of a vaccine here I think we can get groups to step up. For industry, knowing the quantity of the vaccine is critical for manufacturing. And, you know, we can bring in manufacturers from developing countries, we can bring generic manufacturers in, but only if we know how many vaccines over that time, because huge investments need to go into the facilities to produce these types of products.

The CHAIRMAN. Well, you make a very important point, the last, as well as all the other important points you made before that—we've had a problem in this country, this past year, with just a regular flu vaccine. I guess the situation, it's no longer rocket science, but at the same time it almost seems to be as you come along and fall comes and suddenly an announcement is made to the public, "Not everybody is going to be able to get it." You start with high priority groups, people at risk—old people and people in bad health and so forth, and then they run out, you even begin go get some tremors that that might occur in this year, if we're not very thoughtful.

Dr. BERKLEY. That was a market-related issue, and it related to the fact that the old technology, which is the egg-based vaccine, there isn't enough money to drive and to move innovative technologies, and one of the problems with that is that every year you have to make it, so they didn't make a lot of money, so now, as part of the bio-shield work and other work, there's beginning to be an effort from the government to figure out if we can create, now, a way to help those companies make that technological leap which is going to be critical to supplying these type of products.

The CHAIRMAN. Well that is very good news and I hope that both of you can offer some leadership on that in addition. But, you've made the point which is important—that it's really not clear to companies as they start this how they're going to finance it, quite apart from the scientific questions about solving the problem, and how distribution might occur. Many governments involved—some in denial as we've talked about today, or semi-denial—so that even

if we're in a consensus today, around this table, this is a crisis, this is tremendously important, trying to save lives, but then you come up against the political realities, or religious doctrine, realities, what have you around the world, it's a large world, many different viewpoints, and not everybody sees it that way. So, as you say, some companies in some countries are discouraged, really, from becoming too aggressive in this area, or talking about it too much, which is extremely frustrating.

Dr. GAYLE. Just to add, Chairman, I think this issue for being able to show support for buying vaccines is critical, and so for instance, continued U.S. Government support for programs like GAVI are instrumental in demonstrating that if vaccines are made, and if there's a commitment to purchasing them and then making them available, in fact, you can give industry incentive, so I think on the donor side, showing that commitment to purchasing vaccines is critical in kind of breaking this logjam in the long run.

The CHAIRMAN. I agree, and I appreciate very much that there is such entities as GAVI, as you do, Dr. Gayle. But, I appreciate, likewise the Foundation, Bill and Melinda Gates tackling this issue. Now, I suspect often, the thought has been—well, why haven't commercial institutions been involved? Well, in part, because of the controversy we're talking about, and certainly markets, distribution and all of the rest of this, and the fact that it involves very poor people in remote parts of the world on occasion, quite apart from cases in the United States in which is not very clear how, commercially, you support that situation, as opposed to other objectives of firms who are busy saving lives in various other ways.

Now, thank goodness someone in the Foundation Community, in this case, a very large foundation, stepped forward and have said that this is where we can play a very important role, not only in transition, but in leadership. That's the genius of the American scene, that we have philanthropists who have this kind of vision, and it's very important.

But I stress the commercial side of this because as both of you, eventually you finally have to get back to the nitty-gritty of how it is to be done—physically, the product produced, distributed, what the cost will be, how many people can imbibe, and therefore we need to think about the vaccine as well as prevention, and knowing that the treatments, no matter how many treatments you have, this is always going to be one part of the picture, and hopefully a transition phase.

Now, let me just ask sort of a, we call it the $64 question: Are you optimistic that a vaccine can be found, or maybe vaccine is wrong—vaccines or whatever, maybe, finally the protocol in this—why? Why do you think that's the case, this has not been obvious to the world for awhile, and as a matter of fact, even as persons who are citizen amateurs myself are advocating this, people are saying, "Oh, come off of it, that's all well and good, pie in the sky, but as a matter of fact, life is going in earnest, and this is going to be a situation of people dying perpetually, and none of us find that acceptable, but why should we have optimism that the vaccine will happen?"

Dr. BERKLEY. May I, Mr. Chairman?

The CHAIRMAN. Yes.

Dr. BERKLEY. If I could take two points here, first of all, to date, one AIDS vaccine in the world has been fully tested to see if it works, that's 24 years into the epidemic. Now, science is tough, but a lot of that represents the lack of focused attention, finance, *et cetera,* so, when people say, "Well, this hasn't worked," that's the fact.

Well, why do we think it could work? Well, there are two arms to the immune system, one is the cell mediated arm, and one is the antibody arm. We would like a vaccine that does both. We now have pretty good vaccines that do the cell mediated arm, the Merck Company has an exciting vaccine, which unfortunately may have some issues working in the developing world, but that's in testing now, and a number of other vaccines, we have some, the NIH have one that are now striking that——

The CHAIRMAN. When you say several out there? Several possibilities?

Dr. BERKLEY. Well, why is that important? Well, every person who gets infected with the virus it goes ahead and circulates in them and then it gets driven way down by their immune system, and that's why they stay 10 years, 15 years, without getting the disease. So, we know that that part of the immune system can have a dramatic effect, and we think we can reproduce that. But that's not good enough. What we need to do is solve this other problem, and it's an extremely difficult problem. Yet, we now have found some people who make the right type of antibody. We don't know why they do it—in other words, we have a lock, but we don't know what the key is——

The CHAIRMAN. So, human beings on earth could produce these antibodies?

Dr. BERKLEY. And recently our consortium crystallized the different antibodies and showed what they look like, and figured out how they work, and the way they work is they've got these funny shapes that kind of reach in behind the coating of the virus that is very wise to kind of keep the immune system from seeing it, so the challenge for us is can we produce something that will make those type of antibodies? And that's the search that's underway, but that needs to be focused, it needs industry, it needs science, and it needs to be done as a product of an initiative, that's not an individual researcher thing, like Dr. Gayle said, that's coming together to try to solve that type of problem, and I believe it will be solved, but of course we can't definitively say that, so one of the things is to move this forward with the existing antibodies, but also now to search all the people elsewhere in the world, and let's do it on an industrial scale, let's not do it in this lab or that lab, but let's bring the tools of industry, high through-put screening and combinational work to try to accelerate this, and that I think is the challenge. But, we can protect monkeys, we certainly know that people can suppress the virus for a long time, so I am absolutely convinced protection is possible, the question is when, and is it practical and is it going to be cost effective.

Dr. GAYLE. Just to add to that, I think as Dr. Berkley said, the approach has to be a different approach. We can't continue to go down blind alleys and everybody going down that same approach without more systematically looking at whether or not we're looking at each part of the immune system, looking at how to optimize responses, and doing that in a much more coordinated, across the board way and at the scale that is necessary to do that so we can look at all of the ways you can investigate these, but do it in a much more coordinated fashion. We have not given ourselves the opportunity to do that kind of research, and that's what the Enterprise, and the work of IAVI, NIH, and all the other partners are doing, is to really look at this in a coordinated way, and giving ourselves the opportunity to do the kind of industrial-strength, coordinated more strategic research than we've done thus far, kind of taking one lead at a time. And I agree and we all feel the same sort of optimism, there's enough information now to suggest that it is possible.

But also, as I made, said in my comments earlier, this is not a sprint. We do think that it will take at least another decade to be able to get to the point where we have a safe and effective HIV vaccine, so we know that we need to be in it for the long haul, and we know that it has to be a combination of different approached. Microbicides, which may be able to be available sooner than a vaccine—critically important—other prevention tools that might be able to be available, barrier methods for women, other prevention strategies, so we really need to do all of these and they really can't compete with each other. Even when we have a vaccine, it's unlikely to be 100 percent effective, so it will still need to be mixed and matched until we keep having new, successive evolutions in our vaccines, so we have more and more effective vaccine. The first one may not be 100 percent effective, it's likely that it will not be, so we have to make sure that we're maintaining the research on all fronts, as well as putting in place the things that we already know can make a difference, and we believe that we can get there.

The CHAIRMAN. As you said, Dr. Berkley, as opposed to one attempt, sort of on the industrial scale, this means, I suppose, hundreds, thousands of persons, cases, in other words, just a myriad of possibilities as well as many trials, and you need, I suppose for statistical validation a lot of people, a lot of cases, a lot of trying, maybe, to watch the evolution of hat it will be doing, how it works. And as Dr. Gayle speaks about, I suppose even with intensive operation, both of you testifying to make certain you've got something that is as close to being right as opposed to being perfect, and human lives are at stake, you have to have this period of time for validation, I would guess, although that would be disturbing for anyone listening to this hearing, a decade is a long period of time, we've discussed this, both of you have the statistics of the number of developing cases day by day, how that number is racing ahead of however many treatments are occurring as the world becomes more efficient in actually getting to persons as we have to in a humane way.

So, our optimists would hope that the decade idea is realistic, but too pessimistic, as often happens. In the meanwhile, on the other

hand, the purpose of this hearing is really to try to illuminate, so that this is not something that we guess, but people will know from your testimony that there are hundreds of scientists, doctors, researchers, maybe thousands of persons, individual persons in this world looking for the antibodies, for example, or how there can be an arresting of the situation, if not total prevention.

Dr. GAYLE. Mr. Chair, if I may, I'd just like to add a couple of points. I think you emphasized why this must b e a global effort, because we will need to do—once we get suitable candidates—we will have to do trials that will include tens of thousands of people, so we need to have a global collaboration, we need to work with the countries where HIV is having the biggest impact, because that's where the trials need to be done, and we need to make sure that we're working hand in hand with those, and again that's why an umbrella like the Global HIV Vaccine Enterprise is so critical. And I think, while a decade seems a long period of time, if we don't put the resources and the effort in today, then you'll be talking about even further out than that, so whenever we start, we've got to put the effort in—we've already started obviously, but I think if we put in an even more intensive effort, a more coordinated effort than we really will be able to get there, but any delay will continue to push that finish line even further out and that's what we want to avoid.

The CHAIRMAN. We thank both of you, but this committee does not have complete jurisdiction over the situation, and we will work with the other important committees who have equal interests. But, at the same time, as Dr. Gayle has pointed out, the global aspects of this are undeniable. In situations that are really serious, although not at the gravity we're talking this morning, the world is deeply worried about soybean rust, for example, which may have a tremendous impact on soybean farmers, but likewise on agricultural America, and we really don't know nearly as much about that as we need to know as we approach this particular year. We're worried about Avian flu—no one knows precisely how many cases are occurring somewhere in Asia now, and whether particular drugs are used by certain people, maybe Chinese farmers have surrendered whatever they were doing and in fact, with regard to fighting the disease involving human beings, but there is clearly concern about that and it happens because it's a small world, and that is why the global perspective is important. And as small as the world may be, the political divisions, the different views, politically, religiously and so forth that people take of this are very diverse, and therefore the coming together of people of goodwill is not easy. But we thank both of you for your leadership in making that more possible, and those who have sponsored you.

And so saying, we thank all of the witnesses, and the hearing is adjourned.

[Whereupon, the hearing was adjourned.]

APPENDIX

Responses to Additional Questions Submitted for the Record by Members of the Committee

RESPONSES TO ADDITIONAL QUESTIONS SUBMITTED FOR THE RECORD TO DR. SETH BERKLEY BY SENATOR DODD

THE NEED FOR PEDIATRIC TESTING OF HIV VACCINES

Some of the populations hardest hit by the pandemic—infants and youth—are at risk of being left behind in the search for an effective vaccine against HIV/AIDS. To date, the vast majority of HIV vaccine trials have not included children. Because we cannot assume that a vaccine tested in adults will also be safe and effective when used in pediatric populations, it will be important to ensure that promising vaccines are tested in infants and youth as early as is medically and ethically appropriate. Failure to begin planning for the inclusion of these groups in clinical trials could mean significant delays in the availability of a pediatric HIV vaccine, at the cost of countless thousands of lives.

Question. Where are we in testing possible vaccine candidates in children?

Answer. Children's risk of HIV infection, and hence their need for vaccination, varies enormously with age.

Infants of HIV-infected mothers are at great risk if their mother is not treated with antiviral medications, during gestation, birth and breastfeeding. Vaccination at birth, added to temporary antiviral therapy such as nevirapine, could reduce this risk if the vaccine were safe and efficacious, and if the vaccine could induce a protective response within weeks after birth. For infants, the "bar" must be particularly high for both safety of the vaccine and for the possibility that the infant will benefit from the vaccination.

Investigation of HIV vaccines in infants has been carried out in the United States under the auspices of the NIH-supported Pediatric AIDS Clinical Trial Group. The vaccination of these infants raised no safety concerns, but in the U.S., where infants are protected from HIV infection by treatment of mothers with highly active antiretroviral therapy, it is not feasible to assess whether the vaccine protects infants. One of the three vaccines tested in the infants subsequently failed to protect adults against HIV and another is currently being studied for efficacy in adults.

After infancy, most children are at relatively low risk from HIV infection until they reach the age of sexual debut (here called "adolescence," but in fact quite variable). The level of adolescent risk varies enormously by age, by gender, and by region.

Adolescents are vulnerable to infection through blood transmission; sex, including incest, other sexual abuse, and commercial exploitation; and injection drug use. Adolescent girls, in particular, are often at high risk of infection. One of the most effective strategies for controlling the spread of the epidemic will be to vaccinate preadolescents before the onset of behavior that puts them at risk.

IAVI is committed to working with others in the field to ensure timely access for adolescents to a safe and efficacious preventive HIV vaccine. This will, however, require a clear understanding of the requirements of national regulatory and licensing authorities for testing and data on adolescents. Given the special vulnerability of adolescents as described below in question two, it probably makes sense to do most early screening of vaccines in adults and then assure that promising vaccines are further developed for children and adolescents.

To meet these requirements it may be necessary to include a subset of adolescents in efficacy trials, while weighing the risks and benefits for individual adolescents when planning such trials. Phase I (safety) trials are conducted in lower risk communities, while efficacy trials, by necessity, occur in populations at risk for the disease. In regions where adolescents are not at high risk of infection, it would not be useful or likely ethical to enroll them in efficacy trials.

There is an underlying assumption in the field that a vaccine that is effective in adults will also work in adolescents and pre-adolescents. It may not be necessary to enroll large numbers of adolescents in efficacy trials. Instead it seems likely that "bridging" data showing safety and immunogenicity in adolescents and pre-adolescents, generated simultaneously with efficacy data in adult populations, may be adequate for licensure.

Question. What are the logistical, regulatory, medical and ethical issues that must be overcome in pediatric testing of HIV vaccines? How do we address them?

Answer. Before enrolling infants or adolescents into clinical trials, it is critical to weigh the risks and benefits to them, just as we do with adults. Children are vulnerable, both biologically and socially; therefore, it is essential that any research study in children incorporate safeguards. The evidence for vaccine safety and tolerability should be strong and most feel that there should be a relatively high probability of success—infants and adolescents should not be the first group used to test most vaccines. For trials in infants or adolescents, the trial design should incorporate ethical and procedural safeguards to protect these vulnerable research subjects.

In a research study enrolling pregnant women prior to or at the time of delivery, one overriding consideration is that the study be clearly explained to the child's mother so that she can freely consent, and that all reasonable measures be taken to care for the mother and to prevent mother-to-child transmission (the experimental vaccination cannot be assumed to be effective for this purpose). Designing such a study will not be simple.

With adolescents, we must consider the social and psychological risks of trial participation. There are two significant risks from trial participation. One is stigmatization; participants in a trial may be thought to have HIV or to partake in "immoral" behavior, and this may lead to social discrimination, expulsion from the family, or violence. It is important that adolescents volunteering for the trials, and their parents or guardians, understand these risks. AIDS vaccine trials in adolescents must avoid and prevent any social harm that may result from their trial participation, whether this social harm be directed from his/her family, friends or community against the adolescent or from the community against the adolescent's family.

The second significant risk is that trial participants may be tempted to think of themselves as protected and to increase their risk-taking behavior. While this has not been documented as a significant risk in the HIV vaccine trials undertaken to date among adults, adolescents may lack maturity and judgment. On the positive side, the education and counselling involved in a trial may be of great benefit to an adolescent at risk, if s/he has the power to alter that risk, by altering behavior.

Laws regarding the age of consent vary in the United States from state to state, and elsewhere between countries. Some countries make the distinction between the legal age of consent and the age of participation in biomedical research. For example, young women who have already given birth may be considered "emancipated" and be legally allowed to consent for themselves but may not be authorized to enroll in trials. This may vary on a country-by-country basis. The major difficulty in some countries is that the law may not specifically address the age of consent for clinical research involving an investigational agent. Vaccine research conducted in developing countries typically involves infants and children, with parental consent. In some developing countries where adolescents are at high risk of acquiring HIV, regulators may therefore be tempted to take a more conservative approach, precluding adolescents' participation in AIDS vaccine trials.

Some countries typically register only vaccines or drugs that have been licensed in Europe, the U.S., or other countries, a practice that could cost many years.

The U.S. Code of Federal Regulations takes a more conservative approach on preventive-based research, such as for vaccines and microbicides, which involve healthy HIV-negative participants, compared to therapeutic-based research where a direct, immediate benefit for trial participants could be anticipated.

Prior to enrollment in any trial, potential participants are informed regarding the trial and must demonstrate a clear understanding of the potential risks and benefits

of participation. This assessment is difficult for well-educated adults, and may be much more difficult for adolescents, most of whom are not well educated. Further, it may be difficult for researchers to ascertain the level of understanding and maturity of adolescent trial candidates. A traditional approach has been to require both assent of a minor child and informed consent of the parent(s) on behalf of the child. Where sexually transmitted diseases are involved, even asking a parent for consent may put a child at significant risk of expulsion from the family or violence. Hence, it is important to arrive at a proper legal and ethical definition of "emancipation," so that it is clear whether adolescents can be counselled and possibly enrolled without parental consent. In any trial, and certainly later in the deployment of a vaccine in the general population, it will be critical to avoid the tendency for vaccinated individuals to conclude that they are safe from HIV and can increase their risk behavior. This disinhibition factor is of greater concern with adolescents than adults. Research on the best way to inform, educate, obtain informed consent from and assess understanding in adolescents should be supported.

Liability concerns have been raised frequently as a possible obstacle to HIV vaccine trials in children. In the U.S., for licensed and recommended childhood vaccines, the Vaccine Injury Compensation Act provides liability protection for vaccine manufacturers and compensation for children who may have suffered harm from vaccination. There is no comparable system for investigational vaccines, and most large pharmaceutical companies "self-insure," an approach, which may prove difficult for small biotech companies and non-governmental organizations involved in the search for an HIV vaccine. The indemnification clause of the Homeland Security Act may provide a path forward to remove this potential barrier.

IAVI is committed to working with others in the field to clarify the practical, legal and ethical challenges for enrolling adolescents and pre-adolescents in HIV vaccine trials.

Question. Do you have specific recommendations—legislative or others that we could implement to ensure that children are not an afterthought when it comes to preventing HIV infection?

Answer. In addition to the recommendations already mentioned, we believe that participation of adolescents in vaccine trials must occur in the context of strong HIV prevention programs, adolescent-friendly services, and community support of their participation. It is important that a comprehensive and widely accepted package of preventive interventions be made available for adolescents. Everyone engaged in vaccine research should work to establish a receptive and supportive environment for a future HIV preventive vaccine among families, communities, and governments.

The utility of a vaccine, however, will depend not only on its efficacy, but also on the duration of protection. This duration of protection will have tremendous public health implications. For example, if a vaccine is only active for a period of five years, it would be inefficient to vaccinate young children in a population where the average age of sexual debut is 16. Determining a vaccine's duration of protection will take years of follow-up and monitoring of trial participants after the initial efficacy trial is completed. Everyone involved in vaccine studies should commit to doing this, allowing us to extend the lowest age of vaccination to a time before risk activities begin.

Specifically, relevant government agencies should commit to supporting long-term follow-up studies once a vaccine is proven efficacious, to determine the duration of protection.

Regulatory agencies should clarify requirements for approval so that adolescents' access to the vaccine will happen without delay.

IAVI plans to gather data on safety, immunogenicity, and, if required, efficacy responses of adolescents, prior to licensure or registration, so that young people's access will be timely. IAVI's current plans commit to long-term follow-up of immunogenicity and efficacy for promising vaccine candidate(s), so as to best gauge the earliest time at which a vaccine would be useful. We encourage others in the field to do so as well.

Additional Material Submitted for the Record by Dr. Helene Gayle

Speeding an AIDS Vaccine

BY RICHARD G. LUGAR AND PATTY STONESIFER

Washington Post, Wednesday, January 19, 2005; Page A19

Picture two scientists in adjacent labs. They're working on the same problem—how to stop a disease that kills 3 million people every year—but although they compare notes and share findings, they need a better plan to coordinate their research. They labor for years at the same task, but as individuals rather than as a community of scientists.

Although they make important progress, after two decades just one vaccine makes it into large-scale clinical trials—and it doesn't work.

With a few exceptions, this has been the story of the search for an HIV vaccine. While dedicated scientists around the world have collaborated on significant discoveries, they've had no shared strategy for finding a preventive vaccine, no standardized tools to compare results, no forum to identify priorities and share information. Meanwhile, HIV-AIDS is spreading at an alarming pace, with a record 4.8 million new infections in 2003. At the current rate, there will be 45 million new infections by 2010 and nearly 70 million more deaths by 2020.

Preventing the transmission of HIV-AIDS by discovering and making accessible an effective vaccine must be a priority for our government, for the private sector and academia, and for other countries, including the Group of Eight industrial nations. While promising results are coming from new approaches to changing behavior, such as the Ugandan ″ABC″ model—which promotes abstinence, being faithful and condoms—that is clearly not enough.

Fortunately, a group of the world's leading scientists is mobilizing to coordinate and improve vaccine efforts. This alliance of independent organizations, called the Global HIV Vaccine Enterprise, is committed to accelerating the development of a preventive HIV vaccine by working more collaboratively, more strategically and more aggressively.

But such a risky and expensive venture can succeed only if government leaders, donors and researchers around the world work together to make it happen. And while the progress so far has been promising, there's much more to do. This year will present three concrete opportunities to achieve real progress for the Global HIV Vaccine Enterprise.

First, Congress must continue to make the fight against AIDS a priority in U.S. foreign policy and in future spending. Besides causing massive human suffering and loss of life, the disease is undermining the stability of nations, creating labor shortages and making orphans of an entire generation of children. President Bush, through his Emergency Plan for AIDS Relief, has provided new leadership and resources for the worldwide campaign to fight the disease. The federal government, through the National Institutes of Health, already has one Vaccine Research Center and, in support of the Global HIV Vaccine Enterprise, has unveiled plans for a second one. The NIH's continued leadership and support are critical.

Congress, businesses, foundations and others must fund the Global HIV Vaccine Enterprise and its components, including vaccine research centers. The investment we make now in finding a vaccine will not only save millions of lives but could save billions of dollars in future treatment costs. We also need to determine whether tax or other incentives will be necessary to get the most talented private-sector scientists to contribute to this enterprise, and whether we need to help developing countries improve their pharmaceutical regulations to break down barriers that discourage collaboration.

Second, governments, scientists, donors, the private sector and community leaders must act on a set of priorities to help accelerate the search for a vaccine. The Global HIV Vaccine Enterprise brought many of the world's leading researchers together to develop just such a blueprint, which for the first time identifies key research priorities. The blueprint, which was published yesterday, calls for new approaches to crack the major scientific barriers to an HIV vaccine, for affected countries to host more clinical trials and train more researchers, for more private-sector investment in research and development, and for local leaders to encourage volunteers to participate in studies. It is a global summons to action.

Finally, other developed countries must make this project a priority by focusing their resources on it. The G-8 industrial nations endorsed the Global HIV Vaccine Enterprise at their 2004 summit, and AIDS-ravaged Africa will be at the top of their agenda when they meet in July in Scotland. Now is the moment for these countries—Japan, Germany, France, Britain, Canada, Italy and Russia—to make real commitments to support the Enterprise, for instance by creating their own vaccine research centers and linking them in a global effort.

This year we can make genuine headway in the fight against AIDS—a pandemic that threatens mankind in a way no other disease has. In the 1960s we launched the Apollo program to put a man on the moon. In the 1990s we came together to map the human genome. In the decade ahead why shouldn't we demand a similarly urgent effort—this time an international one—to stop this scourge?

Richard G. Lugar is a Republican senator from Indiana and chairman of the Senate Foreign Relations Committee. Patty Stonesifer is co-chair and president of the Bill & Melinda Gates Foundation.

G–8 Action To Endorse and Establish a Global HIV Vaccine Enterprise

1. We reaffirm our commitment to combating the global HIV/AIDS pandemic. Both individually and collectively, we have increased our efforts aimed at HIV treatment, care, and prevention. We acknowledge the important role of the Global Fund to Fight AIDS, Tuberculosis, and Malaria, UNAIDS, and WHO in fighting this pandemic. But the human and economic toll of the AIDS pandemic demands that these activities be complemented by accelerated efforts to develop an HIV vaccine. In 2001 and 2002, only seven vaccine candidates entered clinical trials, and only one entered advanced human testing, but proved to be ineffective. Vaccine development efforts have proceeded slowly, due largely to the enormous scientific challenges. The best way to meet these challenges is for scientists around the world to work together in a complementary manner.

2. We believe the time is right for the major scientific and other stakeholders—both public and private sector, in developed and developing countries—to come together in a more organized fashion. This concept has been proposed by an international group of scientists. Published as a "Policy Forum" in Science magazine. Klausner, RD, Fauci AS, et al: "The need for a global HIV vaccine enterprise." Science 300:2036, 2003. We endorse this concept and call for the establishment of a Global HIV Vaccine Enterprise—a virtual consortium to accelerate HIV vaccine development by enhancing coordination, information sharing, and collaboration globally.

3. The Enterprise should establish a strategic plan that would prioritize the scientific challenges to be addressed, coordinate research and product development efforts, and encourage greater use of information sharing networks and technologies. This plan should serve as a blueprint for helping to align better existing resources and to channel more efficiently to the needs at hand new resources as they become available. Specifically, the strategic plan should seek to:

3.1. Encourage the development of a number of coordinated global HIV Vaccine Development Centers: Each center should have the critical mass and scientific expertise to advance the development of a particular HIV vaccine approach. These centers could be self-contained, as is the National Institute of Allergy and Infectious Diseases (NIAID) Vaccine Research Center at the U.S. National Institutes of Health, the European Research Institutes or could be virtual centers, such as those funded by the public-private partnerships of the International AIDS Vaccine Initiative (IAVI), the European Developing Countries Clinical Trials Program (EDCTP), the Gates Foundation, and others.

3.2. Stimulate the development of increased dedicated HIV vaccine manufacturing capacity: There is inadequate existing capacity to produce HIV vaccines for advanced clinical testing. Therefore, the resources and facilities involved in manufacturing potential HIV vaccines must be increased, particularly for testing of vaccine candidates that are currently in or will soon be in the developmental pipeline, like in the EDCTP.

3.3. Establish standardized preclinical and clinical laboratory assessment: Data gathered from clinical trials on a given vaccine candidate should be available and applicable to trials being conducted on other vaccine candidates. Therefore, standardized protocols and measures of effectiveness need to be

adopted at the preclinical and clinical stages of vaccine development. In turn, laboratories need to be better linked to clinical trials, which will require wider use of novel confidentiality agreements and information-sharing technologies.

3.4. Expand an integrated international clinical trials system: Large, clinical programs capable of conducting phase I, II, and III trials of potential HIV vaccines have been established by the U.S. NIAID, France's Agence Nationale de Recherches sur le SIDA, Italy 's National AIDS Program, IAVI, and the EU. This global clinical trials system should be expanded and coordinated. It should facilitate a multidisciplinary approach which draws in inputs from social and behavioral scientists, alongside biomedical teams.

3.5. Optimize interactions among regulatory authorities: Increased cooperation, communication and sharing of information among regulatory authorities in various countries and regions involved in licensing HIV vaccines are essential. This can be accomplished without reducing safety or manufacturing standards.

3.6. Encourage greater engagement by scientists from developing countries: Since most phase III trials will need to be conducted in the developing countries hardest hit by the disease, the international clinical trials system must involve local scientists, ethical review committees comprised of local and international representatives, and regulatory bodies.

4. We call on all stakeholders in the Global HIV Vaccine Enterprise to complete the development of this strategic plan by our next Summit.

5. The United States, in its role as president of the G-8, will convene later this year a meeting of all interested stakeholders in the Enterprise to encourage their collaborative efforts in HIV vaccine development. This meeting should clarify how the strategic plan is to be implemented. We support this conference becoming an annual event and we look forward to a report on the follow-up of the Initiative at the next G-8 Summit.

From the U.S. State Department web site at: http://usinfo.state.gov/ei/Archive/2004/Jun/10-92350.html

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The Need for a Global HIV Vaccine Enterprise [1]

Since the discovery of HIV 20 years ago and the demonstration that HIV is the cause of AIDS, the world has awaited the development of an effective preventive vaccine. Recent projections from the World Health Organization (WHO) and the Joint United Nations Programme on HIV/AIDS (UNAIDS) indicate that if the pandemic proceeds at its current rate, there will be 45 million new infections by 2010 and nearly 70 million deaths by 2020. [2] Although the scientific establishment has made extensive progress on extending survival of people with HIV and reducing maternal-fetal HIV transmission by antiretroviral therapy, transferring concepts for HIV-1 vaccines into clinical application has lagged.

Almost everyone involved in HIV vaccine development agrees that there is an urgent need to create and to evaluate systematically more candidate vaccines. Despite the wide variety of conceptual approaches to HIV vaccine design, the pace of development of new HIV vaccine candidates needs to be accelerated. In 2001 and 2002, only seven immunogens entered clinical trials. Only one candidate vaccine, aimed at eliciting neutralizing antibodies to a soluble HIV envelope protein, entered human phase III testing. Unfortunately, the recently released results from this trial did not demonstrate vaccine efficacy in the overall trial cohort. [3] Although many approaches to producing immunogens have been discussed and initiated, systematic evaluation and optimization have proceeded slowly, in part because of factors such as the expense and complexities in advancing new candidate vaccines into phase I trials and scientific challenges.

These challenges include (i) the inability of current vaccine designs to elicit effective neutralizing antibodies against the circulating strains of HIV, (ii) the inability of current designs to prevent HIV from establishing persistent infection, (iii) the extensive global variability of HIV, (iv) the lack of understanding regarding the mech-

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[1] "The Need for a Global HIV Vaccine Enterprise," Richard D. Klausner, Anthony S. Fauci, Lawrence Corey, et al., *Science Magazine,* Vol. 300, June 27, 2003. Enhanced online at: www.sciencemag.org/cgi/content/full/300/5628/2036.

[2] J. Stover, et al., *Lancet* 360, 73 (2002)

[3] D.P. Francis, personal communication.

anisms of protection in the most effective HIV vaccine animal model system—the live attenuated approach, and (v) the lack of understanding of which HIV antigens induce protective immunity and which immune effector mechanisms are responsible for protection. The best engine for solving these major scientific challenges is the creativity of individual scientists working together in multidisciplinary problem-solving consortia, adequately resourced and linked to vaccine development capabilities. Two decades after the discovery of HIV, even with a variety of advanced cell and molecular technologies, the need remains for improved vaccine designs that will deal with the genetic and phenotypic variation of HIV-1 and effectively prevent the establishment of lifelong infection. The "enterprise" of HIV vaccine development must be designed as a high-quality collaborative research system that goes well beyond the high-quality but separate research projects that we have today.

We propose a model that could achieve the goals of a more efficient and integrated HIV vaccine research enterprise. We hope this Policy Forum helps open an international dialogue about options to achieve the goal of developing a safe and effective HIV vaccine in the shortest time possible.

Basic Principles for the Enterprise

Vaccine development has historically been empiric and iterative, building on sequential successes to define correlates of immune protection that guide product development. Preclinical and clinical experiments and evaluation systems with objective measurements and analysis have been critical. Perhaps one of the most successful examples of such a concerted, empiric approach in medicine generally is the improvement in the treatment of childhood acute lymphocytic leukemia (ALL). Cure rates for children with ALL have improved from 10% in the 1950s to more than 80% (and for some subtypes, 100%) in 2002. This increase has been produced almost entirely by a coordinated and iterative series of preclinical drug evaluations and subsequent clinical trials, in which partially effective drug regimens have been systematically altered (through studies of the effects of combination and sequence), to produce steady and significant improvement in survival as well as reduced toxicity.

HIV vaccine development has several similarities with developing treatment for ALL: (i) Although animal model data provide major conceptual insights, human clinical trials are ultimately required to define vaccine or drug effectiveness; (ii) the number of possible variables in reagent de-sign and clinical outcome are large but definable; (iii) combinations of reagents (vaccines for HIV, drugs for ALL) are likely needed to maximize benefit; (iv) no single regimen is likely, at least initially, to provide the optimal balance of efficacy, safety, and cost for all regions of the world; (v) a centralized, coordinated clinical trial and laboratory evaluation system facilitates progress in the field; and (vi) the program has substantial support from medical and political communities.

There are also features that are unique to developing an HIV vaccine. The pace of progression of the HIV epidemic, as well as the international, political, and economic toll, require a more rapid iterative process than the multi-decade process described above. A well-coordinated global enterprise necessary to drive this scientific effort does not exist and must be created. The cost and process of developing new vaccine candidates, especially protein-based immunogens or noninfectious particles is typically substantially higher than those of new or modified drugs. Also, as the scientific risk of failure and the cost of vaccine development are high, reliance on industry to carry the major load for discovery and development for HIV vaccines is unrealistic. Thus, creative new public and public-private partnerships are necessary to drive the vaccine discovery effort, with industry's development expertise a key element that must be marshaled effectively.

HIV Vaccine Development Centers

Even with the current paucity of prototype antigens in clinical trials, the portfolio of vaccine candidates contains significant overlap in approach (see "the pipeline project").[4] Increasing the diversity of approaches and coordinating the types of vaccines entering clinical trials are fundamental to speeding global HIV vaccine development. We believe that this requires the creation of a series of coordinated global HIV vaccine centers, each of which has the critical mass, focus, and scientific expertise, especially in vaccine development, to advance the rational development of a particular HIV vaccine approach rapidly and systematically. Features we believe vital to the success of such centers are as follows: (i) a critical mass of re-searchers with experience in basic and clinical research and an appreciation for the empiric aspects of vaccine development, (ii) concentrated dedication to the single goal of a

[4] See www.hvtn.org and www.iavi.org

global preventive vaccine, (iii) long-term commitment free of the strict requirements of the classical short-term measures of success used by academic institutions, (iv) sufficient resources to conduct costly preclinical development activities, and (v) collaborative arrangements with the private sector.

Each of these centers would have the funding, structure, and resources to devote itself to a specific vaccine development need and product. The sole focus would be to test systematically and to improve incrementally the immunogenicity and safety of the immunogens that they develop. The core of an integrated enterprise approach to HIV vaccine development would begin by conceiving of the world of potential vaccine concepts as a grid, with each cell representing a particular approach to immunogen construction, composition and delivery. We propose the development of as many HIV vaccine development centers (VDCs) as are needed to fully cover the agreed-on "cells" of the vaccine product pipeline grid; they would be supported by a variety of international funding agencies. The structure, scope, and scale of each VDC would be organized to explore fully design, development, and testing in preclinical and early-phase human trials of a particular approach with the capacity to examine an adequate range of variables of dose, delivery, adjuvants, and combinations. The goal would be to learn whether their approach is immunogenic, with what characteristics (nature of the immune response, breadth of response, intensity and persistence of the response) and whether any of the variables modify the response in a way that indicates whether and how to produce second- and third-generation candidates.

The structure of the VDCs could vary. These centers may be self-contained, as in the National Institutes of Health (NIH) Vaccine Research Center, or may be virtual centers such as those funded by the public-private partnerships of the International AIDS Vaccine Initiative (IAVI) and NIH. These VDCs may be developed within commercial or academic and/or research institutes, or through novel collaborations between different types of institutions, but would be unified by a central concept or theme. For example, multiple investigators and laboratories interested in the evaluation of a particular approach (e.g., specific viral vectors or protein antigens) would work together to systematically "cover the grid" of vaccine immunogenicity and toxicity for this specific vaccine vector or concept. Each center would be expected to work in collaboration with the larger global enterprise.

Areas of potential emphasis might be the development of novel adjuvants including recently discovered cytokines and chemokines, systematic modification of the envelope protein to maximize immunogenicity, bacterial vector design and delivery, optimized DNA and viral vector delivery, construction of immunogenic particles or structures, practical nonparenteral delivery systems and systematic approaches to define enhanced antigen presentation. Each center would systematically create reagents and conduct preclinical experiments that would provide vaccine prototypes for human clinical trials. We estimate that between 6 and 10 new VDCs are needed to comprehensively cover the various approaches. As the most significant problem relates to developing vaccines that achieve rapid and broad viral neutralization, priority should be given to developing VDCs with this focus.

This system of collaborating vaccine developers would allow centers that work on cross-cutting technologies, such as novel adjuvant development or mucosal delivery, to work with the most promising antigens so that each component of a candidate vaccine would be optimized. This is currently lacking in HIV vaccine development. The purpose of this approach is to create a systematic and coordinated pipeline of vaccine constructs that can be tested, evaluated, and redesigned. It is especially important that combination vaccine regimens are developed and tested early and that there is a systematic evaluation of the strains and antigens used. Ways must be found to address how proprietary issues, such as exclusive licensing deals, can be reconciled with open communication and vaccine development paths that combine materials and technology platforms owned by different entities. Creative solutions to this problem will be required if the critically important role of industry in this enterprise is to be realized.

Organizations like NIH, IAVI, Agence Nationale de Recherches sur le SIDE (ANRS), and the European Union (EU) as well as pharmaceutical companies have funded vaccine development programs that are directed at many of these issues. Their work could form the foundation for this collaborative enterprise. Our concept could facilitate increased scale as well as greater communication and cooperation. This is particularly important among groups working on similar vaccine concepts. We expect that the infusion of funds, intellectual focus, and collaborations brought by such centers will result in increased participation of industry in HIV vaccine development. As product development and process engineering have largely resided in

the biotechnology and/or pharmaceutical industry, incorporation of these skills should be an integral part of each VDC.

Vaccine Science Consortia

Many of the fundamental scientific questions impeding AIDS vaccine development have remained unchanged and unsolved since the identification of HIV as the etiologic agent responsible for AIDS. Answering these questions would provide crucial support to the VDCs and would be aided by the creation of a series of coordinated HIV vaccine scientific consortia. As with the vaccine research centers, we do not propose a specific structure for a given consortium, but the goal is to focus a range of researchers from many disciplines on a specific applied vaccine problem. The ultimate goal is to create effective, novel antigens for the pipeline. Commercial, academic, and research institutes must work together to solve the scientific challenge. Features we believe critical to the success of such consortia are (i) clearly defined goals and effective project management, (ii) dynamic scientific leadership and commitment of consortium members to the mission, (iii) a critical mass of researchers and the resources and infrastructure to rapidly translate preclinical leads toward clinical development, (iv) creative intellectual property agreements to provide incentives for data sharing and cooperative research, (v) long-term commitment free of the strict requirements of the classical short-term measures of success used by academic institutions, (vi) sufficient resources for each element of the consortium and flexibility to move resources between elements of the consortium, and (vii) collaborative arrangements with the private sector and/or the VDCs. Some of the possible scientific challenges are noted above, although these will undoubtedly change over time.

Development of Dedicated HIV-1 Vaccine Manufacturing Capacity

At present, there is inadequate capacity to produce vaccines to the standards needed for human clinical testing and insufficient resources devoted to the process of taking a research construct through the rigors of vaccine production. Therefore, the resources and facilities involved in manufacturing candidate HIV vaccines must be increased markedly. This entails the development of dedicated personnel and manufacturing facilities devoted to the process development, scale-up, formulation, stability, safety, toxicology, and production (in accord with "good manufacturing practice" or GMP) of experimental HIV vaccines, disciplines that are largely found in the private sector. A critical feature of this is the need for assay development to control the manufacturing process, something that is required for each technology and is often responsible for slowing product development. The importance of building manufacturing infrastructure has become even more acute as the major focus of HIV vaccine development has shifted from large pharmaceutical corporations to small biotechnology companies, or nonprofit or academic organizations, all of which have little or no vaccine manufacturing capabilities and experience. This lack of manufacturing capacity and expertise for vaccines and uniformity in production facilities has accounted for repeated delays in the HIV vaccine clinical trials programs. A system must be devised in which experienced industrial colleagues and facilities are devoted to the development and manufacturing of candidate HIV vaccines for human clinical trials. Expansion of this program must be coordinated with expansion of the product pipeline from the HIV VDCs.

Establishment of Standardized Preclinical and Clinical Laboratory Assessment

Although regulators and clinical trial specialists have recognized the need to standardize laboratory measurement in human clinical trials, preclinical assessments of candidate immunogens are still based largely on experiments in single research laboratories. As such, access to the primary data, standardization of the laboratory assays utilized, and interpretations of such data within the context of the field are generally not available. A more transparent and standardized preclinical evaluation system for candidate immunogens is essential for defining and developing successful vaccine regimens. For example, despite a wide variety of prototype vectors, only one standardized preclinical evaluation of their comparative immunogenicity has been initiated, and comparative human trials have not been performed. This issue has been recognized and begun to be addressed by NIH and IAVI, but should be considerably expanded.

Standardized protocols and immunogenicity measurements need to be broadly implemented at the preclinical and clinical stages of vaccine development to measure humoral and cell-mediated immunity and to provide a test bed for reproducibly assessing the immune response to HIV antigens and adjuvants. The preclinical discovery system provides a foundation on which choices for manufacturing and testing of formulations for human clinical trials can be made. Laboratories should be estab-

lished to develop and deploy robust, reproducible, and interpretable assays of immune response; to standardize reagents for such assays; and to incorporate quality-control measures for consistency. This paradigm might prove challenging to academic-based laboratories; therefore, linking these laboratories with clinical trials requires wider use of novel confidentiality agreements, working relationships, and information-sharing technologies. Such a preclinical laboratory program will also improve the pace of developing immunologic assessments in human clinical trials and will increase the likelihood of defining important correlates of immune protection.

Expansion of an Integrated, International Clinical Trials System

Large, comprehensive, coordinated, international clinical trials programs to conduct phase I, II, and III trials of candidate HIV vaccines have been established by the National Institute of Allergy and Infectious Diseases (NIAID), ANRS, IAVI, and the European Union. A rapid, iterative HIV vaccine trials enterprise will require expanded clinical trials capacity with emphasis on speed of accrual and retention of participants, high ethical standards, and enrollment of participating populations appropriate to the antigens being tested. Phase I/II clinical trials to define safety and immunogenicity are an integral part of vaccine development because, to date, animal models have been used with limited success in predicting human immune responses to HIV vaccines, especially to vector-based immunogens. The expanded global clinical trials system must therefore be considered part of vaccine product development and design. The clinical trials themselves must use standardized protocols and immunogenicity measurements. After an initial and rapid safety assessment in phase I trials, phase II trials must be adequately powered to define immunogenicity of new constructs as preclinical discovery and phase I/II clinical trials systems provide the foundation for choosing sets of large-scale phase IIb/III efficacy trials. Initial phase IIb/III clinical trials must assess laboratory and clinical efficacy and also attempt to define correlates of protection with validated assays.

Phase I safety and immunogenicity assessment of candidate HIV vaccine trials average 100 persons per protocol and phase II evaluations to define optimal dose and schedules, between 300 and 600 persons. The number of enrollees into phase III vaccine trials varies, depending on their goals, the nature of the population, and the transmission rate—but in general have averaged from 2500 to 10,000 persons per trial. To keep pace with the expanded pipeline, eventually the vaccine development enterprise would need to support a clinical trials program that enrolls about 5000 individuals in phase I/II and 30,000 persons into the phase III efficacy trials yearly. Multiple phase III trials will be needed to assess the protective efficacy of different vaccine concepts against different HIV-1 clades and in populations that may differ on the route of HIV-1 transmission or genetic background. In addition, gender, diversity in viral strains, duration, and magnitude of the ongoing epidemic are likely to influence vaccine efficacy. Most of these phase III trials will need to be conducted in developing countries, where most infections are occurring, and where a vaccine will have the most benefit. Assuring that true partnerships are developed with the research, medical, public health policy, and civic communities in those countries is essential and must begin early in the design of this enterprise. The international clinical trials system must engage local investigators, communities, ethical review committees, and regulatory bodies and must be coordinated with other national efforts to control the HIV/AIDS epidemic.

Optimizing Interactions Among Regulatory Authorities

Cooperation, communication, and sharing of information among regulatory authorities in various countries involved in licensing HIV vaccines are essential. We are not implying reduced standards in safety or manufacturing. In fact, the proposed system, with its more centralized manufacturing and immunogenicity programs, may be viewed as advantageous by regulatory bodies. This iterative process requires that regulatory bodies in a large number of regions or countries share access to preclinical and clinical information. Risk-benefit analyses for regulatory decisions should recognize regional variations in the social, economic, and health burdens of HIV and decisions by local regulatory authorities. Participation in the Enterprise requires transparency and equality for all countries and regions involved. Vaccines that are partially effective should be made available for regions of the world that might benefit from their use at their explicit request while new trials and improved vaccines are being developed and evaluated.

Coordinating International HIV Vaccine Development

The Human Genome Project provides an interesting model for international coordination as many funders agreed on a scientific road map, voluntarily divided the work, and agreed to an evolving set of production standards. The frequent sharing

of progress and problems allowed coordination, cooperation, and internal competition. The "governance" was driven by an open agreement of the scientists and the funders about the blueprint of the project, which allowed coordination without unnecessary duplication. No one entity actually ran the international genome project, although the leadership was assumed by the major funders and implementers. We believe that the time is right for the major scientific and product-development leaders and the stakeholders involved in the global HIV vaccine development enterprise to come together in an analogous way.

We propose the development of a road map for the Global Vaccine Enterprise that (i) would prioritize the scientific challenges to be addressed as well as product development efforts, (ii) would rapidly develop an implementation plan for all the components of the system, and (iii) would develop a plan that identifies the resources needed. The Enterprise, however, should have multiple models for structures to accomplish these goals and must find solutions that engage the public and private sectors.

For this system to work, it must address several challenges. Funders and major stakeholders of HIV vaccine development must agree to a common vision so that they can coordinate their activities with other components of the Enterprise. There must be considerable sharing of information among vaccine developers regarding preclinical investigation and trial results, with the ultimate goal of advancing to clinical trials. Solving problems of access to reagents, platforms, and technologies of potential commercial interest will be required. Finally, this must be a global effort. The research and development enterprise described here must build and include full participation of the developing world where this pandemic is raging. Tens of millions of lives are dependent on the development of a safe and effective HIV vaccine. It is essential that we aggressively explore all mechanisms that might expedite this process. While comparable vaccine access initiatives will also be required to ensure that HIV vaccines are made available to populations in need throughout the world, the expanded global AIDS vaccine effort proposed here hopefully would be a major step towards accelerating successful HIV vaccine development.

The Global HIV/AIDS Vaccine Enterprise: Scientific Strategic Plan

COORDINATING COMMITTEE OF THE GLOBAL HIV/AIDS VACCINE ENTERPRISE[1]

Introduction

In June 2003, an international group of scientists proposed the creation of a Global HIV Vaccine Enterprise.[2] The authors invited discussion of this proposal, and challenged scientists to identify new strategies and mechanisms to accelerate the global effort to develop a safe and effective HIV vaccine. This paper describes the processes that led to agreement on the major roadblocks in HIV vaccine development, summarizes current scientific priorities, and describes an initial strategic approach to address those priorities. Specific research is not prescribed. Rather, the intent is to stimulate both researchers and funders to explore new, more collaborative, cooperative, and transparent approaches to address the major obstacles in HIV vaccine development identified in the plan, in addition to continuing the productive, high-quality programs already underway.

The motivation behind the proposal for a Global HIV/AIDS Vaccine Enterprise was the recognition that development of an HIV vaccine remains one of the most difficult challenges confronting biomedical research today.[3 4] Fortunately, scientific progress has created new opportunities that could be harnessed more effectively through global coordination and collaboration. These new opportunities include an expanded HIV vaccine candidate pipeline, improvements in animal models, a growing database from clinical trials, and the availability of new quantitative laboratory tools that make comparisons among vaccine studies feasible. Confronting major roadblocks and harnessing these new opportunities requires an effort of a magnitude, intensity, and design without precedent in biomedical research, with the Human Genome Project as a potentially useful model.[5] More specifically, the critical scientific insights generated by the creativity of individual investigators, as well as small groups and individual networks, could be significantly augmented by a properly organized, managed, and systematized international effort targeted on the design and clinical evaluation of novel HIV immunogens. An international collaborative effort that addresses a shared scientific plan, provides information exchange among groups, links clinical trials with standardized laboratory assays and evaluation in animal models, applies new knowledge to improvements in vaccine design in an iterative manner, and supports a transparent process for decision making in

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[1] *Citation:* Coordinating Committee of the Global HIV/ AIDS Vaccine Enterprise (2005) The Global HIV/AIDS Vaccine Enterprise: Scientific strategic plan. PLoS Med 2(2): e25. This is an open-access article distributed under the terms of the Creative Commons Public Domain Declaration, which stipulates that, once placed in the public domain, this work may be freely reproduced, distributed, transmitted, modified, built upon, or otherwise used by anyone for any lawful purpose.

Abbreviations: BMGF, Bill & Melinda Gates Foundation; GLP, Good Laboratory Practices; IP, intellectual property; NIH, United States National Institutes of Health; R&D, research and development; SIV, simian immunodeficiency virus; UNAIDS, Joint United Nations Programme on HIV/AIDS; WHO, World Health Organization.

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Competing Interests: The authors have declared that no competing interest exist. Most of the authors hold directive or managerial positions in agencies and organizations conducting or supporting HIV vaccine research and development.

[2] Klausner RD, Fauci AS, Corey L, Nabel GJ, Gayle H, et al. (2003), The need for a global HIV/AIDS vaccine enterprise. *Science* 300: 2036–2039.

[3] Fauci AS (2003), HIV and AIDS: 20 years of science. *Nat Med* 9: 839–843.

[4] Desrosiers RC (2004), Prospects for an AIDS vaccine. *Nat Med* 10: 221–223.

[5] Waterston RH, Lander ES, Sulston JE (2002), On the sequencing of the human genome. *Proc Natl Acad Sci USA* 99: 3712–3716.

all aspects of vaccine discovery, design, development, and clinical testing will prove critical to success.

The Global HIV/AIDS Vaccine Enterprise represents a novel paradigm to seek and identify international agreement on the critical roadblocks for developing an HIV vaccine and on creating a shared scientific plan that addresses those roadblocks (see Box 1). The Enterprise proposes to coordinate efforts at a global level, facilitate use of common tools and technologies, and help ensure access to optimized resources. Furthermore, the Enterprise approach is a way of behaving as a global community of problem solvers, more openly sharing information, ensuring that the shared scientific plan is implemented, and basing decisions on evidence rather than advocacy.

It must be emphasized, however, that the major difficulties encountered in the development of an HIV vaccine are scientific, not organizational, and arise directly from the complexities of HIV and AIDS. "Small science" should not be replaced with "big science." Both approaches must be undertaken. Creation of research environments that support the creativity both of individual investigators and of larger, collaborative efforts will accelerate the scientific breakthroughs needed to successfully develop a safe and effective HIV vaccine.

Scientific Priorities

Prioritization Process. In August 2003, the authors of the Enterprise proposal invited a group of leading scientists, public health experts, and policy makers to meet at the Airlie House in Warrenton, Virginia, United States, to refine the vision for the Enterprise. The Airlie group agreed that the Global HIV/AIDS Vaccine Enterprise should be developed as an alliance of independent organizations committed to accelerating the development of a preventive vaccine for HIV/AIDS through implementation of a shared scientific strategic plan, mobilization of additional resources, and greater collaboration among HIV vaccine researchers worldwide.[6]

The subsequent initial planning phase of the Enterprise involved leading government research agencies, private industry, non-governmental organizations, and funders involved in HIV vaccine research and development (R&D) activities, including the Bill & Melinda Gates Foundation (BMGF), the International AIDS Vaccine Initiative (IAVI), the National Agency for Research on AIDS of France (ANRS), the United States National Institutes of Health (NIH), the United Nations Joint Programme on HIV/AIDS (UNAIDS), the World Health Organization (WHO), and the Wellcome Trust. The Enterprise is expected to grow with time and include additional organizations and research groups willing to contribute to the implementation of its scientific strategic plan. A Steering Committee composed of representatives from several of the founding organizations provided guidance and coordination, with the BMGF serving as interim Secretariat.

Six Working Groups involving more than 120 participants from 15 countries, the WHO, and UNAIDS were formed to develop the scientific plan of the Enterprise. These Working Groups met from January to April 2004, identified critical unanswered questions, and proposed actions to address them. In May 2004, the Steering Committee of the Enterprise analyzed the recommendations from the Working Groups and identified the scientific priorities for initial action.

Several common themes emerged from the Working Groups. There was clear agreement on the key scientific challenges, as well as strong consensus that the HIV vaccine field has progressed to a point where it should be possible to answer some of the persistent questions more definitively. To meet these challenges, the Working Groups called for enhanced access to reagents and technologies, adequate resources, and strengthened human capacity in several key areas, especially in developing countries, where clinical trials need to be conducted. There was also agreement that the present way of doing business, which centers primarily on individually led research groups or networks, needs to be supplemented by establishing focused, collaborative structures and providing access to common standards and technologies, which would enable comparison of data and candidate vaccines. This would, in turn, support a rational process for decision making to advance candidate vaccines through the different phases of evaluation.

[6] Klausner RD, Fauci AS, Corey L, Nabel GJ, Gayle H, et al. (2004), The challenges of an HIV vaccine enterprise: Response. *Science* 303: 1293.

Box 1.

Key Points in the Scientific Strategic Plan
More new HIV infections and AIDS deaths occurred in 2004 than in any prior year. A vaccine is critical for the control of the pandemic.
Development of an HIV vaccine is one of the world's most difficult and important biomedical challenges.
Harnessing new scientific opportunities for HIV vaccine development will require an effort of a magnitude, intensity, and design without precedent in biomedical research.
The Global HIV Vaccine Enterprise is an alliance of independent organizations committed to accelerating the development of a preventive HIV/AIDS vaccine based on a shared scientific plan.
The scientific strategic plan was developed with the collaboration of over 140 scientists and other participants from 17 countries and several international organizations.
The plan identifies critical unanswered scientific questions along the critical path for vaccine discovery, from antigen design to the conduct of clinical trials.
Novel vaccine candidates need to be designed to induce high levels of broadly reactive and persistent immune responses against HIV strains circulating in different parts of the world.
Standardization and validation of high-throughput laboratory assays conducted under GLP will allow comparison of results from different vaccines, which is a linchpin of rational decision making in vaccine development.
The Enterprise will encourage decision makers to establish clear and transparent processes to identify and prioritize the most promising vaccine candidates.
The Enterprise will seek to engage the best researchers who are willing to work in a highly collaborative manner and to dedicate the majority of their efforts to solve the fundamental roadblocks in HIV vaccine development.
To mount an accelerated global search for a safe and effective HIV/AIDS vaccine, annual funding for such research should double—to US$1.2 billion per year.
Several founding partners of the Enterprise have already committed, or are planning to commit, new funding to support the proposed Enterprise activities, and to create a culture of mutual accountability for the effective implementation of the scientific strategic plan.
Enterprise activities are guided by an international Coordinating Committee, supported by different technical expert groups, including representatives from funders and implementers of HIV vaccine R&D.

Vaccine Discovery. One immediate goal is to design HIV candidate vaccines that consistently induce potent, broadly reactive, persistent neutralizing antibodies, as well as memory T cells that suppress viral replication and prevent escape of virus from immune control.[7] [8] Additional research is also needed to identify how mucosal[9] and innate[10] [11] immunity could be harnessed to develop effective HIV vaccines. The ability to develop effective vaccines would be greatly enhanced by an understanding of what specific immune response or responses correlate with vaccine-induced protection.[12]

The current state of the art suggests a two-pronged strategy to accelerate the development of a safe and effective HIV vaccine. One component should center on candidate vaccines already in the pipeline, nearly all of which are designed primarily to induce T cell responses. In some animal models these T-cell-inducing candidate

[7] Wei X, Decker JM, Wang S, Hui H, Kappes JC, et al. (2003), Antibody neutralization and escape by HIV-1. *Nature* 422: 307–312.

[8] Barouch DH, Letvin NL (2004), HIV escape from cytotoxic T lymphocytes: A potential hurdle for vaccines? *Lancet* 364: 10–11.

[9] Veazey R, Lackner A (2003), The mucosal immune system and HIV-1 infection. *AIDS Rev* 5: 245–252.

[10] Kottilil S, Chun TW, Moir S, Liu S, McLaughlin M, et al. (2003), Innate immunity in human immunodeficiency virus infection: Effect of viremia on natural killer cell function. *J Infect Dis* 187: 1038–1045.

[11] Pulendran B (2004), Modulating vaccine responses with dendritic cells and Toll-like receptors. *Immunol Rev* 199: 227–250.

[12] Pantaleo G, Koup RA (2004), Correlates of immune protection in HIV-1 infection: What we know, what we don't know, what we should know. *Nat Med* 10: 806–810.

vaccines suppress post-infection viremia and prevent or delay HIV disease, rather than prevent infection.[13] [14] In studies of individuals infected with HIV, viral load correlates with efficiency of transmission,[15] suggesting that a vaccine capable of suppressing viral load might reduce HIV transmission.

The second component should address critical gaps in scientific knowledge through carefully designed, focused, coordinated, and well-supported approaches. The fruits of this work will be a clearer understanding of what properties are needed for a successful vaccine and how to design candidates that incorporate those properties.

Scientific areas in which a more collaborative and organized Enterprise approach will be beneficial include the following: vaccine design based on the characteristics of recently transmitted viruses, evaluation of immune correlates of protection in animal models, and design of novel candidates vaccines that induce neutralizing antibodies and T cell immune responses.

Vaccine Design. Strategically, vaccines that are designed based on recently transmitted viruses hold the best hope of inducing relevant immune responses against currently circulating strains. Recent data suggest that the subset of viral strains that are sexually transmitted has unique genetic and anti-genic properties, including greater susceptibility to neutralization than the bulk of circulating virus.[16] While such observations require confirmation, newly transmitted viruses are nonetheless the crucial targets of vaccine-induced immunity. Therefore, virological and immunological characterization of acute/early HIV infection should inform the design of vaccines and also guide the design of trials capable of determining whether immunization impacts virus levels and the course of HIV infection.

To address these issues, a representative number of virus strains derived from recently infected individuals representing those populations who will participate in vaccine efficacy trials, including populations in developing countries, should be obtained. These virus isolates should be subjected to a comprehensive genetic and biologic characterization, together with an analysis of host immune responses and the genetic background of those populations participating in the clinical trials.

This continuous and ongoing effort will require a multidisciplinary global approach, linking investigators who are conducting epidemiological and cohort studies (to allow for detection of acute/early infections), laboratory scientists working on the virology and immunology of acute/early infection and on the genetic characterization of affected human populations, vaccine designers and manufacturers, and clinical trialists. In addition, systems for data management and analysis that will facilitate the rapid translation of new information into improved vaccine designs need to be developed.

Immune Correlates. Nonhuman primate models of AIDS offer opportunities to evaluate potential correlates of immune protection. While a particular immunization strategy that works in animal models may or may not predict protection in humans, important insights into potential immunologic mediators of protection would result from such studies. Several experimental vaccines induce varying degrees of protection against simian immunodeficiency virus (SIV) or chimeric simian/human immunodeficiency virus in rhesus macaques. In particular, studies using models in which a very high level of protection from acquisition of infection was achieved are needed, i.e., immunization with live attenuated SIV and attenuation of SIV infection

[13] Shiver JW, Fu TM, Chen L, Casimiro DR, Davies ME, et al. (2002), Replication-incompetent adenoviral vaccine vector elicits effective anti-immunodeficiency-virus immunity. *Nature* 415: 331–335.

[14] Tang Y, Villinger F, Staprans SI, Amara RR, Smith JM, et al. (2002), Slowly declining levels of viral RNA and DNA in DNA/recombinant modified vaccinia virus Ankara-vaccinated macaques with controlled simian-human immunodeficiency virus SHIV-89.6P challenges. *J Virol* 76: 10147–10154.

[15] Gray RH, Wawer MJ, Brookmeyer R, Sewankambo NK, Serwadda D, et al. (2001), Probability of HIV-1 transmission per coital act in monogamous, heterosexual, HIV-1-discordant couples in Rakai, Uganda. *Lancet* 357: 1149–1153.

[16] Derdeyn CA, Decker JM, Bibollet-Ruche F, Mokili JL, Muldoon M, et al. (2004), Envelope-constrained neutralization-sensitive HIV-1 after heterosexual transmission. *Science* 303: 2019–2022.

by short-term antiretroviral treatment administered immediately after SIV inoculation.[17 18]

To facilitate this process, assays for many different immune responses to SIV and chimeric simian/human immunodeficiency virus need to be standardized, validated, and made available to different research groups. Likewise, agreements need to be reached on those monkey challenge models that most closely resemble HIV transmission and infection in humans. Large numbers of animals will be needed to achieve statistical significance for experimental findings,[19] which in turn will require expanded primate breeding and housing capability. A multidisciplinary approach that links virologists, immunologists, vaccine developers, primatologists, data and project managers, and others will be needed.

Neutralizing Antibodies. There is increasing agreement that a successful vaccine needs to induce both humoral and cell-mediated immunity. Development of immunogens capable of inducing antibodies that neutralize primary HIV isolates from all genetic subtypes and regions of the world remains the most difficult challenge in the field of HIV vaccinology.[20 21] Success will likely require a deeper understanding of the structural motifs of the HIV envelope protein that interact with cellular receptors and/or that are recognized by broadly neutralizing antibodies. This strategy will require numerous well-characterized, broadly neutralizing monoclonal antibodies, the application of peptide and carbohydrate chemistry, structural biology, and genetic engineering approaches to immunogen design, and the use of iterative approaches guided by the immunogenicity of new designs.

Given the importance of these endeavors and the uncertainty as to what path will lead to success, multiple intersecting approaches need to be explored, including, for example, the design, production, and evaluation of (1) envelope proteins that stably reveal neutralization epitopes that may be only transiently exposed during viral entry into target cells, (2) immunogens that contain rigid, stable epitopes that mimic the portion or portions of envelope recognized by broadly neutralizing monoclonal antibodies, (3) modified envelope proteins that better expose existing relevant epitopes, and (4) molecules that resemble a stabilized version of the mature envelope trimer on the virion surface. These are examples of current approaches being explored, some or all of which may prove ineffective. Additional novel ideas need to be proposed and explored.

To achieve the above objectives, new tools and technologies such as those able to detect rare, broadly neutralizing monoclonal antibodies through large-scale screening of human sera will have to be developed. In addition, the very limited existing capacity to translate structural information into stable immunogen products needs to be expanded.

T Cell Vaccines. Nearly all current vaccine candidates in the clinical pipeline are T-cell-inducing vaccines, e.g., poxvirus recombinant vectors, adenoviral vectors, DNA constructs with or without adjuvants, and lipopeptides. The ongoing effort to evaluate these products and to develop new ones is considerable.[22] Identifying which T cell candidate vaccine or vaccines are most promising has become an urgent priority. However, these evaluations are being conducted within separate preclinical research groups and, to a lesser extent, separate clinical trial networks, with the result that candidate vaccines may not be optimally compared preclinically or clinically. This approach may result in delays in identifying the most promising candidates, and it risks devoting time and resources to inferior products, although it is recognized that the specific immune responses needed for a successful vaccine remain unknown. The identification and optimization of promising candidates will require (1) defining clear, transparent processes for decision making, (2) establishing agreement on vac-

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[17] Mills J, Desrosiers R, Rud E, Almond N (2000), Live attenuated HIV vaccines: A proposal for further research and development. *AIDS Res Hum Retroviruses* 16: 1453–1461.

[18] Lifson JD, Piatak M Jr, Cline AN, Rossio JL, Purcell J, et al. (2003), Transient early post-inoculation anti-retroviral treatment facilitates controlled infection with sparing of CD4+ T cells in gut-associated lymphoid tissues in SIVmac239-infected rhesus macaques, but not resistance to rechallenge. *J Med Primatol* 32: 201–210.

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[20] Burton DR, Desrosiers RC, Doms RW, Koff WC, Kwong PD, et al. (2004), HIV vaccine design and the neutralization antibody problem. *Nat Immunol* 5: 233–235.

[21] Mascola JR (2003), Defining the protective antibody response for HIV-1. *Curr Mol Med* 3: 209–216.

[22] Graham BS (2002), Clinical trials of HIV vaccines. *Annu Rev Med* 53: 207–221.

[23] Barouch DH, Pau MG, Custers JH, Koudstaal W, Kostense S, et al. (2004), Immunogenicity of recombinant adenovirus serotype 35 vaccine in the presence of pre-existing anti-Ad5 immu-

cine characteristics upon which decisions should be based, (3) developing and using validated assays to assess those parameters, to allow for preclinical and clinical comparison among candidates, and (4) establishing closer coordination and data-sharing among product developers, which will accelerate the availability of critical information needed to identify and further develop the most promising candidates.

Research is also needed to develop improved novel T-cell-inducing candidate vaccines, especially those that avoid or otherwise circumvent anti-vector immune responses,[23] and those that induce persisting high levels of immunity, especially mucosal immunity. In addition, a thorough, systematic exploration of adjuvants that markedly enhance the quantity, quality, and durability of immune responses to HIV vaccines is needed.

Laboratory Standardization. Comparison of results from preclinical and clinical studies is the linchpin of rational decision making regarding further development of vaccine candidates. Therefore, the initiation of approaches that will permit valid comparisons is crucial.

Progress to standardize and validate a limited number of T cell assays has been made within the laboratories of vaccine developers and within some partnering research networks. This approach now needs to be more broadly applied and extended to the analysis of neutralizing antibody responses. A robust infrastructure that develops, expands, and ensures broad access to quality assay technologies will allow valid comparison of data across trials and networks worldwide.

In order to achieve this goal, the following are required: (1) a decision-making process to select a set of robust assays, standardized and validated across laboratories, for measuring vaccine-induced immune responses in humans and animals; (2) wide availability of common reagents (such as peptides, control sera, and virus panels); (3) capacity for developing novel assays and reagents of potential value and for their translation to preclinical and clinical settings; (4) "core" laboratories that run selected assays and serve as a reference laboratory for satellite laboratories (clinical and preclinical work would take place in separate facilities, and clinical studies would require Good Laboratory Practices [GLP] conditions); (5) satellite laboratories located at or very near clinical trial sites to carry out a range of activities such as processing blood, storing and shipping specimens, and conducting basic immunological evaluation, and to participate in other Enterprise-organized activities such as acute/early infection studies; (6) an ongoing global quality assurance function encompassing all participating core and satellite laboratories and covering both routine safety as well as immunologic and virologic assessments; and (7) transfer of research assays and, when and where feasible, validated endpoint assays to satellite labs, including the necessary training activities.

In addition, new assay development has failed to keep pace with current understanding of the biology of the immune system and recent advances in technology. A more active program of applied research and assay development is needed to explore new concepts that would advance technical abilities and provide a better understanding of the immune responses generated by HIV vaccines.

Cellular Immunity. Two assays are currently used for the primary evaluation and enumeration of antigen-specific T cells: Interferon-λ ELISPOT and multiparameter flow cytometry. The ELISPOT assay was initially developed to measure CD8+ T cell responses. Several observations in both mice and humans have indicated that protective immune responses will likely require stimulation of both CD4+ and CD8+ T cell effector and memory functions; it is unlikely that induction of Interferon-λ-secreting T cells alone correlates with protective immunity. Therefore, additional laboratory assays measuring multiple HIV-specific cell types as well as functional capabilities will be needed to thoroughly evaluate vaccine-induced immune responses. These assays should also permit rapid assessment of the magnitude and breadth of immune responses, and enumerate the specific epitopes that are recognized.

Humoral Immunity. Different laboratories use different assays to measure antibodies that neutralize HIV and related viruses, SIV and chimeric simian/human immunodeficiency virus. These assays vary technically, but the most widely accepted assays measure reduction in virus infectivity in cells that express the receptors necessary for virus entry. Assays that offer the greatest value are those that are vali-

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dated, amenable to high throughput, low in cost, readily transferable, and that can be performed according to GLP guidelines.

The ability to measure the magnitude and breadth of neutralization against diverse HIV strains is essential to evaluating responses generated by candidate HIV vaccines. Only with multiple strains of virus can neutralization breadth be ascertained in a meaningful way. Standard panels of HIV strains are in early stages of development. Expansion or extension of current standardization and validation activities, production and provision of necessary reagents, and access to quality assurance programs are needed to ensure worldwide comparability of assay results.[24] The strains of virus incorporated into a worldwide panel need to be carefully selected to reflect the current epidemic and should include early isolates from individuals at potential vaccine trial sites.[25] Molecular epidemiological studies and elucidation of the role of genetic factors and immune responses of the host in the transmission of HIV at the population level will also help guide vaccine design and evaluation.[26] [27] Another specific priority is an assessment of the neutralizing antibody response generated in the recently completed Phase III trials of HIV envelope glycoprotein 120 candidate vaccines using a global virus panel. The results would establish a baseline level of neutralization potency and breadth that is nonprotective, which would be extremely valuable in reaching informed decisions about advancing future antibody-based candidate vaccines.

A major obstacle to designing a suitable global virus panel is the paucity of information on neutralization serotypes. There is general agreement that if a reasonably small number of neutralization serotypes exist, their identification would guide the creation of an optimal panel of isolates for neutralizing antibody assays and the design of polyvalent immunogens. Although there is some controversy as to whether HIV-1 neutralization serotypes exist, the magnitude of benefit that would result if serotypes were identified warrants establishment of a neutralization serotype discovery program that employs the latest technologies.

Product Development and Manufacturing. Manufacture of vaccine candidates for large clinical trials and to meet eventual worldwide demand requires the development of processes for producing consistent, active vaccine batches on a large scale. Development of these bioprocesses must be integrated with analytical work (e.g., toxicity and stability testing), incorporate validated assays, and be applicable to the manufacture of sufficient vaccine to meet global needs after licensure. These processes are typically individually developed as a candidate vaccine advances from early clinical testing to late-stage evaluation and licensure. Worldwide expertise and capacity for this bioprocess development work is already limiting and exists almost exclusively in the private sector. As more HIV candidate vaccines enter the pipeline, current capacity will be rapidly exhausted.

The initial priority is to identify or establish one or more dedicated HIV vaccine bioprocess and analytical development groups that bring together the skill set and capacity to manufacture different promising candidates for clinical trials. The bioprocess development groups would also help train people and transfer manufacturing skills in whole or in part to manufacturing sites around the world. This training program would address the acute shortage of bioprocess experts.

At a later stage, building, acquiring, or contracting facilities to carry out bioprocess and analytical work and to produce several different types of candidate vaccines should be considered. Such facilities would further assist in transferring manufacturing technology to other production facilities, preferably in one or more developing countries. Decisions about which candidates a facility undertakes would be made through a well-defined, comprehensive evaluation process. The facilities could eventually be expanded to provide production capacity to launch a vaccine for public

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health use, should no manufacturer be available to produce the vaccine quickly upon licensure.

Clinical Trials Capacity. As a growing number of HIV candidate vaccines begin to move through the clinical trials pipeline, the gap between existing global capacity and future requirements for conducting large efficacy trials has grown in magnitude and urgency, especially in developing countries. This gap in developing countries must be addressed through (1) increasing the quantity and quality of research staff, (2) establishing sustainable research facilities to support trials, and (3) expanding access to large, well-defined populations of uninfected people at high risk of HIV infection.

The recommended solutions take a long-term view and are aimed at building site capacity rather than preparing for specific trials. Sites should not be confined to conducting HIV vaccine trials but should be positioned to contribute to other research of public health importance to the community and the country, including, for example, other areas of HIV research (e.g., microbicides and treatment) and/or other diseases. Additional field trial sites must be developed to be able to conduct planned and anticipated efficacy trials. Sites should be selected in a strategic, data-driven manner, and should demonstrate the ability to recruit and retain large numbers of HIV-negative volunteers from populations with substantial HIV incidence. New efficacy trial sites should be developed in regions with emerging epidemics rather than only in areas with already-established disease. "Early-warning systems" must be available to identify these newly emerging sub-epidemics. Defining optimal methods for collection of HIV incidence data from populations at potential efficacy trial sites is essential. Whenever possible, efficacy trial sites should be linked to (1) academic medical centers to enhance research capacity and help train clinical researchers, (2) accredited local and regional laboratory facilities to provide infection endpoint and safety assessments, and (3) centers that can provide appropriate care and treatment to trial participants.

The acute shortage of qualified personnel is a major bottleneck to the conduct of clinical trials in developing countries with severe or rapidly emerging HIV epidemics. Development of intellectual capacity at these sites should emphasize (1) expanding research training opportunities for personnel in the broad range of topics required to conduct high-quality clinical research, (2) establishing and adequately supporting long-term career paths for such individuals, and (3) fostering political and social environments locally and nationally that support the conduct of clinical research. Building HIV scientific and operational expertise at clinical trial sites should be linked to other HIV/AIDS research activities (e.g., identifying and characterizing incident/early HIV infections, collecting newly transmitted strains, and measuring incidence in high-risk populations).

Site development must include strategies to develop or enhance existing capacity to deliver health care, including HIV prevention, care, and treatment, to the local community participating in clinical trials. Provision of, or referral to, basic clinical services such as voluntary counseling and testing and diagnosis and treatment of sexually transmitted infections will be essential.

In addition, site development should include building skills that are ancillary but critical to the actual conduct of clinical trials, such as educating communities, building community partnerships, managing site finances, and piloting applications through regulatory decision-making processes.

Regulatory Considerations. The Enterprise must address a number of problems that currently impact the review of HIV vaccine trial protocols and that could delay future decisions regarding product licensure in developing countries. Most regulatory challenges arise from the fact that regulatory approvals are granted at the national level, but many developing countries lack the expertise, well-defined processes, clear delineation of authority, and/or other system components needed to make regulatory decisions expeditiously. As a result, new products are often licensed in these regions based on prior approval in the U.S. or Europe and/or endorsement by the WHO. Under these circumstances, data specific to developing country populations (e.g., disease burden or childhood vaccination schedules) often do not enter into the decision making. The absence of defined pathways to approve products targeting a country's needs when a product is not also submitted to regulators in the U.S. or Europe remains another obstacle. The Enterprise process has identified these action-item priorities: (1) harmonize and exchange information needed by regulatory bodies within the differing legal frameworks of different countries, (2) facilitate regulatory decision making, possibly using regional approaches for conducting reviews and making recommendations, (3) build regulatory capacity, (4) perform risk/benefit evaluations in the context of differing epidemic dynamics

and country needs and resources, (5) identify and remove potential scientific impediments to rapid regulatory decision making, and (6) address ethical issues that interface with regulatory decision making, such as ensuring informed consent and defining the degree to which trial participants should receive a standard of care that is higher than others in their community.

Intellectual Property Issues. Given the Enterprise focus on stronger collaboration, data sharing, and use of common materials and reagents, an intellectual property (IP) framework that facilitates this "enabling environment" is crucial for success. While IP issues may arise throughout the vaccine development process, at present the top priority is to stimulate early stage research and vaccine design by increasing scientific freedom to operate and sharing of data and biological materials.

Specific areas for further consideration include: (1) minimizing restrictions on freedom of operation, perhaps by early stage covenants not to litigate and followed by later stage agreements based on true valuations of IP; (2) sharing of information (including clinical trial data), materials, expertise, trade secrets, and platform technologies in a protected and secure manner while also remaining in compliance with national laws devised to prevent monopolies and insider trading; (3) recognizing the contribution of different countries to HIV vaccine development through approaches that assure affordable access to successful vaccines; and (4) maximizing access to essential technologies and inventions.

Scientific Plan

Scientific Activities. On October 21, 2004, a group of participants from 16 countries, the European Commission, UNAIDS, and the WHO met to finalize the scientific plan and to discuss how to formulate specific actions.

Participants noted that the structure of an activity should depend on several factors, including, for example, the degree to which the activity can be predefined, the degree to which the creativity of academic researchers needs to be harnessed, and the mechanisms available to the funding organization.

A number of options were discussed, with consensus as to those that would fit various scientific priorities.

First, networks of focused consortia and real or virtual centers are well suited to systematically address many of the major scientific roadblocks identified in this plan. These consortia or centers would link to each other to ensure a comprehensive, systematic approach, sharing information so that each can be as productive as possible, and also to share reagents and procedures so that data among groups can be compared and, where possible, merged for analysis. The specific scientific areas that could be supported by consortia or centers include (1) addressing fundamental scientific problems, such as the definition of correlates of immune protection in selected animal models and the characterization of acute/early infection in potential vaccine trial sites; (2) designing and evaluating novel vaccines, such as immunogens that neutralize primary isolates, and improved T cell vaccines that avoid immunological escape and/or that induce persisting mucosal or persisting systemic responses; and (3) providing for a systematic evaluation of potential adjuvants. The success of consortia or virtual centers will depend on engaging the best researchers, getting them to work collaboratively and dedicate the majority of their effort to HIV vaccine research, resolving IP issues, obtaining support for researchers from their institutions, and keeping the group focused on specific, well-defined questions. More than one consortium may be needed for systematic coverage of vaccine design research (e.g., monoclonal-antibody-identified epitopes, native envelope, and modified envelope).

Second, a global system of central laboratories linked to satellite laboratories that work together (using GLP) would provide a range of standardized functions, help ensure the quality of clinical research, and enable comparison of data from different trials. Together this system could (1) conduct preclinical or clinical assays, particularly critical endpoint assays that require standardization and/or validation; (2) develop, optimize, and validate new assays and platforms; (3) transfer assays from central labs to satellite labs; (4) develop and implement a global quality control/quality assurance program and proficiency testing for assays performed at central and satellite laboratories; (5) implement vaccine-related research that requires validated assays and close cooperation and collaboration among labs globally, such as a Virus Neutralization Serotype Discovery Program, and the characterization of recently transmitted HIV isolates; and (6) contribute to the development of technological infrastructure in developing countries.

Third, a number of contract laboratories capable of developing, acquiring, storing, and distributing common reagents will prove critical to the success of collaborative

research and development projects, and to ensuring reagent quality. These reagents could include (1) peptides, antisera/antibodies, and viral isolates for immune assays, including a standard panel of virus strains and sera representative of the global genetic and immunologic variability of HIV, and (2) additional broadly neutralizing monoclonal antibodies, especially from non-clade B viruses, to facilitate elucidation of the motif or motifs they recognize. These contract laboratories would be expected to work very closely with and enable the work of Enterprise consortia, centers, immune assessment laboratories, and clinical sites.

Fourth, a network of Clinical Research Training Centers in developing countries could work collaboratively to ensure development of quality trial sites. These centers would (1) conduct or facilitate training of trial site personnel in activities that are generic to the conduct of clinical trials, as well as those specific for HIV vaccine trials, for example, an HIV vaccine fellowship program for developing country scientists; (2) coordinate and work together with other Enterprise consortia or centers, such as those established to characterize acute/early infection in developing country settings or to prepare a standard panel of HIV strains representative of currently circulating viruses; and (3) share standard operating procedures, vaccine development plans, and strategies for engaging and ensuring community and political support.

Fifth, a network of individuals and companies with manufacturing experience, particularly process development expertise, could link to consortia, centers, and others involved in vaccine development to provide development and manufacturing expertise to facilitate the advancement of improved HIV vaccine candidates. The above structures are proposed to address the initial Enterprise scientific priorities. Additional consultative groups, reference and centralized facilities, and other mechanisms may be needed to facilitate collaborative work and strengthen the global capacity for the conduct of HIV vaccine research and development as the field progresses.

Different implementing and funding agencies will need to work in close collaboration to ensure harmonious implementation of the scientific plan. Initial actions should focus on the areas of vaccine discovery and standardization of laboratory assays, which are considered critical for the success of the Enterprise and the eventual development of a safe and effective HIV vaccine. Activities to address recommendations in the areas of product development and manufacturing, clinical trials capacity, regulatory considerations, and IP issues should be launched after these initial components of the plan are under way.

Regardless of timing, each scientific endeavor needs to outline specific strategies to ensure information exchange and capacity building among the collaborating partners and institutions. The funding mechanisms employed (i.e., contracts, grants, interagency agreements, etc.) will depend on the task to be accomplished and the needs and capabilities of each funding organization. In the spirit of coordination, collaboration, and transparency promoted by the Enterprise, two or more partners may jointly support one or more activities, taking care to avoid duplication in the use of their respective resources. When a research area is jointly funded, all communication regarding goals, research plans, progress, obstacles, etc., should be openly and transparently shared among all stakeholders—funders, project managers, and researchers.

Guiding Principles. As an alliance of independent entities, the Global HIV/AIDS Vaccine Enterprise will be challenged to carry out three essential functions. One is to continue regular scientific assessments. The scientific priorities outlined in this paper will need to be monitored, reevaluated, and updated. An evolving scientific plan must reflect lessons learned, new opportunities, and the influence of new scientific findings and new technologies. Revised versions of the scientific plan must be made fully and publicly available. The second essential function is to establish global processes. To optimize progress across a large and complex set of activities at the global level, standards, performance criteria, and processes for data sharing, communication, and convening must be established. The Enterprise will convene fora to address policy issues such IP, clinical trials, site development, and regulatory hurdles. And the third essential function is shared accountability. The partners in this alliance will need to create a culture of mutual accountability for the effective implementation of the scientific strategic plan. Since the Enterprise is not a single organization, a shared "way of doing business" is one of its most important defining traits. Articulating an explicit set of "working principles" is therefore crucial to the identity and smooth functioning of the Enterprise.

For the Enterprise as a whole the following conditions apply: (1) the central task is to develop and implement an ambitious scientific plan with the necessary scale,

balance and sequence of activities, and structure to carry it out; (2) the plan must focus on critical roadblocks that would benefit substantially from global collaboration while fostering continued R&D by individuals, small groups, and individual networks; (3) the incentives holding the alliance together will include collaborative arrangements and structures that give people the resources, necessary critical mass, centralized facilities, common reagents, assays and technologies, and data they need to effectively remove critical roadblocks; (4) all activities will reflect the commitment to create an environment that maximizes the ability of participants to share data and biological materials, e.g., through the use of common standards for measurements and appropriate IP arrangements; and (5) the Enterprise also commits to working for rapid global access to a successful vaccine.

For participating investigators and organizations, key principles include (1) the willingness and desire to work in an open, collaborative fashion, sharing data and reagents in a collegial fashion, with the appropriate balance between productive competition and effective collaboration, and (2) the willingness and ability to devote the majority of their time to tackling these problems within a focused environment, completely committing to solve the problems at hand.

Organizational Structure of the Enterprise. The Coordinating Committee will facilitate all aspects of the Enterprise's activities. This committee consists of representatives of the Enterprise founders as well as additional scientific leaders selected from inside and outside the field of HIV vaccine research and development. The committee will develop procedures for term rotation and inclusion of new members, to ensure appropriate representation of all relevant partners, and will engage external stakeholders for advice, expertise, and assistance, appointing technical expert groups as needed. A Secretariat will provide logistical and administrative support to the Coordinating Committee and Enterprise partners. The BMGF will serve as Interim Secretariat until a permanent Secretariat is established.

The Funders Forum will be an open forum of sovereign, independent funding organizations, starting with a nucleus of those who already embrace the principles of the Enterprise and who are actively supporting or intend to support and fund HIV vaccine research and development. Members of the Funders Forum will be high-level decision makers within the ranks of funding organizations and governments, as close as possible to the source of resources. Since the Enterprise is not a discrete organization with a pool of money, funders will support specific areas using their own mechanisms, according to their own practices and policies, and following Enterprise principles. The road to success will be a bumpy one. The scientific plan will provide guidance that may help funders better align existing resources but, more importantly, will facilitate the efficient and focused application of new resources as they become available. Multiple funders who wish to support a single Enterprise-defined project could form collaborative agreements, memoranda of understanding, or other forms of written agreement among themselves to outline their respective roles and responsibilities; address IP, program management, oversight, and other issues; and establish mechanisms for communication and conflict resolution.

The funders with greatest flexibility could provide incentives for sharing reagents and data, and linking projects together, e.g., by supporting the additional work that nationally or regionally funded laboratories would need to undertake in order to participate in a global network, or by supporting a program to develop and share reagents.

In some cases, funders may wish to support an implementing organization that will take responsibility for managing the project and reporting back to the funder and other stakeholders. In other cases, funders may have the capability and capacity to play a substantial role in facilitating the project. In still other cases, funders may have the capability to assume a leadership role in overseeing the conduct of the activity, particularly in cases where the activity is well defined in advance.

In addition, an Annual Stakeholders Forum will be organized to bring together the broader community of scientists, policy makers, public health officials, and community representatives involved in the search for an HIV/ AIDS vaccine. This meeting will serve as a forum to (1) update the broader community on Enterprise activities and progress, and (2) provide the community with a mechanism for feedback and dialog.

Funding Issues. Global expenditures on HIV vaccine research and development in 2002 were tentatively estimated to be on the order of US$624–670 million, the large majority (67.3%) provided by the public sector, followed by the philanthropic sector (17.4%) and industry (15.3%). An analysis of how those funds have been invested revealed that the large majority (43.1%) is being used in preclinical research activi-

ties, followed by clinical trials (28.2%), basic research (20.7%), cohort development and clinical trial infrastructure (6.5%), and vaccine education, advocacy, and policy development (1.4%).[28]

The largest funder of HIV vaccine research and development activities has been the NIH, with almost US$350 million in 2002. The NIH budget for HIV vaccine research has grown from less than US$50 million in 1996, to an estimated US$514.6 million for 2005, corresponding to 17.6% of the NIH total HIV-related research budget for 2005.

The Enterprise Coordinating Committee will analyze the additional financial requirements to fully implement the scientific plan of the Enterprise, and the Enterprise Secretariat will explore options to leverage these funds from the public and private sector. Initial estimates by Enterprise partners suggest that US$1.2 billion per year, or double the current expenditures on HIV vaccine research and development, will be needed. Although this amount may appear unrealistic at present, it would represent only a fraction of the total global expenditures in response to the AIDS pandemic and a very reasonable investment in view of the enormous social, political, and economic consequences of the pandemic. However, it is essential that the proposed increase in funding for HIV vaccine R&D be additional to existing AIDS expenditures, and not at the expense of current prevention, treatment, and care efforts.

The founding partners of the Enterprise, including the NIH, the BMGF, and the Wellcome Trust have already committed, or are considering committing, resources towards new initiatives that will begin to enact portions of the Enterprise scientific plan over the next six to nine months. Each funder will utilize their own funding processes and will align the design, scope, and scale of programs to those laid out in this plan. For example, the NIH National Institute of Allergy and Infectious Diseases will establish the Center for HIV Vaccine Immunology, which will target several scientific priorities identified here.

Political Support. As a sign of global recognition of the importance of better, more strategic coordination in the search for an HIV vaccine, the "Group of Eight" leading industrialized nations in June 2004 endorsed the goals of the Enterprise and agreed to review progress in implementation at its 2005 summit meeting in the United Kingdom.[29] Likewise, on October 19, 2004, Ministers of Health from seven European countries (France, Germany, Italy, the Netherlands, Spain, Sweden, and the United Kingdom) adopted a statement of intent to coordinate efforts to accelerate research for an HIV vaccine within the context of the global effort.

Next Steps

With almost 5 million new HIV infections and 3 million AIDS deaths occurring every year worldwide, the development of a safe, effective, and accessible HIV vaccine represents one of the most urgent global public health needs. This global emergency led to the proposal to harness the power of science to find a definitive solution to one of the most catastrophic health problems of our time. The Global HIV/AIDS Vaccine Enterprise has evolved over the past 18 months from a concept proposed in a scientific journal by a cadre of researchers to a global consensus concerning the major scientific roadblocks facing HIV vaccine development, a strategic approach to address those roadblocks, and guiding principles for the plan's implementation in a manner and degree commensurate with the challenges at hand. Several organizations have already embraced the Enterprise concept and are moving to tackle portions of the scientific plan. Still, much more remains to be done. The road to success will be a bumpy one requiring the energy, commitment, and action of a wide number of government and nongovernmental organizations globally. Recognizing the enormity of the roadblocks as well as the potential benefits of a safe and effective HIV vaccine, it is essential that many more organizations and agencies contribute additional expertise and resources and work together as a global community in a cooperative, collaborative, and transparent manner to fully implement the Enterprise scientific plan.

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The scientific strategic plan of the Global HIV/AIDS Vaccine Enterprise was developed though a complex process of consultation that involved more than 140 par-

[28] Bing A, Gold D, Lamourelle G, Rowley J, Sadoff S (2004), Quantifying global expenditures on AIDS vaccines R&D [abstract]. XV International AIDS Conference; 2004 July 11–16 Bangkok, Thailand. Abstract number Tu-PeE5325. Available: http://www.iasociety.org/ ejias/ show.asp?abstract—id=2170619. Accessed 8 December 2004.

[29] Vogel G (2004), AIDS vaccines. G-8 leaders endorse global effort. *Science* 304: 1728.

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