*The Campaign to Fight AIDS*

# Ensuring Access to the Best Medicines


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## Ensuring Access to the Best Medicines

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# *How to Make Quality Drugs Available*

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**Robert Goldberg, Ph.D.**
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Panelists:
**Dr. Scott Gottlieb**
*Senior Adviser to the Administrator, Centers for Medicaid and Medicare Services*

**Jerry Norris**
*Adjunct Fellow, Hudson Institute*

**Dr. Robert Orina Nyarango**
*Head Pharmacist, ARV Programme, Gertrude's Garden Children's Hospital, Nairobi, Kenya*

**Dr. Segolame Ramotlhwa**
*Director of Pharmacy, Botswana Government HIV Program*

**DR. ROBERT GOLDBERG:** Thanks to enormous private-sector investment in health care, we are on the verge of great public health breakthroughs that will extend the promise of healthier, longer, and better lives not just for rich nations but for each and every individual on this planet. But the quest for health improvements on a global scale requires us to look beyond ideological partisanship and face the most compelling public health challenges and opportunities before us with faith, ingenuity, and honesty. Surely, one of the most pressing-and most contentious-global health challenges is the epidemic of HIV/AIDS in Africa. Our conference today is designed to help policymakers learn what resources are needed by those who must set up, run, and sustain programs in Africa intended to prevent HIV and treat those who are infected with that deadliest of diseases.

We made a decision when we organized this conference

to invite African health-care providers who actually treat patients, rather than relying on abstract conjecture or statistics. We think that it is critically important to give the people on the ground who are actually treating this epidemic a real voice in our deliberations. In an era when technology can practically eliminate communication barriers, provide high-quality scientific information in real time, and accelerate the creation of sophisticated health-delivery networks, health-care professionals in developing countries are demanding direct control over how funds are allocated, how drugs are used, and how medicines are evaluated. The era when any one international agency or donor organization or drug company or NGO can dictate to HIV organizations in developing countries what their priorities are is over.

We are also going to discuss the scientific and economic challenges ahead as we seek to develop medicines to fight infectious diseases, particularly emerging pathogens, and provide a vaccine to combat HIV. The reality is that these treatments will not emerge without substantial private-sector investments, along with an expectation of substantial return on that investment. To suggest that these products can be developed without private-sector investment is not only shortsighted; it will cost lives. But the need for private-sector investment does not suggest that cutting-edge medicines cannot be made available to Africa and other developing countries for little or no cost. They can, they should, and they must be made available at affordable prices, and our speakers today are going to discuss how this can be done.

I would now like to introduce the speakers from our first panel. Our first speaker today will be Dr. Scott Gottlieb, who is a physician and the senior advisor for medical technology to the Centers for Medicare and Medicaid Services Administrator, Dr. Mark McClellan. Before holding that position, Dr. Gottlieb was the Director of Medical Policy Development at the Food and Drug Administration. In addition to his official duties, Dr. Gottlieb still serves as an emergency-room physician.

Our next panelist will be Jerry Norris, an adjunct fellow at the Hudson Institute in Washington, D.C., working on global HIV/

AIDS issues. Before holding that position, Mr. Norris was Senior Director for International Operations for the WebMD Foundation, where he was developing a joint UN private-sector partnership to bridge the digital divide in public health. His research now focuses on trying to find ways to ensure a steady, affordable supply of quality medicines to developing nations.

Following Mr. Norris will be Dr. Robert Orina Nyarango, a pharmacist responsible for coordinating the antiretroviral treatment program at Gertrude's Garden Children's Hospital in Nairobi, Kenya. Gertrude's Garden is the only pediatric hospital in east and central Africa and is the primary referral hospital in that part of Africa.

Our final panelist is Segolame Ramotlhwa, who is Deputy Operations Manager for the National Anti-Retroviral Therapy Project as well as head of the Botswana Essential Drugs Action Program at the Botswana Ministry of Health. As the pharmacist in the ART Project Team, Mr. Ramotlhwa is also responsible for coordination of the pharmaceutical component of the project.

**DR. SCOTT GOTTLIEB:** I want to start by talking about a policy that we instituted at the FDA about a month ago. I recently moved over from the FDA, as Bob mentioned, to work with Dr. McClellan at the Centers for Medicare and Medicaid Services, but I was at the FDA at the time that this policy was developed.

A very high-level group of officials from the Department of Health and Human Services recently returned from a trip to South Africa and India, where they spoke to some of the companies that have expressed interest in developing follow-on versions of existing drugs but in fixed-dose combinations, so that they would be producing new drugs by combining some currently marketed drugs into one pill. These companies are Aspen in South Africa and Ranbaxy and Cipla in India.

I've been told that those discussions went well, and I think that this trip demonstrates opportunities that are going to be created as a result of the new policy promulgated by the FDA. That policy consisted of a guidance document that articulated a very

fast pathway for the approval of fixed-dose-combination drugs through the FDA, and committed the FDA to unprecedented timelines for review of these drugs—as fast as several weeks.

The fixed-dose-combination drugs, as many of you know, are combinations of existing patented HIV medications. So rather than taking six different pills a day representing three different medicines, in some cases you can combine all those different medications into one pill and take a regimen that's as easy as one pill once a day.

The guidance that we put forward has several components, and I don't want to go through every detail, but I do want to highlight four essential elements of that policy that I think make this policy unique. It is an unprecedented step forward from the agency's standpoint. It's important to know that there's nothing really new as far as policy: we didn't require any new regulations or new laws and were able to articulate all these pathways in one document.

The first element of our new policy was to articulate four processes by which fixed-dose-combination drugs can get FDA approval. Some of these processes represent the typical pathways that a branded company or a generic company would use to get approval for a product through FDA, but the issue that emerged was that there were products developed by Indian companies (Ranbaxy and Cipla, in particular) that were being used on the ground in Africa yet had not gone through any formal approval process-certainly not the FDA's approval process. There also might be some desire to use funds from the President's Emergency Plan for AIDS Relief to procure those products. Naturally, we wanted a method by which those products could be brought under some form of scientific review to ensure that they were safe and effective.

So one element of the guidance policy was a process by which these Indian and South African companies could file for formal approval with the FDA under a mechanism known as 505B2. They can go through a formal evaluation and get tentative approval, which would be sufficient for the purposes of procure-

ment by the president's fund. They couldn't get full approval, because patents would block them in the United States. But for the purposes of procuring these products for the countries where the branded companies have already waived their patents under the Trade-Related Aspects of Intellectual Property Rights (TRIPs) agreements-principally, Africa and the Caribbean-tentative approval would be sufficient. But these companies would still go through a process analogous to any scientific review that the FDA does, albeit on a very expedited timetable.

The second element of the policy was a proactive listing by the FDA of where the clinical data already exist to allow this very expedited process. Specifically, to obtain approval for these products, you need two things: first, you need to demonstrate that the combinations themselves-the three drugs used in combination-are actually effective for the treatment of HIV, and that requires clinical evidence where these three drugs have been used in combination in actual patients and have resulted in attenuating viral loads. Second, you need a lot of chemical data to demonstrate that the products don't break down in the sun, that they get into the bloodstreams at adequate levels for treatment, and that they get into the bloodstream in reproducible ways. In short, we need to ensure that every pill that reaches a patient is the same. The first thing usually requires many years of clinical data. We actually have to give the drug to patients and see how the patients do. The second thing can be done very quickly because much of it is chemical data. You can test for bioavailability in a laboratory, where you can actually monitor the drug in the bloodstream with a small group of patients.

So we listed 25 or 30 combinations for which we believe that the clinical data already exist to prove that the drugs would be effective if used in combination. Therefore, if a sponsor wanted to come in with a fixed-dose-combination drug, all it would need to do for those listed combinations would be to provide bioequivalence and chemical stability data, which can be done in a very short time. I could find only one other instance in which the agency proactively listed a case in which it felt that the clinical data

were sufficient for a sponsor to come in with an application for a drug without going through the clinical trials-the normal process of giving the drug to patients and watching for the clinical effectiveness.

The third element of our policy was an articulation of the bioequivalence in the composition that would be needed for approval. This is what the FDA does on a day-in and day-out basis—it looks at bioequivalence and stability of drugs. But here, again, we were proactively articulating what the threshold would be for the approval of these combination products.

The fourth and final element was a pledge on time frames-that the FDA would review these products in time frames as short as three to six weeks.

Shortly after we announced these guidelines, companies expressed interest in developing new combination products. In particular, two groups of branded companies issued press releases expressing interest in developing fixed-dose-combination drugs. We're hopeful that other companies will step forward as well.

Despite the innovative steps taken by the FDA, an enormous political debate surrounded the announcement of our new policy. As many of you know, there was a lot of talk about the Indian companies that were developing fixed-dose-combination drugs—principally, Cipla's product, which consisted of Sustiva, Nevirapine, and Lamivudine. The discussion focused on whether the U.S. would use the president's fund to procure these products. The reason that people in the AIDS community, particularly in the international AIDS community, wanted us to use our funds to procure these products is because they were cheap fixed-dose combinations. The fact that they were fixed-dose combinations is not debatable, and the fact that fixed-dose-combination drugs will probably offer some benefit in a Third World environment without a lot of health-care infrastructure probably isn't debatable, either. The assertion that these drugs were cheaper than other available options is probably very debatable, but I won't get into that today, since it is not my direct area of expertise.

What I would like the audience here today to think about

is the value of a one-size-fits-all drug in Africa and other similar markets. I have talked to many public health officials about this and have heard are various opinions. There is a presumption that these products-particularly, the Sustiva, Nevirapine, and Lamivudine combination-would be a very good pill to introduce into the African market because it is, in many respects, a one-size-fits-all pill, meaning that it can be used in men as well as in women. In women, the medical community wants to be able to offer a product that can prevent maternal-to-fetal transmission, and the inclusion of Nevirapine in this product does just that.

Consequently, if you are looking for a very easy way to procure one product and do not have access to the kind of health-care infrastructure in which you can tailor different kinds of treatment regimens to different kinds of patients, this is the product to use, according to many people. But one thing that we need to think through carefully from a public health standpoint is the limitation of introducing a one-size-fits-all product into any market.

Here in the United States, treatment regimes are highly tailored; a drug would probably have limited market potential here for that very reason. The best case is the situation in which clinicians can tailor treatment regimes to an individual's response to different kinds of medications to ensure that they are responding positively to treatment and avoiding severe adverse effects. For instance, if a patient has liver disease, physicians want the option to give the patient drugs that aren't as toxic to the liver. If the patient is a young woman, you might prescribe a certain drug that prevents maternal-to-fetal transmission. In short, there are numerous considerations that illustrate the limitations of a one-pill-treats-all approach.

Clinicians in the U.S. can avoid that problem because we have the health-care infrastructure to assess patients on a regular basis. That is obviously not true around the world, and that is what makes a combination product like Cipla's attractive in some people's minds. But you also have to realize the shortcomings of that approach. You are, by necessity, accepting a certain percentage of treatment failures and a certain amount of toxicity from the

product itself. In particular, we know that Nevirapine is highly toxic. About 0.5 to 1 percent of people develop a very severe rash called Stevens-Johnson Syndrome, which can be fatal, particularly if you don't have sophisticated health-care support. A much higher percentage of patients will develop liver toxicity that isn't necessarily self-limiting-for example, it doesn't stop once you withdraw the drug. As a result, it is quite possible that a not-unsubstantial number of those patients could go on to develop fatal liver disease.

The unpleasant reality that not many people want to acknowledge is that if you saturate this product in a population without a lot of health-care support, you're going to obligate a small percentage of those people to die just from the treatment, not the disease. Here in the United States, when we use Nevirapine we titrate it on very slowly to patients over the course of a couple weeks and monitor them very closely for liver toxicity. But in an environment where you're using a fixed-dose-combination pill, you don't have the opportunity to titrate it up. It is, by definition, a fixed-dose combination, and you're starting them on the maximum clinical dose right from the start. This means that you are going to have a certain amount of toxicity that's going to be even higher than our experience in the United States with this drug.

I raise this problem to ask the question: What should be our goal? Should the goal be to get patients on durable treatments in settings where they could continue to be successfully treated, or should the goal be to start as many people on treatment as quickly as possible? If your goal is the latter, you want a very cheap drug that doesn't require substantial infrastructure to support. If your goal is to get people on durable treatments, you probably need many different kinds of drugs. This is not to deny that there is a very important place for the fixed-dose-combination drugs, but you need backup drugs to support people who fail on that treatment, and you probably need to tailor your regimens a bit better to men and women and young people and old people and people who might have other comorbidities.

The ultimate question is which treatment scenario will save

more lives. I'm not sure that it is a foregone conclusion that starting many more people on fixed-dose treatments is better than taking the time to develop treatments that could be more sustainable in the long run. There is a real sense of crisis attending this problem, and rightfully so. But we cannot allow our sense of crisis to blind us to the therapeutic trade-offs and alternatives that are available. If we do that, we may wind up regretting our decisions a few years down the road.

**MR. JERRY NORRIS:** I would like to discuss the fixed-dose-combination conference that was held in Botswana, March 29-31. But before that, I would like to go back to October 2003 because it has an effect on the conference itself.

Last October, I wrote an analysis of the scientific dossier for the drug Triomune, which is the fixed-dose-combination product that most of us will be referring to today. About a month later, I was invited to participate in a telephone conversation with the CEO of Cipla, the company that produces Triomune. In that conversation, the CEO, Dr. Hamied, started off by saying that the analysis that I had written was causing the WHO to delay the approval of Triomune, so he wanted to correct the inaccuracies in my analysis.

He said that I was inaccurate in stating that the drug could only be administered by registered medical practitioners. I replied that I was only quoting from his scientific dossier. After a couple of minutes of dueling assertions, in which he kept asserting that there was no such dossier on his company's drug, I said, "I have it in my hand. It is a six-by-nine brochure, three colors. On the back cover, which is blue, in very small white print, it says, 'only for use only by registered medical practitioners.' " After I pointed this out to him, there was a long silence on his end of the line. Finally, he asked, "How did you get it? It's confidential."

At that moment, I was bemused that a copy-drug manufacturer, who reverse-engineers someone else's intellectual property, was concerned that his property rights had been compromised. So indeed, there was a scientific dossier on his drug. At the end of

the conversation, he asked, "Is there anything else that I could show you?" So I asked if he could send the approval from the Indian drug-regulatory authority. He replied that not only would he send it, but that he would send it by DHL. And indeed he did: it arrived a few days later. This document was more revealing than the scientific dossier. It isn't an approval, but rather a permission to produce the drug-manufacture the drug-and it's from the Drugs Controller General of India, which is India's centralized version of the FDA. There were five conditions that I found significant in the approval. One is just what we talked about, that there must be a box-warning label that it can only be used under prescription by registered medical practitioners. Second was that it was for adult patients only. Third was that it is for patients who have been on Nevirapine. The patients must have been stabilized before they are administered Cipla's triple-dose drug. Fourth, the permission to produce the drug was good for a period of two years beginning July 26, 2001, and we were in the end of that approval period. And fifth, which I found puzzling, was the restriction that there shall be no reference in the advertisement or medical literature that the Indian government has approved this drug. None of these restrictions saw the light of day when the WHO prequalified the drug or when the World Bank approved purchase of the drug in its procurement mechanism.

None of these conditions has been publicized, but all of them are very, very critical to our discussion today. In terms of the drug approval in India: I went back to Dr. Hamied and said, "You must have gotten it renewed by the Drugs Controller General." And he said no, that I didn't understand their system and that he would send me their new approval. And the new approval is from the State Authority-Maharashtra State. So it's gone from the central regulatory agency to a state regulatory agency. Apparently, there are 28 different state authorities in India after it goes through the two-year initial process at the central level.

So now let's go to the Botswana conference. As many of you know, it was cosponsored by World Health Organization, UNAIDS, the Southern Africa Development Community, and the

U.S. Department of Health and Human Services. The purpose of the conference was to try to draft scientific and technical principles for fixed-dose-combination products, so it was basically a scientific meeting. And it was an open meeting: anyone could attend. In the week or ten days prior to the conference, there was an incessant drumbeat of articles in the media and letters to the president of the United States calling for its cancellation. These letters claim that the intent of the conference was to subordinate the World Health Organization's prequalification system and to stop the purchase of least-cost fixed-dose combinations (FDCs) from India. Behind it all, they claimed, was the silent hand of the U.S. pharmaceutical industry, the largest financial supporters of the president's reelection campaign. But the media barrage was to avail. The conference went forward. But having failed to stop it, NGOs in particular were able to read prepared statements at the end of the conference, and these statements were picked up by the media, which were quick to claim that the conference had failed to reach consensus.

What the media did not report were the voices from Africa that were at that conference. Let's hear just a few of those African delegates: "We are holding all drugs to the same high standard," said the delegate from Botswana. "Yes, people are dying in Africa, but should we throw out standards and buy anything?" said the delegate from the Food and Drug Board in Ghana. "Poor quality means poor access," said the delegate from the Medicines Control Council, South Africa. "African regulators are not being unreasonable by demanding that generic companies show them the data on their drugs," noted the delegate from Botswana. On April 12, the *Financial Times* carried an article by the director of the Institute of Public Policy in Nigeria, who wrote: "HIV medicines, whether original or generic, should meet the most stringent, rigorous, clinical and testing reviews. If the proposed drugs are rejected by pharmacies in Brussels, London, Tokyo, Geneva, or Washington, accepting the use of the same drugs in Africa with little resources and lack of equipment to do a proper clinical and scientific evaluation may further compound the woes of HIV/

AIDS victims."

The FDCs suddenly captured everyone's imagination over the past six months. But I find it astonishing how quickly these FDCs could gain ascendancy in so many quarters as the silver bullet for AIDS treatment among Africa's poorest. Much of the enthusiasm started in October 2003, when the Clinton Foundation announced its historic pricing agreement with Indian pharmaceutical companies. The Indian companies said that they would be able to produce this triple-dose combination treatment for $140 per year per person. That's an amazing price, and the press naturally picked this story up and ran with it. On December 1, 2003, the World Health Organization announced its support for these drugs as the cornerstone of its plan to treat 3 million people by 2005. Subsequently, the WHO listed these same fixed-dose combinations in its prequalification system for the first time. All this happened over the course of just a few months, and it was what propelled the conference in Botswana. The NGOs jumped on the fixed-dose bandwagon, sending a blizzard of letters to Congress, the State Department, and Secretary Tommy Thompson at Health and Human Services. They claimed that millions of patients would die because the U.S. government would not approve the purchase of cheap fixed-dose-combination products.

The reason that the NGOs asserted for U.S. non-approval? They trotted out the scapegoat of the U.S. pharmaceutical industries and asserted that the WHO prequalification system was just as scientific and just as rigorous as that of the FDA. But when you look closely at the FDA and the WHO, you see that they are not really comparable. The FDA is, for the most part, the gold standard when it comes to pharmaceutical data and approval.

The NGOs also asserted that copy drugs are two to three times less expensive than patented products, and so they seemed- until someone did a comparative study. On May 12, the Hudson Institute released a report called "Myths and Realities on Prices of AIDS Drugs." Hudson found that the average price of the patented product (and these data were taken from Doctors Without Borders publications where they list prices of drugs) was $404.

The average price of the copy drug was $494. Of the 13 most commonly used AIDS drugs, eight copy drugs are less expensive, and the next several are marginally more expensive. The real price differential is found in Nevirapine, which is much more expensive. But Nevirapine is produced by a German company, and the Doctors Without Borders pricing report did not mention-or did not compensate for-the fact that the German company donates this drug absolutely free in mother-to-child transmission prevention programs around the world. When it comes to fixed-dose-combination drugs, the patented version is $659 and the copy drug is $1,178.

At the Botswana conference, something occurred that was significant to the WHO prequalification process. One of the co-chairs was from the Office of Essential Drugs and Medicines Policy in Geneva, and I had been puzzled as to why in 14 separate editions of the prequalification exercise they listed a disclaimer saying that these drugs were not warranted for safety or efficacy in the treatment of AIDS patients. So I asked at the conference of the WHO representative: Why there was a disclaimer noted in the prequalification for these drugs? This was a public meeting, so I was very surprised when he said that he would only answer that question in private. So I moved on, and followed up with another question: How does the WHO intend to ensure informed consent to patients in its plan to treat 3 million people by 2005? Again, he told me that he would only answer that question in private.

Later, during the coffee break, he told me that the reason for the disclaimer for safety and efficacy of these drugs was that it is the responsibility of the manufacturer to ensure those attributes. In terms of informed consent, it's the responsibility of the home government in question.

In the first case, all the drugs shipped out of India are priced freight-on-board, and once the drugs leave Indian shores the companies have no concern about those products and do no post-surveillance or marketing studies to see if there are any adverse side effects with their drugs. Consequently, I don't understand how the World Bank, the WHO, and even the Vatican leap

onto the FDC bandwagon and pretend that these drugs are the silver bullet for AIDS in Africa. I remind everyone here today that this is not a silver bullet that we're willing to use in the West. We're only willing to use it in poor African countries, and that's the shame of it.

**DR. ROBERT ORINA NYARANGO:** The purpose of my presentation today is to relate the Kenyan experience with antiretroviral therapy (ART) and to focus on what the requirements are in our situation. The mission of antiretroviral therapy in Kenya is to ensure the best clinical outcomes and to place as many patients as possible on ART. I must emphasize the first part, of ensuring the best clinical outcomes, because that is what is missing in most of our programs. The idea currently is to place as many people as possible on ARVs (antiretrovirals), as opposed to monitoring the outcome of the treatment.

We have five objectives: to ensure availability of quality and affordable ARVs; to provide a policy framework and structures through which ARVs should be given; to ensure availability of trained personnel to run the program (that is a very big challenge to us); to implement and coordinate the program; and to put into place a sustainable resource fund for the program. The last objective is critical because if we are relying more on donors-if we have a supply of ARVs for, say, only two years and we don't have funds for the following year(s)-we will have a severe problem in continuing that program.

The components of our program are very complex, and I will highlight only a few. Quality political and technical relationships are very important, especially in our setting because from a political standpoint, the government may want to make as many ARVs available as possible without taking into regard the technical aspects of their delivery. But the technical aspect is very important because the political leadership has to be in check. What political objectives are driving the choice of which ARV drugs you bring in? How useful are the drugs for the patients? Has there been adequate quality analysis of these drugs? How do we evaluate the

process through which these drugs are given to patients? These questions are very important, and most of the answers are missing.

Right now, we cannot adequately monitor treatment outcomes. Once we place these patients on ARVs, how do we monitor them? How do we know that they are benefiting from them? At what stage do we decide to move from one regimen to another? That also requires input. We need quality logistical management information. We must have a tracking system to know which patients are using which drugs and how they are benefiting from particular regimens.

The situation in Kenya is as follows. We have 2.1 million infected people, 315,000 of whom are eligible for ARTs (that number could be higher because we don't know exactly what parameters the government is using to decide who is eligible for treatment), but only 18,600, or 0.9 percent, of those who are eligible for treatment are actually on ART programs-about 8,000 in the government and the rest in the private sector. The government has two bodies coordinating the ARV program: one in the Office of the President; and one in the Ministry of Health. We should have only one, in the Ministry of Health, but there must have been political considerations for this setup. With all due respect to our ambassador to the UN, who is here today, I don't see why we should have one in the Office of the President because it's duplicative-money that could be used elsewhere, which gives political leverage to whoever is in power.

We also have about thirteen donor communities involved with our programs. The sad thing is that every one of those groups is doing its own thing-coming into our country with its own drugs and running its own programs. The goals, methods, and standards of these groups are all very different, and the outcomes will be very different in that kind of setting. The quality of all the products and the processes are not assured because they are not evaluated in any centralized way. There are no uniform policies for product quality; the government is relying more on the WHO prequalifications.

But I come from the private sector, and we have a small

unit of antiretroviral therapy. We try as a hospital to have our own way of deciding which products to use. Thus far, we rely on FDA approval, but the government says that you have to place so many people on ARVs, so then we have to use the WHO prequalification instead, which is a problem because the product quality is not as assured as it would be with FDA approval. There are no national guidelines for ARV use in pediatrics and in pregnant women. The government has some guidelines, but they're not adequate. There is no national curriculum for training and certification of ARV providers, which is a very big problem. If there is any curriculum, it is still being developed. There is very little funding for human-resource development. You can bring in all the ARV drugs you need, but if you don't have people who know how to use them, the drugs aren't useful.

The government has trained about 500 people, but at least 2,500 are now necessary. Our hospital is a pediatric-referral hospital, so we have pediatricians practicing-and 90 percent of the prescriptions that we receive are from one pediatrician. This means that most pediatricians are not well versed in the use of ARVs. Some 60 percent of all prescriptions that we receive require pharmacist intervention in terms of wrong combination, wrong dosage, drug interactions, food interactions, and so on. That is why I emphasize the need for human-resource development. If this is happening in the private sector, imagine what is happening in the public sector. There are huge funding gaps, especially for human-resource development.

About 90 percent of our pediatric patients pay from their own pockets. There are no HMOs or insurance under the funding pool for ARVs. Less than 10 percent of patients have laboratory checks at least every three months to confirm that the ARVs are working or to monitor them for adverse reactions and so on. There are 12 sites for dispensing ARVs in a country with 30 million inhabitants, and there is inadequate information technology and infrastructure (warehousing, transportation facilities, and so forth).

Right now, the crucial goal should be to balance clinical outcomes with scaling up our ARV treatment programs. The ARVs

that are available or that should be given must address the need for appropriate structures for delivery. That is very important. We need adequate monitoring of the relations of other products and the process and the human resources. Pharmaceuticals need, as much as possible, OD and BD dosing for the drugs for the obvious reason of adherence. FDCs (fixed-dose combinations)-I don't say which manufacturer-are good in our setting in terms of improving adherence, reducing pill burden, and possibly reducing cost.

Forty to 70 percent of our children are on adult formulations-capsules and tablets, because syrups are very expensive. If you have to put children on ARVs, you need to put the medication, say, in a tablet that you break and crush-and you can anticipate the problems that arise with that. More liquid formulations for pediatrics are necessary. FDCs are most desirable. They should fit in with the work schedules of the parents and of the patients. They could improve adherence and reduce pill burden, but we need a way of certifying that they're working correctly and certifying the quality of the FDCs. The formulation should come with assurance of quality and efficacy. There should be more choice in the FDC regimes available (not just the one triple dose available now among the innovator brands).

FDCs must be developed with the clinical requirements of administration in mind. About 60 percent of our patients are also infected with tuberculosis. If you're putting them on a Nevirapine FDC, I don't know how you're going to manage the interactions that are going to occur with the TB treatment regime.

Ninety percent of our patients are on first-line therapy. I guess that applies to most of Africa. So if we have to develop FDCs, we should keep that in mind. FDC formulations should also allow for dose titrations. Dr. Gottlieb mentioned the toxicity of Nevirapine. If you had to titrate it for two weeks to check liver toxicity, how are you going to do it if it comes in a fixed-dose combination?

There is a pressing need for monitoring product quality and safety, and we need to revamp our national laboratories for doing that. There is a need for monitoring the patient outcomes,

the drug effects, resistance testing, toxic effects, and so on. Resistance testing is a very big problem because it's a major hurdle to change from one combination to another without resistance testing. We've had a big problem with resistant malaria and TB strains in Africa, and we don't want to repeat the problems with HIV.

We need to put into place a management institution for ARVs, and we need government as well as private-sector collaboration. The government will provide leadership and coordination and will mobilize funds while the private sector will provide the human resources. I've just broken it down from the Minister of Health to private sector to commercial distribution and to donor funding with the Ministry of Health's doing a lot of the policy work, development of systems, and logistics and coordination, and the private sector providing personnel, distribution points, and dispensing, education, and training. We need commercial distribution-I prefer commercial distribution because if they're distributing through the government, a lot of bureaucracy slows down the process. And, of course, we need donor funding and logistical and technical support. As the drugs and the funding go through the pipeline to patients, we need to have a way of moving information up from the patients to the doctors and then to the government and to the donors. We need that distribution network working in both directions. We need national, regional, and district distribution centers. We need a way of transport to rush those drugs to the patients. We need equipment-computers, refrigerators, and a computer system that is able to track the product and the patients. We need to upgrade our quality laboratories for monitoring both the quality of the drug and the treatment outcomes of the patient. And human-resource development-it costs about $2 million a year. We need a national curriculum and technical aid.

Central distribution, regional distribution, dispensing sites, information system management, personnel and training, transport, quality-control centers, monitoring laboratories, treatment guidelines: these are the hurdles we face, and the cost of these elements is more substantial than the cost of just buying the ARVs. The funds go more to ARVs than to information, logistics, or

training, but we should focus more on developing the structures and the human resources before we move into mass ARV provision. With the ARVs, the approach is to have revolving funding. We need to have a way of sustaining the process of ARV provision over time.

In conclusion, we need private-sector NGO and public-sector collaboration, with the Ministries of Health taking a lead. We need donor funding. We should address the priority areas-human-resource development, systems and infrastructure, and subsidizing for ARV costs. We need to create revolving ARV funds to sustain the provision of ARVs, and we need to develop drugs that address the needs we face-adherence, cost, safety, and efficacy.

In our hospital, our first priority should be orchestrating our programs using more technical criteria than the need to provide just the ARVs to patients. What we have learned is that we need to have a more objective way of deciding who should be on ARVs in terms of diagnosis and balancing between long- and short-term effects. We have managed as a hospital to develop pediatric guidelines for ARVs, and we think that the government can work out something similar in the public sector. We have a method of training personnel without a well-developed curriculum. It is a great challenge to us, but there is some interest from donors in developing such a curriculum. USAID has shown interest in this area. We have a strict way of monitoring adherence, which includes having to spend the hospital's money to call up the parents and find out how they are administering the drugs to their children. We are now able at least to collect some data. And 80-90 percent of our prescriptions, as I said, are from one pediatrician, 60 percent require pharmacist intervention, and 6 percent of the patients in our hospital who need to be on ARVs are actually on the program, which means that about 94 percent are going without treatment. The average cost of our prescription is up to $200 per month for each patient. The government and private practitioners have shown interest in our training programs. A few groups have also expressed interest in terms of funding.

**MR. SEGOLAME RAMOTLHWA:** I would first like to recognize members of the diplomatic corps present today. I'm going to be talking about our program in Botswana. We call it "Masa," which means "dawn." The name was chosen to reflect our situation at the time; before this program, it was as though the sun had set for people who were living with HIV/AIDS. But with the introduction of this program, the sun began to rise and there was new hope for people living with AIDS. The program in Botswana was initially launched in 2001 after a series of activities and considerations by government.

Initially, like everyone else, we focused primarily on prevention. But because the epidemic was hitting us so hard, the idea of treatment kept cropping up among those responsible for such decisions. From a study done by the Bank of Botswana that examined the economic impact of HIV if left unchecked or untreated, it became clear that without any intervention that targeted the virus itself, there were going to be many problems. There have indeed been many developments in the technical field; in the mid- to late 1990s, the newer class of antiretrovirals-the protease inhibitors-came onto the market. The results from these drugs were encouraging, which made it interesting to consider what it would take to actually introduce antiretroviral therapy. Indeed, the government eventually asked the Ministry of Health what it would take to introduce antiretroviral therapy. A study was conducted to examine two things: First, what would be the demand, or what could be the demand, for antiretroviral therapy if it were to be introduced in the country at that time? Second, what resources would be required to service that demand?

By 2001, we were already in the middle of a mature epidemic, with many people infected and many people dying from the disease. At that time, it was projected that about 300,000 people were infected with the virus, based on an estimate that at least 35 percent of cohort aged 15-49 would test positive. Based on an eligibility criterion of a CD4 cell count of 200 and below or the presence of an AIDS-defining illness, it was projected that the demand for antiretroviral therapy would be 110,000 people.

But it is important to interpret the figures that 300,000 people are living with HIV/AIDS, and 110,000 of those people are eligible for ARV treatment in the right context. These numbers were based only on projections and not necessarily on people who were actually waiting at the door that day who had already been tested and were ready to be started on ART. In fact, at that time, over 90 percent of the people didn't even know their HIV status. So in order for people to benefit from this program, they would have to start with testing, to learn their HIV status. Given the 110,000 people who are thought to be eligible for antiretroviral therapy, it became clear that our health-delivery system could not immediately service that demand; thus the decision to introduce the ARV program in phases or stages. It was not the easiest of decisions, because we are talking about people dying in large numbers. But given the vastness of the country, there obviously were those eligible people who didn't have immediate access to the program. We were faced with a situation whereby we felt that it was better to start small and do something rather than nothing.

What was of great concern to us was the human resources required for the program. We recognized that we needed to increase the number of health-care providers in our facilities and to train them appropriately, including those who were already in the system. The infrastructure and the treatment that are required to service a problem of this magnitude forced us to assess the resources that we would need. Previously, our policies were centered on prevention; with the introduction of a program like this, we needed to review our policies and systems.

This included confidentiality, which, with respect to HIV, had reached the stage of secrecy rather than confidentiality. I'm saying this because as health-care providers, we are trained in patient confidentiality. But when it came to HIV, it was a completely different ball game because of the social and cultural issues involved. As a country, we introduced routine HIV testing in January 2004 as part of a comprehensive management of the epidemic with a specific intention of facilitating access to ART by those in need. This is one area where people become uncomfortable. But

if we had to address the HIV epidemic comprehensively, we needed to be honest about the confidentiality issues involved and do all we could to win the war against HIV/AIDS.

We needed to revisit our information, education, and communication (IEC) strategies so that we could come up with a strategy that would be dedicated to a program of this type. ART and prevention were viewed as mutually reinforcing, and our IEC messages were deliberately designed to reflect this.

A program like this needs a well-organized and functioning monitoring and evaluation component, which meant that we had to implement a nationwide IT (information technology) system that included testing and evaluation on site. We were starting from a situation where our health-care system was not computerized and our IT literacy level was very, very low. We had people who didn't even know how to turn on a computer, so you can appreciate the challenges that we were facing.

Currently, we have about 14 or 15 centers with a total of about 15,000 patients from the public sector and another 7,000 or so from the private sector. So the total number of patients who are now on antiretroviral therapy is about 22,000. We have a mortality rate of, on average, about 10 percent. In our view, that's quite a success because we were initially dealing with very, very sick patients with advanced disease-stage three, stage four of the disease-and we did not expect that we would get that sort of results. An average of 10 percent mortality is very good when we are dealing with patients with such advanced disease.

Currently, there are about 22,000 people enrolled in our program, with just under 15,000 people receiving ARV treatment. As I mentioned, after treatment we are averaging about 10 percent mortality rate, with another 7 percent experiencing toxicity, which requires them to switch treatment regimes.

In terms of monitoring, one issue has always been gender. Some 64 percent of our patients are women. For whatever reason, women tend to enter the ARV program in greater numbers. Perhaps in our situation, women tend to seek medical treatment more often than men do.

When we started, CD4 cell counts, on average, at the time of intervention were about 50. But that figure has increased to about 86. So we are still dealing with very, very sick patients. The monitoring of CD4 cell count and viral load are among the important parameters for patient monitoring. Thanks to the effort that we put into this particular program, we have adequate patient follow-up, which is currently over 90 percent. In monitoring patient follow-up or adherence, we record every deviation: we do not tolerate any deviation whatsoever. For instance, when a patient is supposed to come in for a checkup today, but she comes the following day, even if she still took the drugs as prescribed we record that as non-adherence. In terms of patients taking the drugs under a zero-tolerance policy, our adherence rate is at least 85 percent, and it is a lot higher if one looks at whether the patient actually takes the medications.

When we started this program, one of the biggest unknowns was the toxicity issue. Initially, we thought that important drug toxicity requiring a change of therapy would be more common and thus make implementation of the program very difficult. But our experience so far is that toxicity occurs in less than 10 percent of cases, that is, toxicity requiring a change of treatment from one drug to another. And primarily, we are talking about anemia-related sickness, where the patient has to be switched from AZT to another drug because of anemia. But if you remember that the majority of the patients were anemic already because of their advanced disease, this is a figure we can live with. So in this particular area, we don't feel that there's much of a problem. Best of all, at about six months we find that we have at least 85 percent of patients with complete viral-load suppression. That tells us that our program has been highly successful even in terms of therapeutic outcomes.

We are currently scaling the program and rolling it out to the rest of the country. Our aim is to have a nationwide ARV program by the end of 2004. We only have about 17 sites remaining now. There are a several areas for which we need support from development partners; one is the strengthening of

monitoring and evaluation, which includes IT system improvements. This is one area where we think we may need outside expertise. We do have a system in place that has served us well to this point, but with the rollout and expansion of the program, we will certainly need to strengthen this component.

With the expansion of the program and as the program evolves, we think we might see other problems related to implementation-for instance, development of disease resistance in the next few years. We need the expertise that will help us monitor and manage that inevitable development. Management and coordination is another area that needs strengthening, which could be done with the support from our development partners. In the Anti-Retroviral Therapy (ART) program, you need to ensure that you optimal utilize all available resources. The support and contributions from development partners should be coordinated, including those efforts from the private sector and NGOs, if you are to get everyone moving in the same direction so that we actually get synergy.

Staff recruitment, especially key staff such as doctors, pharmacists, and laboratory scientists, is one very important area where support from partners will be highly valuable. One big challenge is that we don't have the ability to locally train the key health professionals urgently needed for the rollout of the program, such as doctors and pharmacists; all doctors and pharmacists practicing in Botswana obtained their degrees outside the country. A further complication is that the majority of doctors and pharmacists in the country are actually noncitizens and therefore work as expatriates; thus we compete for these professionals with the rest of the world, including developed countries, which often offer far better packages than we can afford as a developing country.

Training is a major component of our program because we have health-care providers who graduated in the early 1980s who were never trained to administer antiretroviral therapy. That means that we have to train each and every health-care provider in the system. You cannot say that you want only to train a certain number of people because of the prevalence of HIV in our popu-

lation. The HIV infection is going to be the single largest morbidity factor in our health system for years to come. So the largest group of patients who will be visiting our health facilities are going to be HIV-positive. If about 35 percent of the population is infected, health facilities will tell you that about 50 percent of the patients they see are going to be HIV-infected. If you are a doctor, it means that when a patient enters your consulting room there's about a 50 percent chance that the person is going to be HIV-positive. All of our health-care practitioners have to be prepared to deal with those patients.

As far as laboratory and testing, we know the special tests that we have to do as a result of this program: CD4 cell and viral-load testing. In addition, we have to put a lot of effort into our existing testing capabilities for other areas, such as hematology and chemistry. We need to strengthen our capacity to meet the increasing demand for these laboratory services.

Space procurement and upgrading is another area where the support of our development partners will be highly valued. The need for adequate facilities is challenging as well, but is a lesser challenge than that of adequate human resources. Human resources are the most dynamic of all the resources that we need, so it is the biggest ongoing challenge. This is so because of all the issues that I've raised during this presentation.

There are several challenges that we face as we move forward. One is the fact that most people in the country, including those who are infected, don't know their HIV status; we all know that knowing one's HIV status is a prerequisite for accessing all available care and support services for infected individuals. Because we began the ART program amid a mature epidemic, we're facing an initial burden of very sick patients. In our experience, there is a tendency for the general public to wait until they are very sick before they seek medical assistance. It takes far more resources to stabilize bedridden patients than those who are up on their feet. And, of course, there are also social and cultural factors that delay members of the public to seek treatment, such as going to the traditional practitioner first and only going to the hospital when

the condition has gotten worse. Fear and stigma remain the biggest challenges in terms of people accessing the HIV/AIDS programs that could help them; the result is that people only go for an HIV test very late and eventually access services late-if they survive long enough.

Another challenge to our national ART program in Botswana is the fact that there is limited civil society activity and NGO capacity. This means that we have to strengthen these organizations so that they can increase or expand their capacity and play a more meaningful role in the fight against the epidemic.

Adherence and drug security-another very important area. Initially, you are dealing with very few patients, but as you expand the program, non-adherence may be a consequence of drug security or lack thereof. There are people who may start sharing drugs with friends or relatives or even diverting ARV drugs to unintended markets. As a country, we have put measures into place, which we continuously review and adapt, to prevent these potential problems. It is critical that drugs are kept under secure storage, fully accounted for, with definite mechanisms and procedures for assessing adherence. The consequences of non-adherence in this particular program are far-reaching; if people don't adhere, you are going to get rapid development of drug-resistant HIV strains and thus start dealing with a completely new strain or strains of the virus. Once you start dealing with the new strains of the virus, your nationwide ARV treatment program is going to be challenged as the new strain spreads, and the new strains can start spreading very quickly.

Management and communications become very important in this scenario because you have to coordinate within the health system and within all the sectors that are involved in the provision of ART. You need to get everyone involved, including the private sector-even in terms of seeing how the private sector can be brought on board to play that part, because in this program you need a multi-sectoral approach; you cannot leave it to the Ministry of Health. It has to involve everyone if you are to reach out to all the people who need to be put on this program and cater for

all their needs, some of which may be outside the mandate of the Ministry of Health.

Capacity building is critical. Ironically, you start with less experienced people, but as they gain experience suddenly they're able to enroll more patients in treatment within a short time. Then it reaches a phase where your capacity to treat patients is saturated. If you don't augment that capacity as you proceed, your patient enrollment is going to stagnate, which may create problems. As you augment capacity, it picks up again. All sites tend to experience the same problems, and our experience is that there is no gain in starting one site at a time once you have passed the pilot phase.

Initially, the sickest patients come first, but it takes a lot more time to stabilize a bedridden patient. In terms of cost, we found that it takes at least three times more resources, especially human resources, to stabilize the sickest patients. So it is important that while you are attending to the sickest patients, you also look at those who are still up on their feet so that you can enroll those who are healthy and maintain them in a productive state while you're also addressing those who are bedridden. If you don't do that, you will face a constant stream of very sick patients and you won't be able keep up with the epidemic.

Another issue that is often viewed as controversial is confidentiality. We think that if you are to address this problem comprehensively, you need to look at routine testing. When we talk of routine testing, some people think that we mean mandatory testing. But we are simply saying that if, for example, a patient comes to your clinic or consulting room and has a sexually transmitted infection, in Botswana that means that there's a much greater chance of that person being HIV-positive. So you need to talk to the patient about getting an HIV test. You want to emphasize the importance of getting the patients tested while you are treating the infection that they already have. If someone comes to you with TB, you have to be aware that 75 percent of our patients with TB are HIV-positive. So it is not adequate management of that particular patient if you're not going to be thinking about HIV testing. We are not saying to do routine testing for the sake of doing it. Do

it so that you can provide for that particular patient; voluntary counseling and testing (VCT) centers and services will continue, as has always been the case. Once you institute routine testing, you can also test patients who are still up on their feet and stabilize them on antiretroviral therapy before they become seriously ill. And when you stabilize them on that antiretroviral therapy, you keep them productive. They can continue to provide for their families and contribute to the community, pay taxes, and therefore fund their own antiretroviral therapy. And that is one of the objectives of this program.

# *Patents and the Availability of Medicines in the Third World*

**Dr. Amir Attaran**
*Associate Professor, University of Ottawa*

We have removed Dr. Attaran's remarks at his request. The paper on which his talk was based, "How Do Patents and Economic Policies Affect Access to Essential Medicines in Developing Countries?" can be found in the May/June 2004 issue of *Health Affairs*. This paper is available for free download at www.healthaffairs.org.

# Drugs and Vaccines Against Global Diseases: The Next Generation

Moderator:
**Robert Goldberg, Ph.D.**
*Senior Fellow and Director, Center for Medical Progress at the Manhattan Institute*

Panelists:
**Karen Bush**
*Vice President, Anti-Bacterial Research, Johnson & Johnson*

**Dr. Emilio Emini**
*Senior Vice President, Vaccine Development, International AIDS Vaccine Initiative*

**Professor Frank Lichtenberg**
*Courtney C. Brown Professor, Columbia University School of Business Administration*

**DR. ROBERT GOLDBERG:** We've addressed one set of challenges to ensure that the next generation of medicines are available to patients in the developing world. We're now going to talk about other sets of challenges, and one of them, of course, is scientific.

We sometimes forget that there are formidable technical, biological, and chemical challenges to overcome before we can successfully design new drugs to combat emerging pathogens. The reality is that our stock of drugs for dealing with infectious diseases is sometimes diminishing not only in the developing world, but here as well. So we are very fortunate today to have with us Dr. Karen Bush, who is a Distinguished Research Fellow and Biology Team Leader for Antimicrobial Agents Drug Discovery at Johnson & Johnson Pharmaceutical Research & Development. She is also a fellow of the American Academy of Microbiology. Her recent work has included drug discovery efforts to identify new

drugs to treat multi-drug-resistant gram-positive bacteria, which includes not only cephalosporins, but a wide range of other agents as well. She received her B.A. at Monmouth College and her Ph.D. in chemistry from Indiana University.

**DR. KAREN BUSH:** My talk today will be focused on anti-infective drugs in general, primarily with regard to small molecules. In the HIV area, that would include the major HIV drugs that are currently being used throughout the world.

To begin, why or when does industry develop anti-infective drugs? (Here I'm including antivirals, as well as antibacterials and antifungals.) Unmet medical needs are one driving force, and we've heard a lot today about how AIDS and HIV present us with a number of unmet medical needs. There is also a responsibility to address certain public health issues that include large numbers of infectious patients. Also, if there is a limited number of drugs available to treat a certain indication, that would be a reason for us to look for new agents. Resistance is another major contributing factor. And one might develop new drugs if there are unacceptable risks with current available therapies.

Frankly, we can't ignore the fact that pharmaceutical companies also have legitimate commercial interests. There has to be some interest commercially in new products, although not every project or every product has to generate significant revenue. This is true in the area of HIV research and TB research. We are seeing pharmaceutical activity in these areas, and it's not only for commercial interests. Research in these areas is being driven by the fact that we have a social responsibility to address these unmet medical needs.

Resistance is the major driving force for developing new anti-infective agents. My career has primarily been focused on discovering new agents for resistant bacteria, but I also think that resistance drives the development of drugs in all anti-infective areas.

There are multiple approaches to drug development. One is to look at older agents that may be used in combinations. We

just heard that some drug companies need to be more proactive in developing drug combinations. We also can look for novel structures in known classes. If we have a fluoroquinolone that we know has some activity against tuberculosis, we may want to develop a quinolone that we know will have very high specificity in the area of tuberculosis.

If we have new drug targets, a wide range of possibilities is opened so that we can develop new agents that have new mechanisms of action. Historically, we developed drugs starting with antibiotics from naturally occurring classes, from natural products-for instance, the original penicillium mold that kills *Staphylococcus aureus*. In the past, we relied heavily on natural sources for new drugs. We looked at soil samples, plants, tropical rain forests, and marine organisms, and then we used synthetic chemistry to improve their properties.

In the twenty-first century, there is very little work being done in the natural product area. It's an area where many people think we have exploited all the good drugs at this point. What we have done is to move to genomics. We've looked for target identification for essential genes in bacteria, fungi, and viruses. We've used genetic and microarray analyses to identify genes that are required for growth, both *in vitro* and in animal models where we know that in some cases an essential gene, or a gene that is required for the bacteria to cause disease, may be expressed only if it's in a mammalian host.

We also look at novel targets. We try to identify drug targets that perhaps have not been used before to develop drugs. This is one way of circumventing resistance that may already be present for a known class of drugs. We then go to HTS (High Throughput Screening) assays. These are assays in which we test hundreds of thousands of compounds. There are compound libraries in some companies that contain millions of compounds for screening. At Johnson & Johnson, we are looking at assays in which we can test 384 compounds simultaneously in about two minutes. So there are many possibilities for finding new agents. We will use hits from our compound libraries to set up directed chem-

istry synthesis programs. We can also use molecular modeling studies and crystal structures to look at the way that compounds bind to a new target and try to identify ways to achieve tighter interactions with the new target that we're looking at.

If we look at the process of going from discovery through development, in the first series of discovery experiments we will identify a target, do HTS, do cell free assays, optimize the inhibitor, and then study the compounds in animal models. From this we get a lead series of compounds and go into a process at Johnson & Johnson that we call Drug Evaluation.

In the Drug Evaluation progression, we go through essentially the same process for every drug in every therapeutic class. We have to synthesize large amounts of material to be able to do toxicology studies at much larger concentrations-much larger doses of drugs than we normally use in a therapeutic setting. We want to find out the potential for toxicity in several animal species. We also want to see how a drug may be metabolized, how it may be broken down by a living system.

In our Drug Evaluation process at J&J, we go into Phase I clinical studies, in which we look at the way healthy human beings handle a drug. Do they excrete the drug in the urine? Does it get metabolized to something that is not closely related to the parent drug? How long does the drug remain in the body in its active form? A number of basic studies like these are done in Phase I.

If a compound at that point looks as though it has good safety and has good pharmacokinetics (the ability to stay in the body long enough to be therapeutically useful), we move toward the commercialization of the product. We must develop formulations that may be commercially acceptable. We then conduct Phase II and Phase III studies in infected patients and apply for worldwide approval in a number of countries. But as mentioned by Dr. Attaran, we do not try to get the drugs approved in every country, because that becomes cost-prohibitive.

If we look at the time frame involved and look at this in terms of the old way that we did things when we started from natural products, we begin with a soil sample, identify an active

compound, look at it in our in microassays, our petri dish assays, and see if it protected animals from infection. Those processes probably took two to three years. (However, when I was at Squibb, we developed the antibacterial drug aztreonam from a natural product, where we identified the natural product in April of one year and had the semi-synthetic compound in humans by the end of the next year. So it's possible to do this within a year if everything works well.)

Preparing large batches of drugs sometimes takes a very long time, depending on the difficulties of the synthesis (at least six months). We need to show safety in animals and then do our Phase I studies. In the earlier days of anti-infective drug discovery, we could do Phase I in approximately 50 to 75 patients. We could then go into our Phase II and III studies with 1,000-2,000 patients and then obtain regulatory approval.

In the past, under optimal conditions with a new anti-infective agent we could take an agent from lab to market in anywhere from four to eight years. If we now look at enzyme inhibitors as a starting point, we find that it takes a bit longer. We have to identify a target; then we have to identify and develop an assay for the enzyme. Rather than killing a whole organism as our first step in the process, we've added another few years to the whole process.

If we look at the total development time, the other places where we've added time to the current process are in our Phase II and Phase III studies. In a number of these studies, we're now seeing patient studies with 4,000 patients, and, in some cases, 8,000. There was an antibacterial drug, Ketek, which was recently approved, that required a Phase III study of 24,000 patients. This is because regulatory expectations for approval are becoming more difficult to satisfy. Overall costs for developing a new drug, as estimated by the Tufts Center for the Study of Drug Development, are around $900 million. Of these costs, about $500 million is related to clinical costs for an anti-infective agent.

However, if we look the anti-infective agents in terms of their success in the drug discovery and drug development process,

we see that anti-infectives actually have a high success rate compared with compounds that are developed in other therapeutic areas. Through the Phase I, II, and III studies, we see better approval rates for anti-infectives than we see for central-nervous-system, cardiovascular, or anti-cancer drugs.

Some of the reasons for this suggest that the anti-infective area has developed very good predictive tests in the early drug discovery process. We have good activity that is predictive in terms of in vitro testing and in our animal models. We have safety issues that are relatively well defined. In many cases, we're looking at drugs in classes that have already been developed and we have some idea as to what kind of safety problems to look for in our testing. We also have very well defined pharmacokinetic and pharmacodynamic models, in which we have a good idea as to how to select an appropriate dose very early in the process.

Hurdles can arise, however, if we are looking at novel agents in new drug classes and we don't know if we have specificity for particular targets. We may have nanomolar inhibitors, that is, very tight binding inhibitors, but these inhibitors may also be binding to other mammalian proteins. They may be responsible for toxicities that we didn't anticipate, or they may be broken down (metabolized) by the body in ways that we didn't expect. Dosing regimens for new compounds may be very different from what we had expected. Resistance, again, can develop to any agent. Many people don't realize that there is no agent for treatment of an anti-infective infection that will not at some point see resistant organisms.

Especially if we're looking at drugs that do not give us a lot of return on our dollar, relative development costs may be very expensive. We also have an evolving regulatory environment. Fortunately, in the AIDS area you are not seeing some of the hurdles that we face as we develop treatments for other conditions. But in other anti-infective areas and in other areas of therapeutics, we are seeing greater difficulties in satisfying the regulatory requirements. Often, regulators have zero tolerance for side effects and are focused on risk-benefit analysis.

In summation, we know that resistance has driven drug

development. We may identify new agents from various sources, but they in turn may generate new toxicities. And the drug discovery process can go anywhere from five to 12 years at costs that may exceed a billion dollars, especially if you're outside the anti-infective area. However, anti-infective agents do have advantages over other therapeutic areas in terms of development costs. The bottom line is that we will continue to need new agents. We can't just sit here with the ones that we have, because resistance is going to become more and more important with any drug that is introduced in any population.

**DR. ROBERT GOLDBERG:** Our next speaker, Dr. Emilio Emini, is currently the senior vice president and head of Vaccine Development at the International AIDS Vaccine Initiative, where he is dedicating his efforts to develop a vaccine to stop AIDS. Before he held that position, he was at Merck, working on the same heroic effort.

**DR. EMILIO EMINI:** Why are we focusing so much effort on creating an AIDS vaccine? I'm sure that everyone here today knows the numbers, but I want to emphasize once again that this epidemic is absolutely frightening. As of December 2003, it was estimated by UNAIDS that 40 million people worldwide are living with HIV and AIDS, 2.5 million of whom are children. In 2003 alone, there were approximately 5 million newly infected individuals and 3 million deaths worldwide from AIDS. The distribution of the infection is obviously well known to all of you. It is particularly striking in countries of sub-Saharan Africa, but with growing epidemics and growing incidence and prevalence in some other populations, including the Indian subcontinent, Southeast Asia, and China. There is no part of the globe that is untouched by this disease. This is an issue that affects the human population worldwide; by definition, therefore, none of us is free from the risk of potential HIV infection.

The most important statistic is that there are an estimated 14,000 new AIDS infections that occur in the world every day.

Between the time you got up this morning and the time you will go to bed this evening, 10,000 to 14,000 individuals will have been newly infected with the virus. And in spite of all of the talk that we heard this morning about the importance of antiretroviral therapy, the only way to stop this epidemic, as has been the case with every infectious disease in human history, is the development of a successful vaccine. Unfortunately, the development of a vaccine for HIV infection has not been an easy task and will not become an easy task anytime soon. Vaccine development will require not just extraordinary scientific resources but also substantial social and political will.

To summarize the last 20 years of research in this field: When a viral particle infects a cell, the cell undergoes a series of biochemical reactions and in the end produces new viral particles that then go on to establish a new infection elsewhere in the body. In the context of an adaptive immune response, a typical immune response against any viral infection, there are essentially two arms to that immune response. There is an antibody component, which typically binds to viral particles and neutralizes them and prevents them from infecting uninfected cells. And there is what is referred to as the "cellular immune response," is a complex interplay of immune system cells that are essentially responsible for eliminating infected cells. Normally, this is a very potent immunological reaction whereby viral particles are neutralized and infected cells are eliminated, cutting off the cycle of viral infection at its root. This is what occurs with most acute viral infections, such as an influenza virus infection. But in the case of HIV infection, the immunological reaction is sabotaged: once an individual is infected with the virus, the infection essentially becomes a long-term persistent infection.

There are a number of reasons for this, because the immune system is still, to a certain extent, functional during the course of the infection. One of the primary reasons is that neutralizing antibodies against the virus are very poorly effective. The virus has evolved to thwart the antibody response, and it has done so by a number of different means, which I won't go through in detail.

But a substantial part of it has to do with the surface proteins on the virus, called "glycoproteins."

These proteins are like little knobs on the virus's surface and represent the primary structures that the virus uses to bind to new host cells and establish infection. Typically, antibodies would bind to these knobs and neutralize the virus, but the virus has modified these structures in such a way as to largely-not totally, but for the most part-defeat the antibody response. There are some potent neutralizing antibodies that have been isolated against the virus, but they are not consistently produced in the context of a virus infection. This is a tremendous hurdle, so most of the effort over the last six years has focused on the cellular immune response.

The importance of the cellular immune response in controlling HIV infection has become, over the last six years, much better appreciated than at any time previously, partly because of the development of novel technologies that have permitted a better quantitative assessment of the cellular immune response and a better understanding of how the cellular immune response actually interacts with the virus and infected cells in the context of the infection.

The degree and extent that the cellular immune response can have substantial long-term consequences. When HIV first infects an individual, the infection is usually characterized by a period of very high viremia. Viremia refers to the numbers of virus particles circulating within the infected host. But this acute phase of the infection usually resolves (in the vast majority of cases) into a persistent infection, which is characterized by a much lower level of circulating virus. This lower-level infection can persist for a long period of time, and gradually increases as the infection progresses over the subsequent months and years.

The important thing is that the acute phase does resolve. It is now well understood that one of the primary reasons, if not the primary reason, for the resolution of the acute phase of infection is the cellular immune response directed against the virus. This is a sort of victory, but in the absence of an effective neutralizing antibody response, it is very difficult to actually clear the virus from

the host. Still, the viral infection can be kept under control by the cellular immune response for some time.

The interplay between the immune system, particularly the cellular immune response, and HIV infection is established very early on during this acute phase. And that interplay between the virus that is infecting the host-and indeed, infecting the immune system itself-and the desire of the immune system (so to speak) to eliminate the viral infection influences how rapidly the initial viremia in the acute phase resolves and also substantially influences the level of virus that is expressed during the persistent phase of the infection.

It's well known that the level or degree of virus replication during the persistent phase of the infection directly influences the progression to actual clinical disease, which is why, for instance, antiretroviral therapy works so well. When it is used effectively, antiretroviral therapy restricts virus replication during the persistent phase and therefore lengthens the time to progression of clinical disease.

Based on what we now know about the relationship between the immune response and persistent HIV infection, the objective of vaccine development is focused on the elicitation of a cellular immune response in such a way so as to alter the balance that is established during acute viremia primarily in the favor of the cellular immune response. This won't necessarily prevent infection, but what it might do is to substantially lower the amount of virus that is present during the acute phase, resulting in a much more rapid resolution of the acute phase, and at the same time result in a much lower virus load and in a much lower level of virus replication during the persistent phase. This would, for all practical purposes, duplicate the effects of antiretroviral therapy by producing a prolonged period prior to the actual development of clinical disease.

This may sound like a draw, but it isn't. Because even more important than delaying clinical expression of disease is disrupting the epidemiology of the virus. That is, by significantly lowering the initial viremia, we can prevent individual transmission even after

initial infection. There is a growing body of convincing evidence that most of the transmission that occurs from host to host actually occurs primarily during the acute phase of the infection. And there is a clear relationship between the amount of virus that is present within the infected individual and the actual probability that a subsequent infection will occur. By substantially lowering the amount of virus that is present during acute phase and restricting the period of this acute phase, we should (at least in theory) have a substantial positive effect in lessening the likelihood of transmission within a highly endemic population.

To reiterate, the objective with a vaccine is to provide an advantage to the immune system during the early, acute struggle with the virus. This will, we hope, allow for long-term suppression of virus replication, certainly with beneficial individual consequences, but also beneficial epidemiological consequences. If we can inhibit the amount of circulating virus during the acute phase, we can lessen the likelihood of transmission from host to host.

Establishing a cellular immune response is not a straightforward matter. What one needs to do is deliver genes from the HIV virus to certain specialized cells of the immune system, called "antigen-presenting" cells. To do this, one has to use what is called a "vector-delivery system." Novel vectors (taxis for the immune system, if you will) are used in which genes expressing HIV proteins of interest are stitched in by molecular means; those vectors are then inoculated into an individual. Once inoculated, the vectors deliver these genes to the appropriate antigen-presenting cells.

Vaccine development is an effort that has taken on quite a large commitment from a number of academic, government, private-sector, and nongovernmental organizations. There is a very large number of vaccine vector-delivery systems. These range from what is known as naked DNA, which is simply DNA without any covering, to various poxvirus delivery systems, to so-called alphavirus replicons. Several of these are undergoing either early- or late-stage clinical trials. Replication-defective adenovirus is a particularly effective delivery system. Adeno-associated viruses are another interesting vector-delivery system that is currently in study,

and a whole series of others are being studied pre-clinically.

The nature of vaccine research is such that one can learn only so much pre-clinically. In the end, it is only through human clinical study, looking primarily for safety and for immunogenicity, that we can define whether any of these vector-delivery systems holds any promise. It's a very long process, and it requires a great deal of expense and commitment to makes one's way through all these iterative processes, but we are doing it.

Will such a vaccine-elicited cellular immune response work? A study that was published several years ago was one of the first studies that actually indicated that elicitation of such a cellular immune response could be effective (this was a monkey model of immunodeficiency virus infection). In that study, the monkeys that weren't immunized expressed very high virus-load levels that subsequently resolved. A number of these monkeys go on to die a number of days subsequent to infection. On the other hand, of the three animals that were immunized (in this case, with a replication-defective adenovirus vector that expressed an appropriate immunodeficiency virus gene), a good cellular immune response was established prior to the challenge with infectious virus. After infection, the animals' immune systems established a favored balance between the immune system and the virus. This was manifested by a much lower virus load and viremia, as well as a much lower virus load during the persistent phase of the infection.

It has now been four years since these animals were infected. The immunized animals all remain healthy. They're still infected, of course, but virus loads were substantially lower during the acute phase, and virus loads have remained lower during the persistent phase of the infection.

So there is some hope, but we are still far from actually determining whether this hope is going to translate into an effective vaccine in the context of HIV infection in humans. At the moment, the vaccines-at least, those that are focused on cellular immune responses-are not likely to prevent infection, but they can have some potential beneficial effects. But the primary question is, how effective will they be in mitigating this initial virus infection in

the humans? Also, how long will this mitigated infection be maintained? If they're found to be reasonably effective, can a vector-delivery system be developed for widespread use in the developing world, where HIV infection is the most significant? Will the genetic diversity of the circulating virus thwart the vaccine's effectiveness?

These are important issues that are not addressed in any of the pre-clinical studies simply because they cannot be. The genetic diversity of circulating HIV is very substantial. By definition, a vaccine is always going to be genetically restricted relative to the genetic diversity of the circulating virus population. Very careful clinical studies are ultimately going to have to be designed to address this question. There is also the problem of whether the vaccine will actually drive genetic escape, which is a hallmark of HIV infection.

So this is our research agenda for the remainder of the decade, because that is how long this effort is going to take. There are a number of ongoing studies, but there's a lot of work that still needs to be done to render them practical should the whole concept work. I would argue that current efforts in this regard are certainly inadequate.

A critically important aspect of what needs to be done between now and the time that a large-scale efficacy trial is conducted is that efficacy trial sites have to be prepared in which the molecular epidemiology of the circulating virus is very well understood. Again, efforts in this regard to date have been inadequate. This is going to be needed in order to properly interpret the results of trials that are based on uses of genetically simple vaccines, which by definition will always be simple relative to the virus that's circulating.

It's critical that the field focus on the effort to understand the interplay between the virus and the immune system so that those earliest events, which we're attempting to influence with the vaccine, are better understood so that we can then ultimately design better vaccines. It's critical that the field enhance and focus the effort to design immunogens that will consistently elicit potent vi-

rus-neutralizing antibodies, because in the end, unless this latter goal is accomplished, I suspect that we're not going to produce a vaccine able to prevent infection. Preventing infection is not an impossible goal, but it's a very hard one that's going to continue to require a lot of time and effort by researchers in the field.

So what's our human challenge or policy challenge? The process of scientific discovery, as we all know, is inherently individual. But the magnitude and difficulty of this problem goes well beyond any individual person or any institution or, for that matter, any individual country. Coordination, focus, and cooperation-particularly, scientific cooperation-are absolutely essential. If we continue to say, as many people do, that such cooperative scientific endeavors can't happen, then they won't happen.

It is very important not to have that attitude and instead to say that, yes, it is not an impossible task and we will proceed; cooperative scientific endeavors are critical, and they have to happen. What we do in the next several years, given the magnitude of the problem, will determine whether a vaccine becomes available in the next ten years or whether this is a problem that we will have to leave to the next generation. If we fail for reasons other than the purely scientific, then history will not-indeed, should not-be a kind judge.

**DR. ROBERT GOLDBERG:** Our next speaker is Professor Frank Lichtenberg, the Courtney Brown Professor of Business at Columbia University. Professor Lichtenberg is one of the world's leading experts on the role that new pharmaceuticals have on lengthening and improving human life and the underlying factors required to encourage investment in medical innovation.

**PROFESSOR FRANK LICHTENBERG:** The previous two presentations were about science; mine is focused on social science. The U.S. government and American pharmaceutical companies have embarked upon a new plan to rapidly develop and distribute a low-cost and convenient combination pill to treat HIV in the developing world. The goal is to provide people in poor

countries with the same quality medicines available to Americans at a much lower cost. I'd like to discuss the economics and a bit of the politics that this project entails.

As you are no doubt aware, the pharmaceutical industry is perhaps the quintessential knowledge-intensive industry. There are others, such as software and entertainment, but what all these industries have in common is that they are characterized by extremely high fixed costs and very low marginal costs. In other words, it's very, very expensive to get the first pill on the market; we can easily assume a cost of about 800 million or a billion dollars to develop the new drug, shepherd it through clinical trials, and finally get it approved by the FDA.

This process is mind-bogglingly expensive, but once you've manufactured and marketed the first pill, the cost of producing the second through the millionth pill is quite low. The industry is characterized by very low marginal costs and very high fixed costs. That creates fundamental economic issues that distinguish it from other kinds of commodities, such as pork bellies or timber. It also raises issues about pricing.

Let me suggest two possible kinds of pricing: uniform pricing; and nonuniform pricing, or price discrimination. Uniform pricing is quantity pricing: if you go to McDonald's and buy ten Big Macs, it will cost you ten times as much as if you buy one Big Mac. The total expenditure is proportional to the number of units that you buy. Suppose that there were uniform pricing for HIV medications: everyone is going to pay the same price for HIV medication. Then the question is, under uniform pricing, are we going to have a very low price-perhaps a price equal to marginal cost, the manufacturing cost of the drug and maybe a bit more-or are we going to have a high price? A low price, one roughly equal to the cost of production, does allow broad access to the drug, but it does not allow firms to recover their development costs. If, in fact, it only costs a dollar per pill to manufacture, but the company had to spend a billion dollars to develop the drug in the first place, if the price is only a dollar then firms will not recover their development cost.

In the long run, this pricing will undermine the development of new drugs. Firms are not going to want to develop drugs if they cannot recover their development costs. My research has shown that development of new drugs has large social benefits, including longer life, higher productivity, and reduction of other medical costs such as hospitalization bills. So it would be unfortunate if firms exited from the development of new drugs because of inability to recoup development costs.

The other option would be not having a price equal to marginal cost. What if we have a higher price-a price well above marginal cost? The good news is that it allows firms to recover their development costs; however, it inhibits broad access to the drug. If it only costs a dollar to manufacture a pill but we're going to charge $100 per pill, then some people are going to be denied access; that's inefficient as well as very unfortunate for those individuals.

Under uniform pricing, there is an inevitable trade-off between innovation and access. You could have a very low price that is good for access but decreases incentives to innovate, or you could have a higher price, which produces good incentives but less access.

The question is, can we have our cake and eat it, too? Is there any way that we could enable broad access and encourage innovation at the same time? Since I'm an economist-and we all know that economics is the dismal science-you probably think that I'm going to say no, we can't have our cake and eat it, too. But I'm an optimistic economist. So I'm going to say yes, in theory we might be able to have it both ways. We can encourage broad access and still promote innovation. The way that we can do that is to have price discrimination.

The basic idea of price discrimination is that we're going to charge a low price to consumers with a low ability to pay, such as people in sub-Saharan Africa, and a higher price to consumers with a higher ability to pay, such as Americans and people in other industrialized nations. By charging different prices to different populations, we can in principle have both broad access and innovation.

It's useful to think about there being at least three stakeholders here. One stakeholder is consumers in low-income countries in Africa. A second stakeholder is consumers in high-income countries such as America. And the third stakeholder is the manufacturer, the pharmaceutical industry. In fact, there is a fourth stakeholder we ought to consider, and that is future generations of patients. We should think not only about the needs of today's consumers but also about future consumers.

But for the moment, let's just think about the three stakeholders: low-income consumers, high-income consumers, and manufacturers. It turns out that one can show that price discrimination can be win/win/win. That is, all three stakeholders can be made better off than they would be in a world in which price discrimination was impossible, that is, if manufacturers were forbidden from charging a higher price in the United States than in Africa. In that case, it might be that pharmaceutical firms would not find it profitable to develop HIV drugs at all, and that would harm consumers in low- as well as high-income countries, and it wouldn't be so good for the industry, either. So while it is not always true that price discrimination will benefit everyone, it is certainly possible. Examples exist in which everyone can improve by the market's ability to offer price discrimination.

The fly in the ointment, of course, is that high-income consumers may resent paying a higher price than low-income consumers. If I see that a drug is selling for $5 in Africa and I'm an American AIDS patient paying $5,000 for ART, that could very well strike me as annoying and unfair, even though perhaps it is the essence of fairness, since I have a greater ability to pay than people in Africa. However, people may resent these price differentials and may demand the same prices that people in much less affluent countries receive.

The problem with attempts to eliminate price differentials, if they are successful, is that they hurt the fourth stakeholders I mentioned earlier: future generations. Uniformly low pricing today may undermine innovation tomorrow. If everyone tries to get the low price now, making price discrimination impossible, the

whole win/win scenario unravels.

One could interpret the current American debate on drug reimportation as a rebellion against price differentials. American consumers see that prices are much lower in Canada than they are in the United States. They say that we want those low prices, too, and it is becoming increasingly difficult to maintain international price differentials. If it becomes impossible for the industry to charge different prices in different markets, that could unfortunately have the effect of reducing future investment in research and development.

But as Karen Bush said earlier, we need to develop new drug agents. We can't rest on our laurels now, because the pathogens aren't going to stop evolving or developing resistance. We're not done yet because we face too many challenges. We must continue to innovate, and if price controls strangle innovation it would be a great tragedy.

So to engage in price discrimination, which may be in everyone's best interest, there are several prerequisites that have to be met. One is that manufacturers have to be able to distinguish between consumers with a low ability to pay and a high ability to pay. In this case, that's not much of a problem. It is fairly obvious that people in Africa have a much lower ability to pay than Americans do. But there's a second condition required for price discrimination: the absence of what economists call "arbitrage." Arbitrage is the ability of some people-for example, middlemen-to buy AIDS drugs cheaply in Africa and resell those drugs at a higher price in America or Europe. If reimporters have that ability, it will undercut the manufacturers' ability to engage in price discrimination. Essentially, for price discrimination to be successful, companies must be able to prevent the resale of commodities from low-price markets to high-price markets. Last, but far from least, intellectual-property protection is important for enabling price discrimination to occur. Obviously, if a generic company can violate a patent and sell a patented drug for significantly less than the developer, it will also prevent price discrimination.

If our program is to develop rapidly and distribute a

low-cost and convenient combination AIDS drug—which clearly has the potential to benefit the current generation of citizens in developing countries—we can do that without jeopardizing the interests of future generations in low- and high-income countries. But that requires us to continuously remind the public that price discrimination is not a corporate crime. In reality, it is good economics and good medicine.

# *Luncheon Address*

**Dr. Mark Dybul**
*Office of Global AIDS Coordinator,*
*U.S. Department of State*

**DR. ROBERT GOLDBERG:** Our final speaker this afternoon is Dr. Mark Dybul, who is currently on detail from the Department of Health and Human Services as the Deputy Chief Medical Officer for President Bush's Emergency Plan for AIDS Relief. At HHS, he is the Assistant Director for Medical Affairs, National Institute for Allergy and Infectious Diseases. He is the co-Executive Secretary of the HHS HIV Therapy Guidelines for Adults and Adolescents and has taken the lead for HHS for President Bush's initiative to prevent mother-to-child transmission of HIV in Africa and the Caribbean.

He is a former member of the World Health Organization's writing committee to develop global HIV therapy guidelines, the principal investigator for clinical and basic research for U.S. and international protocols with an emphasis on HIV therapy. He received his B.A. and M.D. from Georgetown University, completed a residency at the University of Chicago, and a fellowship in infectious diseases at the National Institute of Allergies and Infectious Diseases. He's here to speak about the President's Emergency Relief Plan for HIV in the developing world. We're very honored and pleased to have him as our speaker. Please help me in welcoming in Dr. Mark Dybul.

**DR. MARK DYBUL:** I'd like to thank the Manhattan Institute for having me here today. It's a great privilege to represent Ambassador Randall Tobias, the U.S. Global AIDS Coordinator, and to represent the President's Emergency Plan.

President Bush has embodied the leadership, compassion, and commitment of Americans in two international HIV/AIDS

initiatives. In less than two weeks, it will be the second anniversary of the announcement of President Bush's international mother-and-child HIV prevention initiative. This was a five-year, $500 million initiative. The goal was to reach 1 million pregnant women annually in 14 focused countries in Africa and the Caribbean and to reduce mother-to-child transmission of HIV by 40 percent.

The 14 countries that are targeted as focus countries represent 50 percent of global HIV infections and 70 percent of infections in Africa and the Caribbean. As we reach women and protect babies, a fundamental pillar of the president's initiative is to build capacity so that we can move from short-course Nevirapine treatment to full therapy for mothers, children, and fathers; to protect the entire family unit and to prevent a generation of orphans.

We are moving quickly with this initiative. We will soon have the report from the first piece of the initiative, which represents $133 million since October 2002. The results will be out next week, and we believe that we have done a good job of beginning. We are on the move and are developing more successful programs.

The leadership, compassion, and commitment of the United States were demonstrated through the creation of this initiative. We had to act in the face of 2,000 new HIV-infected babies born every day. But not only are women, children, and their parents and their immediate families suffering; each day, 8,000 deaths occur because of HIV/AIDS, and there are 14,000 new infections. In the words of President Bush, "Global treatment of HIV is rooted in the simplest of moral duties. When we see this kind of preventable suffering, when we see a plague leaving graves and orphans across a continent, we must act." Therefore President Bush launched his Emergency Plan for AIDS Relief in his State of the Union address in 2003. This initiative demonstrates leadership by compassion and action. It is the largest initiative in history dedicated to a single disease. It budgets $15 billion over five years, $10 billion in new funds.

These are staggering amounts. In 2003, before the first

appropriation for the President's Emergency Plan, the United States, representing the compassion of U.S. citizens, was already providing half of the global donor aid for HIV/AIDS. In 2004, as a result of the President's Emergency Plan, the United States will provide twice as much as the rest of the world donor community put together. The United States is committed to turning the tide against HIV. But these dollar amounts, as impressive as they are, are not enough. Action and results are necessary, not commitment of dollars. What the dollars represent are the goals that the president outlined in his State of the Union address: to prevent 7 million new infections; to care for 10 million HIV-infected persons and those who are affected by AIDS, including orphans and vulnerable children; and to treat 2 million HIV-infected persons.

This initiative builds on the mother-and-child initiative that we just discussed. It is focused on the same 14 countries, with a 15th country to be identified. It's a pleasure to be in the room with representatives from two of those countries, Kenya and Botswana, who spoke this morning. This initiative has moved at an incredibly rapid pace. As I mentioned, the mother-and-child results will be available next week. Within days of the first appropriation for the President's Emergency Plan, we were actually treating people in rural Uganda by motor scooter-getting out to their homes by motor vehicles to deliver therapy in their homes.

Within weeks, we had opened and started to deliver treatment in multiple sites in several countries, whether it be for a faith-based site in a slum in Uganda, or in a site in rural Kenya. We had already begun treating people weeks after the appropriation. In May and June of this year, we finished plans for many more treatment sites. Drugs have been ordered. In the first year of the president's initiative, we expect to provide therapy for 170,000 people, doubling the number of people on therapy and almost doubling the number of people on therapy in Africa.

An important thing that we are doing now is ensuring access to high-quality therapies. Several weeks ago, Secretary of Health and Human Services Tommy Thompson, along with Ambassador Randall Tobias, announced the U.S. government strategy

allowing drug companies to come in through the Food and Drug Administration to receive full or tentative approval for drugs through a rapid approval process, within two to six weeks of an application being received by the U.S. government.

We are taking as many steps as we can, in many different directions, to ensure the success of the initiative. We are acting with the international community, which is necessary if we are to fight this disease. Part of the President's Emergency Plan is a billion-dollar pledge for additional resources for the Global Fund, bringing the total pledge from the United States to $1.6 billion. The U.S. government was the first donor to the fund. It was the first donor to give the second gift to the fund. We remain by far the largest contributor to the fund, contributing 40 percent of resources available to the fund.

As you know, Secretary Thompson is chairman of the fund, demonstrating the clear commitment of the U.S. government to the success of the fund. Under Ambassador Tobias, we are working at the headquarters and at country levels to ensure that we are collaborating with our international colleagues. We work with the WHO, UNAIDS, the World Bank, and UNICEF.

I understand that there are high-level representatives here today from the World Health Organization, UNAIDS, and other international communities, and we're delighted to be partners with you. We're working closely with the WHO to expand therapy for HIV and tuberculosis. We were one of the sponsors several weeks ago in Washington of the UNAIDS-initiated proposal for "three ones"—one national strategy, one coordinating mechanism, and one mechanism for monitoring and evaluation. We are taking the lead in ensuring that we have one uniform monitoring and evaluation procedure so that we're not burdening our partners and other countries with having too many people to respond to for accounting purposes. This is a very important step.

We continue to work with our partners and are proud to be a member of the international community fighting this global disease. More important, as we coordinate globally we are focusing our efforts on localities. Local efforts are critical to our success.

We must develop-and the president says this every time he speaks-a sustainable program. If we reach all our planned goals in five years but do not develop local medical capacities to respond to HIV in the countries where we offer aid, we will have failed.

In our focus countries, our HIV/AIDS teams for the U.S. government are building on 20 years of active partnerships. The United States government has been on the ground through USAID, through the Centers for Disease Control and Prevention, through the Department of Defense, and through the Department of Labor for up to 20 years in the focus countries. The reason that the focus countries were selected was because we were already on the ground there. These were places where we could move quickly because of the relationships we had developed with our important partners in those countries, beginning with the ministries-the Ministry of Health, the host government, as well as our other partners on the ground. We have now, under Ambassador Tobias, brought together all those pieces of the U.S. government under the U.S. ambassador in a coordinated fashion to ensure that we can coordinate our efforts as we interact with our partners on the ground.

We must recognize that we are fundamentally guests in the host countries in which we work. As we move along, we will coordinate our strategies with those countries to develop sustainable programs. Drugs alone will not solve this problem; expanded health-care capacity is necessary. As with the mother-and-child initiative, capacity is one of the most important pillars of our initiative.

We will serve the local governments in whatever ways that we are able, within the limits of our legislation, to help develop capacity in ways that are important. This includes training at extensive levels, twinning where you have institutions in the United States or Brazil, in the case of Mozambique or other places, funded by the U.S. government to help develop capacity so that we can remove ourselves from the actual performance of care. Volunteers in the early going may be important to help with training. We do not envision American volunteers doing the work in Africa and

the Caribbean. This is fundamentally an African disease and a Caribbean disease, not a U.S. government disease. So we are working to ensure that we help develop the hands and train the hands on the ground to perform the work. We have instituted, with our first round of contracts, contractual requirements that all our partners develop indigenous capacity. If they do not do so-even if they achieve their prevention, care, and treatment goals-we will reduce their funding.

We are moving very quickly: within four weeks of receiving an appropriation, we put $350 million into the hands of providers. We have submitted to Congress our intent to expand the additional $500 million that is available for the focus countries, bringing the total to $850 million available to service providers by September 30 of this year. There will be a total of $2.4 billion around the world where the emergency plan is active. We are very proud of that, but we need to work together to move with our international partners and-most important-with our local partners to ensure that the job is done. As Americans, we should be very proud of the bold leadership of President Bush and Congress on behalf of the citizens of the United States in this compassionate effort. We now look to the world to work with us. We are doing our part. We call on others to join in our efforts, to work together, to work compassionately, and to help the host nations turn the tide against HIV/AIDS.

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