So good evening everyone on this beautiful spring day. My name is Pat Thomas. I'm the Knight Chair in Health and Medical Journalism at the Grady College of Journalism and Mass Communication. And I want to welcome you to the conclusion of season three of the Voices from the Vanguard Global Diseases Lecture Series. You know, I see a lot of familiar faces out there. And we really appreciate those of you who have been impelled to come by your teachers, or by your individual interest in these important topics. I guess now we know that works. These lectures are a collaborative venture between Dan Colley, the director of the Center for Tropical and Emerging Global Diseases at UGA, who's down in the front row, and my programs. And we've just had a great time doing them, and we really appreciate you joining us for them. Remember please, that we have a reception to follow the lecture, where you get a chance to talk with our speaker in person. Now tonight it's a real pleasure for me to introduce Doctor Annie DeGroot to you. The program notes will tell you that Dr. DeGroot was educated at Smith College, and at the Pritzger School of Medicine at the University of Chicago, and that she trained as a physician and a researcher at some of the top places in the country, Tufts New England Medical Center, and the National Institutes of Health. And you know that she teaches, and...
research in Providence, Rhode Island, at Brown,<br/>and now shifting to the University of Rhode Island campus there.<br/>And you know that she founded a biotech company, and an international HIV vaccine foundation.<br/>Just the typical kind of slacker we like to have for these lectures.<br/>But the inside front cover of a program is not near big enough to tell you all the things that you might want to know about this fascinating woman, who has been committed not just to science, but to social justice for many, many years.<br/>And I'm pleased to have known her for about the last ten of those years.<br/>One of the things that you won't really read in any detail here is some of the programs that she's done domestically and internationally, that have to do with people who are pretty much disenfranchised in our world.<br/>And I'm thinking here about some of the health programs for incarcerated people that Dr. DeGroot has been working in for the past ten years.<br>Along the way she founded a newsletter and a continuing medical education program to help the healthcare providers who work in prisons do a better job taking care of people with HIV and AIDS.<br>And this little newsletter which she started actually has some fourteen thousand subscribers around the country.<br>And she told me over lunch today about to lose its funding, because you know, about to lose its funding, because you know, people in prison, they have nothing to do with us. Except the important thing to remember is that most people in prison come out of prison, and prison is not Las Vegas, and what happens there doesn't stay there, and it does have an impact on the rest of us.
On a different front, an entirely different front, Dr. DeGroot founded the GAIA Vaccine Foundation, which she started to help create a globally relevant HIV vaccine. Not just a vaccine that would be helpful to those of us in industrialized countries, but a vaccine for the world. Furthermore, she wants to do this in a non-profit model, so that the vaccine not only exists, but is accessible to the people who need it. This is actually not a crazy idea. Back in 2006, the first ever lecturer in the first Voices from the Vanguard lecture series was Victoria Hale, the founder of OneWorld Health, a non-profit pharmaceutical company. So we know that this can be done. Dr. DeGroot is going to talk to us about why it would be an enormous mistake, even given all the bad news you've been reading about HIV vaccine development, to abandon the quest for such a vaccine. Dr. DeGroot. Well it's wonderful to be here, and the weather is gorgeous, I can't believe you're inside. So thank you for being with me tonight. I hope that I will inform you and inspire you, mostly I want to inspire you. I think it's important for all of us to be active, and to demand improvements in healthcare for everyone, including people who have very limited access, whether they're here in the United States, or whether they're in Africa, as this picture so graphically shows us. So I'm going to talk about why we shouldn't abandon the ship, and we should stay on course, and we should believe that
there can be a new HIV vaccine.<br/>
And I'm going to talk a little bit about the work<br/>that we're doing to develop such a vaccine,<br/>and kind of where we are in the process.<br/>So first a frame, the picture I think<br/>you're familiar with the concept<br/>that AIDS is killing a lot of people,<br/>in 2007 2.5 million people.<br/>Five million people got infected, so<br>more people are being infected every year than people<br/>who are getting killed, which means that<br>of course the global epidemic is expanding.<br/>And of those, and if we continue this<br/>in this course, there'll be a hundred<br/>and twenty million people dying of AIDS in<br>2010, in one year there will be a hundred<br/>and twenty million people dying of AIDS.<br/>And that's a pretty scary figure.<br/>The other thing that's very concerning is that there are countries<br>that are disproportionately affected.<br/>I'm sure from Jim Kim you heard that Africa and<br>Asia are the hardest hit, with 70% of the people<br>in the world living in the sub Saharan area of<br>the world, 70% of the people living with HIV,<br>living in sub Saharan Africa, and 95%<br>living in developing world countries.<br/>So what else is going on,<br>children are being affected.<br/>And if you go over to Africa, and you meet<br>the kids who are bearing babies at the age<br>of twelve, you can understand why they<br>might also be at risk for HIV infection.<br/>So seven hundred thousand children, aged<br>twenty-four or younger became infected with HIV<br/>in 2007, sorry age fourteen or younger.<br/>And of those, over 90% were babies.<br/>And this is actually one of the great tragedies<br>of HIV, that is that HIV positive mothers<br>who know that they're infected are
at risk of transmitting HIV to their babies.<br>
And if we know they're infected, there's actually means to prevent that from happening.<br>
We know that that's true, because in the United States the number of children who are actively infected with HIV as babies is dropping to near zero.<br>
But more than six hundred thousand babies are acquiring HIV infection in Africa, and that is a huge problem that's completely preventable.<br>
So by the end of 2007, the impact on children has been dramatic.<br>
Twenty million AIDS orphans, which is actually something that we will have to contend with, because how those children are growing up in the developing world is unknown.<br>
Who is going to be teaching them to become adults, what behaviors are they learning, how are they going to become citizens of this society.<br>
And that is something that has to be dealt with as a social disaster.<br>
All of this in the context of the fact that we have treatment for HIV infection.<br>
Treatment is cost saving.<br>
You probably know also from Jim Kim that when Brazil made a decision to break the patents on HIV drugs, and make their own HIV drugs, and spent the money to make those drugs, and distributed them to people in Brazil who were HIV infected, they actually came back and found out that after a few years they were saving money by treating people with HIV.<br>We know that we can save lives, and if you want to look at it in the most kind of cost effective sense, we can save money by treating people with HIV.<br>But the problem is that the need for treatment outstrips available funds.<br>So the need grows every year. You can see on this graph
here that the bar is going up.

<time begin="00:09:06.25">How much it will actually cost to treat people living with HIV infection is going up, whereas funding has remained relatively flat.</time>

<time begin="00:09:14.63">And when you put this actually in the context of other things that we spend money on,</time>

<time begin="00:09:20.42">we ask is this idea, this concept that everyone in the world should have access to treatment for HIV, asking too much.</time>

<time begin="00:09:29.04">Are we caring about something that is simply not achievable on a dollars basis.</time>

<time begin="00:09:34.47">Well it has been projected by Jeff Sax, a noted economist, how much it would actually cost to treat everyone in the world, if we were to make that decision.</time>

<time begin="00:09:44.45">And the total is 4.4 billion per year.</time>

<time begin="00:09:47.60">Is that a lot of money?</time>

<time begin="00:09:48.61">Well billion dollars sounds like a lot of money,</time>

<time begin="00:09:51.37">but in actuality we've spent already five hundred billion dollars in Iraq alone.</time>

<time begin="00:09:58.43">not counting Afghanistan, just talking about Iraq.</time>

<time begin="00:10:02.15">So when you put the numbers in context, you see that this is actually achievable.</time>

<time begin="00:10:06.13">It would cost twenty dollars per person in the United States, per year.</time>

<time begin="00:10:12.96">to treat everyone with HIV infection, and that seems like a totally achievable number.</time>

<time begin="00:10:18.91">for which we have no leadership, and it is really leadership that we need.</time>

<time begin="00:10:24.06">The problem is that we don't have those medications, they're not getting out to the people who need them, and this young child who lives in Sikoro, which is where we're working in western Africa, has really no clinic to go to.</time>

<time begin="00:10:33.73">which is where we're working in western Africa, has really no clinic to go to.</time>

<time begin="00:10:38.92">She has no doctor to go to, she has no medicine that's accessible to her.</time>

<time begin="00:10:44.50">She in fact, if she were to become sexually active doesn't have access to condoms.</time>
because in west Africa to<br/>
purchase a condom costs as much<br/>
as a meal, and most people choose to<br/>
eat.<br/>
So her hope of preventing herself<br/>
from getting<br/>
HIV infected in the future becomes slim to none.<br/>
So a vaccine is really the<br/>
best hope for HIV infection.<br/>
It is something that you could<br/>
give to people, and prevent,<br/>
theoretically, HIV for the rest of<br/>
their lives.<br/>
It could save millions of lives.<br/>
Even a vaccine that's not completely<br/>
effective.<br/>
For example, what's shown here is if<br/>
you had a<br/>
30% effective vaccine you could actually save<br/>
5.5 million lives.<br/>
A 70% effective vaccine would save<br/>
twenty five million lives, oops,<br/>
my glasses, twenty eight million<br/>
lives.<br/>
So you can see, even with a vaccine<br/>
that's not 100% effective, we might actually be able<br/>
to save that little girl's<br/>
lives in Sikoro, Mali.<br/>
Now why does it take so long<br/>
to make an HIV vaccine.<br/>
We've known about HIV for years,<br/>
since 1983 as a matter of fact.<br/>
Why does it take so long.<br/>
In truth, as many of you sitting in<br/>
this audience who are biologists know,<br/>
it does take a long time, first to<br/>
discover the<br/>
pathogen, then to figure out what are the correlates<br/>
of immunity, what are the critical<br/>
antigens, how to make the vaccine,<br/>
how to formulate it, how to test it.<br/>
And we'll talk about that a little<br/>
bit.<br/>
Twenty five years is average.<br/>
But we are at that point right now.<br/>
And what you have heard in the news<br/>
perhaps is<br/>
the Merck vaccine trial failed.<br/>
And so people are beginning to<br/>
despair.
Will we ever have an HIV vaccine.

So let me just go over a few of the aspects of HIV. I promise you not too much immunology for those of you who are not aficionados, and just enough for those of you who are.

But I want to talk about why it's so difficult to come to the point of making an HIV vaccine. One of the reasons is that HIV is a retro virus. It is a virus that makes RNA as its message. It's a virus that is an RNA virus. Hepatitis C, for example, we don't have a vaccine for Hepatitis C either.

So when HIV gets into the cell, it basically uncoats, it takes its RNA message out, it converts that into DNA. The DNA actually can integrate into the host genome. So people living with HIV have the HIV genes integrated into some of their cells, for a very long time. And then once that cell becomes activated, then the genes start getting transcribed and translated, making protein, making the virus, and then bursting out of the cell.

The biggest problem in HIV vaccine development is this. When it enters the cell, normally you can make an antibody to protect against entry. That's how we protect against many viral infections. We make an antibody that blocks the entry. The HIV virus has a special trap door. When it approaches a cell, it opens that trap door, and then a protein comes out, and allows it to enter. That happens in a microsecond.
The space involved between the HIV virus and the target cell is so small, that an antibody can't even actually fit into that space. So no antibodies have ever been identified that really effectively protect against HIV entry into the cell. They are looking at single chain antibodies that might fit in there. But basically, one of the biggest problems is how to protect using antibodies, and it's not ever been shown to be effective with the exception of just a few, which we can talk about later. This is what a CD4T cell looks like, a target of the HIV virus. The CD4T cell is the factory for HIV infection. In fact, it makes, all of the T cells in the body make a hundred billion new viral particles every day. Now remember the other point about this, each one of those particles might not actually be the same as the one that came before, because this is an RNA virus, and it mutates. The other point about this virus is that it attacks the T cells, so that factory is destroyed in the process of creating new HIV particles. The T cells decline, and then the person has immune paralysis. Without T cells you can't fight off infection, that's why we have AIDS. Now to go back to the concept of the HIV virus mutating, this you probably are very familiar with the concept of evolution. And in every HIV infected person's body, HIV evolution is going on. What happens in the person's body is the virus is mutating, it's trying out new forms. If an immune response occurs to the virus, then it will mutate away from that immune response,
and become immune to the body's attempt to fight it down.

So the host cell is infected, the virus is being produced, the virus is mutating, the immune response is occurring, and yet it is ineffective.

There are two processes between HIV evolution, and one is drift, and the other one is selection for more fit virus variance. When we first started talking about this in 1996, people were unsure that this actually went on. But in point of fact now, we know due to the mutation of the HIV virus, that it is able to create versions of itself that completely escape the immune response.

How does that happen? This is a picture, for those of you like graphics, of a virus entering a cell, the target cell, which is the CD4T cell, and then it's making more copies of itself. That cell is actually, when it's able to present immune information to the immune system, is breaking up the virus, and presenting at the surface of the cell a very small piece of the virus called a peptide, or a peptide epitope. It is just a nine amino acid sequence that is derived from the viral proteins presented on the surface of the cell. That peptide epitope is recognized by a T cell, that's where all the action happens.

Once the T cell, as shown in this picture, recognizes the viral epitope on the surface it will try to kill that cell. So what does the HIV virus do? But it changes its epitopes. And that's actually shown in this slide. What happens in the course of a single person's infection, if you follow this sequence of the HIV virus from the point that they infected, to just several years later,
you can see that their virus evolves, and it evolves variance with mutant epitopes that escape the immune response. This is a picture of the sequence of a child infected in Philadelphia at birth. And only four years later you can see how many different sequences of HIV are circulating in this child's body. This has also happened worldwide.

What happens in a child happens in a population. So within a population, HIV again is trying to escape the immune responses of the collective population. The result is that in different regions of the world, different variants of HIV have emerged. These are called clades. In the United States we have clade B, in Europe clade B, in Africa which is the epicenter of the epidemic we have five, six, ten different clades. In a single country, Mali where I work, the clades are mixed, and you have both the A and the G clade circulating in the population.

This is a dramatic problem in terms of making an HIV vaccine, because you can't make a vanilla vaccine and expect it to protect against chocolate. It simply isn't going to work. This picture actually shows how great the variation of the HIV virus has been, compared to one of the viruses that we are most afraid of, which is the flu virus, shown over in the corner of the picture right here, I don't have a pointer do I? I don't think so. But you can see there's a little dot in the corner of the picture over here, and that shows you how variable the flu virus is in the course of a year, compared to the expanding sequences of HIV. When we really think about this,
it's amazing that HIV can hold itself together. How can it be so variable and still function as the same virus. So this is really, summarizes the immunopathogenesis, the generation of the bad immune response to HIV, from the vaccine perspective. First of all, the near impossible task of preventing HIV entry makes it difficult to make the most standard type of vaccine against HIV, which would be an antibody directed vaccine. The HIV variability is also a huge problem, because if the immune system must recognize those epitopes that are presented on the surface of the target cell, and the virus mutates the epitopes, the T cells can't keep up. They can't keep on recognizing an HIV that is mutating away from their immune response. The other problem is latency. You may be able to clear HIV infection with drugs in the body, but there's always the coding sequence for HIV hiding inside of a cell, waiting for the cell to be activated. So you can't clear HIV, it's very difficult. The other problem with HIV is that it destroys the very immune system that we use to fight it off. So the T cell which is the target of HIV infection is also the cell that is destroyed, and leads to the disease that is known as AIDS. So those are all huge problems in terms of HIV vaccine development. So what do we think we can possibly do? There are ways that we could perhaps develop a vaccine, and that's what I'm going to get into right now. We're thinking that one of the ways that we could possibly direct our
HIV vaccine effort is to prevent infection. And one of the greatest problems with that is that most of our preventive vaccines, like the Hepatitis B vaccine, or the cervical cancer vaccine that you've heard about are based on antibody response. Most vaccines that prevent infection are based on antibody. So it's difficult to conceive of an HIV vaccine that could actually be effectively prevent infection. So now we're thinking perhaps a vaccine might be able to prevent disease, meaning yes you still get infected, but then we're able to control the infection, and we turn you into a person who has HIV infection, but may be like having diabetes, or high blood pressure, you live with the disease rather than being killed by it. The other thing that is a potential goal for a vaccine is preventing secondary transmission. So let's talk a little bit about the different types of vaccines, and then I'm going to talk about why the Merck vaccine has been such a failure. The ways that we can work on vaccines are shown here, and I'm just going to first talk about the simplest approach to making an HIV vaccine, which is what scientists seized upon in the 1980s when the virus was first identified. And that is if you look at the surface of this virus, you can see a knob on the surface, that's called the envelope protein. When people saw that it had an envelope protein they thought ah, this is just like Hepatitis B, we can simply sequence that protein, create a...
whole lot of it in a big vat, make just tons<br/>
and tons of this particular protein called<br/>
GP120, and we can inject that into people,<br/>
and we will create an effective<br/>
antibody response.<br/>
By now you should be familiar with<br/>things that absolutely make that impossible.<br/>
So one is the variation of the<br/>virus.<br/>
This particular envelope protein is<br/>most variant protein in the whole virus.<br/>
So maybe it's not so simple to<br>select<br/>one single protein that will be effective<br/>against all strains of HIV, that<br/>would be problem number one.<br/>
And problem number two is that<br/>nobody's been able to figure<br>out what antibody can effectively<br/>prevent entry into the cell.<br/>
So there are the two problems with<br>that approach.<br/>Nonetheless, as Pat Thomas says in<br>her book, Hot Shots, nonetheless,<br>even though most scientists were<br>well aware<br>that that approach would not work for HIV,<br>vaccines were developed, trials went<br>forward,<br>people volunteered all over the world<br/>for the VaxGen<br>trial that came off about two years ago.<br/>And were we surprised that the<br>results were<br>that there was absolutely no protective effect?<br/>Most of the scientists in the<br>field were not surprised at all.<br>VaxGen went on to capture some<br>defense money,<br>and is now making Smallpox vaccine<br/>somewhere on the west coast.<br/>But that particular vaccine<br>effort completely failed.<br/>At that point, what do we do as<br>scientists?<br/>We go well, maybe that didn't<br>work, we'll try something else.<br/>So two of the leaders of the NIH<br>vaccine<br>effort, Peggy Johnson, a good friend of mine,<br>and Tony Fauci, who<br>is the director of the division of Aids,<br>decided that perhaps we would have
to think
about a different way of making an HIV vaccine,
maybe a less than perfect vaccine would be okay.
Maybe something that didn't completely prevent infection,
but actually diminished disease would be something that would be acceptable.
And the reason for this is that we know that some people can actually control HIV infection.
There are people who are living with HIV today, twenty years after being infected, who have never been ill.
Something about their body allows them to contain the HIV infection,
and so people started looking into that.
They measured the amount of virus in their blood, and they saw that if you had a low load, then you were a controller.
somebody who was an elite controller they're called.
And this is what people started to study.
They found, low and behold, that the most important correlate of protection from disease was T cell mediated immune response.
The T cells, those same T cells recognizing epitopes, sometimes were able to keep the virus in check.
So people started working on T cell mediated vaccines, instead of antibody mediated vaccines.
And this illustrates a complete shift in terms of the vaccine paradigm.
Most of the time we think about a vaccine that protects completely against infection,
that's what's shown in the second panel here.
You would have a virus entering the body, and absolutely no virus ever occurs.
because you get clearance with the antibody.
A second type of vaccine would either give a very low amount of virus,
or give you a lower level of
virus than complete protection.<br/>
And that's actually what was proposed in 2002, in Barcelona,<br/>
and that is to basically lower the viral load with a vaccine.<br/>
This just recalls what happens in HIV infection.<br/>
You get an acute infection which drops your T cell count.<br/>
They come back up, and then they slide down towards AIDS.<br/>
The CD4 T cells are preserved, and the viral load varies,<br/>
generally is low in chronic HIV infection,<br/>
but eventually at the end when AIDS occurs,<br/>
and there's a complete immune suppression comes up.<br/>
So the idea would be that we would be trying to lower the viral load<br/>
to prolong life, and limit the impact.<br/>
There's actually good data showing that people who have lower viral loads live much longer.<br/>
So people who have, as shown on this slide, less than a certain number of copies per CC are more likely to survive,<br/>
89% surviving if they have less than five thousand copies.<br/>
Whereas people who have thirty six thousand copies in their blood,<br/>
62% of those people are dead within the next five years.<br/>
So a vaccine that can lower viral load is one of the targets that we're trying to achieve.<br/>
This was actually described at the Barcelona conference in 2002,<br/>
and the idea was that we would be trying to make a T cell mediated vaccine that would contain infection.<br/>
There is good data that this would actually protect against transmission.<br/>
Remember that's one of the goals of the vaccine that we'd like to develop.<br/>
This is a study that was done in Rakai,<br/>
where they looked at discordant couples, one person with HIV,<br/>
the other person either a spouse or a partner,
without HIV, and they looked at the virus load in the person who had the HIV infection. They're more likely to transmit to their partner if their viral load is high, and less likely to transmit if their viral load is low. And people have actually modeled, mathematical modelers have projected that a partially effective vaccine might actually be able to reduce HIV transmission in a population, and eradicate HIV, get the HIV transmission below that magic number that allows it to continue to propagate in a population.

So then what became the focus? Well the focus became T cell mediated vaccines. Here are some of the approaches that people have looked at, and I'm really just going to talk briefly about live recombinant vectors. These are virus packages that contain the genes from HIV infection, and the particular virus package that was chosen by Merck is the adenovirus. That's the standard cold virus, most of us have actually been infected with adenovirus. They used this as the package to deliver the genes from HIV to create an immune response that was T cell mediated. They studied this vaccine all over the world. The studies actually started about three or four years ago. A large phase three trial 2B, actually a 2B trial, which is a particular type of clinical trial. They enrolled about six thousand people in different regions of the world, and in parallel there was a study in South Africa with the same strain, the same particular vaccine, but being performed by the HVTN, the HIV vaccine trial network. Most of these studies are actually paid for by the U.S. government, even though Merck made the vaccine.
Now a note about this particular vaccine. This vaccine is a clade B vaccine. It is not developed for other regions of the world, it does not contain epitopes, those little messages to the immune system that represent the flavors of HIV that are being transmitted in Africa. And yet it's being studied in Africa. From what I've just told you, you would think that even generating an immune response against a clade B virus, it would be unlikely to protect against the clade C's that are found in south Africa, because the epitopes are not the same. Merck waved its hands, did some fancy T cell assays with lots of overlapping peptides, and came up with an answer that seemed to suggest there might be enough cross reactivity with the whole genes that they were expressing, to perhaps protect. And they argued that this might be a good idea to at least test this vaccine, and see if we could get protection against different strains of HIV. Now I also want to note that most of the pre-clinical studies are done in monkeys, non-human primates, that are infected with not HIV, but a strain of monkey virus, SIV. Whenever they're testing vaccines in these monkeys, they usually immunize with the vanilla flavor, and then challenge with the vanilla flavor, and when they get protection they go oh, we can protect monkeys from HIV infection, or SIV infection, therefore we should go ahead and do studies in humans. There are very few studies in monkeys that have been performed with the type of variation that exists in the real
world.<br/>
<time begin="00:32:18.32"/>So again, the scientists have been concerned,<br/>
and they have said you're vaccinating<br/>
<time begin="00:32:24.35"/>with clade B, that makes sense, you're<br/>
a Merck, you're gonna be making a vaccine<br/>
<time begin="00:32:28.60"/>for the United States of America where<br/>
you can sell it for lots of money.<br/>
<time begin="00:32:31.67"/>You're really not that interested<br/>
about making a vaccine for other areas<br/>
<time begin="00:32:34.95"/>of the world, we understand that.<br/>
<time begin="00:32:37.06"/>You argue that it will provide<br/>
protection,<br/>
but the scientists were very concerned.<br/>
<time begin="00:32:41.87"/>They were concerned there wasn't<br/>
going<br/>
to be enough breadth of immune response,<br/>
<time begin="00:32:45.23"/>and that there wasn't going to<br/>
be protection in this trial.<br/>
<time begin="00:32:48.56"/>So the news was not surprising to<br/>
many of us in September, and then in November<br/>
<time begin="00:32:55.03"/>when the data finally came out that<br/>
there was absolutely no protection.<br/>
<time begin="00:32:58.94"/>The two trials that I talked to you<br/>
about, the<br/>
Merck study that was in north and south America,<br/>
<time begin="00:33:03.63"/>and then this South African<br/>
study were both discontinued.<br/>
<time begin="00:33:07.95"/>But even worse, even worse, and I'll<br/>
show you what actually happened.<br/>
<time begin="00:33:13.51"/>And that is as shown here, people<br/>
who got the<br/>
vaccine were more likely to come down with HIV.<br/>
<time begin="00:33:23.37"/>This is about the worst possible<br/>
outcome for a vaccine trial.<br/>
<time begin="00:33:27.40"/>Imagine you're a vaccinologist,<br/>
you're me,<br/>
I'm standing up here, and I've just told you<br/>
<time begin="00:33:32.93"/>that people who got a vaccine, and<br/>
not<br/>
placebo, were more likely to get HIV.<br/>
<time begin="00:33:39.71"/>This is the worst possible outcome.<br/>
<time begin="00:33:42.04"/>The numbers were small, so here you<br/>
can actually see in the vaccine arm,<br/>
<time begin="00:33:47.26"/>forty nine people got infected out<br/>
six hundred when they broke the code here.<br/>
<time begin="00:33:52.02"/>And in the placebo arm, thirty<br/>
three got infected.<br/>
<time begin="00:33:55.65"/>And it turned out, what was very
strange about this particular study was that the people who had high pre-existing antibody titers to the adenovirus, the package that they had put the HIV genes in, were more likely to get HIV when they were exposed to it. So twenty one people out of the high adenovirus titer group were infected, whereas only nine of the placebo group. So there was something about the reaction to the vector that made people more susceptible to getting HIV if they got the vaccine. So they stopped the study, they actually do this as a standard in all clinical trials. They have what's called a data safety monitoring board that looks at the data to determine to see if there's any problem with the vaccine as the trial is going on. They stop the studies, and they started trying to think about what was actually going on. And I'm only going to present to you a summary slide, because I you know, there's so much data coming out about this, I just want to really hit the time points. And basically what they looked at was how the study was designed. They looked at both groups, the placebo group and the vaccine group. They saw no behavioral differences, that was almost the first question that they wanted to ask, were the people in the vaccine group taking more risks and more likely to be HIV infected than the people in the placebo group? Both the doctors and the patients and the subjects were blinded, nobody knew which person got placebo and which person got vaccine. But when they unblinded the study, they found no differences in terms of risk behavior. So it wasn't a behavioral issue.
their intermediate study goals,

One was to either prevent infection, clearly

that didn't happen, and they also looked to see

if there was a lower viral set point, the amount of virus

in the blood after infection was decreased.

And I'll show you a little note about that in a minute, but in general there was no difference.

The people who got HIV infection in the placebo group got just as much virus

as the people who got the vaccine.

So there was no difference in terms of the initial control of HIV infection.

There was clearly more infections in the vaccines than placebos.

This is a dramatic problem for HIV vaccine trials.

Imagine you're the next HIV vaccine volunteer, and the researcher is trying to convince you to participate, when in fact you know, it's been in the paper that the last vaccine trial caused people to get infected.

Are you going to sign up for that? I think people are going to be a little bit hesitant.

So there's a huge amount of work to do in fact, around vaccine trials, and a lot of basic research that actually needs to be done.

The lack of efficacy did not appear to be explained by suboptimal immune responses to the vaccine.

People did get T cell responses, I think that's in this slide.

Now I have to note here as an immunologist, these are not whopping T cell responses.

You can see here that they did pools, they looked at pools of peptides from the HIV virus, and you can see to the different proteins the average response was really one pool.

Most people only responded to one pool of
peptides, overall the average was three.<br/>
This is probably not going to be effective.<br/>
If you think about how variable the HIV virus is, and how many different pieces of information it can show to the immune system, what we're saying here is that this vaccine caused three pieces of HIV to be recognized by the immune system, in a virus that starts mutating the minute it hits your body. Recognizing three pieces of HIV is not going to be enough. So I think that that's probably one of the main problems here, and what we actually think is that there's going to be a difference between the vaccine epitope, remember they picked vanilla as the flavor that they wanted to vaccinate against. And if you're coming in with a different strain of HIV, the epitope, the piece of information presented to the immune system is going to be different. So you might as well not get vaccinated because what the immune system is going to see is a different kind of HIV than the one it was trained to recognize. And that's actually what they're thinking in terms of this particular vaccine, possibly, that the challenge virus was different enough from the vaccine virus that we will not see protection. And that's what I'm trying to point out here, is that when the challenge virus gets into those cells, they start presenting the information to the immune system, the T cell's looking around for the vaccine that it was trained to recognize, and it doesn't recognize the HIV infection, so it's not able to protect. How will we know this? We'll know this by studying the people who were somewhat protected. And this actually shows that in the
in the vaccine group there was actually some, a number of people who had very low viral loads after infection. So they were somehow able to contain the infection. That tells us that perhaps their T cells actually recognize the challenge virus that they were challenged with. So they're going to look at their T cell responses, they're going to sequence the virus that they were infected with, and they're going to compare that to the vaccine strain. I will bet anyone in this room lunch that the epitopes in the vaccine are the same as the one, as the HIV they were infected with, and therefore they were able to control the infection. But we know this. We already know that HIV mutates, three T cell responses is not sufficient. Why do we go forward with this kind of study? It's a good question, and I'm going to have Pat get up here and answer the questions with me when we go to the questions section. So what's going to happen now? Basically, most of the vaccine trials have been put on hold. We're going to try and figure out, this is what they're doing with these subjects who were exposed to HIV, they're looking at their type of T cell responses, they're going to look at how the T cells responded to the HIV infection, they're going to look at the different roots of exposure. was a certain sexual practice more likely to cause exposure. There is some discussion actually that circumcision might have played a role here. They think that the people who were more likely to get infected were uncircumcised men, and that's certainly played out in Africa. We know that circumcision can protect against HIV infection.
So they're going to start looking at that. And they're going to stratify future vaccine studies by circumcision status, which makes it very complicated for HIV vaccine researchers. They're going to sequence the virus, and they're going to follow the HIV positive patients to see if the vaccine had any impact on the course of their disease. If you remember what I said, that is one possible endpoint for a vaccine program. There's lots more to do. They need to look at the set points, they need to look at the immune correlates of protection, they need to figure out if the breadth of T cell response, which is what we would argue is critical, was important in terms of the patients who were able to actually control their initial infection. Meanwhile, what is the vaccine world, research world going to do. So basically, if you were working on an adenovirus vaccine for HIV, you're dead in the water. You might as well forget that program, put your RO1 grant on the shelf, and start working on something else, because that's not going to get funded. nor is it going to get into trials now. People are looking at alternative ways of delivering the HIV information either by a DNA vaccine, which we can talk about, or the Smallpox vaccine. The three vaccine trials here, if you go on the website, which is what I did a couple days ago, to get this information, the three adenovirus vaccine trials that were in process, including one funded by a consortium of donors, including the Europe and the CDC called the PAVE trial,
all adenovirus
virus directed vaccines, are dead in the water.

The vaccine trials have been
cancelled, the people who recruited
to participate basically being told
that right now we cannot go forward.

Now the list of potential candidates is pretty huge.
What I want to point out about this list, in this huge list of vaccines that are actually in the pipeline, is that they are all vanilla vaccines.
They are all basically based on whole protein, they are all basically based on delivering a whole protein to the immune system, and never really focused on the variability of the HIV virus, and some way of stimulating a broad immune response.

There are three vaccines that are pointed to with arrows on this slide where they are actually considering that.

But again, they're using one or two or three epitopes, which really would not be sufficient to protect.

One is the Wyeth vaccine.
They're using four CTL epitopes, and they seem to think that might be effective, and I really doubt that.

So here's the issue that I have, and a lot of scientific researchers have with the vaccine development field so far.
And that is HIV is a global problem.
HIV doesn't just exist in the back yard of the Merck vaccine company,
where only the clade B flavor is circulating.
HIV's incredibly variable, and we really need to think outside the box.
And how best to address this problem.
So that's actually something that we've been working on since about 1996 at Brown,
and that's what I'm calling a new vision.

I'm not the only researcher working in this area.

And this is kind of what we're hoping to develop.

We want to develop an HIV vaccine that's effective everywhere in the world, where all the different flavors of HIV occur.

We want to make sure that we induce a broad T cell response, not something that just recognizes three little tiny pieces of HIV, but a broad T cell response that can recognize any variant of HIV that you would throw at it.

We want to reduce the chance of transmission, we want to use low risk vectors, I would not use adenovirus.

We want to make it low cost, if not entirely free, because the average income in countries like Mali is thirty dollars per year.

We want to make sure that this vaccine could actually be made in the developing world.

Why should we make the vaccine here, can't we transfer that technology to Mali, or to Kenya, or to Cambodia, where they can actually make the vaccine themselves.

And we need to make it with a technology that's scalable, so we can make small research batches and quickly translate to make larger batches in developing world countries.

So that's really what we've started out to do.

And the other very important point is that this has to be done in collaboration with developing world scientists.

If the target is the developing world, you cannot do this in a vacuum, you cannot do this without actively getting scientists in the developing world engaged.

So that's what we've been working on, I'll just give you my example
which is the Guya HIV vaccine, which we hope to be globally relevant and globally accessible.

The way that we're approaching this vaccine program is to basically build it based on epitopes.

And this is actually a picture of an epitope lying in the MHC molecule.

We use computer programs to predict these sequences, that are highly conserved in all strains of HIV.

So epitopes are the minimum essential unit of information that stimulates an immune response.

We use our immuno informatics tools to identify what we now call these Achilles heels.

If the HIV virus is so variable, it still needs to function.

There are pieces of the HIV virus that stay the same, those are the vulnerable targets for HIV.

If you can find the sequences that stay the same no matter which flavor of HIV you're looking at, then you probably have something that will work in a vaccine.

So we've focused on these very conserved epitopes.

These epitopes that we've selected are not just conserved in one particular year, but we show that they're conserved over time.

In the twenty years of the HIV epidemic, as long as we've been sequencing HIV, we know that our epitopes are conserved in all of those viruses.

And we also tailor this vaccine so that it can be presented in the immune response of all peoples of the world, no matter what their genetic background is, or no matter what their HLA is.

And the other concept, as Pat so well summarized, is to make this vaccine a not-for-profit endeavor.

So we take computer programs, we basically digest down all of the sequences.

Fortunately for us, most of the work has actually been done.
They have created a huge database of HIV sequences, they're also available in Gen Bank.

We basically dump those into the top of the computer, and what we're selecting, if you want to think about this in a different analogy, if we have all the dialects of French in the world, Haitian Creole, Senegalese French, all the different dialects of French. We're picking out the words, Bonjour, Comment ca va, Tres Bien, Aujourd'hui. The words that are conserved in the French, in the HIV virus, that are conserved in all the different dialects. We use computer programs, and those are the epitopes, putting into our vaccines. We start with the genome, we predict the T cell epitopes, we confirm them using blood from HIV infected patients. We've had donors from all over the world, from Thailand, from Cote D'Ivoire, from west Africa, and also from Providence donate their blood to have these T cell epitopes tested.

We then clone them into a DNA vector, and we produce also the peptides, and we've been vaccinating. So far just in mice, but we have pretty dramatic results.

This really kind of summarizes the informatics approach. You take all the sequences, you dump them into the top of the computer, you ask the computer to find the letters that are actually conserved, nine amino acids, strings of letters, it's as simple as that. This program is called Conservatrix, it's an algorithm that we wrote to do this. We then find these conserved sequences. This just basically shows how it might look in the sequence.
You find this nine amino acid string, and that's your conserved epitope.

We've also developed another program called the Epi Assembler, which assembles those conserved sequences into longer ones, so we can get longer sequences that contain highly immunogenic, and very highly conserved T cell epitopes to turn on a T cell response.

When you look at them over time, this just basically illustrates how well conserved they are. In orange are the epitopes that are conserved, not just in a single year as shown in one of the columns, but across time over the ten, fifteen years of the HIV epidemic that we have selected epitopes that this virus cannot change, because it uses that piece of its protein to do something critical.

So we've found the Achilles heel of the HIV virus, and that's what we're putting into our vaccine. Basically where we are in terms of the epitopes, we mapped four hundred epitopes, we confirmed two hundred of them, and that's pretty good when you look at computer programs.

We're now aligning them so that when you put two of these words together you don't create a new word at the junction. This is a computer program called Vaccine CAD, or Vaccine Computer Assisted Design.

That allows you to put epitopes in a string and not create gobbly gook. And then we clone the strings of words into a DNA vector, and that's shown in this picture. We basically take the amino acid sequence, we create the DNA, we then make a vaccine using that DNA. That's our delivery vehicle. We also use proteins to boost the immune response, this is a prime boost vaccine.
that we're working on. And we test them in mice that have human immune systems. That's how we test our vaccine. And I can't show you results from challenge in mice, because basically HIV doesn't infect mice. So the best proxy I have are two proxies. One is a vaccine that we've made, a DNA based vaccine using epitopes alone, and showing here that we can protect against a very virulent bacterial infection. With a vaccine composed just of fourteen epitopes. This particular example is Tularemia, a biodefense project that we now have funding on thanks to the Bush administration, to protect against bio terror. But it's a great model for our HIV vaccine. And we will be doing studies in mice that have a chimeric virus that is created to look like HIV, that does infect mice, and we will show that we can protect against HIV infection using this chimeric virus in the mouse models. So that's basically where we are. It's also important to point out that we're working in collaboration with Ousmane Koita of the University of Bamako, And a wonderful collaborator who has his PhD from Tulane here, and is very interested in vaccine. Is building a vaccine research building in Bamako, so that when we have our vaccine, we can actually test it there. In the meantime, we're working in west Africa, so I have roped some Brown students into doing some basic research with me in the neighborhood where we hope to test our vaccine. And they've been doing what are called KAP studies, knowledge, attitudes, practices, looking at HIV risk behaviors, and
asking people what they think about getting an HIV vaccine,

We've done this in a particular region of Bamako, which is the poorest neighborhood in the poorest, one of the poorest cities in the world. The neighborhood is called Sekaro, and over the course of many trips to Sekaro I finally met the chief. The chief said look, you know, I know this is a lot to ask, could you please build me an HIV clinic in my neighborhood. And I said well you know, if you never ask, you never get. So let me ask. And I went home, and I asked my board, and basically that's what we've been doing. This is a picture of the new HIV clinic that we've built in the neighborhood of Sekaro over the past three years. It took us about two years to raise the money, and about six months to build the clinic. But basically what this clinic will be doing is providing state of the art HIV care, accessible HIV care right out at the fringes in the village system, the village infirmary of Bamako, Mali. And we're setting an example. There are seven hundred such infirmaries in Mali. If we can show that we can provide HIV care in this center, they can replicate the model in all the other sectors. So I don't want you to go away from this discussion and think we'll never have an HIV vaccine. I think we will have an HIV vaccine. It takes ten years to really get a vaccine through trials. But what we have to do as a group is decide that we want an HIV vaccine. And what does that mean? The vaccine trials that we're...
currently in process, that took years to get to this point,

they were just starting the clinical studies,

they were projecting that we would have the actual data either this year or the year after from these studies that were now stopped.

You can see that it takes years and years and years.

So if we don't make a decision now that that's what we want to do, these vaccines that are in the pipeline will never bear fruit.

So we are actively carrying our work forward, even though that there is no NIH funding for this particular program right now, we continue to try to compete for funding.

But the funding for HIV vaccine research has really gone down to just a trickle.

Meanwhile, this is a world map or picture of AIDS deaths in the world.

Meanwhile the problem gets bigger and bigger.

So AIDS deaths are predominantly concentrated in southeast Asia and sub Saharan Africa, whereas health spending again, disproportionately in Europe, Japan, and the United States.

There is money being invested, so this is actually a picture of the funding being spent by different countries of the world, 759 million dollars in the year 2005, about 4% of the gross domestic product of the United States, a little bit less for Ireland and Australia, Brazil, and a number of countries way down at the bottom of the list spending less than 0.5% of their GDP on vaccine development.

But remember this in context. The war budget, 1.4 trillion U.S. dollars in 2008, that's what's projected.

The U.S. will be spending 711 billion dollars on war.
Meanwhile 759 million dollars is being spent on AIDS vaccines, which is less than 0.1%. So I do think that we can change that dynamic and to do that we have to be politically active. Not necessarily scientifically active, but politically active. And there are lots of people who have written about this, some of the journalists like Pat Thomas, who's been a leader in terms of questioning how HIV vaccines have been developed, but also John Cohen, who says basically you know, we need a March of Dimes. There was a March of Dimes to make a polio vaccine. There was a public support for the creation of a polio vaccine to keep kids from getting paralyzed. And 25 years later we had a polio vaccine. But we can't say the same about AIDS. The way funding goes, and the researchers among you know this very well, trying to publish, look around, figure out how they can possibly create publishable information with the research that they're doing. Because if they don't publish, then they don't make a vaccine. We really just need to go back to basics here, and say just make a vaccine. Use your best tools, we will fund you, let's let a thousand flowers bloom, let's try lots of different approaches and let's get an AIDS vaccine. Is this asking for too much? And this is Pat Thomas's book if you haven't read it. It only takes really 20 million dollars for one vaccine from start to finish. And yet we spend 500 billion for Iraq. So I just want to leave you with
the concept that hope is a vaccine.<br/>
<br/>
This is the direction that we're going in, we really want to get there,<br/>
and that is all I have to say tonight.<br/>
So thank you for your attention.<br/>
I'd be happy to take any questions.<br/>
[ applause ]<br/>
You better get up here and answer questions with me.<br/>
So read Hot Shots.<br/>
Burning questions.<br/>
Yes.<br/>
[inaudible-too far]<br/>
It's, it would be a therapeutic preventative is what we call it,<br/>
because basically we would be trying to induce that immune response that would lower the amount of virus in your body after you got infected.<br/>
So that's really what people are hoping to achieve right now,<br/>
is a vaccine that would contain infection, like the elite controllers.<br/>
It's a DNA prime and protein boost. <br/>
So no live viral vectors either.<br/>
[inaudible-too far]<br/>
Would problems arise,<br/>
misuse of the Merck vaccine?<br/>
GAIA vaccine?<br/>
Well first we have to have the vaccine,<br/>
and then we'll see if it's misused.<br/>
In what way do you mean?<br/>
If it's made in developing world countries, or?<br/>
[inaudible-too far]<br/>
One of the points about the vaccine that we're trying to develop is<br/>
that it actually doesn't contain any viable genes from the HIV.<br/>
In fact, all vaccines are made that way now.<br/>
They're either whole virus killed, or<br/>they're just pieces, like a single protein,<br/>
talked about that Vacs Gen made.<br/>And ours is made of even smaller
You can kind of think of a whole virus vaccine as being the whole book, the encyclopedia, some people make just the protein which is like a chapter, and we're just putting words. So you can't actually make anything with those words, the virus, that machinery's not functional, it can't cause a bad effect. So that's so, and also when you give a vaccine, the dose is controlled. You actually do dose ranging studies to look at the most effective and the safest dose before you decide on how it's going to be marketed. So even in developing countries, the dose would be identified, and it would be controlled. It would always be the same dose. Maybe a little bit less for children, but it would be the same dose. Yes. [inaudible-too far] So the question is whether this vanilla vaccine would work in a country where vanilla is the form of the virus being transmitted. When I, I sort of oversimplify when I say vanilla clade B. And when you talk about the virus in the United States, it is mostly clade B, but even within clade B there's so much variation. Remember the kid that I showed you, that pediatric patient? That was a clade B infection, but over four years he developed what, a hundred different strains of the same clade B virus, each of it which has different epitopes. So I don't think that a single protein from a single virus will actually protect. You do have to use the computer approach to find those Achilles heels, the piece of the virus that is conserved.
And that hasn't been done, that simply hasn't been done yet, until we started doing it.

And also now the Gates foundation is starting to think about doing it.

Yes.

It all depends on funding.

So if some wonderful person, Larry Ellison, Bill Gates were to come along and give me the twenty million dollars that I need to make the vaccine, it would happen very soon.

It's all about money.

And it doesn't have to be my vaccine, it could be the Gates vaccine that they're working on.

There's a multi-epitope, multi-clade vaccine.

It's just about funding.

I do not believe, that's what I hope you go away with.

The Merck vaccine is not the end of this story.

It shows a failed approach, one that we really didn't think was going to succeed, even from the get go.

Now we need to abandon those failed approaches and start funding the approaches that will work.

And if we do that, we will have a vaccine.

And a note about the funding of vaccines.

I mean I think that historically one of the problems that's happened is that we've been able all along to see the people most at risk for AIDS as other than ourselves.

At first in this country we said well, it's homosexual men, it's IV drug users, it's not us sitting here.

And then there was a tremendous wave of political activism, which proved that the government does listen, and the government can be made to allocate money on the basis of an outcry from the citizenry.

And that's when funding really increased in the 1980s.

I mean that's a remarkable story,
and AIDS activists showed the way
to breast cancer activists, and
every other patient advocacy movement
that has gotten substantial tax dollars for its research.
But now more recently, we during the last decade
or so, we have conceptualized HIV and AIDS
as a problem of people on other continents.
And so the demand side from the citizens
and voters is not there, you know?
We're not saying to congressmen or
republican senators, you know what?
We really think that getting an HIV vaccine for the world is important.
We talk about the University of Georgia's commitment to international careers
for our students, and I love that, that's an important thing.
I don't know what marvelous things people in this room may accomplish
working outside our own country.
But you know what? It is just one world, and a disease of this magnitude,
with these kinds of modeling projections for transmission and spread,
we have to see it as our problem, we have to say this is a political issue.
We think this is a top health funding priority, but we've not done that, so it's been,
and you know, great ideas.
They are in a sense a dime a dozen.
Not to denigrate the kind of accomplishment of a lab like [inaudible],
but what's really expensive is moving those ahead into factories to make vaccines,
and then moving them ahead into clinical trials, which are enormously expensive.
but cost less than the wing of a stealth bomber.
Yes.
Well there's, what's interesting about drugs these days is that there was a big effort
to get tiered pricing, part of which...
was led by Paul Farmer and Jim Kim, who Jim Kim spoke here. And that has actually happened.

So there is tiered pricing, and developing world countries are able to purchase drugs at a discounted price. And that, and Bill Clinton, to his credit, has been a major driver as well, reducing the cost of drugs in developing world countries. And that, and Bill Clinton, to his credit, has been a major driver as well, reducing the cost of drugs in developing world countries from fifteen thousand dollars per patient per year, which is untenable, to three hundred dollars per patient per year, which is paid for by the global fund, usually.

I will actually talk about this in the journalism class tomorrow, is that it still doesn't get out to the people who need it. So in Mali, the country I know the most about, there are probably about a hundred and twenty, a hundred and eighty, a hundred and fifty thousand people living with HIV in that country, three times the size of Texas, but only eighty thousand people on medication. Because there aren't enough doctors, and because there simply isn't enough push or pull to get the drugs out. So there, the same level of activism that we have in the United States, act up, all of the gay men's health crisis, all of those groups don't exist in developing world countries, and there isn't the same level of advocacy.

There's still a huge amount of stigma, even the doctors are afraid of treating patients with HIV, because they haven't seen them live with HIV the way we have. So getting the medications out is one of the biggest problems, and yet that's not going to be enough, that will only treat the people who get infected, and it won't prevent people from getting infected. 

Treatment, the expansion of
treatment programs globally is a great thing.

Jim Kim, when he spoke to us two months ago talked through about how the centerpiece of his time, as leader of the World Health Organization's AIDS programs, was a so called three by five program.
The goal of treating three million people in the developing world by the year 2005, it simply didn't happen.

It hasn't happened.

Same reason failure of funding, not sufficient funding,

and we talk about the numbers that were you know, twenty dollars per person in the United States per year would get funding to everybody on the planet.

So it's, there, you know, this is doable, but it's just lack of leadership.

So we actually mapped our epitopes with some of those patients.

So we were able to get a cohort of patients in Providence who are elite controllers,

and when we predicted our epitopes, we then confirmed using their blood that they donated, whether we were right.

And so that was the great news, that paper was published in 2005.

Very good question.

There was one in the back, yea.

So we were able to get a cohort of patients in Providence who are elite controllers,

and when we predicted our epitopes, we then confirmed using their blood that they donated, whether we were right.

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Very good question.

There was one in the back, yea.

So we were able to get a cohort of patients in Providence who are elite controllers,
are actually at the functional part of the scissors, and that's why they're conserved. But you can't actually ascribe a function to something that's only nine amino acids long, usually. You can say it's within this particular region. So I think we can take this discussion next door to [inaudible] Hall, where refreshments are waiting for us all. And let's thank Doctor Degrut for coming. Thank you. [applause]