Welcome to the third lecture in this 2009 series on global diseases, Voices from the Vanguard. This is a joint effort between the Center for Tropical and Emerging Global Diseases and the night chair in Health and Medical Journalism, Pat Thomas of the Grady College of Journalism and Mass Communication and I am pleased that each of you is here.

I know outside if it is very tempting, the first nice day in about four days.

As most of you know, the lecture series is intended to create interest in global diseases across the campus from north to south campus and today we have Dr. Barney Graham, who will talk to us.

But let me first remind you that we have a reception immediately following the lecture over in Dennison (assumed spelling) Hall, right next door.

The next Voices from the Vanguard will be April 14th and that will be Dr. Jennifer Freidman from Brown University and she will probably talk to us about her work in the Philippines on a variety of neglected tropical diseases.
So tonight, Pat and I have asked Dr. Barbara Schuster to introduce Dr. Graham to you.

But before I do that, it is first a distinct pleasure to introduce Dr. Schuster to you.

Dr. Barbara Schuster is the new campus dean of the medical college of Georgia, University of Georgia medical partnership, campus in Athens.

She is a proven educator, physician and administrator.

Barbara comes to us from Wright State University and Ohio and there she chaired internal medicine and has most recently taken a year to work with the American Medical Association in terms of doing some research.

So it is a pleasure to introduce her.

She is new to the campus and I think it is terrific that she took the time out from putting together her medical school, which is literally what she is doing to be with us tonight.

So it is my pleasure to introduce Barbara to you.

I would ask you to welcome her and her husband Richard, who is a professor of UGIA's public of college health and they are both here tonight.

So please introduce yourself to them too.
Barbara: Thank you very much for that wonderful introduction.

My husband is here in the second row with me, so I hope I will get to meet each of you later after Dr. Graham presents.

It is really my pleasure to introduce a colleague.

I don’t know Dr. Graham, but we have mutual friends in Rochester, New York, people who also work in the field of virology, but Dr. Graham is a graduate of Kansas, the University of Kansas where he received his MD degree after graduating from Rice University.

He went on to do post medical school work called residency in Vanderbilt and completed a fellowship there after internal medicine in infectious disease.

The infectious disease folks are always close to my heart, because had I chosen a specialty I had thought about infectious disease and so microbiology and infectious disease is something I have always had an interest in.

He, of course, has you know rose in the ranks, became a professor and has done outstanding work in the fields of RSV, also known as Respiratory syncytial virus and HIV and today he is going to speak to us on the HIV vaccine development,
what is the next step, so please welcome Dr. Graham.

( Applause )

>> Dr. Graham: Well thank you very much and it is my pleasure to be here.

I have to tell you a little bit about my connection to Dr. Collin (assumed spelling)
because he rescued me during my dissertation work when I was getting my PhD at Vanderbilt,
even though I was a virologist and wanted to be a virologist and he was a parasitologist,
he helped me finish that dissertation project and I think it may be his only virology paper ever, but he does have one.

( Laughter )

The thing I learned there though that most of the really big ideas about immunology have come out of the parasitology field and it is mostly things borrowed from parasitology that has populated the viral immunology literature

and so I owe him a debt for that as well.

Okay. And I thought of him not too long ago when I was in Uganda and had an opportunity to go rafting on the Nile River.

And they said it was a class five rapids
and so the shisto (assumed spelling) really shouldn't be there.

( Laughter )

Because they should only be present in very calm waters and so we did go rafting.

I was at the head of the boat and we had a terrific time

and my antibody titer a few months later was negative.

( Laughter )

So I just, but I did think of you during that trip.

So why do we need an HIV vaccine, this is the main reason that there is still more

than 7,000 infections every day occurring throughout the world and despite the delivery

of anti-retro virals in a more efficient way globally,

there are still about 10 new infections for every new person that is started

on anti-retro virals and if that is the trend, we are never going to be able
to treat our way out of the HIV epidemic.

Unfortunately, many of these infections are in low and middle income countries and they are

in our most vulnerable populations, women and young, young children.
The United States, the epidemic has
gotten as much attention recently
as I think it should have,
but it still is significant.

There is still 55 to 65,000 new infections
every year and as you see it has moved more
into minority populations, more vulnerable
populations and it has become a disease
of young people particularly
within those minority populations.

So we do need a vaccine.

So why do we think vaccines would work for HIV?

The main reason is because
of their track record.

Vaccines are the most effective
and efficient way to managing
and I am showing you just a few
examples here of vaccines for viruses.

The year of the peak incidence of that infection
in the United States, the number of cases
at present in those years, for instance,
mumps in 1967, almost 200,000 cases.

In the early 60s, half a million cases of
measles, those diseases have almost vanished
and have become very rare, except for last
year when there was 7,000 cases of mumps
because people stopped taking their vaccines,
because they forgot how bad mumps could be.
We have eradicated smallpox that happened in 1980, so no place on earth is having smallpox now and polio is very rare, if ever present, in the western hemisphere. So vaccines do work, vaccines work even when they are partially affective or partially administered. So this is an example from the mumps epidemic, when the vaccine became available in 1967, before very many people were immunized, the epidemic started going away and it is one of our best examples of how just taking a few transmitters and a few susceptible people out of the population, these kinds of epidemics that are requiring a large number of susceptible people for transmission can start going away. So even before the recommendation was made for some people to be vaccinated in a more universal way, the epidemic was vanished. But there are problems for HIV, very significant biological hurdles that have not been accomplished in any other vaccine effort and so HIV has a list of problems, for instance, the lack of natural immunity.
There is not an example of where our natural immunity response was able to fully clear a virus from an infected human being and so the absence of the ability to study the natural clearance mechanisms is not present in HIV.

There is also evidence that if you are infected with one strain of HIV, you can be affected with another strain of HIV so natural virus infection doesn't necessarily prevent you from having another natural virus infection.

The genetic diversity is difficult for two major reasons, one is the question is what do you put in the vaccine, how do you select the antigens for the vaccine when there are so many tens of thousands of choices to make.

And secondly, because if you do become infected, even though you are vaccinated the genetic variation in the virus growing in you can help you escape those immune responses.

So it is problematic on both the population and the individual level.

Thirdly, there is an infection in a deficit created in the first responders for the immune system, both antigen presenting cells are impacted and the (inaudible) 4 T cell that organizes the rest of the immune response are either destroyed.
or their function is diminished and then HIV can infect immune privileged sites like the eye

or the immune system has a hard time reaching.

It can become integrated into your genome and become latent and so it can exist in a state in which no antigens are seen and the immune response can't see it

or it can become sequestered so a lot of HIV in an infected person is actually sitting outside of your cells.

It is sitting attached to the outside of the drake (assumed spelling) cells in the lymph nodes and that is not a place it can be cleared by the immune system.

And then for vaccine developers, one of the biggest problems for HIV is the failure to induce neutralized antibodies, which is the basis for most effective vaccines that we have today.

So I will go through why despite these biological problems,

I think it is still possible to have an HIV vaccine and then I will tell you about some of the difficulties we have had in the HIV vaccine development field in the last two years and then at the end I will let you help me decide what we should do next,

what should be the next step.
So when you are infected with the virus, it is interesting that despite the diversity of viruses that a person might be exposed to, a typical infection is a single Varian crossing over and infecting the next person.

We know that because sequencing virus early in that infection period only gives you a single genotype and it doesn't, it takes about 4 to 6 weeks before the genotypic diversity to start developing, so unless a person has ulcer disease, most infections occur from just a single varian and so the transmission efficiency is not that high with HIV.

It is not a very contagious virus and it may be a very minimal immune response of the right time and the right place that had a big impact on HIV transmission.

So when it infects, it infects usually through a mucosal service, dendritic cell grabs the virus and feeds it to a CD4 T-cell nearby and within just a few hours it is spread and can be detected in regional lymph nodes.

Within a few days, it is systemically spread and you can find it in all the lymph nodes in the body and at that time, it achieves a dynamic equilibrium where there is a lot of virus being made and a lot of virus being cleared, but you reach a set point
where you have a steady state virus level, but that process of making virus and killing virus is what eventually erodes and destroys your lymph node architecture and allows you to develop immune deficiency.

We know that if we had an antibody that was effective at blocking HIV that could neutralize HIV, we could potentially block infections.

That would be our best option.

That is how most good viral vaccines work, but as I will explain later in more detail, we do not have antigens identified that can elicit broadly neutralizing antibodies to HIV, so antibodies that can block the most commonly transmitted strains of HIV are difficult to identify.

We also know that when we have our normal adaptive immune response, particularly the T cell response, when it happens, it cannot fully clear virus. It just achieves this steady state of virus resistance and we know that in the meantime before that T cell response can occur, this state of latency can be establish in a sequestration.
So the big question for vaccines as we are now working on vaccines is what happens if you move the T cell response sooner.

If the adaptive immune response can happen a little bit earlier and a little bit higher magnitude, what effect could that have on virus replication.

So when you are infected with HIV, it takes about 3 to 4 weeks for the virus to reach its peak point of virania (assumed spelling) and at that point, the T cell response kicks in and a specialized type of T cell, the CD8 T cell, the killer T cell or the CTL, cytotoxic T lymphocyte is able to recognize the virus and start clearing virus infected cells and that is what reduce the viral load to this set point of virinia that you would have for 7 to 10 years untreated before you developed AIDS.

If we had an antibody response preformed antibody response, we may be able to block infection, but it is not likely we will be able to generate antibody response like that in the near future, so most of the vaccines that were being tested right now are T cell based vaccines, hoping that these specialized CT8 T cells that recognized process virus on the surface proteins called
MHC molecules, type 1, class 1,

MCH molecules can rapidly clear those virus infected cells and then

if potent enough could potentially clear your body and have an abortive infection,

but more likely is what is seen in animal models reduce the (inaudible) virinia

and achieve a lower set point viral load that results in a very delayed illness progression.

You might also have a situation where it doesn't really reduce viral load in the host,

but maybe it reduces the output virus and maybe it reduced transmission to the next person.

That could also have a beneficial effect on the epidemic and then

because things don't always go the way you want them to go,

there is also the possibility of disease enhancement.

That has been something that has happened with respiratory syncytial virus in the past

with measles virus in the past with some (inaudible) viruses in the past.

So when you think about starting to make an HIV vaccine and you look back at history,

how long does it take to make a vaccine.

Can you do it even in one career?

And the answer is only if you are lucky and start soon, start early,
because it usually takes decades to develop a vaccine.

From the time a virus is discovered to the time the vaccines are available for human use is usually majored in decades.

Right now, we are in 25 years and counting with HIV, but there are other difficult viruses with difficult biology that we also still haven't conquered and they are common viruses. Like RSV is more than 50 years, herpes simplex virus is more than 90 years.

These are viruses that have properties of latency like herpes or that inactivate some of the early immune responses like RSV that share these properties with HIV, so not all viruses are easy.

In 1997, President Clinton gave an address at Morgan State commencement and said maybe we should put more effort behind the HIV vaccine development process and proposed a new center be built on the NIH campus and so that project was started in 98, the building was finished in August of 2000 and we started occupying these laboratories.

In 1997, President Clinton gave an address at Morgan State commencement and said maybe we should put more effort behind the HIV vaccine development process and proposed a new center be built on the NIH campus and so that project was started in 98, the building was finished in August of 2000 and we started occupying these laboratories. I went from Vanderbilt University at that time to help start the center and partly because it has unique features. Most of the easy vaccines have already been made.
for the viruses that we have and the formula,

[00:18:49.236]the risk benefit and the cost benefit formula
now for vaccines is such that it may not be

[00:18:55.386]that industry alone will be able
to develop very many more vaccines.

[00:18:59.336]And so the unique feature of our
program is there is government money,

[00:19:06.836]public money for public health
in vaccine manufacturing.

[00:19:10.976]That has not occurred very often.

[00:19:12.826]If it has occurred, it is mostly
been in the setting of the military.

[00:19:16.456]It is a very mission oriented
program, unlike many programs at NIH

[00:19:23.046]that are more free flowing,
basic research, follow the idea.

[00:19:27.846]This is very mission oriented group and self
contain means that we cover a broad array

[00:19:34.766]of activities all the way from
atomic structure of the proteins

[00:19:39.376]to clinical trials in a relatively small group.

[00:19:44.336]So these are some of the
principal investigators of the VRC.

[00:19:47.626]We work out of Building 40 on the NIH campus,

[00:19:51.426]but now the program also includes
what we call the pilot plan,

[00:19:55.556]which is a GNP production facility in
Frederick about 20 miles north of campus.

[00:20:00.406]
It is a state of the art facility that is every bit like you would see at a Merck or a Glaxo.

[00:20:09.396] There is a clinic here now in this building.

[00:20:13.696] This is the new Building 10, so we can do phase one clinical trials.

[00:20:18.156] This is the clinical trials group and we also have a processing cite in Gaithersburg, a few miles away that processes our clinical samples and does good laboratory practice end point analysis.

[00:20:24.256] We also can do small animal work and we have a primate colony spread out throughout the world of about 500 Indian (inaudible) that allow us to do the studies we need to do pre-clinically before we get into clinical trials.

[00:20:32.136] And because the gates are imposing and the fence around NIH is imposing,

[00:20:38.386] we now have a mobile clinic to see if we can reach out beyond the gates to do these clinical trials.

[00:21:00.356] And since 9/11 in 2001, our mission has expanded somewhat and I won't say anything about these other programs, but in addition to HIV, we now have a programs or have done programs on Ebola Marburg, smallpox vaccine, alternative smallpox vaccine,

[00:21:19.146] West Nile Virus, SARS coronavirus,
and influenza viruses.

So the story of HIV vaccine development has been kind of staggered and it has its ups and downs.

Pat Thomas has written a book about some of these ups and downs, some of the peaks and valleys that she has witnessed, but there has been a clinical trials program for HIV vaccine evaluation since 1987.

Vanderbilt was one of the founding sites and since that time, a number of different vaccine products have been developed and may be as many as 60 different concepts.

And but those have only resulted in a small number of efficacy trials where you actually test to see whether a vaccine works or not.

And the first one was this Vac Gen GP 120, which was based on a purified protein.

It was based on the same thing that the Hepatitis B vaccine was based on.

And the problem is because we weren't inducing antibodies that could neutralize the common virus, it did not work.

So that trial ended in 2003.

A purified protein can induce antibodies in CD4 T cells, but it cannot CD8 T cells,
the ones that can clear the virus infected cells.

And so from that time, even before that time, studies were being done with vectors, vector based vaccine delivery.

So this RV 144 is a trial using a canary post vector boosted with this GP 120.

It is in 16,000 people in Thailand.

They had an interim analysis in 2007 and 8, the trial is continuing and we will hear about the results of that study, I think this year in October.

And then there was the Merck studies, where they took an ad nil virus based vaccine and add 5 vector, I will tell you more about that and did something called the step study.

That is where the title of my talk came from, because the step study was a good idea.

It was testing a very important vector that can induce CD8 T cells that could have a chance of clearing the virus early and it was conducted first in North America and then in people who are adnil virus naive, add 5,0 negative and then extended to add 5 immune people and then it was extended to a sister trial in South Africa called Pambilly (assumed spelling),

so these 6,000 people were studied with the Merck vaccine and you see these big red Xs.

There was something that happened in this
trial and that was at the interim analysis

[00:24:10.996] when they were evaluating this first
trial that was primarily in North America,

[00:24:15.386] they found that among the
vaccinees there was a higher rate

[00:24:18.896] of infection then among the placebo recipients.

[00:24:21.816] So the vaccine was causing an increased rate of
infection at least among some of the sub groups

[00:24:28.536] and we will talk about those sub groups
later, but the consequence of that was

[00:24:32.666] that the Pambilly trial was immediately
stopped and this pay 100 trial

[00:24:38.546] which we had been planning for the last 7
years, which was slated to start on September 28

[00:24:46.646] of 2007, 10 days after this
Merck announcement never started.

[00:24:52.306] So this pay 100 study that was going to evaluate
a different gene based vector concept did not

[00:24:58.536] start, so I will tell you the
basis for that vaccine product.

[00:25:04.996] I will tell you the differences
between it and the Merck product

[00:25:08.146] and then I will ask you what you
think about starting the 505 study

[00:25:12.796] and you can help me decide
whether it should go forward.

[00:25:16.656] So the VRC vaccine candidate was multi-valient.

[00:25:21.866] It included envelope genes from plates
A, B and C that covered about 85 percent
of the incident stains in the global epidemic, attempting at least to have broader coverage of a greater number of viruses.

And it included multiple genes, not only the gag and paul genes, but the nef gene and these envelope genes.

So it included a lot of genes and a lot of plates to cover a lot of viruses and it used two different types of platforms, a DNA vaccine platform to prime the response and an antinal virus based platform to boost the response, the DNA was delivered by this needle free injection system and the boost had a set of matching genes.

And so what we knew about that vaccine is that in non-human primates, among the vaccinated animals, you could lower the peak virania relative to the controls and you could lower the early set point virania in animals who had been vaccinated with a similar type of vaccine and challenged with SIV, a simulated immune deficiency virus.

We also knew that vaccinated animals had a survival advantage in this very stringent SIV challenge model and so that DNA ad combination had better protection in monkeys then the adnil virus alone product from the Merck studies.
We also know that in this example where compared to the sham or the mock vaccinated animals, animals immunize just with the DNA add (inaudible) gag and paul, which had a relatively small reduction in the set point virania, had a much larger reduction in the semen viral load. So the amount of virus in the semen (assumed spelling) that could be detected was even greater, more reduced in the vaccinees than you would have guessed from just looking at the plasma virus. We also know from early phase one clinical trials that giving either DNA alone or adnil virus alone compared to the combination of DNA and adnil virus that the heterologist (assumed spelling) gene based combination gave a much higher antibody response, more than 100 fold higher antibody response and if you measure T cell responses and this is an ell-(inaudible) essay, but it is a measure of these CD8 T cells that I have been talking about. If you combine the DNA and adnil virus, you can see about a 5 to 7 fold higher response of T cells in the combination than you can
in either of the modalities by themselves.

And the response was also qualitatively different.

One of the big features of this new center is all the ways we can measure T cell responses and Mario Roater and Rick Kelp there have pioneered this use of poly functional T cell analysis using flow based methods where we can phenotype cells and then define whether they are making these degranulation markers or putting out the things that can kill the target cell or making these various (inaudible) that are a measure of the CD8 T cell function and we can measure all of these things at the same time on a single cell basis.

So there is really a large number of phenol types in these cells, but we condense them down into just how many functions are present and we can ask in the HIV response is it poly functional or relatively oligal functional and what you can see in both CD4 and CD8 T cells compared to just adenyl virus by itself, the DNA ad combination is much more poly functional.

There are many more cells that are making 3, 4, or 5 functions instead of 1 or 2. And so in the DNA ad heterologist prime boost combination, we are seeing more T cell response
and a more functional T cell response.

So this product was moved into phase 2 studies and this was done on three continents and three major regions by three major networks, so we had network partners, the HVTN, which was domestic and also in South Africa, US Military Research Program, the International AIDS Vaccine Initiative, a nonprofit and a military program work together in East Africa with a very diverse group of investigators and we accomplished a 920 person study that we called the Triad and in that I will just show you this one table and bottom line that either at our facility in Gaithersburg, the HVTN labs in Seattle, the IOVI labs in London or the military field site in Tanzania, if you measured T cell responses in the field in these vaccines in populations at risk, you could see about a 70 to 80 percent response rate, which was considered good at the time. But then on September 18th, our September 18 was worse than September 11th, in some way, but this report from the Merck study showed that there was increased rate of infection among vaccinees compared to placebos and it was even more profound in people.
who were prior, previously exposed to adenovirus 5, so ad 5 zero positive people,

[00:31:08.706]
there was a risk rate, odds ratio of some place of around 3

to 1 vaccinees to placebos getting affected.

[00:31:17.586]
So the question is first of all what is going on there and second of all is it safe
to do any more gene based vaccine studies?

[00:31:26.266]
So the next analysis broke it down into whether a person's ad 5s were all negative or positive

[00:31:34.286]
and whether they are circumcised or uncircumcised

[00:31:38.126]
and what you see here is the greatest risk among vaccinees was among the uncircumcised men

[00:31:45.856]
and this entire analysis was done in men.

[00:31:49.266]
So of the 83 infections in that first analysis, 82 of those analysis were in men.

[00:31:55.746]
This analysis is only evaluating gay men in North America.

[00:32:02.376]
[00:32:03.456]
And so, the odds ratio is highest in uncircumcised whether they are ad 5, 0 positive

[00:32:09.846]
or not, but there also appeared to be some risk among circumcised men

[00:32:15.616]
if they were add 5, 0 positive.

[00:32:18.796]
So the question is if you just focus in on this group of circumcised ad 5 naive individuals

[00:32:30.316]
where the relative risk of vaccination was less than 1,
could you do a safe vaccine study in that population?

The other piece of data that came out of the Merck study was that among people who had a low ad 5 antibody before vaccination, if you looked at their LE spot response compared to the viral load after they were infected, there appeared to be a correlation in those people who are ad 5 naive, ad 5, 0 negative, as opposed to the people who are ad 5, 0 positive prior to vaccination where there was no correlation at all.

So the question became was it safe to do a vaccine trial in ad 5, 0 negative circumcised men and ask the question can we identify a T cell measurement that correlates with reduce viral load and at least take another step toward finding an HIV vaccine.

So that is one piece of information that you need.

Now I am going to compare the VRC vaccine to the Merck vaccine and you can then judge if it is different enough.

So the VRC vaccine includes these plasma primes with an adnil virus boost.

It is an ad 5 based vector.
included in ours is represented here.

In the Merck vector, there was a gag paul naf adnil (assumed spellings) given repeatedly at 0, 1 and 6 months.

So the genes differed somewhat, our product included gag and paul and nef, as did the Merck product, but we also included envelope genes, so there was a little bit difference in antigenic content and then this is a nuance to some people, but it may be one of the most important differences in these two vectors.

There is different ways of making adnil virus vectors, the Merck vector used the E1 region to put the trans-genes, so the gag and paul and nef were put here, so that when the adnil virus was used to deliver the gene, those genes were expressed out of this site, but that means the rest of the genome backbone for the adnil virus was also making RNA and making adnil virus proteins.

In our construct that was made by Gen Vec, not only was the E1 region used for expressing the trans gene, but the E3 region was deleted, partially deleted that is a region that adnil virus uses to modify immune responses.

It has analogs to different cemokin
(assumed spelling) receptor genes.

It has proteins that will down regulate the MHC molecules and so this contains a lot of immune avoidance genes that was deleted.

And importantly, this E4 region was deleted and E4 region has a set of genes that allows the other adnil genes to be expressed and so if you just look at the blots here of the kinds of proteins in adnil virus that are made by either an E1 deleted or E1, E3, E4 deleted vector, what you see is the hexon and the panton based in the fiber that makes up the capsule of the adnil virus or made from the E1 deleted vector, but not made, so there may be a lot more adnil virus proteins being made if you don't believe the E4 regions, so that is the other difference in these vector systems.

So in the field studies, we saw that not only in the phase one studies, but in the field studies, six months after the adnil virus boost, you were able to maintain a fairly high level of T cell response to the different envelope A, B and C proteins or peptide pools and the gag, not so much against Paul and nef. But against the envelope and gag proteins, even after six months,
there was a good T cell response.

So the question is and this is what we believe and I would like to hear comments from the audience on whether I have made the case to you.

That is that we think it is safe to proceed with this type of product, an ad 5 antibody negative circumcised MSN because of the partial protection in SIV challenged monkeys, we think we have a slightly different possibility for efficacy, because there are differences in the antigenic content and the pattern of immune responses with a more balanced CD4 and CD8 and more envelope and gag rather than paul and gag response and because importantly we have the opportunity to identify T cell responses that could correlate with reducing virus load, which were made to take the next step in vaccine development.

We think there is a good scientific basis and ethical basis for moving forward.

So there is a trial called HVTN 505, it is much smaller than that original pay 100 study.

It is designed to study this vaccine in this group that I just described and it would enroll about 1,350 people, half of who would receive this vaccine and half of who would not
and the major end point would be able to see if they could reduce viral load by at least a log

[00:38:05.546] in those people that became infected despite being vaccinated.

[00:38:11.206] So if we were able to start that study and it has now been submitted to the FDA

[00:38:15.316] as of just a few days ago, the crew would again around July and that means that sometime

[00:38:24.726] in 2012, we would know if this vaccine was having the affect that we thought it was.

[00:38:31.916] So I am going to stop there for just a moment and I would like to take a few questions

[00:38:36.896] and I want to go on to finish what alternative strategies there may be.

[00:38:42.586] So if anybody has a question or would like to make a comment here, let me hear it?

[00:38:47.756] >> The Merck study was done just in (inaudible) is that correct and if so, what?

[00:38:54.876] >> Well the Merck study was done initially in people who are ad 5, 0 negative in 1,500

[00:39:03.726] and then it was extended to ad 5, 0 positives in North America and the Caribbean.

[00:39:09.376] It turns out that about 1,200 of those 3,000 were women, 1,800 were men,

[00:39:17.456] but almost all of the infections were in men.

[00:39:23.336] It says a couple of things.

[00:39:24.826] One it says that we aren't very good

[00:39:27.386] at identifying high-risk cohorts of women in the United States.
It also probably says that women follow directions better than men.

You can interpret it either way.

>> In terms of phase twos for something like this, how much does putting on the trial change behavior, I mean.

>> Well when you go into start preparing sites for a vaccine trial, the question is how much does preparation change the dynamic of where you can do the trial.

So when you start preparing sites like this for vaccine work, it often takes years of preparation of cohort development, education, testing and treatment, exercises and so generally if you go into a place with a zero incidence of 3 to 4 percent a year, after a year or two that incidence will be halved.

It will go down to 1 to 1 1/2 percent per year. So in general, it will go down about 50 percent.

It is hard to get it to go below 50 percent with just educational intervention, but it does start making a big difference in the number of infections that you might expect from a given cohort.

>> Bernie, you didn't make it completely clear in my mind, are you testing them
or us that you have refined it and
(inaudible) more at this time (inaudible)

and what is your deadline going to be,
failures do you figure okay no more.

>> So, the question is where are
we going to do the trial, I think.

The trial as it is planned right now, originally
it was going to be planned in those same reasons

where we did the phase 2, but because of
the zero prevalence of ad 5 is so high,
especially in Eastern Africa, it is about
95 percent, recruiting a population of ad 5,
0 negative people there was
untenable and because

of the issues involving safety the trial is
going to be done in North America where at least
to ad 0 prevalence range is at
50 percent instead of 95 percent,
so we at least have a chance
of enrolling people.

So this trial would be planned for North
American MSM, men having sex with men, ad 5,
0 negative circumcised men, but
the subgroup in the Merck study

that actually may have had
a benefit from the vaccine

at least had a lower odds ratio
for infection with the vaccine.

The second question is how
many times will we fail
with an HIV vaccine approach before we stop testing and developing HIV vaccines.

Well if I tell you that there is 7,000 new infections every day with HIV,
do you think we should stop trying?

>> Oh no (inaudible).

>> So our goal is to never stop trying and either we are going to find a vaccine
or we are going to change the dynamic of HIV in the world by trying to develop a vaccine

and the question is you know what is it going to take to develop a vaccine

and I am going give you a few additional slides about some of the new approaches

that are being taken and some of the technology that is being applied to this problem

and hopefully to get us to the point that we can have a more effective AIDS vaccine,

but you know if you look at the malaria field, there have been at least 20
to 30 failed efficacy trials for malaria vaccines.

If you look at the development process of almost any other vaccine product,
you have to go through a lot of failure to ever achieve something that is working.

We are still working to improve the influenza vaccine, something that is already licensed.

So I think that in vaccine
development in general,

there is a lot of failure before success typically.

So one of the problems for achieving the kind of breadth we need, not only the breadth of response in an individual, but the breadth and response in the population to cover all of the possible incoming HIV viruses is being addressed and an informatics approach and Betty Corber (assumed spelling) at Los Alamos is a brilliant mathematician who also is a trained immunologist and she has brought a lot of innovation to HIV vaccine concepts.

So one of the things she has done is using bioinformatics, she takes sequences from a large population of individuals. So for instance, all these different lines might represent a population,

well these would be the different viruses within a population and then she puts it through her computer algorithm and asks if I start recombining these sequences at natural recombination break sites, because HIV does a lot of recombination and I keep remaking recombinations of viruses and then I ask within those new virus recombinants, how many of the T cell epitomes that have been mapped
within these viruses have been retained
and can I achieve a virus sequence

that is relatively natural with the normal break
points, but that has achieved a higher level

of epitome coverage for the
different virus possibilities.

And what she has found by doing that,
she can find winning sequences from each

of these recombination experiences and
then by using a combination of these,

in silica recombined sequences, she can
achieve about a 20 to 30 percent higher level

of coverage with new epitomes above any given
single natural isolate or even a combination

of natural isolates and that is now
proving to be true in animal experiences.

So if you use a cocktail of two or three
mosaics or four mosaics compared to a cocktail

of three natural isolate sequences, you can
achieve a much broader range of response

and so instead of having the
three or four epitope response

in a normal setting you might achieve
in some of the monkey studies,

they have gotten up to 12
to 20 epitope responses.

So the thought is especially in T cells,
if you can achieve multiple responses
to multiple epitopes, it will be much harder for
that virus to escape, just like three drugs is
when we really started making a big impact on HIV instead of just single treatment

where the virus can serially escape.

So this new concept of mosaic inserts is now being combined with a whole variety of new vector choices which are being developed, not as DNA and ad 5,

but there is a whole variety of gene based vectors that are being used and combined in different ways using these new insert designs to see if we can really maximize the breadth and the magnitude of the T cell response.

But the real problem is antibodies, so I am going to end with a brief series of slides on the antibody problem and most vaccines have worked because we introduce an antibody and it turns out for various reasons, because this protein, this GP 160 protein on the surface of HIV is so highly cligoscualted, it is hard for antibodies to reach the most vulnerable sites.

It is very flexible and so there is a lot of different forms that it takes before it locks into the sector making it hard for an antibody to ever lock in on a single confirmation and the sites that are most vulnerable are hidden in these places.
If you were looking at the top
of this molecule even in a groove

[00:48:29.196]
that requires an antibody coming
in at just the right angle,

[00:48:33.236]
just the right specificity to neutralize.

[00:48:36.396]
So over all these years, there has only been
a handful of antibodies that have been found
to broadly neutralize the commonly
transmitted strains of virus.

[00:48:41.796]
Two of them are against this
membrane proximal region in the GP 41

[00:48:51.916]
that is anchoring the protein to the
viral membrane and then two of them are

[00:48:58.416]
in this GP 120 head, one of them is where
the CD4 binding site is for main receptor

[00:49:06.826]
of the virus, that is the B12 antibody.

[00:49:09.346]
The other one is 2G12, which recognizes
a combination of glocisolation sites

[00:49:15.806]
that is not particularly well understood.

[00:49:18.536]
So the question is if you
apply structural biology

[00:49:21.686]
to understanding exactly the atomic structure of
these GP 120 molecules in their different forms,

[00:49:29.476]
can you use structure based
vaccine design to find something

[00:49:34.726]
that might actually work
for neutralizing antibodies.

[00:49:38.146]
So one of the big findings early on
using this structure based approach is
that if you compare this core structure over here, which Peter Cong solved in 1998,

this is taking off a lot of the GP 120 just looking at the core molecule and asking

in the CD4 bound confirmation, bound to its receptor, what is the GP 120 look like

and this domain right here, which is called the bridging sheet.

This is where the CD4 binds, this is the inner domain and the outer domain.

This is the place that binds the coreceptor for HIV, the CCR5 or CCR4,

so this is one of the early important vaccine targets thinking that we could use

that as a target for vaccine development.

Well it turns out a few years later when Harrison solved the unbound, unleaded structure,

if you look at GP 120 before it is bound to its structure, these two regions that make

up the bridging sheet are not even together and so that region doesn't even exists in the virus,

before it is already bound to its receptor.

So using this kind of structure information,

we can have a much better idea of what the targets are for HIV.

So making antibodies to the bridging sheet is obviously not an option based on this and

but in contrast if you focus not on the inner domain and its changing position,
but the outer domain, the outer domain in both the unliganded
and liganded position is very constant,
so this region of the GP 120 molecule remains very constant.
So Peter and his group at the VRC have used a series of experiments
where they co-crystallize these antibodies, these broadly neutralizing antibodies the GP 120
or the GP 41 and they determine exactly what the structure of the binding stuff is
for neutralization and one of the more important papers was this one
where they used the B12 antibody pictured here interacting with the CD 4 binding site here
and then they mapped the region of the antibody footprint to the CD 4 footprint to try
to really show how the antibody was binding to neutralize the virus.
So if you have that information, what do you do with it?
So the different approaches now that are being taken with the proteins,
based on this structural information is the following.
First of all one of the problems with HIV is this reason here
where CD 4 binds is somewhat blocked by the other primers and these regions in here,
if you just present the single monomer, if you just present one of these to the immune system,
all of the antibodies response is happening to this
which is not even present in the natural virus.
So one option is to make the more native primer as a vaccine hoping that the antibody will find that little groove right there to go into.
The other approach is to make an artificial protein in which you try to single out that one area where you want the antibody to bind by cloaking the rest of the protein in glucosylation sites.
So you can build these glucosylation sites into your protein so that this now is covered with sugar and you are hoping that it will make the antibody focus on that one green spot.
Another approach is just simply presenting the outer domain of the protein to the immune system hoping that it will see that CD 4 binding site and an even more elegant approach is scaffolding where that exact structure for neutralization is preserved and a guy at Washington University, University of Washington Seattle, Bill Sheaf (assumed spelling) takes that structure and he does a threading program and so he threads that structure
through the entire protein database and he finds other proteins that can hold that structure in the right conformation, so then he can then lift that exact determinate and put it in 10 different proteins that are irrelevant of themselves other than the fact that they can hold that one little structure in just the right shape.

And so all these approaches are being taken and some of the more successful approaches have been the trimer in which some of the pieces have been locked into place with disulfide bonding so that it won't be such a flexible molecule and it will have less entropy. That approach is starting to have some promise and this scaffolding approach and the outer domain approach are starting to have some promise that we can start directing more of these antibodies at the right angle to the right spot, but the question is still whether we can ever develop that into a real manufactured vaccine, which is still several years away.

So that is what is happening in HIV vaccine research.

We still have a long way to go, but we will believe that somewhere over here
after we finishing walking on this path that we will get there eventually

and I will stop there and take any more questions.

( Applause )