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CURRENT APPROACHES TOWARD THE CURE OF HIV DISEASE

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[video transcript]

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Welcome to Physicians Research Network. I'm Jim Braun the course director of the monthly meetings of PRN in a New York City. Since our beginning in 1990 PRN has been committed to enhancing the skills of our members in the diagnosis management and prevention of HIV disease as well as its co-infections and complications. We hope this recording of Daniel Douek's presentation and Current Approaches Toward the Cure of HIV Disease will be helpful to you in your daily practice and invite you to join us in New York City for our live meetings in the future. PRN is a not for profit organization dedicated to peer support and education for physicians nurse practitioners and physician assistants. The membership is open to all interested clinicians nationwide at our website PRN.org. Now allow me to introduce Danny Douek from Bethesda Maryland who will be speaking as a private citizen rather than as a representative of the National Institutes of Health. It's a pleasure to be here. I'm going to be talking about current approaches towards the cure of HIV disease. Now this topic is a topic of quite a bit of controversy and there are many things that we disagree on about and there are many things that we agree about and I'm going to start with the things that we agree about. We agree that when somebody comes in becomes infected with HIV they reach a peak virus load which then settles down to some set value that you can see up there. The the setpoint we also agree that when somebody goes on antiretroviral therapy you can get that virus slowed down to all intensive purposes and undetectable levels.

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And we also agree that if you stop antiretroviral therapy virus comes back within two to four weeks. OK. Almost everyone virus comes back within two to four weeks. You could write it on a big flag and put it at the top of the Empire State Building. It's that important. OK. It's the very different definition of what is not fake news. And the reason the virus comes back is because of the HIV reservoir cells that harbor replication competent virus that can rekindle HIV replication and transmission and the absence of drugs. So let's begin by talking about this HIV reservoir. So here you can see an acutely infected person and then chronically infected and off therapy lots of productively infected cells there in red making virus. And if you put someone on therapy as we discussed what you're left with is a few quiescently infected T cells the productively infected ones have gone quiescently infected cells remain. Now these quiescently infected cells can live forever for the lifetime of the infected person and they can clonally expand not producing any virus but just dividing and carrying that HIV genome with them so that if he were to interrupt A.R.T. virus rebounds from those latently infected cells. So the goal of a cure is to kill or suppress or take away that infected cell in some way. So let's start with a definition few definitions. Three definitions. First of all the HIV raised what we just discussed the cells harboring replication competent virus that can rekindle replication and transmission. In the absence of A.R.T. cure a full cure is the elimination of all replication competent HIV.

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And what we might call remission or what is also referred to as a functional cure I would define is a sustained period of viremia in the absence of A.R.T. and I would add the inability of that individual to transmit HIV to another person. Now what we're going to try to achieve. I'll tell you what I think we should try to achieve at the end of the talk and we'll see if you agree with me. So if we continue talking about the reservoir we can ask some pretty broad questions. They seem broad they seem a bit dumb but they're not that dumb because we don't really know the answers such as how big is the HIV reservoir. Where does the HIV reservoir reside. Where is it in the body. What is its transcriptional state. Can we see it. Can the immune system see it. Where is the HIV reservoir that matters. That reservoir that when you take someone off therapy will rekindle and try and kill an individual because developing treatments that target those HIV infected cells is by definition a part of the path towards a cure. So how big is the reservoir that matters. Well we don't really know if you take all the infected cells in the body. Sorry in the blood were talking about the blood here. It's a thousand infected cells per million CD4 T cells and 100 percent of all the HIV genomes. And then you go down to the integrated genomes intact genomes all the way down to the genomes that are actually capable of producing replication competent variants the virus that matters.

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What you see is that only a tiny and very difficult to quantify fraction of HIV genomes in blood CD4 T cells actually produce replication competent variants in people on antiretroviral therapy. So how big is the reservoir that matters. We don't know but it's somewhere between the pink and the grey. So it's a bit of a really grey area. So how do we cure HIV infected people. Well the subject of another talk that I have is to show you all the multiple mechanisms that account for HIV persistence. So I'm not going to be talking about that today but if we accept that there are those multiple mechanisms then a unifying theme of a cure would be to find and diminish the size of that HIV reservoir. And you can do it a number of ways and I'm going to talk about these this evening. You could reduce seeding of the latent pool with early or more A.R.T. you can reverse latency with shock and kill that most of you will have heard of you could increase HIV specific immune function with vaccines or immune checkpoint blockade. You could do gene therapy to disable the virus or you could remove infected cells with HIV specific antibodies but because there are multiple mechanisms I want you to appreciate that combination therapy may be necessary probably will be necessary by definition but you might say to me whoa! Danny and I say whoa what! and I say well we've already cured HIV infection and indeed we have. Right? We've done that once and you know this man this is Timothy Ray Brown and he's doing very well off antiretroviral therapy. Ten years of therapy and he received a hematopoietic transplantation with cells from a donor who was resistant to infection.

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CCR 5 delta 32 homozygous mutation. And he's doing well can't find any virus in him. He's got no antibodies no specific T cells. We look every now and again we've got his cells in our freezers there's

nothing there and it's fantastic. But even though this procedure works it's highly unlikely that it will ever translate into an accessible approach. Can you imagine doing allogeneic hematopoietic transplantation in a resource limited setting in Africa somewhere like that. It's not going to translate and this point is reinforced even more by the experience with the Boston patients. Now these were two guys in Boston who had almost the same thing as the Berlin patient hematopoietic stem cell transplantation. But this time with cells that were susceptible to infection. And look what happened. Despite a 1000 10000 fold reduction in reservoir size virus rebounded off therapy in both of them. This guy it took eight and a half months for virus to come back but it came back now some very interesting studies using mathematical modeling showed that the latent reservoir will have to be depleted at least 100000 fold to achieve a cure. Okay that's the figure that we have in the literature. But I think that's wrong. Two reasons one. That study was made up because it was mathematics wasn't real. It's just modeling I don't like modeling two if you ask the question by sequencing viruses How many viruses accounted for a recrudescence in this guy here was a single virus. All right.

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So yeah you can reduce the size of the reservoir 100000 fold but if you've got two viruses left and one of them has a viable genome they'll come back because that's what it does. Right. HIV likes to run hot ok cure approaches. I'm going to go through some cure approaches now. A whole bunch of things. Everything that's being tried. And you will be able to gauge my enthusiasm for these various approaches. By the look on my face and the tone of my voice I do very good disdain the early antiretroviral therapy it's a good idea but all right here we're looking at some early HIV reservoir dynamics. I'd like to make what I think is a very important point here. Two cohorts of people here followed from very early infection. One cohort the red guys went on treatment early. The blue guys did not go on treatment at about the time that HIV RNA becomes detectable which is here the reservoir begins to increase dramatically with an apparent hundredfold increase over the next two weeks a hundredfold increase in two weeks. So if any of you are wondering should I start treatment early start. The reservoir is therefore largely established by week four of infection. There it is. It's done now as you can see early A.R.T. can significantly reduce the size of the reservoir that's this solid line here. All right. And I can show you the same data here. This is integrated HIV DNA in P.B.M.Cs. If you start within two weeks of infection of exposure size of the reservoir is very small. If you start two to four weeks it's a lot bigger if you start as you approach the chronic phase it's much bigger. So very early A.R.T. significantly reduces HIV reservoir size.

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Does that make any difference to the person who's infected. So what happened here was people would take an off therapy right. And time to rebound was measured. So if therapy was started very early stage one time to rebound a virus was made in 26 days. If therapy was started two weeks later. Time to rebound 22 days. Therapy was started in the chronic phase times rebound 14 days doesn't make any difference. Mathematically it makes a difference and it's significant. But to the person who's infected

with HIV there's no clinically significant delay in time to virus rebound. So folks we're up against a wall here right. We're up against the wall. You can't treat any because if you're going earlier then you're in the realm of PEP and then PrEP. All right. So we're not going to treat our way out of that shock and kill. You'll have heard a lot about shock and kill. You'll have heard a lot about it because a lot has been published not because it's any good. OK. So what is shook and kill. This is a cure approach where you take an individual and you reactivate HIV Transcription by activating the T cells with an LRA a latency reversing agent a drug such as Vorinostat that makes the cell produce virus coming out here. The idea is that the virus or the immune system will kill the cell. You can see here. So the infected cell has gone. So the HIV reservoir is now one cell smaller and you do this under the cover of A.R.T. to stop any new infections. All right.

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There's a whole bunch of different approaches different drugs that are being used these are all LRAs the underlined ones the ones that are in or soon will be in clinical trials and there's a whole bunch of other metabolic pathways other pathways that of being considered so numerous LRAs have been identified in studies with cell lines and primary T cells they can activate cells in vitro. And that red line there is maximum activation and each one of these is a different drug and it shows you the extent of activation but relative to T cell activation few of these LRAs work very very well with cells from HIV positive people in clinical trials. There is evidence for an increase in cell associated and plasma HIV RNA. Right. So the LRAs are working. They are making virus wake up and it's being transcribed but there's no reduction in the reservoir size yet demonstrated. So this should be a concern. Here's a list of some of the studies that have been done since the beginning. This is one of the latest that was published just a few months ago. And you can see all these arrows going up these are measures of the size of the reservoir cell associated RNA plasma RNA thats the virus load cell associated DNA. That's the size of the reservoir. You can see all the arrows either going up or sideways which is not a good thing. We want the arrows to go down. This study here. In fact if you look closely the size of the cell associate to DNA amount actually went up a bit.

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So what we're doing at the moment is increasing the size of the reservoir with this shock and kill approach. So what's going wrong. Well remember the point of shock and kill was to shock and kill clear the infected cells. Does the virus kill the infected cells. Well I'm quoting here from a paper from Bob S Connor's group at Hopkins after the reversal of latency in an invitro model infected resting CD4 T cells survived despite viral psychopathic effects. So the virus doesn't seem to be killing the cells effectively. Maybe the immune system can help. Well the problem is as you well know that in most of our patients most of the virus has mutated to escape the immune response and escape variants of the virus dominate in the latent reservoir of chronic subjects. Well maybe you can vaccinate with the therapeutic vaccine to increase the size or the functionality of that immune response and indeed you can you get transient expansions of T cells but they don't recognize the escaped HIV epitopes and you recognize the original ones. So your immune response doesn't do anything and while we're on the subject of

therapeutic vaccines where do we stand with that. There have been about 40 clinical trials of therapeutic vaccines to date. DNA based vaccines RNA based peptide based virus vectorbased lenti viral vectorbase and of course that good old standby dendritic cell based vaccines which have been shown to be safe and generally immunogenic. So who knows what it means when the title of a paper is blah blah blah therapy is safe and generally immunogenic. It means that doesn't work. Okay so in most of the studies there was no benefit at all in some studies. There was a questionable benefit.

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I would say yet after two decades of largely failed approaches. Despite this the therapeutic vaccine field remains alive and well very active. I'm going to discuss this study in a few slides time and if you don't believe me here is a bunch of ongoing trials just to show you. Well maybe we're doing things wrong here. Maybe we should combine shock and kill with other modalities so maybe we could combine shocking kill with a vaccine like here with an antiviral agent like type 1 interferon or with a broadly neutralizing antibody. So let's look at a few of those studies. Okay early A.R.T. plus Vorinostat that is an LRA hydroxy chloroquine is an anti-inflammatory and maraviroc. You know what that does. These were people who were started on treatment and febic stage 3 or 4 so pretty early 2 years and then either got placebo or the mixture of these drugs. And what you can see when therapy was stopped when anti retroviral therapy was stopped is that there was no delay to virus rebound after A.R.T. interruption. So that didn't work. What about a peptide vaccine plus a very potent LRA. Romidepsin that's the darling of the field these days. This was a non randomized observational study of 20 people. They were immunized with an HIV vaccine here then they were given Romidepsin in the LRA and then therapy was stopped here. So the days here correspond to the days up here. What you can see is there was no change in integrated DNA or infectious virus but here you can see there was a decline in total HIV DNA that was statistically significant.

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So there was a slight decrease in the size of the virus reservoir but when therapy was stopped two to four weeks it all came back no clinically significant delay in time to virus rebound what about something more complicated. Start people really early with therapy anti retroviral therapy. Vaccinate them right at the beginning with a really good vaccine. And then you boost them with another vaccine and you give them Romidepsin in the latency reversing agent and then you stop antiretroviral therapy. This is a small study. It was uncontrolled. Eight of the 13 individuals came back two to four weeks. Five of the 13 when the data were presented at CROI they said five individuals sustained HIV control its not really controlled because they all viremic just not very viremic. And I've heard recently that a few of them are not controlling at all. So it doesn't seem to work very well. So you all really depressed now? It doesn't sound good. But this is the tray I'm going to depress. I don't want you to go home to when you go I'm happy this is New York you can party do what you like. So the stuff that you've read about doesn't look great you've read about it because it's relatively easy to administer these drugs to people. The studies were published. There was a lot of hope in the field but it doesn't seem to have borne fruit. So I'm going to

turn to some things approaches now which are far more preliminary but I think far more exciting this is immunotherapy. This is this is amazing. You've heard of cancer immunotherapy right. Everyone's familiar with checkpoint blockade this.

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This is incredible. I was one of most immunologists who would say you know 20 years ago 10 years ago this will never work. You guys why are you doing it. I mean at immunology meetings the immuno-therapy session would be like the Sunday afternoon of a weeklong meeting and there would be five people in the room and it was the five speakers and no one else was there. And they've revolutionized the field. This will win a Nobel Prize soon. So I think cancer immunotherapies reshaping a fatal and progressive disease cancer in much the same way as antiretroviral therapy reshaped HIV disease. Is that important. Most therapies aim to enhance the capacity of CD8 T cells to eliminate cancer cells inflamed cancer environments and they aim to act by inhibiting either immunosuppressive checkpoints. I'll talk about those or immunosuppressive cytokines or immunosuppressive cells or all of those things. So what is T cell exhaustion? This is an exhausted CD8 so it's been recognizing its antigen for a long time. A cancer antigen B HIV. How do we know it's exhausted. It expresses the immune checkpoint marker its called PD 1 so that when the CD8 T cell meets its target a cancer cell or an HIV infected cell which happens to be expressing the likened and PDL 1 that interaction will send the message the T cell receptor to shut that CD8 T cell down so it won't recognize and kill its target cell that's an infected T cell. What we want to do is to reinvigorate that T cell and we do it by blocking this interaction so that the T cell receptor recognizes the target cell and kill the target.

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And monoclonal antibodies to PD1 it's like an PDL 1 and another marker CTLA-4 have been used for melanoma lung and bladder cancer. And one of the drugs Pembrolizumab also known as Keytruda was licensed recently by the FDA. This is really amazing and it's been shown that xViva the blockade of PD 1 PDL 1 CTLA-4 enhances HIV specific CD8 T cell responses. So this may work for HIV infection. Now I mentioned antibodies against PD 1 PDL 1 and CTLA-4 but is just the tip of the iceberg. There are more blocking antibodies to inhibitory receptors and activating antibodies to activating receptors so it's just the beginning. There's another very interesting wrinkle very specific for HIV infection which is that checkpoint blockade may act as a latency reversing agent. All right. This is really cool. What was found is that the more immune checkpoint markers a CD4 T cell expresses so if it expresses PD 1 and PDL 1 and CTLA-4 and tigit and Tim 3. There's a whole bunch of them. The more it expresses the more likely it is to contain HIV the more likely it is to be a source of the latent reservoir. So how does that work. Well if a cell gets infected with HIV. Right. And it's expressing a checkpoint marker and that checkpoint Mark is restimulated it'll show that cell down will become quiescent and that cell will become a latently infected cell. All right. And that last forever. So if you block this with an immune checkpoint blocker like one of the antibodies I just talked about is being used for cancer.

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What it will do is to reinvigorate that cell and HIV will be released from that cell which means you're reinvigorated CD8 T cell will be able to recognize that cell and kill it. So it's a kind of two for and this xvivo and invivo evidence to show you for latency reversing activity of anti PD 1 and anti-CLA4 this is a guy with metastic melanoma and HIV who was on ART and was given ipilimumab that's anti-CLA4 an immune checkpoint blocker. And what you can see every time he received the antibody virus load peaked like that single copy assay. It peaked like that. So it's waking up the virus. All right. Doesn't do any damage because he's on antiretroviral drugs. He was given another checkpoint blocker Nivolumab and that increase the amount of HIV that was being made. Unfortunately it also increased the size of the reservoir because HIV DNA went up. Okay that doesn't sound so good. But what I want to show you the results of a study that was published two weeks ago this is remarkable so this is a 51 year old HIV positive man with relapsed non small cell lung cancer after a lumpectomy and chemo. And he was given anti PD1 Nivolumab administered every two weeks from August 2016 to July 2017. This is what happened so HIV RNA went up this green line here transiently. So they're activating the reservoir to produce some bits of virus there was a reduction in the frequency of exhausted CD4 CD8 Tcells you can see this going down here. So that's good even better than that. Look at this green line.

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There was a dramatic increase in the frequency of HIV specific T cells. All right. That being reinvigorated this is what we want to happen even better than that. There was a dramatic decline in the frequency of HIV DNA containing cells and blood. This is pretty staggering. Now there are problems with the study problems in which the way the virus was measured it's not controlled but this is the first indication of a dramatic effect in an individual. That makes sense because it all fits together. So this individual is involved in a bunch of immune checkpoint blockade clinical trials. I'm showing you them here. They're currently recruiting no terrible adverse events have been reported. No events on virus effects yet apart from that one individual. All of these trials are underway and HIV positive people with malignancies future trials of combinations and new drugs have been approved to be performed in HIV infected people with no malignancies. So I think this is great and I really look forward to coming back sometime in the future and reporting this to you. However these drugs these antibodies are potentially dangerous. These are the results of a study HIV infected individuals. Eight people. No effect was detected on virus load size of HIV frequency of HIV specific T cells increased a little bit. The study was stopped due to preclinical retinal toxicity. In a parallel study of this this approach in rhesus mechanics infected with this I.V. they went blind. OK. So there are auto immune toxicities. Some of them can be severe.

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We're figuring out in the field which ones are worse which approaches are worse than others but they may limit the use of certain of these antibodies in non-malignant conditions. So that's just a little caveat that has to be borne in mind. All right gene therapy the aim of gene therapy is to deliver a therapeutic agent to a cell using a gene. You could provide something to inhibit or kill HIV. Cut it up with some

enzymes. For example you could do something to remove something that HIV needs like CCL 5. A lesson that we learned from the Berlin and the Boston patients that I showed you at the beginning of my talk is that you need to remove both the virus and the target cells. Remember you can't just give chemo and wipe out the blood to remove the virus. You also have to give back cells from a donor whose cells don't express CCR 5 so I'm going to give you an example of a nucleus based gene therapy targeting CCR 5. Some of it has been published some of it not so individuals will take in people infected with HIV. Total CD total cells or CD4 cells or CD 34 positive stem cells from the blood removed from these individuals and grown up in culture and they were infected with a replication deficient adenovirus vector that expressed a zinc finger nucleases. This is an enzyme that recognizes a specific target in DNA. In this case CCR the core receptor for HIV. And it cuts it and it kills CCR5. So those cells can't express CCR5 anymore. All right those cells are then expanded formulated tested and infused with a without Cytoxan into these individuals.

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Now this is a very attractive approach. It's minimally invasive. No severe side effects. It's much more accessible than stem cell transplant and there's no need for compatible donors because there's no risk of GVHD because it's autologous. All right so what happened in trials in aviremic HIV positive people on the A.R.T. what was found was that a single infusion of gene modified CD4 T cells persisted for a very long time. InVivo we're talking years. Durable increases were seen in CD4 T cells enriched for the modified CCR 5 remember that resistant to infection so you'd predict that they have a survival advantage all participants had reduction in the size of the HIV reservoir over three years. See I'm showing here that's the reduction in the size of the reservoir. The kinetics of which suggested replacements of infected cells over time is good and the therapy interruptions six weeks after infusion showed that the reduction in plasma virus load setpoint correlated with how many CCR5 modified CD4 T cells you had. So the more gene modified cells you had circulating the lower was your virus load setpoint. After the therapy was removed early days. Very encouraging results. The real question is can we translate this how generalizable it is to the world of HIV infected people so finally I'm going to talk about therapy with broadly neutralizing antibodies against HIV envelope. You may have heard some about this has been a flurry of papers recently. And I think this is particularly exciting. So we use HIV specific antibodies to treat people or to prevent infection and prevention and treatment with antibodies are very different.

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I just want to spend a second going over this. Prevention is going to be a lot easier. All you're doing is preventing acquisition of infection. It's like a couple of viruses. You have to stop them. You might do it in these cases here. You just have to block transmission treatment. That's what concerns us is much more difficult because you have to deal with greater virus diversity but there is certainly a potential to reduce the size of the HIV reservoir or cure by blocking virus entry into cells or killing cells that are infected. This is a picture of the HIV envelope doesn't quite like that but the colors are all genuine. I can vouch for that

these are the names of all the antibodies which we have generated in the field and the red ones are in or will be in clinical trials soon. So you can measure antibodies potency and breadth potency is this way more potent is that way greater breadth of coverage. The more virus variants it recognizes is that way the original neutralizing antibodies we discovered were not potent and not broad. That's where we are at the moment with most of the antibodies pretty broad pretty potent in clinical trials where we'd like to end up. Is there a very broad very potent here are the results of a Phase 1 trial of viremic people after single infusion of one of these antibodies VRCO 1. And you see 3 patents you see profound and maintain suppression of virus that's that transient suppression of viruses and two guys who did not suppress virus at all. That's these guys here number 21 and number 26 why did they not suppress virus after antibody treatment.

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Well we can measure the sensitivity of the existing virus variants in these individuals before we gave them the antibody and the non responders had virus quasi-species that were resistant to the antibody before infusion of antibody. It's like a drug resistant mutation that's in there. Another trial showed very similar results profound maintains suppression engines suppression. Another trial that came out a few months ago. Same thing with one antibody different antibody this time profound suppression presence no suppression and the people who did not suppressed had viruses that were already resistant to the antibody. Here are 2 Phase 1 trials of this antibody VRCO1 one during antiretroviral therapy. So this is people who are now aviremic and then therapy was stopped. The majority rebounded by week 5 even though plasma levels of the antibody was still quite high. But there was a modestly delayed but significant delay in virus rebound compared to historical controls. So that's pretty encouraging. That's all monotherapy right. You would expect it not to last very long. We had this experience with monotherapy with antiretroviral drugs. So what's the second generation product going to look like it's going to be tenfold more potent current antibodies much more broad. It's going to be given by subcontaneous injection once every four to six months instead of infusion every eight weeks and is going to have a low cost. Are we getting there. Yes. I'm going to show you very quickly. So what I'm showing you here is each one of these is one of these broadly neutralizing antibodies.

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That's the breadth here the bigger the number the better and potency more potent the further down you are in this growth. So these antibodies are broad and potent. We also have antibodies that are less broad. You can see here but a lot more potent and look at this. Here's an antibody 10E8 that is very broad basically recognizes all HIV in the world is not very potent. We mutated it just a few little residues we when mutated the antibody and we ended up with a very broad and a thousand times more potent antibody. So engineering these monoclonals improves potency and breadth we can combine monoclonals I'm showing here the dotted lines the monoclonals being used on their route. This is a combination of antibodies in the solid lines and you can see as we combine them they become more potent and with greater breadth of coverage. So we can engineer antibodies we can combine antibodies

and we can increase the half life of the antibodies. So two amino acid mutations lysine and a serine luceine and a serine increase affinity of the antibody I was showing you just before VRCO1 for the neonatal F.C. receptor. What does that do. It protects the monoclonal antibody from being degraded in the endosome when it's taken up inside the cell. Which means the cell then chucks out the antibody and it's fine and it goes back into the circulation. So what we did at the Vaccine Research Center was to inject people with either VRCO1 the normal antibody or VRCO1 LS. LS The one with this mutation that should increase the half life what did it do. Well the VRCO1 half life was very low so you'd have to give it every maybe six weeks to maintain levels.

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VRCO1 unless it's still at super therapeutic level six months after a single injection. We're still waiting. We can't even calculate the half life yet. We're still waiting. This is amazing. That's an at least four fold increase in the half life in healthy adults which means that you would decrease the size of the dose five to ten fold you may extend the interval of dosing to every six months. Right. This is really wonderful. It also means it makes it very very cheap finally two approaches which are being looked at in vitro and in monkeys by functional antibodies that whole bites or darts whatever you want to call and the work like this. You take an antibody. One arm is specific for envelope and it'll bind the infected CD4 T cell. The other arm is specific for CD 3 molecule expressed by the CD8 T cell. It brings them together and the CD8 T cell can kill the infected CD4 T cell. These products exist and have entered clinical trials for cancer and they're looking really good in terms of HIV. These products have been made. They've been tested in vitro and here are the papers. So at the moment it's just a proof of concept in vitro and they're being studied in vivo in rhesus macaques at the moment it's a very new very exciting to conclude we have a greater understanding of the size shape location and maintenance of the HIV reservoir now. We can reduce reservoir size with early A.R.T. but is it clinically significant. No.

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Latency reversing agents shock and kill show poor HIV reactivation and no reduction reservoir size potentially an increase in reservoir size therapeutic vaccines maybe showed some effects in monkeys I didn't show you those studies but in humans it's really debatable immune checkpoint blockers aren't proof of concept studies. I would say does it look promising. It looks very promising. Hematopietic transplantation works once but is not scalable. All right. So how do we translate that well maybe gene therapy is a is a version of that clinical study shows some reservoir reduction. But again how scaleable is it can we deliver it and of specific monoclonal antibodies are it promising proof of concept studies with more potent MABS combination of MABS and by specific MABS being developed. I'll end by saying reinforcing that I think it's going to have to take a combination approach. I really think that the onset of the solution is going to come from immune approaches some kind of vaccine monoclonal antibodies. Maybe if we could make gene therapy deliver it'll be there as well but I think that's going to be. Are we going to achieve complete complete absolute cures. I don't think so. I think we're going to have to come to terms that we're going to achieve functional cures or remissions. But nevertheless it will be an HIV

infected individual off therapy with these other modalities controlling the virus and he or she won't transmitted to anyone else. It will be a combination. Go out there try all the kinds of things that you want and try. Have fun. Thank you for listening.

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