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In a Race to Cure HIV : Gene Therapy, Vaccines and Other Approaches

Progress in antiretroviral therapy has considerably reduced mortality and notably improved the quality of life of individuals infected with HIV . However, drug resistance, treatment-associated toxicity, adherence to medication, and the need for lifelong therapy have remained major challenges. While the development of an HIV vaccine has remained elusive, considerable progress in developing innovative cell and gene therapies to treat HIV infection has been made.

We are talking to Dr. Pablo Tebas M.D., Director of the AIDS Clinical Trials Unit at University of Pennsylvania's Center for AIDS Research (CFAR) on HIV gene therapies, vaccines, limitations of antiretroviral therapy (ART) and scope of new approaches for an HIV cure.

Full Transcript:

Priya Menon: Hello and welcome to CureTalks. I'm Priya Menon your host. The topic for today's CureTalks discussion is 'In a race to cure HIV- gene therapy, vaccines and other approaches. HIV research has come a long way since the disease was discovered in the 1980s. Antiretroviral therapy was a major milestone that changed the lives of millions, but the goal now is to find an HIV cure. And we have with us Dr. Pablo Tebas Director and principal investigator of the AIDS Clinical Trials Unit and Professor of Medicine at the hospital of the University of Pennsylvania. Joining Dr. Tebas on the panel is patient advocate David Stanley. Welcome to CureTalks, everyone. Dr. Tebas, it's a pleasure to have you here with us today. Me and David, we have a bunch of questions for you. I will start with a few of mine and then hand over to David for his. About 10 years ago, an HIV patient was cured of the disease for the first time anywhere in the world, the Berlin patient Timothy Ray Brown. He received a bone marrow transplant from a donor who was naturally resistant to HIV. He has been made of Antiretroviral therapy since the day of his transplant. And recently last week, we have a second documented patient to claim an HIV cure the Esperanza patient whose immune system seems to have naturally cured her of HIV. Dr. Tebas, my first question is, what does a cure mean for HIV? And why is it eradicating HIV proving to be so challenging?

Dr. Pablo Tebas: Well, cure means a lot in HIV because it's an astigmatism disease that the way that you can be cure for is incredibly powerful and meaningful for HIV infected patients and there has been more cases of curing HIV, there was a London patient similar to Timothy Ray Brown that received an organic bone marrow transplant from somebody that doesn't have the core acceptors for HIV, and we know, it seems that you can cure HIV by doing that by removing completely, your immune system, putting a new immune system, does a bone marrow transplant, that kind of replicate the HIV virus. The case from Esperanza that was published a month ago, it's a little bit different because that patient didn't receive a bone marrow transplant and was infected with a very quickly and it seems that the infection never took over. And then finally, she has not rebounded, and they cannot find the virus in her, so they call it is a cure. It is sometimes difficult to define what a cure is, there are two types of cures and let us start with the definition. One is what we call a sterilizing cure, that means that if you look into the cells of the individual infected with HIV, you cannot detect the virus. That's what happened with Timothy Brown, happened with the London patient, that happened with another patient, the Dusseldorf patient, now they call them depending on the city that the bone marrow transplant was done. But that's incredibly difficult to do because this is a retrovirus it infects the cells and stays there. So, eliminating completely all the traces of the virus is difficult. Well, we call a functional cure is a different concept is that you don't have to take medicines every day. The treatment now

for patients, living with HIV, is that you have to take pills every day. It is a chronic disease. So, we want to do those things to the immune system of individuals to try to maintain the virus suppress and that, so people don't need to take medicines every single day of their lives, and that's what we call a functional cure. And I think that our aim right now, it would be great to have sterilizing cure, that's a very difficult aim for but instead functional cure not having to take pills every day. I think is possible. I don't know if we will do it, but I think it's possible.

Priya Menon: Thank you, Dr. Tebas. For the benefit of our listeners, I want to take a step back and ask my second question Dr. Tebas. If a person gets an HIV positive diagnosis, what is the current standard of treatment for HIV that would be available to the patient now?

Dr. Pablo Tebas: So, we could understand there are many what we call combination retroviral therapy. It used to be three different molecules, but now they combine them in a single tablet. Now, we know that we have very powerful drug sometimes, you come under this impression that the virus doesn't replicate, just taking two different molecules, also a single tablet and that's the current standard of care. And we have medicines that are much better tolerated that 20 years ago, when they have a lot of side effects. The medicines nowadays are very well tolerated, and they have side effects, any medicine has side effects, but the side effect profile is tolerable. So, most of the people living with HIV, they are taking one or several pills a day to control the HIV virus, they maintain viral suppression. So, the virus cannot replicate, and they live a completely normal life. They can have kids because if your level is suppressed, you don't transmit HIV virus to others, it's called undetectable equals and transmissible. And they can have a completely normal life. It doesn't mean that HIV is not a stigmatizing disease, it is still incredibly stigmatizing, particularly in some social groups. The general feeling in society about HIV has improved dramatically with a new treatment and now the understanding of people has different sexual orientations, and everybody needs to be respected. The disease is very stigmatizing particularly in some communities. I have many patients that live in West Ville, West Africa, they're still hiding their medicines. They're still not telling their families about their diagnosis, and it is still very stigmatizing decisions because of all the connotations around HIV and all the history about HIV. The situation has improved but not completely clear. So, the standard treatment is taking two or three molecules that block, the HIV virus from replicating. And now the different molecules have been put in single tablet. So, the patients tolerate it much better.

Priya Menon: So, do these patients have to be on this treatment for the lifetime or can they take therapy breaks?

Dr. Pablo Tebas: Now for all we know this is a disease that if you stopped the treatment, that is successfully treating you, the virus comes back very quickly. It takes around two to four weeks to come back from the reservoirs. And as far as we know now it is a treatment for life. There are very few people that can control the virus in the absence of therapy. We call them viremic controllers or elite controllers, but they are interesting because that's what we want to go is the immune system controls the virus, but they are very infrequent, less than 1%. So, for 99% of the people, having HIV means that you have to take medicines every day of your life, which is another problem with HIV is that every day, you got reminded that you have this infection.

Priya Menon: Yeah, so as I understand what makes HIV so dangerous is that it attacks the immune system leaving people unprotected against infections. Dr. Tebas, gene therapy can be used to eradicate HIV or immunotherapy can be used to contain HIV and these are being explored as potential approaches. What according to you like, which do you think is more likely to lead to an HIV cure?

Dr. Pablo Tebas: I think we are learning that is like, in the old days with HIV, we started giving one drug to patients with HIV. We figure out that the virus gets around one drug, then we needed two, and then we realized that we needed a combination of three. So, in order to get to this functional care of HIV I think we're going to need a combination therapy. We're going to need multiple interventions that will do something to your immune system that will allow the immune system of individual to control HIV virus. So, it might be something to decrease the HIV reservoir where the virus hides, and that can be targeted gene therapy for example, with car, T cells, or with monoclonal antibodies, plus something that is going to modify your immune system to control the virus maybe a therapeutic vaccine against HIV. I don't think it's going to be a

single magic bullet that is going to get rid of this. There is going to be a combination approach and after that hopefully these significant proportion of people will be able to control the virus in the absence of antiretroviral therapy. That's the Holy Grail, that's where we want to go and we're in a good starting position because people if you take the pills you're doing well. So, we have to figure this out, but it is not that people are dying like the early nineties.

Priya Menon: But what do you think that these kinds of therapies both immunotherapy and genetic therapies, can be scaled up for use in lower-income settings as well?

Dr. Pablo Tebas: I mean that's also the ultimate goal. I think at the beginning all these therapies are very fancy. They are only done in a few centres around the world, but later on things evolve and it might be easier to do globally. So, gene therapy, now is very expensive and he's only done in a few centres, in the world. But maybe in the future, we can deliver gene therapy with an injection and then you might become something that is affordable for the whole world. At the present time, these are really small studies, proof of concept studies, ideas that need to be tested. And then when something works, then we had to figure out how to implement for the whole world. There is around 40 million, people living with HIV in the world. It would be great to have the potential of functional cure for them. And when we figure it out in small studies, then we can figure out how to do it at the global level. But it's, as I said, is the Holy Grail, The Impossible Dream.

Priya Menon: One last question before I hand over to David, Dr. Tebas the success of covid-19 mRNA vaccines from Pfizer, BioNTech and Modena has given many HIV hope that a preventive mRNA vaccine for AIDS is on the Horizon. What is a vaccine scenario for HIV AIDS?

Dr. Pablo Tebas: I mean we have had HIV infection for almost 40 years. It was described in June of 18, 1981. And by we don't have a vaccine despite that at the beginning we thought this was going to be a piece of cake which was not. There is an incredible diversity of the virus and the virus changes quickly with pressure. So, creating a vaccine is difficult. Now, people are very tune about different strains of viruses because of Covid. You have the Delta virus and everywhere it is spreading. And so, your immune responses are when you get vaccinated you develop an immune response, very strong against the protein that they are injecting you or mRNA or that is producing the protein that you are getting antibodies too. But the virus can change, and those antibodies might not be protecting. So, we know, for example, with Covid you have vaccines that are very effective but for some strain of the virus they are less effective, Dr. Fauci, loses sleep. I am 100% sure, he is thinking about a string of virus that will not be sensitive to the antibodies produced by the vaccine. So far, the vaccine seems to be working well, so if you have not got vaccinated, please do but that's the issue, the virus changes and then the immune response are not responding. With the covid vaccine, we have learned that this is an incredible technology and then was part of the discovery and the development of this technology is a way to deliver this mRNA vaccine, a way to deliver the antigens your muscle makes the protein, and your immune system reacts to that protein making protective antibodies. It is an incredible technology and it being developed so quickly because of Covid, and we hope that that technology can be applied to HIV, to develop a better preventive vaccine. The NIH is starting a study right now as we speak using mRNA technology to deliver trimer. So, the protein that the virus uses to enter the cell is a trimer it has like three things and it binds to the CD-4 and they are injecting trimers delivered by the mRNA technology, so people develop neutralizing antibodies against HIV. Will it work? I don't know. We're at the beginning of the development. We need to learn more about how to present the antigen to the immune system. So how to present this protein to the immune system to see if we can develop neutralizing antibodies. There is a lot of interest to develop, to use this technology, both for prevention and for therapeutics as part of a new strategy for a full-on cure to vaccinate people that had already infected with HIV to see if we can improve the immune response against their virus and see if they can control the virus. So, there is an intersection in fields in medicine all the time. And so, the Covid vaccine was made possible by a lot of the research that was done in HIV and now a lot of research that has been done for covid will impact back into HIV in antiretroviral therapies are other things, but there is continuous dialogue, between different areas of medicine. And I think there is a lot of promise with these new methods to deliver boxing. So, we'll see, I mean it is not because we are not trying, we are trying very hard to try to develop these new vaccines into a prevention and therapeutic intervention.

Priya Menon: Thank you. Dr. Tebas. I'd like to get David on now and David Stanley is a cancer and men's health advocate. He's also an author, teacher a voice-over actor and an audiobook narrator. David, all yours.

David Stanley: Doctor, pleasure to meet you. And I love doing these cure talks because I get to talk to some of the most interesting people in science. So, when free ask me to do this, I was pretty excited because your, your work is renowned. Now, my question is kind of jump all over the place because I didn't submit them to you ahead of time, so I'm going to ask them to maybe a little bit out of order. Also, in respect to the some of the answers you've already given to previous questions. I'm old enough to remember the original AIDS epidemic, and I lost some friends. My dad was a proctologist and here at the height of the AIDS epidemic in our County 500,000 people, he was the only Proctologist that would treat men with HIV/AIDS at that time because the rest of the Physicians whether they were scared or they were Prejudiced and biased, they weren't willing to take that on and then Arthur Ashe died in 93 from AIDS that he got during the blood transfusion, of course, during a heart operation and it seemed to me at the time that there was a kind of a big sea change in attitudes towards AIDS, if an icon who was known to be heterosexual like Arthur Ashe could come down then it could happen to any of us. And at that point, we start seeing by the way, a step up in funding. Do you think 30 years later HIV/AIDS is receiving its fair share of governmental funding to continue the research, that was really kicked into gear during that era.

Dr. Pablo Tebas: I think so. I mean HIV is also a pandemic studied in the 80s we started. Well, I remember Rock Hudson was the prototype of masculinity in movie or all TV shows at that time. And he was a closeted man who had sex with men and died of HIV. Early, Freddie Mercury, who was the singer of Queen or a, I mean, Arthur Ashe, a famous tennis player, I think all of that famous people contributed to normal lives, to make the community more aware that this happened to a lot of people. And if they help to reduce the stigma about HIV, that trigger funding that is started in the beginning of the 90s, and I think the main trigger was a kid called Ryan White. Ryan White was a kid that had haemophilia and he was kick out of several schools because he had HIV. And then there was this cry of communities saying, oh, he's an innocent victim. There are no innocent and good people, there are just people living with a problem. Anyway, then Congress passed this act called the Ryan White Title act, which is still ongoing that provides funding to cities and to communities to provide care for HIV and also created economic incentive for pharmaceutical companies to develop drugs because then they would be covered by the insurance that the Ryan White provided and that changed the field completely. The pharmaceutical industry got together and developed new drugs to treat HIV and the combination, there was funding to do this research also at the NIH level and has remained flat, which means has decreased a little bit over time because inflation but the level of funding for HIV I mean, it's not extraordinary but it's reasonable for the amount of people that are infected with HIV. But the impact of that funding goes well beyond HIV. I know that there is these criticism in a community and in some groups that say, oh the HIV exceptionalism that all, they get too much funding, they have funding to do research when you fund HIV research, you are not only funding HIV research it helps us to understand how to use retinal vectors. All the developments in cancer treatment to treat cancer using gene therapy comes from HIV. Because the vectors that we use are basically retroviruses that you put the genetic information that you need to fight against leukaemia. So, as I said, there is a lot of interaction between different fields. The level of funding, for HIV, I think is, is reasonable. I don't think we can ask for more because they are other priorities in society. But unless we have a dramatic impact, not only on HIV, but also in other areas of medicine. Thank God they found previous treatments, the stigma of HIV as I said before has decreased, and now we can talk about HIV. There are groups where there is a problem with that. I don't know if I answered your question.

David Stanley: No, I think that was spot-on because yeah, there's a lot of crossovers as you've mentioned between the different disciplines in epidemic, and health and medicine and it's the rising tide lifting all boats, idea that hey, this is working for that guy. In fact, I'm a melanoma Survivor and Dr. Nubig who's been working with some essentially, the some MRNA technology to interrupt MRNA transmission, he came upon that, one of his postdocs came upon that because they were doing some work in Scleroderma. And somebody said, hey I wonder if this might work over here and obviously very early on in the concept, but it has been showing promise. This thing that they were doing in Scleroderma is showing promise for melanoma. So, I think it's important that the funding be even-handed. That's exactly what you were talking about. Now, you mentioned retroviruses, you and I understand what that means but HIV being this double

stranded RNA retrovirus. Can you explain that in layman's terms? Because it's a term, we use a lot more talking about this, but it's a term that not many people actually understand?

Dr. Pablo Tebas: In biology things normally go from DNA to RNA to protein and then that used to be a dogma until retroviruses were discovered that the information goes backwards, well, from RNA to DNA and then back to protein. So, retroviruses are viruses. Every virus has a life cycle, I mean, it's like people or animals too. I mean, everybody has a life cycle, retrovirus enter the cell and then instead of replicating in the cytoplasm they retrogress like RNA virus becomes DNA and then integrating into the nucleus, in the chromosome. And then from there they start replicating and making an RNA copies, they start transcribing protein and making the copies of themselves and that's the problem of retrovirus is that they become part of yourself, part of your DNA. So, viruses, like the flu virus or covid virus, they don't replicate, they don't integrate in the chromosome, they don't become part of yourself. And that's what makes HIV so difficult to eradicate because they become part of your DNA. You cannot eliminate all of the copies of the virus. You can cure Covid, you can cure flu, you can cure hepatitis C because these are viruses that the life cycle doesn't involve integration into the chromosome. And that's the problem with retroviruses. Retrovirus have been here for millions probably billions of years and there has been many retroviruses, there are some retro viruses they have become part of our DNA. So, nine percent or significant amount of our DNA comes from retrovirus is called endogenous retrovirus, and it is just sitting there not doing anything. HIV is a retrovirus it integrates and that's what makes it so difficult to cure. Because it's part of everybody, it is the cells in your body. And in order to eradicate, you have to eliminate all the cells and you can only do that with a bone marrow transplant that happened with Timothy Brown. So, it's just what it is.

David Stanley: That's like the best explanation I've ever heard of that. So, thank you for that. Now, Covid has about twenty-nine thousand base pairs, most of the strains we're looking at about twenty-nine thousand, different base pairs in its genome. Spanish flu epidemic as we can tell was around 13,000. HIV according to what I've read is around 10,000, maybe even less. And does the size of the genome contribute to the difficulty, or it is primarily the retrovirus issue because Spanish flu and covid are not retroviruses?

Dr. Pablo Tebas: Yeah, I think it is more than the type of life cycle. Viruses are these small things. I mean thousand base pairs is not that many proteins, but they have is the amazing thing about life isn't it that some people don't consider virus is alive but is the capacity to replicate and continue. You don't need that much information. I mean, the HIV virus has a few proteins and then the genome and a few enzymes, few critical enzymes. So yeah, it is ten thousand base pairs that are just very difficult to completely eliminate. But the part of the problem, as I said before is the life cycle that goes through integration in the chromosome. If it was a virus that it was replicated in the cytoplasm of the cell, like the flu, or the Covid or Hepatitis C or other viruses they don't have a reservoir, they don't integrate. So, your immune system mocks a response, eliminates it and that's it. The other viruses like retroviruses are difficult to eradicate. There is another virus Hepatitis B, that doesn't integrate. It creates like a circle of DNA in the nucleus but is also very difficult to eradicate because it becomes part of your genetic information.

David Stanley: This is not strictly speaking, an HIV/AIDS question. But we have in our human genome three billion base pair roughly, a lot of that DNA, doesn't code for anything that we've been able to discover its essentially spacer that sometimes they call it junk DNA to the best of your knowledge is a, is any of that space filling DNA in our genome retroviruses?

Dr. Pablo Tebas: Yeah, significant amount of the DNA are retroviruses, fragments of retroviruses that have been there for evolution. It's very difficult to know. I mean called something young DNA is difficult because we don't know a lot of the functions of the genome but some of the parts of information are not transcribed. They don't make a protein and they just sit in there because a few million years ago in the mammal were infected and they became part. And that's the way that the increases diversity. So, if you look at for example a mammal, some of them have placenta, some of them don't have placenta. So, you have the kangaroo, they don't have placenta, that's why they have the babies in this bag because they don't have a placenta, so their pregnancies are outside. And the information to make a placenta, which is a truffle blast is anyway comes from an endogenous retrovirus. So, a mammal was infected and that provides a survival advantage and that's how that evolution happen. So, retrovirus provide genetic information and genetic information is

transferred from one place to the other and it can affect evolution. So yes, a lot of our genome is all retroviruses as part of the evolution from billions of years before we were humans and they have been part of our evolution. So yeah, they are important.

David Stanley: Listening to you, it reminds me of that quote, all biology is evolutionary biology. I think Stephen Lander said that it's a great quote. Let me ask you a couple questions about HIV/AIDS and Covid. In general, is the Covid-19 vaccine safe, efficacious for those who are HIV/AIDS positive?

Dr. Pablo Tebas: Definitely, I mean, vaccine is efficacious, in HIV patients and in patients with immunosuppression vaccines are less effective than in the general population, but they are still effective. My wife takes rituximab, the vaccines are less efficacious on her, but she definitely takes the vaccine. The same for HIV, some patients with HIV are taking medicines. They have a normal completely normal immune system, normal response to the vaccine, some people early on the treatment of HIV when low CD4 count and more immunosuppression the vaccine works less, but it doesn't mean that it doesn't work, it works, and we use it a lot. Patient with HIV do not seem to have more severe Covid than people without HIV. However, they have more risk factors that affect. Among patients with HIV, there is more diabetes, there is more cardiovascular disease, there is lower socioeconomic background. All of those are risk factors that predispose people to have more severe Covid. HIV patients because they belong to those groups, they can have more severe Covid, but it doesn't seem that is related to being infected with HIV per se, which is different. So, it's not just HIV viruses, it's all the comorbidities that go together with HIV. Hypertension that's cardiovascular disease, obesity, those kinds of things make people with Covid sicker and because HIV patients are part of the same group, they can have similar problems.

David Stanley: Are you seeing any interesting or different side effects in your patients with the covid vaccine people in your groups or just the normal side effects that most of us are experiencing after the covid-19 vaccine?

Dr. Pablo Tebas: I mean, Covid vaccine side effects are rare. Of course, you have a bias in a hospital, because you get the rare event for evaluation. So, I have seen a couple of cases we've from some regions associated with the Covid vaccine. Those things are something very rare, the main side effect of the Covid vaccine is not taking the Covid vaccine, and I have seen a lot of patients needed to go into the hospital because of not taking the Covid vaccine. And I will encourage everybody to take the Covid vaccine, it decreases the risk of complications. It is not a perfect vaccine, there is nothing perfect in the world, but it increases, your risk of being admitted and having a complication. Look at Philadelphia, in Philadelphia there has been a hundred thousand cases of Covid, more or less, 100,000 cases, 2000 people close to 2,000, people have died. So, if you get Covid, I mean, you might be young and everything and you might not have any problem. But your chances overall in a population level is around 1 or 2% of death. Problems with vaccine is one in a million. So, if you're a better and you are a gambler and and want to do good, so to do good is the vaccine and side effects sure arm pain and those are the more common things you feel lousy the following day, that's it. I think that's it. And then it's over. So, on the balance of things is always in favor of the vaccine. Is it perfect? It's not perfect, but it's a lot.

David Stanley: Respecting your time, doctor, I've got two questions, two more questions for you because Priya said 9:45. So you're currently working on a couple of gene therapy projects that look really interesting. Could you break down how gene therapy works for the listeners and what you feel are the outlooks for these trials that you're meeting right now?

Dr. Pablo Tebas: So as part of these continuous dialogue between oncology and infectious diseases, one of the gene therapies is that we are doing it taking advantage of all the improvements on Car T-cell therapy. So, Car T is Chimeric Antigen receptor that's the car which is a nice acronym. So, you put a T-cell receptor, you are basically engineering T Cell receptor and T cell receptor is the molecule in the surface of the cell that the cell uses to bind or to recognize cancer cell and we are doing the same idea to try to recognize HIV infected cells. So, HIV infected cells, the reservoir, what we were calling before the reservoir, those cells express some proteins in the membrane that tells the immune system oh, this is an infected cell. So, I need to eliminate this cell. So, we are trying to create those cells that are going to recognize HIV-infected cells to

eliminate is Car T cell therapy. The same thing that was developed a few years ago to eliminate leukemic cells for the CD19 Car T. So, basically, they recognize a protein in the leukemic cells CD19 that these T cells bind and then start secreting molecules to eliminate those cells. The same idea we are trying to develop to eliminate HIV-infected cells with car T cells and that's the gene therapy study that we are doing. We have enrolled a few people. There are interesting results in one or two people, it seems that the virus doesn't even come out, but it still will you were in the exploratory phase. But basically, with that gene therapy we are trying to create a T Cell immunity against HIV. There is a lot of people doing many other things, fancy things with gene therapy. So now we know that if you give an antibody, monoclonal antibody to people with HIV. You give enough of the monoclonal antibodies that you maintain the levels, the virus kind of come out is like a long-acting and the retroviral therapy. So, the idea is that there are some groups delivering the antibodies instead of an infusion every three weeks or eight weeks. They are delivering the antibodies with gene therapy. So, they take cells, they put information, they put them back and those cells make antibodies to suppress the virus. Of course, everything is still on the development phase. There are people for example, in Temple Dr. Khalili is working using CRISPR CAS9 technology to try to remove the HIV virus from the infected cells. Very difficult because there is a lot of copies of the HIV virus, but they are starting trials to try to see if they can clean the infected cells using CRISPR CAS9 technology. So, there is gene therapy approaches against HIV. Some of them are developing new responses. Some of them are trying to make the body produce something that is going to prevent the virus from coming out and some technologies are trying to remove the HIV virus. After a few years, what will stay, I don't know. But maybe it will be a combination of the different approaches, that's what we're doing for gene therapy for HIV.

David Stanley: Very interesting. One last question from me and then back to Priya. When you began your career as an infectious disease expert, what was your interest to HIV/AIDS. I mean, it's a heck of a puzzle. I get that from a science perspective. It's a great puzzle, but usually there's some passion in your voice. So, I sense that there's something else at play here and if you don't mind talking about it for a minute or two, I'd love to hear that.

Dr. Pablo Tebas: Sure. My first patients with HIV, I saw them when I was in training in Spain in 1988-89. I was in the hospital doing my residency and we saw some of these patients with HIV. And as you said nobody, there was a lot of rejection including into the Medical Group, into the medical people and I really like infectious diseases and I thought, I love I really like to take care of these patients. I was always a contrarian that my parents will tell you that. I was always a contrarian and I say so nobody wants to take care of you. I'm going to do it and then I enjoy doing it. I learn so much from the taking care of these patients. At the beginning, it was very overwhelming for them and for me personally, and overtime all the progress in science, but it was at the beginning it was mainly a human interest on people that were rejected from the medical establishment. And that drove me to HIV. Then first job that I had after finishing school, in Spain, you have to do an exam after a few months. So, you have time to prepare for exam, but you can work as a physician. I was substituting for somebody in prison. I was a prison doctor for a couple of months, and I learned an unbelievable amount there. There was a lot of heavy drug use and a lot of people in that place were having HIV and I start seeing patients with HIV. I realized that really, we need to work on this disease because it was incredible what was happening. And that basically made me passionate about It. And it stays with me for my whole training. And then when I came to the U.S. to train infectious diseases, it was at the peak of the epidemic, and I really like it. So, I started continuing to do it.

David Stanley: You're such an engaging speaker, Doctor. This has really been a pleasure and such great information. It's been a great experience for me to listen to you to speak about this. Thank you very much.

Priya Menon: Thank you, David. Thank you, Dr. Tebas. Although there are several approaches that would eventually bring a functional HIV cure Dr. Tebas as you mentioned there are still some challenges ahead. The virus insurges it's DNA, into long live cells in the body that may lie dormant for decades. The so-called HIV reservoir and add to it the ability to quickly mutate and develop resistance. However, given the remarkable advances, and cell and gene therapy, over the past years, as we just heard Dr. Tebas talk. The field is well positioned to address these challenges and the immense potential open new venues for developing a cure for HIV. So, with that we are wrapping up today's discussion. Dr. Tebas, I totally agree with David. It's been a pleasure to listen to you and thank you so very much for taking time to join us on

CureTalks today. David, thank you and I think those were some of the great questions and you drew Dr. Tebas out to talk about how he came and started working on AIDS. I think that's something that AIDS Community should definitely know, how much he loves working with them. So, it's been really great talking to you today. Thank you so much. And we also thank the University of Pennsylvania. The talk will be available on your curetalks.com. Thank you, everyone, and have a great day.

Dr. Pablo Tebas: Thank you very much for the invitation and enjoy the holidays for to you and your audience. And it is days an important day to bring attention to HIV, and to his goal of curing HIV. And we had to warn these together with the community effectively. Thank you so much for the invitation.

Thank you.