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Applying mRNA Vaccine Technology to HIV/AIDS

DR. TURCK:
Amid the ongoing COVID-19 pandemic, countries in Sub-Saharan Africa are also facing high rates of HIV prevalence. And with so many of these patients struggling with the burden of both, newly emergent vaccine technology may provide hope for a new treatment.

Welcome to *COVID-19: On the Frontlines* on ReachMD. I'm your host, Dr. Charles Turck, and joining me to share his insights on mRNA vaccines and their potential impact on HIV and AIDS is Dr. Chris Beyrer. Dr. Beyrer is a professor of epidemiology at Johns Hopkins Bloomberg School of Public Health. Dr. Beyrer, welcome to the program.

DR. BEYRER:
Good to be with you.

DR. TURCK:
Before we dive into mRNA vaccines, let's start with some background on HIV and AIDS. Dr. Beyrer, given the advances in HIV management over the past few decades, why is it been so difficult to develop a vaccine?

DR. BEYRER:
Well what we've learned about HIV is of course that because it is an immunodeficiency virus whose principal cell targets are critical to immune functioning, it has always been enormously challenging to get the human immune system to respond to antigens, however packaged, in ways that would really generate protective immunity against the virus.

DR. TURCK:
So mRNA vaccines are currently being researched for HIV. Dr. Beyrer, what do we know so far?

DR. BEYRER:
With Coronavirus, we had really one very good piece of luck for humanity. And that is that the spike protein of coronaviruses is the attachment to the ACE2 inhibitor; it's a critical antigen on the surface of the virus. And so we have a clear target and all the current vaccines against SARS-CoV2 use that spike protein in one way or another as a principal target.

With HIV, we have a real problem there, which is that first of all, it has a slippery glycoprotein coat. It has always been harder to find those targets. And to pick the right antigens. They have to be, as it turns out, expressed in trimetric form to really generate the kinds of neutralizing antibody that we want to see. And this has really proved devilishly difficult.

So with HIV and the mRNA platform, the question is really going to be: what are the antigens you pick? In what form are they going to be presented? From that, you basically then need to get the right mRNA messages from HIV to be able to get the human cell to make those critical antigens. So that's going to be the task and it's not going to be simple because one of the things we already know a great deal about in the most acute and early phases of HIV infection, the critical step, is of course integration. This is a virus that has a reverse RNA genome; it is read backwards by reverse transcriptase into DNA. And then that proviral DNA integrates into human DNA.

And that is the basis both of infection with HIV, but also the establishment early on of the reservoir, which has also proven to be enormously challenging and difficult to address. So that's why we also why we don't have currently a cure. We've had essentially one known cure of the many, many, tens of millions of people who've been infected with this virus over the last 40 years.

Contrast that with SARS-CoV2 where the majority of people spontaneously clear this virus and are cured. And that's why we know that the human immune system with the right stimulation from vaccines is capable of vigorously defending itself against SARS-CoV2; HIV, not so much.

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DR. TURCK:
Could you tell us about some of the clinical trials exploring the efficacy of an mRNA vaccine for HIV and what their results are if we have them?

DR. BEYRER:
So we're not at efficacy trials yet. Efficacy trials, of course, are the large Phase 3 trials in folks who are at risk for HIV acquisition. The earliest trials, of course, have been, first of all, in basically lab studies. And then there have been a couple of smaller Phase 1, 2 studies. Moderna has been working on this. There are a number of other companies, looking at this. And of course, there's been ongoing work at the Vaccine Research Center at the NIH.

We have not yet gotten to what are normally considered, the second phase of trials, which are larger than a few small volunteers. And, of course, those generally speaking aren't people at low risk or no risk. And what you're really looking for is immunogenicity signals and early safety signals.

So we're in the early phases of this work. And it really will depend on how the early stage trials go, if the current generation of products makes it to a Phase 3 efficacy trial. Right now, there's really only one efficacy trial with an HIV vaccine out in the field. That is the Mosaico trial, which is being sponsored by the NIH and the HIV Vaccine Trials Network. Susan Buchbinder at University of California, San Francisco is the PI. And Mosaico is a more of a classical approach, which is looking basically at multiple antigens fit to circulating virus. It's being done among men who had sex with men and transgender women who had sex with men in the Americas, and there's few sites in Europe.

So that's one we're awaiting the results of. And that's the next HIV efficacy trial ahead of us.

DR. TURCK:
For those just tuning in, you're listening to *COVID-19: On The Frontlines* on ReachMD. I'm Dr. Charles Turck, and I'm speaking with Dr. Chris Beyrer about mRNA vaccine technology and its potential impact on HIV and AIDS.

Dr. Beyrer, staying on the topic of research, do we have a sense of what the role is of mRNA technology in the development of an HIV vaccine?

DR. BEYRER:
Well, I think the success of the mRNAs for COVID-19 has opened up this whole field. In HIV, the key is going to be getting the right antigens, figuring out what actually are the targets that the immune system can attack if primed with mRNA. And this has been an elusive challenge. You may know that the only trial of all the many Phase 3 efficacy trials we've done in HIV, mostly had no impact. We had two trials that showed exactly what you never want, which is enhancing immunity. In other words, the people who were immunized had higher rates of acquisition than the placebo recipients. So those were really, of course, enormously challenging. Those were adenoviral vector vaccines.

But we've only had one signal of success. And it was a pretty weak and transient signal. This was the trial done jointly by Walter Reed and the Thai Ministry of Public Health entirely done in Thailand, an enormous trial with 16,000 people. That did show some reduction in acquisition, about 31% reduction in vaccinees. And then a great deal of work was done post hoc to try and figure out what that vaccine had stimulated in the immune response and to what antigens. And it turned out that, for example, one of them was an area on the glycoprotein loop that hadn't really been heavily targeted before. So you know, that kind of empirical learning is going to have to shape what we use as the right antigens for an mRNA vaccine. And, of course, what that means is getting the right transcript for those antigens into the mRNA.

DR. TURCK:
How do you think the development of a vaccine using mRNA technology would impact the HIV AIDS disease landscape?

DR. BEYRER:
Well, there are potentially several ways. Of course, the Holy Grail here, what everyone who has been in this field has been working on these many decades now, is a primary preventive vaccine. A vaccine that could really prevent acquisition and onward transmission. So that would be the first goal. And that could have an enormous impact.

Now secondly, there might be some advantages, for example, for patients who are doing well who are living with HIV, but who are on therapy and who are virally suppressed if we could use adjunctive immunotherapy. So say an mRNA vaccine to handle breakthrough infections should those people go off antiviral therapy. And many, many people have challenges staying on antiviral therapy. Right now, it's daily oral therapy for life. We do have some long-acting injectables, of course, that are coming online. We're gonna have potentially

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some longer-acting orals as well. But for the most part for most people in the world living with HIV, it's still a lot of pill burden. So an adjunctive mRNA vaccine that could help reduce that and help people live without daily oral pill taking could be an enormous advantage.

I think the third area which we would really, really love to see is that there is an intense amount of work going on in the cure area to see if we can use new technologies like mRNA to target the reservoir, the resting memory T-cells, for example, and other reservoir cells that we know continue to harbor the sequences of the DNA provirus inserted into those cell lines. That may be a way that we could really move toward a cure. And that would be extraordinary.

For many years, there was very little movement in the cure space. But in the last decade, this area has really taken off. We've been able to much more carefully categorize the reservoir, understand it, and have even now moved into the therapeutic area trying a number of different approaches. You may have heard of the shock and kill and the shock and lock, and other approaches to trying to address the reservoir. So far, none successful. But, you know, mRNA may change that.

DR. TURCK:
That's such a great way to round out our discussion on mRNA vaccines and HIV/AIDS. I want to thank my guest, Dr. Chris Beyrer, for joining me to share his insights. Dr. Beyrer, it was great having you on the program.

DR. BEYRER:
Well, Dr. Turck, I thoroughly enjoyed it and it was great speaking with you and let's hope one of these approaches works for HIV. We've been at it a long time.

DR. TURCK:
I'm Dr. Charles Turck. To access this and other episodes in our series, visit reachmd.com/COVID-19, where you can Be Part of the Knowledge. Thanks for listening.

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