PODCAST TRANSCRIPT

# An HIV Vaccine—Looking into the future with Nina Russell

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**Jeanne Baron:** I'm Jeanne Baron and on this episode of PxPulse we are anticipating HIV Vaccine Awareness Day on May 18th and thinking about how the field of HIV prevention research is confronting extraordinary breakthroughs and extraordinary challenges. It's considered one of the most important and most difficult scientific enterprises in the history of modern medicine—that's the hunt for an HIV vaccine. It has led researchers to vast knowledge and breakthrough technology, (think Covid vaccines and mRNA platforms). But developing an effective HIV vaccine is still out of reach. Meanwhile, the world still needs an HIV vaccine. Incidence is very high in hard-hit corners of the world, intractable, high. Asyund meanwhile, also the world is struggling to speed up access to longer acting PrEP. It's a complex landscape alongside an incredibly complex science in HIV vaccine research and development. So what should be the goals for an HIV vaccine? With PrEP expected to be more available in the years to come? How are researchers, developers, and donors thinking about the challenge, where do they see promise in the science? Here to explore these questions with us is Dr. Nina Russell, the director of TB and HIV Research and development for the Bill and Melinda Gates Foundation, one of the world's largest funders for HIV prevention research. Thank you for joining us, Doctor Russell.

**Nina Russell:** Thanks so much for having me.

**Jeanne Baron:** So there's been a lot of good news coming from researchers about the high level of protection that can be achieved with antiretrovirals used as prevention or PrEP. Longer acting options are starting to become available, and daily PrEP is finally being offered at scale. But vaccine trials are a different story. There's no efficacious options yet, and there's just been years of toil and effort. Can you start by telling listeners why, for you and for the Gates Foundation, it's clear, and for the world for that matter, it's clear that an HIV vaccine can and must be a priority.

**Nina Russell:** You're absolutely correct that in recent years, daily oral PrEP is being offered at a larger scale. But it's been a long, hard road to get there, and there's still many challenges ahead to make sure that daily oral PrEP is widely accessible to people. And we're also at the very early stages of rolling out the first injectable PrEP with a drug called cabotegravir. And several other long-acting PrEP options are on the horizon. And another exciting and different alternative is a once-monthly oral pill. So,

this toolbox of PrEP options will hopefully be transformative, but it is critically important that we still prioritize a vaccine. And I say that because a vaccine will be, we think, the most promising and sustainable way to end the AIDS epidemic that could be deployed at large scale and at a lower cost to prevent millions of new infections and deaths, and save billions of dollars in health care and social costs. And a vaccine with the right characteristics, and we can talk about that more later, could be administered before sexual debut in an individual and with a simple regimen, provide protection throughout the course of one's sexually active life, and, unlike PrEP, would not require recurring use either prior to or around the time of sexual activity. But while it may be hard work to get to a vaccine, we think it's critically important that we as a field keep working on and keep investing in it.

**Jeanne Baron:** Some of the vaccines that have been tried, investigated in past trials, did need some re-upping. So it sounds like what that so-called target product profile needs to be in order to actually make an additional contribution to the toolbox is evolving. So could you explain what a target product profile is and why we need one? And then what attributes an HIV vaccine would need to have so that it is additive to our current prevention toolbox?

**Nina Russell:** So what you do in the target product profile is you define what are the populations that you're aiming to reach with the vaccine. Is it adults? Is it children. Is it men. Is it women? Is it both? What does the vaccine itself actually have to look like in terms of the way it's administered, in terms of the dose of the vaccine and the volume of the vaccine? And then you also think through what are the characteristics of the vaccine in terms of safety and tolerability, and what would be required in order to have a deployable vaccine? You also consider durability of the effect of the vaccine, the efficacy of the vaccine, as well as cost. So all of these critical components to your product, you lay out in advance so that you can make sure that you're working towards actually hitting that target with your product. And so I think for a vaccine—going to, you know, the other aspects of your question—one of the critically important things that we think about in a target product profile is durability, simplicity and cost. So we really need a vaccine that's simple, cheap and durable. If we had a vaccine that met those characteristics, it would be absolutely complementary to what we have in terms of the toolbox of PrEP options.

**Jeanne Baron:** I want to drill into another, another ingredient in a target product profile, which I hear often referred to as effectiveness or, level of protection, how high level it needs to reach. And there was a time where the field was talking about a vaccine could be successful if it was 50% protective. But are we not at a moment where that number needs to be much higher if it's going to again, be additive to the toolbox, because PrEP is achieving such high levels of protection. How are you going to get people to move from PrEP to a vaccine, or add a vaccine if they don't see protective levels as high or better?

**Nina Russell:** We fully expect that these long-acting PrEP options are going to be highly efficacious. We may be wrong about that, but if we assume that these long-acting

PrEP options are going to be highly efficacious, you're exactly right that a vaccine is going to have to do as well or better than long acting PrEP, but I think the efficacy that we need to target for a vaccine is going to have to be very high, and that is a shift from where the field has been historically. We're moving the bar in terms of what the expectation needs to be around a vaccine.

**Jeanne Baron:** I understand. So let's dig into the science a little bit. What kind of advances do you expect the field to be building on that have already occurred? And where do you see momentum for vaccine research and development?

**Nina Russell:** Yeah, I think there's actually some really exciting science that's been going on over a number of years, which is only building over time. One is in the area of trying to design vaccines that will induce broadly neutralizing antibody responses. We know from animal models and from some studies in natural infection in humans, we know quite a bit about the importance of broadly neutralizing antibody responses and believe that if we can induce those, they will be protective and that that's sort of the holy grail in terms of an HIV vaccine. And there are some very sophisticated and nuanced approaches being attacked by multiple groups in the field, trying to use different approaches to designing a series of vaccine immunogens to sort of nurture a broadly neutralizing antibody response.

**Jeanne Baron:** I just want to inject here, an Immunogen is something that prompts the kind of response you want from the immune system. And, this approach you're describing is referred to in the field as germline targeting.

**Nina Russell:** Exactly. So there are signs that some of these very sophisticated approaches to trying to stimulate these responses are beginning to work. We're starting to see that these vaccine immune agents are actually behaving in humans the way we designed them to work. And so that means that the science is on track. If we continue to do what we call iterative studies in humans, which are studies where you have a hypothesis, you test it, you learn from it, and then you build from there. If we continue to do these kinds of studies— and we call them experimental medicine studies, they're really learning studies— we think that we can design a regimen that might be able to induce broadly neutralizing antibody responses.

**Jeanne Baron:** And they're also called discovery medicine sometimes. Right.

**Nina Russell:** Yes, yes.

**Jeanne Baron:** Is that the primary area, the bNAb research that has you most excited? Or are there others?

**Nina Russell:** The other area I was going to mention, which is something that the field has been thinking about for a long time, are actually vaccines that stimulate T-cell responses, which is the other arm of the immune system. And there's been a lot of historical work on T-cell based vaccines, but there are some newer ideas that have

been coming along that we think are very interesting. And the hope would be if we could, in this sort of discovery phase, demonstrate that we find a vaccine that could stimulate T-cell responses and find another that could stimulate broadly neutralizing antibody responses, that we could bring these together and actually have a vaccine that would have a combined response. And I should elaborate, that sounds complicated. We're talking about multiple vaccine components, which really doesn't jive with what I said earlier around simplicity of a vaccine. So once you sort of demonstrate that you can get the right immune responses, how take what might initially be a complicated regimen and work backwards from there to simplify it? These are the kinds of things we need to be thinking about, is how could you get to a point where you might take a regimen that might initially seem to require three or 4 or 5 shots, but deliver it in a way that you could actually get away with giving it only once.

**Jeanne Baron:** Got it? So it's too soon to say exactly what the efficacy level has to be. If I heard you correctly from earlier, but above 50% for sure.

**Nina Russell:** Yeah, I can't give you an exact number for that. And we're actually doing modeling work right now to address exactly that question, which is how good does a vaccine need to be to have impact alongside PrEP. It's probably going to be upwards of 80 to 90% efficacy, not in the range of the 50 to 70% that we've been working with historically for vaccines.

**Jeanne Baron:** I want to take you back to the success, at least in terms of efficacy of PrEP. And now we're starting to see it reach scale, at least for daily PrEP. And folks who say that we should be shifting resources into delivering what we got because we know that PrEP works if you take it. What do you say to people who say, 'we've taken decades of time and money to try to chase this HIV vaccine. It's time to move on. It's just too hard.' How do you respond?

**Nina Russell:** Yeah, my response to that is that it's premature. I understand the question and why people are challenging vaccines in that regard, but I think there are a couple of reasons why I think it's critically important to not do that. One is there are considerable challenges with rolling out and deploying and providing access to long-acting PrEP in the populations globally that are that are the most impacted by HIV. We are still not there yet in terms of making PrEP accessible, making it affordable, and those challenges are going to remain. There's a long-standing history with vaccines. There's infrastructure and experience globally with vaccines as a public health intervention. So with the right vaccine, it's a proven intervention in terms of being able to deploy at a low cost and have major impact. So for those reasons, I think a vaccine has to remain front and center. And I also think that there's considerable progress being made on the scientific side. We are actually seeing the hypotheses that are being put forward are bearing out in humans. We are actually seeing progress in terms of generating the kinds of responses that we think are going to going to be needed. So it would be premature to walk away from that when we actually see real progress.

**Jeanne Baron:** When it comes to the challenges that it will take for a vaccine to be effective, the challenges of vaccine will have to overcome— myriad factors are in play. There's the science, there's the funding, there's the politics, the partnerships, the policies, questions of equitable development and delivery, public awareness and acceptance. Long list there.  Not to overwhelm you. I'm not going to ask you to address each and every one of these. But among this list, what worries you most and what gives you the most inspiration, the most hope?

**Nina Russell:** For me, it's the science, gives me the most hope. And it also worries me the most. Because the science is the hardest part. And I think that all of those other issues, we won't even have the need to address many of the other issues on your list if we can't solve the science is the reality. Because this is very challenging scientifically. But I'm a believer in human creativity and innovation, and there's been many examples in history where there have been unexpected discoveries in science that have been transformative. We've all seen that, and I'm optimistic that the HIV vaccine field will get there someday. And we've seen, over and over again, and Covid was a great example of this, that the science that's been coming out of the HIV vaccine field has been driving innovation across sectors in global health. And so there's real progress being made there in terms of innovation. And I believe that will continue to happen.

**Jeanne Baron:** Excellent. So, would you say that we have to both see getting a vaccine as do-or-die, and simultaneously we must work urgently as if it may not happen, scaling what we've got and keeping a robust pipeline of options in research and development.

**Nina Russell:** I absolutely agree with that. And I think along the way, you know, we can't be naive and think that, if all of these things are expensive, that the world is going to be able to afford to do it all. So we have to be at the same time really driving down costs, really pushing on efficiency of delivery and access, finding creative ways of delivering the full toolbox of options to people so that it's feasible to continue to offer all of these different options to people who really need to have prevention opportunities.

**Jeanne Baron:**Thank you, Dr. Russell. It's been a real pleasure.

**Nina Russell:** Thank you, I enjoyed it.

**Jeanne Baron:** As we approach HIV Vaccine Awareness Day, May 18th, watch for new resources and webinars announced in our Advocates Network, explaining the role of Discovery Medicine and other topics advancing HIV vaccine research in 2024. To find a round-up of all this news and information go to avac.org/hvad. Thanks for listening, I'm Jeanne Baron.