



PODCAST TRANSCRIPT

HVTN 702 and the Quest for Vaccine

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Jeanne Baron: You're listening to *Px Pulse*, a regular podcast bringing you fresh voices on critical issues facing HIV prevention research today.
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Jeanne Baron: Today's episode is about a major HIV vaccine trial that stopped vaccinations early—called HVTN 702, or Uhambo. The vaccine is safe, but a scheduled review of the data showed it offered no protection. The announcement came on February 3rd, and since then the field has been grappling with what it means.
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Jeanne Baron: Talking with us today will be the protocol co-chair of the study, Linda-Gail Bekker, who also, full disclosure, serves on AVAC's board. And Nandisile Luthuli, AVAC's Stakeholder Engagement Advisor based in South Africa. Nandi previously led community and stakeholder engagement in sub-Saharan Africa for the HIV Vaccine Trials Network (the HVTN), which conducted the 702 trial at 14 sites in South Africa. For the sake of consistency, we'll call the trial "702" in this discussion.
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Jeanne Baron: A scheduled evaluation of the data showed no efficacy and vaccinations have ended, but the trial will continue for another year. There's still much to learn from 702. Linda-Gail, what are the big questions to pursue over the final year of the trial?
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Linda-Gail Bekker: I think probably the most critical question on everyone's mind is 'if this was based on RV144 (the Thai trial), which showed a 30 percent reduction in HIV, why did it not work here in South Africa?' I would think that the most critical question to try and answer in the next few months is just that. We took the same vaccine products, we slightly modified them so that they were more amenable to the Clade C (or the subtype C)
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circulating virus in this part of the world. We added a different adjuvant, which was supposed to increase durability and potency. And we added a couple of boosts to pay attention to durability. We fully expected this to work better and for longer than the vaccine product did in Thailand. And of course, that did not happen. So, the most important question is to understand 'why?'

Jeanne Baron:

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And for listeners who are not aware, the Thai Trial (RV144) was the first vaccine trial to show efficacy—31 percent—in 2009. And 702 was based on that vaccine.

Linda-Gail Bekker:

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As concisely as I can, let me explain what happened after RV144. When there was the recognition that we had, hallelujah, a vaccine that actually did protect, the world galvanized into action and all the laboratories of the world came together to say 'we need to find a correlate of protection. What is it that this vaccine did to the immune systems in those people who were protected?' And we discovered a number of very key factors that we could attribute to potentially being protective. And we looked for those in the lead up to HVTN 702.

Linda-Gail Bekker:

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So, we didn't go straight from RV144 to 702. We went via two other very important trials: one was called HVTN 097 and the other one was called HVTN 100. We were only looking for safety and immune responses. We weren't looking for efficacy. But we were also asking ourselves at that time, 'will we see these critical 4 or 5 factors that we called our "go criteria"?' In order to, if you like, put the flag down on 702. And indeed, we saw those responses—those very critical immune responses—that we call the "correlates of protection". And we went into 702 believing that those correlates would, according to [HVTN] 100, also come up in 702, and would lead to efficacy down the line. We did not get the efficacy.

Jeanne Baron:

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In the 12 months to come, you're going to continue to follow the participants. What exactly might be learned about how people's immune systems responded to the vaccines they received in the first part of the

trial?

Linda-Gail Bekker: So we are following them also for safety, first and foremost always safety — 'are we sure that nothing untoward happens in the time following vaccination?'. That's an important question. The second will be 'what happens after the last vaccination? What happens to immune responses from there out?'. We will be asking, 'those correlates of protection that we thought were so critical and that we saw in RV144, are they present? And in those people who went on to acquire HIV versus those who did not (in the vaccination arm), was there anything different about those individuals? And how did they look similar or dissimilar to the individuals who did and did not get infected in the Thai Trial?'

Linda-Gail Bekker: So, the data is enormous. We have more than 260 infections in the South African group. There were far fewer in the Thai study. But doing comparisons between those who became infected and those who did not is really going to, I think, deliver a lot of information about non-neutralizing antibody type vaccinations, what worked, what didn't work and what we should do differently in the future.

Jeanne Baron: And just to explain, HVTN 702 relied on a strategy to induce non neutralizing antibodies. Other vaccine trials—HVTN 706 and 705 (which is called Imbokodo)—use *different* vaccine ingredients also to induce *non neutralizing* antibodies. Yet other vaccine candidates are trying to switch on *neutralizing* antibodies or deliver them through an infusion. This last strategy is being studied in the AMP trial. To learn about these different approaches, go to avac.org.

Jeanne Baron: But in the meantime, when it comes to 702, Linda-Gail, I hear you clearly that you're going to be looking to see if the expected immune responses showed up. What does it mean if they did show up and what does it mean if they didn't?

Linda-Gail Bekker: So we need to check, 'did we get those immune responses?' In other words, 'were there the active ingredients in the vaccine that we really

thought should be there? And if they were not, why not?' We may need to really understand manufacturing and other aspects that might have played a role. If we saw those immune responses, but we have not got efficacy, then there might have been other factors that could have been playing a role. For instance, we already know our incidence was much higher, particularly in young women, than what was seen in the Thai study. Is it that we overwhelmed our vaccine candidates just through sheer force of infection?

Jeanne Baron: Could these answers to the kinds of questions you're posing be applied to other vaccines being tested right now or to vaccine concepts in earlier phases of development—to the larger quest for a vaccine?
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Linda-Gail Bekker: It's another really good question. Because, after all, the correlates of protection investigation goes both ways. You get an efficacy trial, you then look to see 'are there markers that help you understand why you have efficacy?'. And then you go into the next trial to say, 'if I get those markers, I expect efficacy, and I need to confirm those were indeed correlates of protection'. Now, we have not had that confirmation in 702, but is it possible that it works in some subset? So, if we look at younger men or older women, do we begin to see the impact of those correlates? So, I think because we've got 260 odd infections, it is going to be possible to do some of that teasing out.
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Linda-Gail Bekker: Having said that, the other vaccine trials that are in the field [are] coming from quite a different angle. And so it is anticipated that those may very well have different correlates of protection down the pike. So, all of these are pieces in the puzzle and every single puzzle piece is very valuable to complete the picture. [It's] important to know—the people who enrolled and got involved in HVTN 702, did not waste their time. Their efforts, their samples, their contribution is greatly valued and will be put to very good use in our quest to find a vaccine.
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Jeanne Baron:

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More than 5000 people across South Africa participated in the trial. Participants learned of the stop to the vaccines before it was public—not an easy feat. Getting community engagement right is crucial to the success of any trial. I'd like to invite Nandisile Luthuli into the conversation. Nandi, you led community engagement for the HIV Vaccine Trials Network. Site staff who work as community liaisons have talked about intense disappointment among participants and their urgency for the search to continue. These community engagement staff describe a need for escalated and ongoing community engagement. Nandi, how would you speak to this?

Nandisile Luthuli:

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Thank you, Jeanne. To add to that, when I was with the HVTN, one of the things we did was a stakeholder consultation—inviting various stakeholders, advocates, civil society members, representatives from Ministries of Health—to get their input on how the trial should be implemented, some of their concerns, some of the things that we should do better. So, I think I'd just like to find out if the HVTN has a plan to engage and continue educating stakeholders as well as our communities, so that they can truly understand what these results mean and what they mean for future vaccine trials moving forward.

Linda-Gail Bekker:

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Certainly the protocol team (not wanting to speak for the HVTN as a whole), but the protocol team feel an enormous debt, I suppose, and obligation to, first of all, the trial participants—to be sure that they understand in the next weeks to months as more data comes in. And there is a very strong commitment to keep, first of all, as I say, first commitment is to the trial participants and then of course to the broader communities in which the trial sites are situated. And then in the ripple effect beyond that, to South African communities and to the region at large. We were designing a vaccine for clade C—that is Eastern, Southern, Central Africa. And we need to respond to that region as to what is next, what are we planning [that] could really follow on.

Nandisile Luthuli: There was a plea from community engagement staff from sites to intensify engagement and education efforts. Have sites been given a budget to continue with this engagement and education?
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Linda-Gail Bekker: In terms of the resources to do this, we are just re-negotiating the new protocol amendment. I'm sure there will be ongoing negotiations around what community engagement should look like. Ongoing advocacy on behalf of the co-chairs will definitely be in place to make sure that those resources are put in place and [are] well-placed and well-used.
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Linda-Gail Bekker: I think, as I look at the next few months, there are going to be many reasons why we need to stay in touch with the community. We've got the AMP neutralizing antibody study coming out around October. Definitely we're going to be needing to speak to South Africans at-large, but of course, the participants in our clinical trial sites, in particular, about those results. The Imbokodo study is ongoing. There are going to be community information around that. And of course, in the next 12 months, as we start to piece together what actually happened in HVTN 702, we are going to need to feed that information back to the community.
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Jeanne Baron: I have a final question for both of you. During a February 19th webinar (which listeners can find on avac.org), researchers and community liaison managers from the sites gave updates to each other on the trial—what's next and how communities are responding. It's the community liaisons who explain the trial results to participants. Participants had questions and words of encouragement for the researchers to continue the quest.
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Jeanne Baron: And I was struck that each of the liaisons talked about the disappointment of the participants that this vaccine was not protective. One compared it to giving birth to a stillborn baby and finding the courage to have another. Another liaison said I could feel the disappointment. You could actually cut it with a knife. I was wondering what it makes you think of when you hear about the incredible investment by trial communities and the hope and the pain around the need for a vaccine that will work.
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Nandisile Luthuli: I think for me, and I think for most South Africans, 702 was more than just a study. We have lost so many brothers, sisters, mothers, fathers. HIV has caused havoc in our communities and we are really desperate. We know that the only thing that can really help us defeat this epidemic is a safe and effective vaccine against HIV. So, that's why it was disheartening and disappointing for all of us when we heard about the results of 702.

Nandisile Luthuli: Having said that, though, we should use this disappointment. We should try to turn it around, continue educating our communities, continue working with advocates, stakeholders, civil society, so that everyone, first of all, understands what these results mean. And as Linda-Gail pointed out earlier, what was observed in 702 [no efficacy], will not necessarily translate into future vaccine studies. We should continue to support all prevention research that is going on in our field to end HIV, because we know that as South Africans, we need it the most.

Linda-Gail Bekker: I want to echo everything Nandi's just said. I would just add, I think particularly 702, because it truly felt proudly South African—it really felt like this was designed for us and if anything was going to work, it was this. In addition to which, you can't do it without investing a huge amount of belief and hope and optimism. Those emotions also fall very hard when we get a result we weren't expecting. Somehow, in the next couple of weeks, and I think we've already started to do this, we have to go at this twice as hard. Because what 702 tells us, is we are far from the end of this epidemic, far. Prevention is absolutely leading that charge. There is no doubt we have to get treatment to 38 million people around the world. We've got to do it in the best possible way we can. But the best thing we could do today is stop infections happening in the first place. And that really needs each of us to recommit to finding those solutions and using the best of the solutions we've already got at hand.

Jeanne Baron: As the field continues to discuss 702 and prepares for important data in the months and possibly years to come, AVAC will be following closely.

AVAC's Stacey Hannah, who heads up research engagement, is joining us now. Stacey, what are some of the key insights you've had as you listen to these discussions?

Stacey Hannah:

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One of the things that I've really been thinking about [is] we know community engagement is a bedrock of conducting these HIV prevention trials from beginning to end. And HVTN has an extremely strong community engagement program. And it struck me that those people who did that work in this trial, they're heroes and they're experts.

Jeanne Baron:

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These community engagers and recruiters.

Stacey Hannah:

[00:18:04]

Yes, I think that they deserve so much credit for finding this at-risk population. We don't want to celebrate the fact that we're finding people at-risk, but what we know from prevention programs, is that it's really hard to find the people who are at such high risk that they're going to need interventions like PrEP and are going to take up interventions like PrEP. I think that [being able to find the right people] is something that's growing in South Africa. From an external perspective (I think people who are there, who are doing the work, know way better than I do), from the work that we do at AVAC, we know that it's a challenge. They just ran a really strong community engagement program in order to find those people, to find that population, to recruit them into the trial, to retain them in the trial, and to have people so committed.

Jeanne Baron:

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The participants, as well as the community engagement personnel.

Stacey Hannah:

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The participants themselves. In terms of building that relationship. And that is what community engagement is about.

Jeanne Baron:

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So one silver lining from the bad news that the product didn't work was that the community engagement program was strong and that there's something to learn from it.

Stacey Hannah:

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So I would say two things. First of all, it was so strong [that] they got the right people into the trial, they kept the right people in the trial and because of that, we got an answer. We got a very clear answer and we got it quickly. That's how you want to conduct research. And so it's this great opportunity. It's a great case study of how doing strong community engagement can really benefit the trial. We got a clear answer. We got it quickly. We know what to do. And people loved being a part of it. You know, I think there are things like: they throw birthday parties, they have support groups for participants. And so, I think there are some real tangible lessons.

Stacey Hannah:

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It doesn't just benefit this trial. I think it can benefit other trials. I think it can also really benefit prevention broadly. There is a concrete action that we can actually take in terms of learning lessons from the community engagement team and 702 around how they tapped into this population, which I think can be transferred to things like PrEP scale-up in South Africa. Most people are probably aware South Africa has been announced the biggest PrEP rollout program in the world. They're going to need to know how to do this.

Jeanne Baron:

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As communities and researchers work hard to understand the results of this trial, many of the headlines have used the word "failure", because, sadly, the product didn't work. But at AVAC, it's clear to us that 702 did not fail. It delivered essential answers—ones scientists and advocates will explore and build on for a long time to come, and the field is better for it.

Jeanne Baron:

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You've been listening to *Px Pulse*, recorded in the New York City studios of the Radio Foundation and The Relic Room. Our theme music was composed by Alexie Stevens. Our engineer is Sam Bair.