PODCAST TRANSCRIPT

Dive into the AMP Trials

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Jeanne Baron [00:00:03] You're listening to Px Pulse, a regular podcast bringing you fresh voices on critical issues facing HIV prevention research today. Early in 2021, the field began to hear about exciting but complex findings from two trials studying a broadly neutralizing antibody. This antibody is called VRC01, and the two trials studying it are called the AMP Trials for Antibody Mediated Prevention. They were conducted among six gender women in sub-Saharan Africa and among gay men and transgender people in South and North America and in Europe. And in each trial, people received infusions of the VRC01 antibody every eight weeks. The AMP studies hoped to test a concept. Can a broadly neutralizing antibody, bNAbs for short, protect against HIV? Sounds simple enough, but the complicated findings have prompted discussion and debate. In this episode of Px Pulse, we learn what questions the AMP results have answered and what new questions they raise. We talked to a leading bNAb researcher, IAVI's Devin Sok, and a veteran HIV research advocate, Mark Hubbard, who served on AMP's protocol team. But first, my colleague AVACer Dasiy Ouya joined me to ask Gail Broder to go through the findings with us. Gail is part of the team at the HIV Vaccine Trials Network that conducted the AMP studies, and she's one of the trial's chief explainers.

Gail Broder [00:01:48] You know, when you write a study objective, you write this question thinking that you're going to have this really simple, clear sort of answer, and that's actually not what we found. What we found was this really nuanced, really layered kind of data that needs a lot of interpretation. And some of it was surprising. We now know that a broadly neutralizing antibody can indeed be effective at preventing HIV

infection, but it all boils down to whether the virus is susceptible to that antibody, whether it's vulnerable to that antibody.

Jeanne Baron [00:02:31] You say susceptible or vulnerable, researchers will say, is the virus 'sensitive' to that antibody?

Gail Broder [00:02:38] Yeah, and we think about sensitivity in other contexts. Right. So if you have an allergy to a medication, that means you're sensitive to that medicine. Right? It's the same kind of idea. But we're now thinking about whether the virus is sensitive to this antibody. The second key finding for me is that we now have an assay in the lab- an assay is just a fancy word for a lab test. We have a lab test that can tell us ahead of time what we think the sensitivity of any particular virus is to any particular antibody. And so before we were able to do this test in the lab, but we didn't know if the lab finding would actually match up to what we saw in human being[s]. And now we know that the lab test does match up to what we see in people.

Jeanne Baron [00:03:41] So before this trial, the lab test, which, by the way, has this clunky name TZM-bl, this test was used in the lab to get a sense of the strength of a bNAb. But now the AMP trial has used this lab test to show that VRC01 can be as potent in someone's body as it was in the lab, as long as it's fighting the right virus. And I just want to clarify, when we talk about the sensitivity of the virus, we're not talking about HIV as a whole. We're talking about one strain versus another, of which there are how many?

Gail Broder [00:04:21] Zillions. We know that there are these major clades or strains of HIV that circulate in different geographic regions of the world. And so we saw, for example, that this particular antibody did somewhat better against Clade B strains than it did against Clade C strains.

Daisy Ouya [00:04:40] So I'm going to go back to that idea of clades and sensitive viruses. My first question is when we see clades and strains, do I mean the same thing? And because AMP tested only in clades B and C, what does it mean for Clade A, which is circulating where I'm sitting right now in East Africa?

Gail Broder [00:05:02] So clade is the scientific name. Strain is the sort of layperson term to describe a clade. But I think of them as being the same thing. And your question is a really good one because we know that there are these strains in other parts of the world. And so one key finding is that one antibody by itself isn't enough. We're going to need to look at combinations because some antibodies are better at neutralizing and other antibodies are better at addressing a broader spectrum of viruses. And it's not necessarily one antibody that can do both. The terms in science for that are the breadth and the potency. So we need it to be strong and we need it to be broad. We need to look at these antibodies that can have coverage against a wider array of viruses.

Daisy Ouya [00:06:02] Thank you. Yeah, indeed. My other question is: how do you tell what is circulating? Because you talked about this test that can tell you what viruses are actually sensitive. And so I guess you need to match that information with knowledge, very good knowledge of what is circulating. Because what I've understood with AMP is that the prediction of what would be circulating did not come to pass. And so how are we going to be sure what's circulating so that we can match up those two things?

Gail Broder [00:06:39] Yeah, you're exactly right. So we designed the AMP study with the assumption that there would be 70 percent of the viruses that would be susceptible. And what we found was that only about twenty-five percent or a little less than a third were susceptible. So you're right, we have to focus in on making better predictions. We have to be more on top of sequencing blood samples from people living with HIV in these regions to really make sure that we have a good understanding of what viruses are circulating and then using the assays that we have to determine whether these are viruses that are susceptible to a particular antibody.

Jeanne Baron [00:07:27] So AMP shows us we need a much better way to track the sensitivity of the viruses that are circulating in a community, for bNAb prevention product to work. I want to ask you, Gail, about a key figure in the findings. It looks like an equation. IC 80 at less than one microgram per milliliter (IC80 <1 µg per ml). This equation describes the concentration of this antibody needed to neutralize 80 percent of the virus. And this is a readout from the lab test, the TZM-bl assay, right?

Gail Broder [00:08:02] Right. Exactly. Exactly what the TZM-bl assay does, it can tell us how much antibody is present in your blood and what that level in the blood needs to be about one microgram per milliliter of blood. If it was a strain that was sensitive to the antibody, one microgram per milliliter of blood could be actually as high as eighty-five percent effective at neutralizing. But again, you have to hit all the targets. You have to have a sensitive strain and you had to have enough antibody in your blood. And if the conditions were right, it works. Now, we have proven this concept. We actually can do this. And so now the research moves to, how do we make it better? How do we make sure that we have the right antibody, or antibody combination, that has the potency and the breadth of coverage so that it's going to work against a wide array of viruses? And then how do we make sure that you're going to have enough antibody in your blood to be successful?

Daisy Ouya [00:09:21] I just have a very quick clarification about this, TZB?

Gail Broder [00:09:24] The assay. We'll just call it the lab test.

Daisy Ouya [00:09:29] TMB? Let's call it the assay! At what point do we use this assay? For me, it seemed like it's something that you do in the lab. You put the bNAbs that you think will work through this assay and up pops, I guess, a number or something? And you can then take them straight to humans. Right? Because if you know that number, maybe you don't even need to go through non-human primates, or maybe you do?

Gail Broder [00:09:54] Yeah, no. I think, you know, we still want to pay attention to our animal and laboratory studies because that's where we get our initial look at safety. At toxicity. So that kind of a study is still going to give us really important information.

Jeanne Baron [00:10:13] On that note, Gail, there is some disagreement in the field among antibody researchers about whether this assay does show us something you can use in other studies. It's a complicated debate, and in the months ahead we'll continue to watch and learn. But how do you make sense of this discussion?

Gail Broder [00:10:31] I have to say that I'm not up on the technicalities that are involved there, but I think it's important to have people who have a different position, and that they can back it up with the data that they're seeing in their own work, and challenge our ideas and challenge our concepts. What that says is that our scientific community is really healthy.

Jeanne Baron [00:11:04] More data is still to come from the app trials. Two people who will be paying close attention, are researcher Devin Sok, who's the executive director of Antibody Discovery and Development at IAVI, and advocate Mark Hubbard, who has been part of the AMP protocol team from its first draft, as a community representative. Daisy began our conversation.

Daisy Ouya [00:11:27] As we've seen, the AMP results were a little bit more than complicated, with a lot of nuances and a lot of scientific jargon that we saw when the HTPN presented the results. I wanted to ask you Mark, what questions did the AMP study answer for you that you had around antibodies and what new questions did it raise?

Mark Hubbard [00:11:51] So I think there's things that that we know from the AMP studies and then there's things that the AMP study results suggest. I think the top line

we have to be frank about is that VRC01 was not effective in a large efficacy trial, no qualifications about that. That's the truth. I think what's suggested by the data from the trial is, it's possible that we might find a product that's a combination of antibodies that could be useful for HIV prevention. It's possible that the TZM-bl assay will be useful in screening candidates. I don't think we know that. I think the study results suggest that it will be useful. I think we-- the trial results suggest that it may be difficult to develop such a product. You know, the product we tested only worked in viruses that were really sensitive. So how do you come up with a product that is potent against a broad spectrum of strains? And I think we learned that our understanding, even though we brought the best experts to the table, we've seen that some of those assumptions were not valid.

Jeanne Baron [00:13:04] Mark, can you dig into that a little bit? Tell us more about what some of those assumptions were.

Mark Hubbard [00:13:09] You know, we went into this trial thinking that we were going to be able to tell from the two doses that there was this magic level of antibody present in the blood that would be effective. And as it turns out, and this is complex, it had more to do with sensitivity than volume of the product present, at least at the doses that were tested in this trial. So that's one assumption. And another assumption was that it was useful to use a specific lab assay to predict how many strains would be susceptible. There was an assumption about what strains would be present in the tested population that didn't turn out to be reflective. So I don't think that these were bad assumptions. I think they were best efforts. It's a cutting-edge mode of prevention and our understanding was not well developed. And I think, maybe we thought it was more well developed than it turned out to be. And so that's useful information to come out of a clinical trial, in my view.

Daisy Ouya [00:14:09] So I think we'll turn to Devin. What questions did AMP answer for you and what new questions did it raise?

Devin Sok [00:14:18] Yeah, thanks, Daisy. So I guess just to build off of what Mark had already mentioned, the AMP trial wasn't designed like your typical Phase II, Phase III efficacy trial. I think it was designed with the expectation that we're going to learn things, but we're not going to necessarily hit it out of the park and have a product that's going to be ready for prime time. I think the big question for me that was answered was "can antibodies protect against infection?". If they can protect, in what conditions do they protect. Despite, overall, the efficacy not being high, antibodies are protective and they are protective, if you are exposed to a very sensitive virus to that antibody, which is kind of what we kind of knew but didn't expect to see such a clear cut off for sensitivity in the field. So viruses that are supersensitive, you are protected against. The second aspect was what concentration is required for protection. The way that a study was designed, there's no true measurement of "this is the concentration of the antibody that when someone was exposed to the virus enabled protection." The best we can do, with the way that a study was designed, is give a really rough estimate of "it's within this range." And that estimate matched a lot of the preclinical study that we've done in non-human primates.

Jeanne Baron [00:15:36] OK, so we're talking about a range that estimates the level of antibody you need in your blood to be protective against HIV. And of course, this antibody has to be fighting a virus that's supersensitive to it. And the estimate that AMP came up with echoes what researchers have been seeing in preclinical studies and in animal studies. AMP's the first time we're seeing this protection in humans.

Devin Sok [00:16:05] That's exactly right. Yeah, exactly. All the data we generated in preclinical, and in animal models, the data we see in the field [from the AMP trial] actually match quite well, which I think is really encouraging. The outstanding question from that is, is that broadly applicable to all antibodies? What happens if you have combinations of antibodies and what happens when you have a larger diversity of viruses?

Daisy Ouya [00:16:27] I wanted to follow up. Do these results apply to single antibodies? Can they apply to the combo antibodies? Are we able to use this type of prediction to narrow down what it is that we need to use in the future?

Devin Sok [00:16:44] So that is the big question in the field. How much can we extrapolate from the AMP trial? Have we got enough data and information to say, "OK, it's applicable to all these different antibodies, targeting different regions of HIV and different combinations?" That's a big unknown. And that's where I think that a lot of the scientific debate is, is how universal are these findings? So I think the big question for the field, for us all to kind of grapple with, is do we continue to run AMP like trials for other antibodies- targeting other regions on HIV, targeting different epitopes or combinations of antibodies- and kind of march down this really structured, scientifically driven, hypothesis-driven, experimental medicine approach? Or do we say we got a bit of an answer, and say "let's put our best combination forward and run a large efficacy trial."

Jeanne Baron [00:17:42] Some have raised the idea, since we have such great progress with antiretrovirals to protect against HIV, how do we justify, what rationale do we use to say we should continue to invest in antibody research? How do you answer that question?

Devin Sok [00:17:59] I think it comes back to the veterans of the HIV world [who] know this very well. It comes down to choice. And the more choices that we have available, the more that we can empower people to choose what makes the most sense for them.

Jeanne Baron [00:18:12] Mark, do you have a different answer than Devin?

Mark Hubbard [00:18:17] So the question comes back as, "is an antibody injectable better than an ARV injectable?" And we can have that argument all day. The other piece

that, you know, that's not in the simple question is what will this tell us about the development of a vaccine, which is really where we want to be.

Daisy Ouya [00:18:36] Can I follow up on the question around masked infections?

Jeanne Baron [00:18:40] Oh, yeah. Because researchers are exploring if some of the HIV infections that occurred in the AMP study may have been undetectable for a time. But let's start with a definition. What is a masked infection?

Daisy Ouya [00:18:57] And is there a test that can tell that you have a masked infection?

Mark Hubbard [00:19:01] First of all, I want to say this is a newly coined term. So it is not a scientific term. It is not a solidly defined or validated term. And the protocol was actually changed to strengthen its ability to protect participants and detect this. But I think for participants [who may have acquired a mased infection] what it means is there was some period of time when you had a virus or an infection on board that was not detected by the test used in the study, which are probably a little more sophisticated than you would get on the street. My understanding, and Devin did say this, this is inferred at this point.

Devin Sok [00:19:40] It's a hypothesis. With a masked infection, that timeline to that peak viremia that's very clinically typical is delayed or suppressed. And so it enters this gray zone of "is this person infected? Are they protected? And at what time were they infected? And what is the role of the antibody?"

Mark Hubbard [00:20:05] So that partially answers Daisy's question. My understanding is, this is not about them going back to prior blood samples and being able to see that the person was infected [at a particular time]. So the question, of whether or not we could create an assay that would detect this, is open. So I think as advocates, we need

to be more robust in our question, asking at the beginning of any new prevention trial, "how are we going to deal with this? Are there better ways to detect it? Are we more careful in informed consent?" That's on my to-do list immediately, that this has to be disclosed in the informed consent. But I think we have to be very careful not to pretend that we understand this completely yet.

Jeanne Baron [00:20:46] And Devin, you're drawing lessons from what we know about antiretrovirals.

Devin Sok [00:20:51] Yeah. Remember, we want to look at the antibody product with the same lens [as we have for antiretroviral].This is a single drug product. It's not a combination. If we take the same parallels with antiretrovirals, it's the same thing. You wouldn't expect that a single antiretroviral would be effective. That's why we have these combination treatments,

Jeanne Baron [00:21:09] You've both been thinking and talking about 30 years of effort to overcome HIV, an incredibly challenging virus. How does the AMP study fit in this history? What do these results mean for the big picture?

Mark Hubbard [00:21:23] I was thinking earlier about language around this. Doing trials on the cutting edge is an exercise in risk-taking. By no means do I mean risk to participants, but risk in terms of use of resources, decision-making and expectations about outcomes. Whatever decisions made six years ago would have been an exercise in risk-taking. So this was really a trial designed to try to answer a number of scientific questions simultaneously. And I think it succeeded at some level in doing that. I believe, and I have no way of knowing, that we will continue to learn more.

Devin Sok [00:22:03] From my perspective. I think it's a huge, huge, huge milestone. The same way that RV144 is a huge milestone. I think these are big conceptual theories that we have been kind of advancing in the lab without a clear signal that it's going to

work in the field. And this is the first validation that, speaking personally, that the past 10 years of research is going somewhere. It's not there yet. We still have a lot of things to work out, but at least it's going in a direction that makes sense. And to me, that's a huge win. And I'm very optimistic and enthusiastic that we're going to be able to build off this positive signal moving forward. That being said, I think there are questions. I'm not a true believer. If antibodies don't work, they don't work. But I do think if there is a positive signal, how do we maximize that to public health benefit?

Jeanne Baron [00:23:02] The trials are raising complex and important questions about the direction of research and broadly neutralizing antibodies. On AVAC.org, you can find our companion publication to this podcast, Understanding AMP, to explore some of these questions in more detail. And keep watching. AVAC will have more tools and resources coming your way to keep you informed about the potential and progress of this cutting-edge area of prevention. Thanks for listening to Px Pulse. I'm Jeanne Baron. You've been listening to Px Pulse, recorded in The Relic Room. Our theme music was composed by Alexi Stevens. Our engineer is Sam Bair.