PODCAST TRANSCRIPT

CAB-LA is a Highly Effective HIV Prevention Option; Now What?

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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. I'm Jeanne Baron

Jeanne Baron [00:00:24] Some of the best news of 2020 came in the field of HIV prevention. Two related trials from the NIH-funded HIV Prevention Trials Network, or HPTN, found very high efficacy from a long-acting injection of Cabotegravir or CAB-LA for short. Each trial showed less than 1% incidence in their study populations. HPTN 084 studied the product among cisgender women and HPTN 083 studied it among men who have sex with men and trans women. In this episode of PxPulse, we talk to lead investigators of the studies about the findings; and to advocates and implementors about the promise and pitfalls of adding CAB-LA to the package of prevention options that exist today. It's important to note these two trials compared CAB-LA, a long-acting injectable drug, to a daily oral pill (an already highly effective product) TDF/FTC brand name Truvada. The question both trials explored is will people see even higher levels of protection with a product that does not require daily adherence? And the answer in both cases was yes. Sinead Delaney-Moretlwe headed up the women's study and Raphael Landovitz led the study among men who have sex with men and trans women. Raphael, Sinead, lay the groundwork for us. What specifically did you find?

Raphael Landovitz [00:01:47] We ultimately found in the individuals [who were] randomized to the cabotegravir arm of the study 13 incident HIV infections, which ended up translating to an HIV incidence rate of 0.41 per hundred person years. And in the TDF/FTC arm, we found 39 incident HIV infections, which correlated with an incidence rate of 1.22 per hundred person years, which was almost exactly a two-thirds or 66% reduction in incidence HIV infections among those randomized to cabotegravir compared to TDF/FTC.

Sinead Delaney-Moretlwe [00:02:33] And what we showed was that an eight weekly injection with cabotegravir prevented more HIV infections in women than a daily oral pill.

Jeanne Baron [00:02:43] And talk about what's at work there. Why would the protection be better with a long-acting injectable of this drug cabotegravir compared to an oral pill with TDF/FTC?

Sinead Delaney-Moretlwe [00:02:53] We think that's because the injections provided some adherence advantage over pills,.

Jeanne Baron [00:02:59] Adherence advantages and [disadvantages] such as?

Sinead Delaney-Moretlwe [00:03:03] Habit, but also the many social pressures that women have experienced around PrEP use, including assumptions that they're living with HIV, judgments about their sexual behavior...And what injectable cabotegravir gave was a discreet

and convenient product that women were able to use, which translated into [approx] nine times more infections prevented in the cabotegravir arm of our group compared to the Truvada group. But as Raphael pointed out, the overall incidence in the trial was incredibly low at around 1%. And so we think it's important to affirm that both products are highly effective in preventing HIV infection in women.

Jeanne Baron [00:03:43] So we're talking about two products that, when used correctly, are super efficacious. How would you differentiate cabotegravir from oral PrEP for people trying to make a choice?

Raphael Landovitz [00:03:55] You know, I think some people may prefer a pill because it's more easy-on easy-off, if you will. But for people whose lives are complicated and make regulated or planned pill taking challenging, this clearly works better. And that could be really advantageous for particularly young people, particularly people who are highly mobile, are going to be moving around a lot. As Sinead said, from communities where HIV is still so stigmatized and being seen in possession of medications that could be used for HIV treatment, could be not only stigmatizing but even violence-inducing. So this is really a powerful product in those particular cases, especially.

Jeanne Baron [00:04:46] Sinead, what would you highlight about CAB-LA if you were trying to explain the differences to someone trying to make a choice?

Sinead Delaney-Moretlwe [00:04:52] You know, one of the advantages that we had in the cisgender women trial is that women already had articulated their preference for an injectable. And I think that's because, particularly in sub-Saharan Africa, a substantial proportion of women actually use injectable contraception. And so I think the important thing to lay out in the real world is that from a provider perspective, I'm going to tell someone about efficacy and safety. But I think it's also important to understand client preferences and what they want. Many people might want something that's long-acting, that's convenient, that's discreet. But also, what we would talk about would be the other side of what long-acting means. It's not something that you can switch on or switch off.

Jeanne Baron [00:05:39] So I want to turn now to the infections that did happen in both studies. Raphael I've heard you report on this a bit. Five of 13 infections in 083 occurred that can't be attributed to adherence. These were folks who showed up for all their injections. Sinead, there were 38 total infections in the trial, among more than 3,000 participants, but only four in the arm testing cabotegravir in the 084 trial. So I don't know if you can address the same question, but to both of you, what factors might be at work? What questions are you pursuing to understand more about these breakthrough infections?

Raphael Landovitz [00:06:20] These five particularly provocative cases we're still in the process of analyzing and I'm sorry I'm going to frustrate you and not be able to shine any more light on our understanding. At this point we are still working very carefully to understand the cabotegravir drug concentrations in these five people, not only at the time that the infection was detected at the site, but sort of going backwards and trying to understand, were there dips for some explained or unexplained reason in the concentrations, the levels of cabotegravir in the body, at some point that might have unfortunately coincided with a period of exposure to HIV? And what we do know from the Phase II studies of cabotegravir, in both individuals born male and individuals born female, is there's enormous heterogeneity in people about how fast

they remove cabotegravir from their systems. Sometimes, you know, after you stop taking a cabotegravir injection, it can wash out of the body extremely quickly. Sometimes it can last for years. And that's something that we only have a fairly rudimentary understanding of the factors that go into that variability, those differences.

Sinead Delaney-Moretlwe [00:07:48] For all of us, it's going to be, I mean, in the end, we have very few breakthrough infections on cabotegravir in cisgender women. And it is going to be the entirety of the data across the two trials that's going to provide us insights.

Jeanne Baron [00:08:03] Let's talk about the tail now. Once people decide to go off CAB-LA, it takes a while for the drug to completely wash out of someone's system. In that period, and it can be up to a year, people will be offered oral PrEP because there's concern that waning drug levels of cabotegravir could interact with an HIV exposure and lead to resistant strains. What further research needs to happen to understand these risks, and what are the implications for someone using CAB-LA?

Raphael Landovitz [00:08:34] We all handwring about this, the tail and what it means. But I would like to reframe. I prefer to think about it as: If you are coming off cabotegravir, the real question that needs to be differentiated is why. If you are coming off cabotegravir because you no longer are at risk, maybe you've landed in a stable relationship that is mutually monogamous. Maybe you've decided that you're in a period of life where you're going to be abstinent. But if you are no longer at risk for HIV infection, then it doesn't matter. You don't need to do anything in particular. If you're ongoingly at risk, to me, the perspective is NOT 'you must take a year, or however long, of TDF/FTC'. [Rather,] 'You must protect yourself by whatever manner is going to be congruent with your sex life to keep yourself HIV uninfected for at least a year until we think the majority of the cabotegravir is going to have washed out of your system'.

Jeanne Baron [00:09:42] And will the data from these two trials help us understand the tail better?

Raphael Landovitz [00:09:47] We're not going to have enough HIV infections to really interrogate the characteristics of the tail because there were so few infections. And we are really going to have to wait for more widespread implementation and use to fully understand if the tail is a period of vulnerability and what those vulnerabilities are.

Jeanne Baron [00:10:07] I hear you. I think it's important to say, how people cycle on and off CAB-LA or any prevention option can be complex and it's not fully understood yet. When the time comes for CAB-LA to roll out, the field has a lot to learn and we'll need to track this closely. And implementers and researchers will need to work closely with users to support safe and effective prevention for everyone who needs it. And speaking of people who need prevention, I want to turn now to the question of pregnancy and breastfeeding and CAB-LA. The trial among women was not designed to answer these questions.

Sinead Delaney-Moretlwe [00:10:43] This is obviously a big concern and a big issue for many women who may want to avoid HIV, but not necessarily avoid fertility.

Jeanne Baron [00:10:51] Can you give us an idea of when there might be useful data for women who want to become pregnant or breastfeed and whether they can consider CAB-LA as an option?

Sinead Delaney-Moretlwe [00:11:00] Sure. So I'm hoping that in the open label extensions, we will be able to learn more about use of cabotegravir during pregnancy and also during lactation, so that at the time of licensure, or shortly thereafter, we can also give cisgender women guidance about safety and pregnancy.

Jeanne Baron [00:11:21] So, watch for a readout from the open label studies and hopefully those findings are in time to answer people's questions when CAB-LA becomes available. Let me ask you both: CAB-LA is a new option which will be added to what's available now, when it gains regulatory approval. What's the final word you want people to know about how CAB-LA fits in with oral PrEP, a tool that already exists?

Raphael Landovitz [00:11:48] Thank you, the real take home is that now we have multiple, highly effective products for HIV prevention.

Sinead Delaney-Moretlwe [00:11:58] Just to note that Raphael and I are very aligned. Both products are highly effective in preventing HIV infection in women.

Jeanne Baron [00:12:12] We just heard from Sinead Delaney Moretlwe and Raphael Landovitz, the two lead investigators from the twin studies that tested CAB-LA. Now that both studies show the product is highly effective against HIV, the next step is regulatory approval and rollout. The field has seen ups and downs at this stage in the life of a new intervention. The right policies, the right investments, the right planning are essential to bring prevention that works to the people who need it. Longtime advocate Definate Nhamo, from Pangea's Zimbabwe AIDS Trust, and veteran implementor Dr. Jason Reed from the US-based Johns Hopkins affiliate Jhpiego, have joined me to discuss the ins and outs of getting roll-out right for CAB-LA. Definate, what priorities should guide policies related to CAB-LA?

Definate Nhamo [00:13:03] I think, first of all, for me the introduction of CAB-LA represents increased choices and I liken this to family planning where we don't have one or two family planning options, but we have a variety. And the reason behind choice is so that each and every one is able to peek in that basket, [and find] a choice that suits their lifestyle.

Jeanne Baron [00:13:30] And Definate, layout for me some of the advantages and disadvantages that have to be considered with CAB-LA that you would want to point out to policymakers, and even to communities.

Definate Nhamo [00:13:42] So for me, where I'm coming from, Zimbabwe is one of the low resource settings. With CAB-LA, there's less reliance on the health care providers. So having a product that is low-reliance on the health system is actually perfect because then the health care providers don't need to worry about having people queuing for CAB-LA every day. They come in once every 8 weeks, they are done. And I think another advantage is we've had some challenges with oral PrEP; in terms of daily dosing, adherence, in terms of packaging, and the need to find a safe place to store your pills. But with CAB-LA, it's just you go to the facility, you get your injection and you don't need to carry any product with you. And in terms of the disadvantages, I'm sure policymakers would also want to know this, and even community

members, it's systemic, meaning once it's in, it's in. You cannot say 'oh today I don't want it' because it's already in.

Jeanne Baron [00:14:48] Jason, what about you? Anything you'd add to Definate's list of key considerations for how CAB-LA should fit into the landscape of prevention options?

Jason Reed [00:14:57] You know, Definate touched upon the key points. One of the advantages I would add is the important role of clinical providers and the extent to which they buy into the feasibility and effectiveness of any given product.

Jeanne Baron [00:15:14] Tell us more about that. In the case of oral PrEP, what's been your experience with the doctors and nurses who prescribe PrEP, and are gatekeepers in that role?

Jason Reed [00:15:24] We encounter a lot of providers who minimize the potential impact of PrEP as HIV prevention and often do so by citing the fact that a lot of people don't use oral PrEP for the duration that the clinician had in mind for them. And to that extent, I think there is some work we need to do, helping clinicians better understand the real potential of the daily oral PrEP.

Jeanne Baron [00:15:51] And let me quickly contextualize some of what you're getting at here. The field is learning, as evidence continues to mount— for example from a big, long study known as the SEARCH study— that flexible, shorter-term or imperfect PrEP use by an individual is still reducing HIV in the community at large, at the population level. So, that's a point about existing oral PrEP.

Jason Reed [00:16:19] And beyond that, the introduction of CAB-LA is an opportunity to engage providers again, and address their concerns. And I think we could also see some real progress in the overall scale-up by having providers not just trained, but really advocating to have CAB-LA.

Jeanne Baron [00:16:41] I'm hearing clearly there's a need to engage deeply with providers, that's a major lesson to be learned from the rollout of PrEP. What other lessons should be drawn from past experiences in order to prepare for introducing CAB-LA?

Definate Nhamo [00:16:57] I think we've learned a lot from oral PrEP. And CAB-LA introduction I'm sure, and I hope, would be more efficient. How we message CAB-LA is going to be very important. I'll give an example of when we started with our PrEP in Zimbabwe. Because we had just had the demonstration project among female sex workers, communities thought this was a product for female sex workers. So literacy is going to be very important in how we message and position this product.

Jeanne Baron [00:17:33] Jason, what would you add?

Jason Reed [00:17:35] There's a good bit of market research and product introduction work. And getting that work right and getting it done early is definitely critical. And it's been my impression that we understand far too little about the end-users and the product or service that we're proposing to provide, and that a lot can be gained by drawing more heavily upon the experiences of the pharmaceutical industry and market researchers, behavioral economists, design experts.

Jeanne Baron [00:18:13] Right, with all this in mind— the need to apply the lessons of the past, train providers, conduct market research, reach policymakers, have the right messages to the community— donors are instrumental. What should donor priorities be? And is there any risk that CAB-LA might be seen by donors as a silver bullet? Is there any risk of underfunding oral PrEP or the Dapiverine Ring which is going through the regulatory process now?

Definate Nhamo [00:18:41] So to donors, my key message is they should fund all options that are available at any point in time. They should fund oral PrEP, they should fund the ring if it's available. They should fund CAB-LA if it's available. And I'll juxtapose this with family planning. When you're funding family planning, you give the whole array of options that are available because [there's] not one that works for everyone.

Jason Reed [00:19:09] Absolutely. And I think in particular with CAB-LA. It's interesting that you posited, 'is there a risk that donors could be overly intrigued by CAB-LA, similar to the way that they may be for longer-acting versions of contraception as opposed to shorter-acting?' I think, because of the unique characteristics of CAB-LA and the tail, CAB-LA looks more like antiretroviral therapy probably to some donors. So in the past, when we've had stock-outs or funding shifts away from prevention, it was no problem to put people on a waiting list or to simply scale back the service. [But] once a donor commits to putting somebody on CAB-LA, they have to be certain that they can either provide them with the next dose or cover them with a full year potentially of oral PrEP, and all of the work that is entailed in doing so. Some donors may be more attracted to the longer-acting products. With this particular product, there also can be some apprehensions about a more consequential commitment that's harder to back away from.

Jeanne Baron [00:20:24] That does provide a picture of some of the complex factors that have to go into planning. The BIOPIC, short for the Biomedical Prevention Implementation Collaborative, which AVAC coordinates and which both of you are involved in, is taking on some of that planning.

Definate Nhamo [00:20:40] The BIOPIC, which essentially is comprised of about 100 people coming from different disciplines, which includes civil society, researchers, donors, policy makers, people from nominative agencies, program managers, and implementors, it's having a platform for people to map a sort of framework for HIV prevention option introduction going forward.

Jason Reed [00:21:09] So, at least we do have a blueprint as to what needs to happen and in what order, based upon the input, as Definate said, from over 100 different experts representing a diverse array of professional disciplines.

Jeanne Baron [00:21:26] Got it. The BIOPIC is starting with CAB-LA to create a blueprint for roll-out that could be applied to future products. I'm thinking about Definate's example of contraception now, and how offering diverse products ups protection across the population. And since every HIV prevention option has unique advantages and disadvantages, no one option will work for everyone. We need them all.

Definate Nhamo [00:21:53] Absolutely.

Jason Reed [00:21:55] And for some people, even though we have a lot of options—international stakeholders may say, well, look at this ever-expanding pool of prevention options in the toolbox—for any particular end user, there may only be still just one.

Jeanne Baron [00:22:13] At AVAC, we'll be working with stakeholders to advance the strategies developed in the BIOPIC. Those strategies will speed and extend the reach of CAB-LA and future prevention products, and we'll be watching. ViiV has publicly committed to seek a label for all populations at risk. Those applications for approval will be submitted to a number of regulatory agencies by mid-2021 and ViiV is currently in discussions with the FDA, regulators in Europe, South Africa and the WHO about how to ensure global access to CAB-LA.

[00:22:52] 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 Alexey Stevens. Our engineer is Sam Bair. I'm Jeanne Baron