



PODCAST TRANSCRIPT

A Leap Forward For the Dapivirine Vaginal Ring, the Next Steps Are Critical (37:10)

<https://www.avac.org/podcast/dapivirine-vaginal-ring-gets-greenlight>

September 17, 2020

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. On July 24th, the EMA (the European Medicines Agency) gave the Dapivirine vaginal ring a positive opinion. The EMA is one of a small number of bodies in the world that provide what's considered a highly stringent evaluation of new medicines for public health. The FDA is another. After the female condom, this the first HIV prevention product to get a green light [that is] designed exclusively for women. It's hard to overstate the importance of this, with adolescent girls and young women continuing to have breathtaking rates of HIV in many countries. In this episode of Px Pulse, we mark this milestone and explore crucial questions. What advocacy must happen now? What research questions remain? What further regulatory steps must be taken? And where will the ring be available? First, AVAC's Manju Chatani-Gada began by talking with the ring's developer, Zeda Rosenberg from the International Partnership for Microbicides.

Manju Chatani-Gada [00:01:33] The ring has been many years in the making since 2004, and now there's more to do for the ring to become available.

Zeda Rosenberg [00:01:41] Well, it is the first step in a long road of important steps to make the ring available to women in resource-poor settings. This is a victory for women. So, with a stringent regulatory body, which the EMA is, granting us this positive opinion, it allows the next steps, which are for the World Health Organization to convene a committee that looks at their guidelines for HIV treatment and prevention, and hopefully include the ring in those guidelines. It allows for the ring to be put on the WHO's List of Essential Medicines. It allows for WHO to pre-qualify the ring, which is a necessary step of quality that the African regulatory agencies really like to see. It also, in parallel, allows us, in collaboration with WHO, to apply for regulatory approval to African countries. So, there is a lot of steps that are going to follow immediately and in parallel, so that the hope is, by sometime early, hopefully, in 2021, we will have an approval in at least one country and begin the even harder steps of ring rollout.

Manju Chatani-Gada [00:03:04] That's a lot of steps. Just a quick recap. WHO hopefully adds the ring to its guidelines on HIV treatment and prevention. The ring then can be added to the List of Essential Medicines. The WHO also prequalifies the ring, a quality control standard. At the same time, applications will be submitted for approval in key countries, and then, hopefully, you will have an approval in at least one key country

in early 2021. So that's great. The ring will be a new option and will be added to what's available today, like male and female condoms and oral PrEP. But these have high efficacy if you use them. Whereas the EMA's opinion for the ring was based on research that found 35 percent efficacy. What does partial protection mean for an individual woman?

Zeda Rosenberg [00:03:56] So, the 35 percent, in a simplistic way of describing it, was almost an average risk reduction across a study of nearly 2000 women, some of whom used the product extremely well. Maybe 25 percent of the women used it extremely well, as measured by how much drug was left in their ring. About 25 percent of the women likely didn't use the product at all. And then about 50 percent of the women used it inconsistently. So, what we really don't know is for those 25 percent of women who use the ring really, really well, what their level of efficacy is compared to a control group. That 35 percent number is really, from my perspective, a lower limit number. We don't know how high it can go. We know the product can't protect against anal sex. So, if women are having anal sex and using the ring consistently, they may still get infected. So again, in an abundance of caution, we know that using oral PrEP consistently and correctly has extremely high efficacy because oral PrEP is systemic. It covers all routes of HIV transmission. If you can adhere to a pill a day, this is your prevention option and it will be the same for cabotegravir, I am sure, once that data come out. If a woman can't use oral PrEP, or chooses not to use oral PrEP or male or female condoms, then the ring should be offered to her.

Manju Chatani-Gada [00:05:40] Among the steps to come, in the regulatory process and rollout, what are you most confident that will go smoothly? And where do you think more support will be needed—like watchdogging from advocates, pressure for policy change, engagement with the community for the ring to finally get into women's hands?

Zeda Rosenberg [00:06:00] You know, I think so much groundwork has already been done, especially by the activist community, in generating positive support for the ring, that my sense is that all of the countries are looking forward to having the ring be an available option for women. IPM has been very transparent all along about the positives and challenges with the ring. I think all of these countries see very clearly the incidence rates not going down in the populations of women for whom this product will be very, very useful. And so, I'm really optimistic. And a lot of the heavy lifting has to come from IPM right now. It is up to us to get these dossiers where they need to go. Once they're where they need to go, I am really hopeful. We need to give the agencies the time they need. And according to what we see, those timelines are actually quite short. So if these countries adhere to their internal timelines, I think we're going to see rapid approvals and rollouts by 2021.

Manju Chatani-Gada [00:07:22] I hear you—you're hopeful for rapid approvals and rollouts by 2021, but lessons from rolling out oral PrEP tell us critical and hard work is still ahead. The FDA approved oral PrEP in 2012, but rollout was slow, by any measure. It's improved in recent years, so there's much to learn for what it can take for a faster and better rollout of the ring. And the role of advocates will be critical.

Zeda Rosenberg [00:07:48] Absolutely. I mean, we really don't have... IPM itself doesn't have the experience in rolling out a product. So, we clearly are going to have to rely on organizations that have done this, especially for oral PrEP. It's a good thing that we're not first in some ways. There are all these lessons and thankfully there are a lot of groups, including AVAC, that have put together all these lessons learned. So, yes, there is going to be a huge amount of work. We're all going to have to band together and IPM is going to have to be instructed as well, "what are those pitfalls?".

Manju Chatani-Gada [00:08:27] I want to turn to ongoing and still needed research on the ring. The EMA is looking for further data on safety and efficacy in 18 to 25-year-old young women. Why is this data needed, how are you going to get it, and how will it affect all those steps we talked about earlier to make the ring available?

Zeda Rosenberg [00:08:49] So, in general, younger people do not adhere to product-use as well as older [people]. If we could do a follow-on study and enroll women who are 18 to 21 and compare them to women who are twenty-one to twenty-five now, since we've shown the product to be safe and to reduce the risk of HIV infection, would we be able to see efficacy in that group? And that data can occur in parallel to ring rollout, because it is not a condition for ring rollout. But most scientists agree that there is no difference biologically between women under 21 and over 21. And so, the goal really is what can we learn about ways to roll the ring out to younger populations? The same lessons that we're learning for oral PrEP, you know, how do we help younger people adhere better to prevention strategies?

Manju Chatani-Gada [00:09:49] With that picture in mind of further research to come—there's so many women who've participated in trials investigating the ring. Large trials are not unique to the ring. And yet the ring itself is unique as a product exclusively made for women's discrete use. [The EMA positive opinion] is an achievement shared by literally thousands of women who joined these trials.

Zeda Rosenberg [00:10:11] We could not have done this work without all of the women who enrolled in these studies, especially in the very beginning. Totally altruistically. There is nothing to be gained from early clinical studies for yourself. It is only for others. And then to the thousands of women who participated in these long studies, I mean, these women were giving of their time for years. And so, to them, a huge thank you.

Manju Chatani-Gada [00:10:57] As HIV continues to pose a grave threat to young women in many countries and current HIV prevention options don't meet many women's needs, this milestone is so important. The only other product designed exclusively for women is the female condom. Now, women may soon have a product that is long-acting, discrete and under their control. It's taken vision and commitment from a generation of advocates, researchers and funders to get here. And we're going to talk to all three. Joining me are Cleopatra Makura, a 2019 AVAC fellow and HIV prevention youth advocate leader in Zimbabwe, one of the many countries where the ring was tested, and may be among the first places it'll roll out. Cleo also provided testimony to

the EMA as it considered the Dapivirine Ring. Sharon Hillier, who heads up the NIH funded Microbicide Trials Network (the MTN) at the University of Pittsburgh, and Benny Kottiri, the Research Division Chief in the Office of HIV AIDS at USAID. Let me start with you, Cleo. With this announcement from the EMA, there's going to be a lot of work to do before the ring becomes available. The intention is for the countries where it was studied, such as Zimbabwe, to be the first to get access. Cleo, share with us what the opinion means to you personally and what the ring could mean to young women in the communities you know and work with.

Cleo Makura [00:12:28] Thank you so much, Manju. So firstly, women require multiple prevention options that fit within the context of their life, just like we have many contraception options to choose from. For example, in my early teenage years, I used abstinence and in my late teenage years I used condoms, and they were the best because I used them to prevent myself from HIV and unplanned pregnancies. But now I would want to have a baby. But I also do not want to contract HIV. So probably the pill, the PrEP pill, could be the best for me. However, the pill comes with its own problem, like taking a pill daily, which really does not suit me. I also live in a patriarchal society where I have to seek consent to take the pill. And the stigma which really surrounds the pill is still associated with ARV's and it really makes it difficult to take pills daily if they can just be seen by my boyfriend, my husband or even my mother. So, this is my story. But I know a lot of other young women out there. I'm aware also of the high number of young women in child marriages where there's extreme power imbalance and sexual exploitation. So in my engagements with other young women, I was hinting on the Dapivirine ring as another HIV prevention method in the pipeline. And most of the young women showed excitement for this intervention. I'm sure the positive opinion by EMA will just be good news to them as much as it was to me.

Manju Chatani-Gada [00:14:09] Could you just tell me, you've been advocating for HIV prevention options for women for a couple of years now. Tell me, what's the work of advocates now, right now, to make sure the ring becomes available and without delay?

Cleo Makura [00:14:24] So I think there's need for building social movements of women to demand the intervention, specifically the ring. There's also a need for us to engage community leaders so that they are also aware of the ring and the positive opinion by EMA. However, advocates need to be very clear on messaging and make sure a lot of voices are demanding the ring. So, of the influential people, like those who have the power to make things happen, get the pressure from the women themselves. Advocates also should be very strategic. We have the power to bring the ring home. So now is the time where we should be mapping the way forward, to know who to meet, who has the power to make sure that the ring is delivered in-country and the end-users can actually use it. Last but not least, we need to make sure that those who contribute to the health budget also understand the positive opinion and the advantages which the ring will bring to young women, so that the advocates have adequate resources to do their work.

Manju Chatani-Gada [00:15:26] Cleo, you've been working to get oral PrEP into the hands of young Zimbabwean women. What lessons can we learn from this work as we consider rolling out the ring?

Cleo Makura [00:15:37] With PrEP, what we have learned is that the communities took ownership of the initiative, like I was saying before—when the ring is being demanded by the end-users it gives that influence that people really need the intervention. And the most challenges we have observed with PrEP are really being solved by the ring, for example, the pill and the stigma. So that's something to celebrate about.

Cleo Makura [00:16:03] But the major lesson which really touched my heart was the issue of our health workers. We would go into communities and advocate for pre-exposure prophylaxis. People have the information but when they visit their service providers in local clinics, the health workers were not aware, they didn't have adequate information and they were very reluctant and sometimes unable to offer the service. So currently we have to make sure that our health service providers have adequate information and they are also ready to be offering these services.

Manju Chatani-Gada [00:16:34] Thanks so much, Cleo. Now I want to give Sharon and Benny a chance to ask you any questions.

Sharon Hillier [00:16:42] Cleo, it so great to hear your voice. And I remember so fondly the time we spent together earlier this year in Zimbabwe and the meetings we had with groups of young women to talk about the Dapivirine ring agenda. So, my question for you is, if you had to say one thing to a young woman, maybe 18 years old... you talked about your own journey using condoms and abstinence at different points in your life. What message would you give to a young woman who is thinking about trying to use the ring?

Cleo Makara [00:17:17] I would talk about the issue of the efficacy because with young women, like I say, a very diverse group and they would want to experiment. So, I guess I'll first talk about the efficacy and I'll just note that the ring also comes as an addition to the other HIV prevention methods that we have so that young women will know that they are not being forced to use this new HIV prevention method. But it comes as an addition. So, they have the autonomy to choose what they would want. To either use PrEP or just the ring or to use abstinence or choose whatever they think suits them best because the ring gives us those options which we have been crying for for years.

Benny Kottiri [00:18:00] Very clear. This is Benny. I really want to thank you for all your efforts in support of the ring. So, the level of engagement by policymakers and the government officials, especially in Zimbabwe, based on your interactions with them, are they supportive of making this product available to women or are there any reservations?

Cleo Makura [00:18:24] Every time we discussed about ring they showed interest in the ring. But Zimbabwe is having the issues of support and the issue of resources. So, the

interest would be there but advocates still need to do a lot of work to make sure that the ring is available and accessible to the end-user.

Manju Chatani-Gada [00:18:45] Making the case for resources is really going to be so important for both rollout and ongoing research. Sharon Hillier at the MTN, you've led the charge into the study of microbicides, which are products to be used at the site of infection. The Dapivirine ring is the first microbicide to get this far in the game. And the MTN led a lot of the basic clinical and behavioral research on the ring that helped us get to this point. So first, let me congratulate you.

Sharon Hillier [00:19:16] Thanks, Manju. And it's been such a privilege to join with IPM as we've partnered with them to bring this on this long journey from their earliest studies to where we are today, poised, almost to get it into women's hands. So very exciting.

Manju Chatani-Gada [00:19:33] The ring is a localized intervention, slowly releasing the active drug into the vagina to prevent against HIV infection during vaginal sex. Most of the drug is in the vaginal tissue and not absorbed in the rest of the body. In other words, it's nonsystemic protection. That's in contrast to daily oral PrEP, which works systemically. The active drug builds up in the bloodstream and provides protection all through the body. So, Sharon, why do we need a product like the Dapivirine Ring? What's unique about this product?

Sharon Hillier [00:20:04] From my perspective, as both a woman and mother, I cannot say how strongly I share Cleo's passion for choice. And it's really true, Manju, that the Dapivirine Ring is most remarkable because the amount of drug that women are exposed to when they use it is so tiny. So, if you think about a day of daily oral PrEP, that's 300 milligrams over the course of a month, you'll get maybe exposure to nine grams of drug. With the Dapivirine Ring because it's such a tiny amount, it's four milligrams spread over a month. So, what does that mean? It means your exposure to systemic drug is so low, it is super safe. In my 30 years of doing research in reproductive health, I have never seen a product with such an extremely positive safety profile. What that means is we didn't see problems with kidneys or with bones or with liver. We don't see the kinds of problems that people have sometimes with taking systemic drugs. So, while I am a huge supporter of oral PrEP, I'm even more a supporter of choice and options. As I said, the Dapivirine Ring is amazingly safe. It has very few side effects and that's my favorite thing. It's also extremely discreet. It lives with you. It's part of you. It sits in the vagina. Nobody can see it. Nobody knows you're using it. And I think the last thing is that it's easy because you don't have to be reminded every day, like you do with the tablet, to remember it.

Manju Chatani-Gada [00:21:54] You've talked about choice. Help us understand the options available to date and how the ring fits into this big picture. I'm thinking about oral PrEP, among others, but also products in the pipeline. For example, advances with long-acting injectable prep called Cabotegravir suggests that it may not be too long before there's a long-acting systemic option. Who and when might someone choose the ring over other options?

Sharon Hillier [00:22:21] We heard from Cleo today that at different points in your life, you need to use different things and you have different circumstances. When I look at what people talk about in terms of HIV prevention: circumcision—fantastic, but it's really just for men; condoms—overwhelmingly under men's control. Women can try to negotiate their use; and we have oral PrEP—but only Truvada is approved for women, not Descovy. Right. So oftentimes we have this menu of options that really can't be chosen by women because they're not available—either because the research hasn't been done or because they're not under women's control. If the ring is approved, we will have increased the number of biomedical options available for women. But it's not going to be enough either. And we look forward very much to the results of the HPTN 084 study, which will tell us whether or not injectable cabotegravir can be as effective in women as it has been in men. But really, many people struggle with adhering to visit schedules that require frequent visits to a clinic to get an injection or to getting daily oral PrEP, and they need to figure out what works for them.

Manju Chatani-Gada [00:23:43] Cleo and Benny, do you have a question for Sharon?

Benny Kottiri [00:23:47] Hey Sharon, this is Benny. One concern for programmers and policymakers at this point is the partial efficacy of the ring, especially true for younger women. Some people say it can be explained behaviorally. But there are some other people really thinking about, is there a biological reason for that? So, I'd love to hear your opinion on that. Second, what would be your advice, given that we don't really, we lack that data, right now. We are not able to make a decision to really program this product for adolescent girls. So that is a clear concern. What would be the next step and what would be your advice to policymakers at this point?

Sharon Hillier [00:24:34] Thanks, Benny, for asking those two questions. Key key issues. We all know, I think, that oral PrEP has never been proven to be effective in young women either. Right, because non-adherence to daily oral PrEP was so high. Now, what we did see in the Dapivirine Ring studies was lower adherence. But the young women actually told us "yeah, actually, I took it out". We have looked so hard to see if there are biological issues. And quite frankly, we haven't been able to identify any reason the Dapivirine Ring wouldn't work well in young women. Using modeling that's been very similarly used for oral PrEP to predict how effective it is, we think the protective benefits about 75 percent. But think back 10 years ago with oral PrEP, we know the effectiveness in men who had sex with men in the clinical trials was 44 percent. Does anybody ever say, you know, oral PrEP is only 40 percent effective? Nobody says that, right. Because it's taken many years to have other studies that have taught us that when it's used very well, it's extremely effective. We're much earlier in the process with the Dapivirine Ring. We only have the open label studies and the randomized placebo-controlled trials. The second question, what do we need to really move into younger women, I think additional data is needed just as it was needed with oral PrEP.

Manju Chatani-Gada [00:26:12] Got it. We've heard more data is needed on the ring to better understand efficacy in younger women especially, but the data is there showing benefit in general and the ring is moving forward toward rollout. Benny Kottiri from USAID is a longstanding funder and supporter of the ring. Benny, there have been microbicides doubters along the way. In the early days, we heard from funders and policymakers that women would never be open to using something in the vagina, that I would never be efficacious enough, that this is not optimal investment of resources. But USAID has been a supporter of microbicides research and the ring all along the way. Why did the ring make sense to USAID?

Benny Kottiri [00:26:55] For USAID, a guiding principle has always been to respond to the so-called unmet need focused on women in sub-Saharan Africa. So, in that regard this is a product with a clear safety profile. This is the very first product that is discreet, long-acting and nonsystemic for HIV prevention to address the unmet needs of women. So definitely it makes sense for USAID to continue our commitment and support for this product.

Manju Chatani-Gada [00:27:30] But Benny, you had to be convinced, too. What made you personally change your mind about the ring? Why are you a champion of the ring now?

Cleo Makara [00:27:39] That's a great question. Yes, it is true. There have been ring doubters throughout this process, and definitely I was one of them. I was hesitant at first because of the low adherence and moderate efficacy observed in the two clinical trials. The Phase III trials. But as time passed, we know that in the open label extension studies, the U.S. adherence and effectiveness improved very substantially in the open label extensions. So that data indeed convinced me to support the continued development of the ring. And because of the product characteristics, I believe that for HIV prevention, the ring is a significant advancement

Manju Chatani-Gada [00:28:30] How do you make the case to other donors that it's time to join the effort to support the ring?

Benny Kottiri [00:28:36] For USAID we feel that it is our responsibility to listen to the community, what Cleo was talking [about] all along, and respond to what women need and what they want. So, there is strong community support. We have seen that in clinical trials. We are seeing more and more women clearly supporting the ring. For USAID we see it as a mandate. We all know that donor resources are limited. One or two donors alone cannot make this happen. To achieve our goal of providing a ring to women who need them, we need to come together. We had to show our strong support and also, we need to pool our resources. That's what we tell the other donors.

Manju Chatani-Gada [00:29:24] With many voices saying the future of the ring depends on a coordinated, proactive effort, one voice in particular is also drawing powerful lessons from the history of microbicide research for HIV prevention. The drive to find a microbicide came from the ground up, advocates demanding attention from

funderson and researchers. Lori Heise, now at Johns Hopkins, was among those in the 1980s and 90s who began to lay the groundwork for this moment. Lori, it's been a decades-long pursuit and now here we are.

Lori Heise [00:29:59] It's really fascinating to finally be at this moment. It's sort of like a dream that we never actually thought would happen. I don't know how many different times we said, "Well, we're five years away from a microbicide". And then it was the next year, "Well, in another five years..."

Manju Chatani [00:30:17] I'll just share a little of your background. In 1998, you were one of the founders of the Global Campaign for Microbicides. Although the campaign no longer exists, many of the advocates it nurtured continue to be at the forefront of microbicide advocacy efforts. The campaign also helped to inspire the establishment of the African Microbicides Advocacy group AMAG and the International Rectal Microbicides Advocacy group IRMA, along with many others. I said earlier all this came about from women and women's health advocates. What were the early challenges? What was happening and why—to generate this demand for a discreet, women controlled, nonsystemic, or as we call them, topical, HIV prevention products?

Lori Heise [00:31:03] In the early days, and I'm now talking the late 1980s and early 1990s, I think that the field of HIV prevention was really naive and it was very technocratic. And so, the analysis of the challenge was: if we could just get condoms to people, we would be able to control this epidemic. And there wasn't a discourse even on the structural challenges, the inequities—none of [the] recognition of people's lives and the lived reality. And that was partly because [the HIV epidemic] started in high-income countries; at least the focus of agenda setting [started in high-income countries], which is always part of the challenge, right, of who gets to set the agenda. There was a very strong perception that it was gay men who are most at risk in the corridors of power. And it took a lot to get people to recognize that women were a group at risk. Also, it was very hard to develop a grassroots movement for prevention. So, we faced a really uphill battle. Most of the early activism around this came from women's health advocates. And it took almost a decade of really bringing together [from] HIV activism and science with the women's health activism and researchers to really forge an integrated field of microbicide development.

Manju Chatani-Gada [00:32:44] What would those early moments events or people that compelled you to get involved?

Lori Heise [00:32:50] For me, the real turning point was this meeting in 1990, I think it was. And one of the enormous intersecting issues was: what does it mean when women don't have control over their sexual or physical safety for their ability to protect themselves from HIV? And so, I organized a workshop at this conference. A classic story of microbicide advocacy in the early days—it got pushed to during the happy hour. And I thought, 'oh, great. Well, no one is going to come to this.' And the room was overflowing. All of the frustrations that people were feeling—because this was the first time that I had seen at a conference either frontline, not even activist, but peer

educators in Uganda or in Kenya interacting with the global HIV establishment— and this young woman stood up. She was from Uganda and she said, 'Imagine this, I'm talking to a woman who is married, who's not supposed to be having relationships outside of her marriage, who's supposed to not challenge her husband. Her husband may be having affair... [she'll say to me] If I ask him to use a condom, he's going to think I'm cheating or I'm challenging him.' She said, 'I can't even start that conversation'. She said, 'I just don't understand how people think condoms are going to be the end of this. They sent a man to the moon. Can't they make something that will allow you to get pregnant, but protect you from HIV?'. And I said 'I will try to find out an answer for you, because I think we all need that answer.'

Manju Chatani-Gada [00:34:39] So you began to bring researchers and advocates together from both HIV and women's health to explore the need for a product like this and how to get it developed. The struggle for women's social and economic empowerment continues. So, what would you tell us to keep in mind as we work to bring the ring and other HIV prevention tools into the hands of women who want them and can use them? What keeps you up at night?

Lori Heise [00:35:04] There is this tendency, especially among research and product development people, to think that the end goal is the product. But the slog to create real, consistent uptake in use is as long as the slog to get the product in the first place. And just as important. These things could easily sit on the shelf. It's a huge issue and it's been underestimated for almost every woman's product in the past. And I just hope advocates and donors keep their eye on that prize. You know, as we went through a series of successes with some of the biomedical—treatment as prevention and PrEP—I became quite worried. The focus became, again, so much on technology being the answer that it echoed back to the early days where condoms were the answer. You know, the fact is, they're just tools. They're not like magic bullets. So, things like gender inequality and secure livelihood, criminalization—[are] big issues that really need to be part of a strategy if these new tools were really going to make a difference to women.

Manju Chatani-Gada [00:36:20] The ring will be a powerful option if it's part of a comprehensive response that takes in the many facets of a woman's life. All this takes leadership. The field must look to leadership from advocates, policy makers, implementers, funders and the communities themselves, country by country, where the ring could make such a difference. And the time for that leadership is now. You can learn more about the ring and find resources for your advocacy at AVAC.org and PrepWatch.org.

Jeanne Baron [00:36:57] 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 Aleksis Stevens. Our engineer is Sam Bair.