PODCAST TRANSCRIPT

Inclusion of Pregnant and Lactating People in HIV Research: What you need to know

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Jeanne Baron: Welcome to PxPulse! There's a new push for research to finally confront a major gap in HIV prevention. People who are pregnant or lactating have historically been excluded from research and this continues right up to today. This has led to a huge problem- while pregnancy might raise your risk of acquiring HIV or add complications when exposed to COVID or other threats, providers will rarely find data that directly addresses the effect of new interventions during pregnancy. It's a data desert, and in the HIV response it means pregnant people are among the last to get a new drug for HIV prevention…after it's been proven safe for everybody else.

But some researchers, and advocates for women and public health, have been taking aim at this problem. Their efforts are paving the way for a paradigm shift, one that will redefine this population from needing protection *from* research to being better protected *through* research. In today's episode of Px Pulse, AVAC's Manju Chatani-Gada will take us through conversations with researchers, policy-makers, and with trial participants who became pregnant. Manju has been bringing together these stakeholders to help the field understand why this population gets excluded, and what to do about it.

Manju Chatani-Gada: I have been thinking about the disconnect between research in HIV prevention and people who are pregnant or lactating, for many years now. It's a critical problem in HIV prevention. But in recent years, there's been momentum to change this.

Dr Anne Drapkin Lyerly of University of North Carolina in Chapel Hill, is going to give us a researcher's perspective. She's a Professor of Social Medicine and also in Obstetrics and Gynecology. She led the NIH-funded *PHASES Project* to advance equitable inclusion of pregnant women in HIV research, which produced formal ethics guidance. She's been on the forefront of this issue and the urgent need to bridge the data gap and see this population included early in research.

Welcome Anne!

Before we start, I want to define who this population is. Anyone who can become pregnant and choose to breast or chest feed their baby, belongs in this category, which can include cisgender women, trans men or gender non-binary individuals. This podcast is primarily focused on cisgender women, but it's important to underscore that a lot more work needs to be done to bring other affected communities into the conversation and to prioritize their needs because, all of these populations may see a greatly intensified risk of HIV acquisition when exposed - when they are lactating or pregnant.

Anne, does the risk go up a lot? And what do we know about why?

Dr. Lyerly: The risk does go up during pregnancy and lactation, and there are many factors that contribute. One is the physiology of pregnancy. We think that the tissues of the vagina, the cervix are different, and so that exposure during pregnancy may make you more likely to get HIV. Other factors are behavioral. So if you're pregnant, you may be less likely or less able to use barrier contraceptives, which interfere with HIV transmission. So we do think there are a number of contributing factors that I think the jury is out on which are most important. But what we have settled on is that there's about a threefold risk of HIV infection if you're pregnant in the third trimester and that a fourfold risk in the lactating postpartum period.

Manju Chatani-Gada: So, why has pregnancy excluded or precluded people from participating in research - and is it all research, to your knowledge - as the norm in clinical research, or is there something different about HIV prevention research?

Dr. Lyerly: In general, there has been a tendency across clinical research to exclude pregnant people for decades. In some ways, HIV has been an exception to that tendency, most notably in very important studies that were done in the early 1990s that pointed to our ability to reduce the chances of vertical transmission. 076, that trial has always been held up as sort of a moment of success for HIV research. But there are some really important exceptions when it comes to even HIV. So despite the fact that we have this success in terms of preventing vertical transmission, we have a very robust research portfolio around that need. Evidence gaps remain even in HIV. And those include gaps around what the proper dosing of antiretrovirals and drugs for co-infections are in pregnancy. And we know that the pregnant body is different and often processes drugs differently. We also have not done a good job of gathering data about the impact of antiretrovirals on maternal health outcomes. So we know pretty well how to prevent HIV in the fetus. But what is the impact on women's health? One of the worries that has kept pregnant people out of studies is whether the drugs have any effect on the healthy development of the fetus, HIV aside. And then, of course, one of the key areas where research has lagged far behind is in prevention. So, despite the fact that we've done a really good job of figuring out which drugs are most effective in preventing maternal-to-child transmission of HIV, keeping pregnant people from getting HIV in the first place seems to have fallen off the radar screen, and pregnant people have been historically excluded from prevention studies.

Manju Chatani-Gada: What has been the impact of this exclusion, across decades now?

Dr. Lyerly: Yeah, well, so there have been a number of impacts. Sometimes the impact of exclusion has been that because there is no data or limited data on a drug, that pregnant people have not been able to access the drugs that are the most effective, have the least side effects, etc. So some of the newer antiretrovirals have been made less accessible to people during pregnancy. So we call that sort of reticence both at the clinical level and at the policy recommendation level. Another impact has been that when those medications are used, it's not clear that the dose has been correct. So they may not provide adequate protection in pregnancy or there may be a side effect profile that's unacceptable. A third problem has been that as the AIDS community has made very, very clear to the bioethics community, if you will, participation in research can be a benefit to an individual as well as to a population. And pregnant people

have been widely excluded from studies that they could benefit from, either individually or as a as a community. And what we've heard from engaging advocates over time that they value the direct and the indirect benefits of research participation, but they have not been afforded those benefits by and large.

Manju Chatani-Gada: It sounds like there's a lot going on here. We'll be talking to a donor, a policy maker and a former trial participant a bit later— but now, from a researcher's perspective, what challenges do you need to overcome to be able to include people who are pregnant or lactating in research?

Dr. Lyerly: Well, there are challenges at every level. Some of them are challenges in the hearts and minds of researchers who have a lot of fear around conducting studies that are necessary and valued by the population. Some of the challenges have to do with regulatory structures that are in place and legal structures. But, you know, I think one of the really important challenges that has been overlooked is that the community members and civil society has really not been central enough in this effort. And, you know, as we learned from our work together in development of a think tank, Manju, you and I heard how powerful it can be to bring those advocates, to bring civil society to the center of these conversations to help solve the many barriers that are before us, when we think about how to move research forward.

Manju Chatani-Gada: At AVAC, we have long been calling for this kind of early engagement. But speaking as a researcher, what is it that changes when you are collaborating with potential trial participants, the people who are weighing their concerns about pregnancy and if it's safe to join studies?

Dr. Lyerly: Yeah, well, I think it is absolutely critical in all the work that I have ever done in bioethics. A key part of it is listening to trial participants, listening to those in the community and understanding. What they value and understanding what their priorities are in shaping not just individual studies, but in shaping the research agenda. Bioethics, which is my field, has tended to be sort of insular, if you will. So we identify what we see as the key ethical issues and we sort of hash that out among ourselves. What I have found time and time again is that when we engage the community, we hear ways of thinking, moral priorities, ways of framing debates that are not necessarily intuitive to the research community but move the conversation forward dramatically.

Manju Chatani-Gada: Yes! Thats beautifully said. Commuity voices are absolutely essential to getting this right. The think tank you mentioned earlier, which included researchers, relevant donor agencies, ethicists, civil society advocates and former trial participants, it brought about a consensus, I think one of the first times that inclusion of pregnant and lactating people is a matter of reproductive justice, and approaching it that way is extremely important. And what's happening in the US right now is a good example. Women's health has become highly politicized, since the Dobbs decision overturned abortion rights. Other countries are watching. How is this affecting the effort to make research more inclusive for people who are pregnant?

Dr. Lyerly: Yeah, well, I think there's kind of two things that have happened from what we see happening in the United States. One is a lot of worry that finally we have gotten some

momentum around research in pregnancy and we are making some progress. So we have seen momentum at every level from WHO, down to national organizations. The Food and Drug Administration has issued draft guidance that foregrounds research in pregnancy as an ethical priority. So at this moment, when we have broad based momentum, there is a worry that abortion restrictions might have a chilling effect on research.

From a bioethics perspective, there is ethics guidance that says in jurisdictions where safe abortion cannot be assured, you should not do research in pregnancy with some exceptions.On the other hand, there has been, as you say, a galvanization around this because as women have less choice around whether or not they're pregnant, the importance of information is emphasized. So to have no choice about whether or not you're pregnant and to face profound gaps in evidence about how to ensure that your pregnancy is safe is what I would call a double injustice. No choice about pregnancy and no information about how to ensure safe and healthy outcomes. So in many ways, what is happening in the United States, as problematic as it is for women's health, is something that has made research in pregnancy ever more important. If it was a moral imperative to do this research before the Dobbs decision, it's an even more forceful moral imperative right now. Even though it may be harder, it's more important.

Manju Chatani-Gada: f you could capture exactly what the gains will be, if we get this right, how would you put it?

Dr. Lyerly: I think the more information we have, the healthier the pregnancies are going to be. I think we're never going to be able to eliminate HIV if we don't know how to prevent HIV in pregnancy. That is a key area. It's a high-risk population. And without the data that we need to optimize medication regimens in that community, assure people that prevention is safe and effective. We're never going to achieve the goals that have already been set. So what I see with more information is that policymakers and clinicians are going to feel more confident in their recommendations. The recommendations are going to be better and more specific when it comes to pregnancy and the.

People who are pregnant are going to be able to feel more comfortable and have better access to the drugs they need to ensure ideal outcomes. So when we think about research in pregnancy, there is always fear that comes along with it. And when we think about medications and pregnancy, there's always fear. And fear has gotten in the way of optimizing outcomes. And I think the best antidote to fear is information. And so if we do the research, if we do it well, if we honor the priorities of the people who are most affected by it, then the world is going to be a healthier place.

Manju Chatani-Gada: Dr Lyerly painted us a picture on the challenges for researchers and why excluding people who are pregnant or lactating from research is a serious problem that deserves more attention. But there's one voice who can really bring to life why this matters. This trial participant was enrolled in the HPTN 084 trial in Zimbabwe that tested injectable cabotegravir as PrEP, which went on to be shown as highly protective. And then, in the midst of the trial she became pregnant. Per the study protocol, she had to then stop using the product. I asked her to tell me what her hopes, or fears were, when she joined the cabotegravir study.

Elisia Madende: I wasn't given any fears. But I was hoping that everything was going to move well. When I just think about what can help me, or others in this society where I'm living, I saw it was great for me to start the product first- to be an example

Manju Chatani-Gada: I see, being a role model was important to you. I understand. And once you were fully involved, what was your experience like?

Elisia Madende: It is helpful. It is very helpful. I was happy, just because I mentored other women and we discussed all of us, we were interested. It was the fourth year when I became pregnant.

Manju Chatani-Gada: So you had been on the study for three years and then you became pregnant?

Elisia Madende: Yeah.

Manju Chatani-Gada: So when you became pregnant, what did that mean for your involvement in the study?

Elisia Madende: I was supposed to stop. We were not allowed by the monitor to be pregnant. They said that it was not proven for pregnant women. They were not sure about the side effects that may affect the child. So I was stopped.

Manju Chatani-Gada: When they told you that you had to stop taking cabotegravir, were you happy to stop using the product, or did you have questions or concerns about being taken off using it, especially knowing that you were pregnant, a time when your risk of getting HIV is higher?

Elisia Madende: By that moment, it pained me. Just because it was my option of preventing me [from getting HIV]. But then they said, I'm supposed to stop, and I was given no option. It pained me. It pains that when you will be a way that you be at big risk, and knowing that the product was there which was supposed to help you, you are not being allowed to continue. It pains.

Manju Chatani-Gada: Did they talk to you about other ways to keep yourself safe while you were pregnant?

Elisia Madende: Yes, there was, the one of the tablets. But the tablets, sometimes they are forgettable. It is better for an injection than a tablet.

Manju Chatani-Gada: The tablets...that's oral PrEP. How did the trial team explain to you that you needed to stop taking the injectable product, and what was your reaction?

Elisia Madende: Yeah, I really wanted to stay. But they said, 'we can't risk yourself.'

Manju Chatani-Gada: I see. You wanted to stay but they said they couldn't risk it. So, what would you want to say to researchers and to the Ministry of Health about the importance of including pregnant and breastfeeding people in research?

Elisia Madende: They must consider if the person is willingly, they must consider him and just bless them. When she needs to start, it's how, even it is not been proven, they should explain to them. And know exactly what they will be doing. Explain thoroughly. But if she considers it, they must leave her to join.

Manju Chatani-Gada: It's a clarion call from Elisia; Women who find themselves pregnant should get the information they need to make their own decision about how to navigate the risks and benefits of research. Donors, regulators and policymakers who play decisive roles in determining both what research is undertaken and how it is conducted will need to heed this message, for things to change.

Some donors and policymakers are already champions for the inclusion of people who are pregnant or lactating in research. Dr. Ashley Lima of the US Agency of International

Development joined the conversation, speaking as a funder of research. And Dr. Takunda Sola from the Ministry of Health in Zimbabwe has monitored the ups and downs of trying to get HIV prevention products into the hands of the people who need them.

First, I asked Dr. Lima why *she* is convinced that pregnant and lactating people must be included in HIV prevention research.

Dr. Lima: When women are left out of research, we don't have data. When we don't have data, we're less aggressive or we as practitioners maybe are less aggressive with our messaging. And then therefore there's a lack of scale up, there's a lack of adoption that really all of that does stem from the exclusion in the first place of women from the research process.

Manju Chatani-Gada: Dr. Sola you saw this play out firsthand in Zimbabwe as the Ministry of Health began to scale up oral PrEP. What happened and what are the lessons we need to learn from this example?

Dr. Sola: So yes, there is a lot that we can learn. I think as a country we started the oral prep program around 2018. Our guidelines when we knew started off, it was mainly restricting oral prep to key populations, but yet there were at risk pregnant and lactating women who could have benefitted from PrEP early on. And it is only recently that we are having now a trust to say, 'okay, how do we look at our messaging for oral PrEP and how do we get many more pregnant and lactating persons to access PrEP?'

So what it already meant is that there was a delay in our communications in terms of getting pregnant and lactating women to understand that this product is readily available and they can use it. And what we are now noting, for example, when we're trying to analyze why we were particularly struggling with pregnant and lactating persons in terms of access to oral PrEP, we carried out some small focus group discussions. And we were given a quite an interesting response. Some of the women say we do not want to take oral PrEP because they are ARV's.

So in their minds, the very fact that PrEP is an ARV, they were associating with it being necessarily a bad thing in quotes. And they were not willing to take up the product. So we feel that if we had more data, and also had we been aggressive with our messaging early on, some of the stigma related to oral PrEP acceptability would have been sorted out earlier. And we would have managed to scale up access for at risk pregnant and lactating women at a much faster rate.

You realize that there is a lot of lack of awareness about the benefits of PrEP, which I do feel that we could have sorted earlier if we had involved pregnant and lactating women earlier on. Even when we're carrying out our implementation research or when we rollout. But the fact that we rolled the product and it was more associated with key populations— there was a lot of stigma that we could have addressed early on and these populations would have been benefiting.

Manju Chatani-Gada: Those are such powerful lessons from Zimbabwe...leaving pregnant and lactating people out of the conversations—as research, policies and programs are developing—resulted in serious delays. And even when it was available, people didn't trust oral PrEP. The ground had not been prepared for people to understand and use the products.

Dr. Lima, I want to turn back to you as a donor, the need to start this engagement early is very important, but it's not easy. There are many stakeholders who have a part to play. How do we get there? And in particular, what do funders need to do?

Dr. Lima: Sure. So I think that taking a step back even, I think that we as donors, as industry, as regulators, you know, as civil society, as researchers, we have to first get on the same page. Right. I think whether we're talking enrolling women earlier in the research process or whether we're talking about community engagement, both involve all of us getting on the same page and adopting those conceptual shifts, right, related to the attribution of risk in research. So the shift toward considering pregnant women complex versus vulnerable, the shift from protecting women from research to protecting women through research, and the shift toward promoting fair inclusion rather than presumptive exclusion from clinical trials. I think that there's this cascading effect when we're not first on the same page.

Taking a step back from what funders can do, we first have to get on the same page, regardless of which stakeholder you are. And then from a donors perspective, I think it's really our responsibility to understand the science behind moving from **protection from** [research] to **protection through** research. And to really elevate the importance of evidence on maternal and fetal safety so that it's kind of on the main stage. So some actionable steps might be to actually fund pregnancy PK studies for all investigational ARVs before a drug registration; to support the expansion and the strengthening of active surveillance of drug safety in pregnancy; and all activities to meaningfully engage and center pregnant people and the organizations that work with them in setting HIV prevention research priorities.

Manju Chatani-Gada: It's great to hear specific steps like this, to start gathering really essential data– You mention PK studies, which measure how a drug is taken up, metabolized by the body; and the need for more data on surveillance of drug safety; and just the general call to build out a

research agenda led by the priorities of people in their reproductive years, pregnant and lactating people in particular, and their communities.

Let me ask both of you, where do you see momentum on this issue?

Dr. Lima: I think there's certainly been some momentum, especially over the past five years. If you think beginning with the 2018 WHO convened meeting. And I think since then there's been a number of meetings and reports from WHO, IMPAACT, PHASES, AVAC, major players in that area. A JAIS issue dedicated to the topic. I think we've seen a lot more momentum since COVID and seeing what happened with pregnant women's access to treatments and vaccines post COVID, I think we've definitely seen momentum here. And I think that most of the reports and meetings have actually resulted in explicit action items for various stakeholder groups. And so I think it's clear what different stakeholders need to do and now we need to actually see action from those different stakeholder groups.

Manju Chatani-Gada: Are you seeing momentum, too, Dr. Sola?

Dr. Sola: So definitely there has been a change when we are rolling out the implementation research for products like cabotegravir and the dapivirine vaginal ring, we did manage to get regulatory approvals. But I also then also realized that even when we we're getting that approval, there are still more discussions around dapivirine vaginal ring and the implications for pregnant women who use the products in terms of how safe is it for them and what if, in the case of miscarriage, how do we deal with such matters? And we realized that there was a lot of pushback.

So generally there is a bit more openness. But there is still some engagement that needs to be done from us as policymakers even engaging the regulatory authorities, because definitely the protectionist attitude is still there, to say that mindset can then infringe on access for at risk populations.

Manju Chatani-Gada: So some steps forward, but also pushback. When you talk about further engagement, with regulators for example, what's the role of policymakers in bringing about the changes that we've been talking about, "protecting" pregnant people ***through*** research rather than "protecting" them ***from*** research.

Dr. Sola: I think from a policymaker perspective, we probably are the best placed in terms of getting all the partners under one roof or getting the discourse to really start at scale. We also recognize that whatever policy that we're driving or whatever policy that we are setting up, a lot of it has to be guided by the feedback that we are getting from the end users of any products that we are rolling out. So I think there should be a concerted efforts towards research that gathers insights from what the end users themselves are saying.You need local data that suggests the validity of whatever request that we are going to make with our regulatory authorities. Once that is available, it then becomes easier to say, 'Okay, this is the guidance from the World Health Organization, and this is what our local data is suggesting. It gives us enough ammunition to actually carry out the right sort of engagements. That's how I'm looking at it.

Manju Chatani-Gada: And Dr. Lima, in terms of the critical next steps, where do you see pain points that must be overcome to leverage the momentum that we've been talking about?

Dr. Lima: When I think about all the stakeholders involved, I think that researchers and industry are kind of following in the lead of regulators and policy makers and I guess even funders. But then when I think about myself as someone in my own role at a donor agency we are limited by FDA, for example. So I think that if we have clear marching orders and clear guidelines and strong recommendations and alignment from regulatory agencies, and that enables us as funders to have clearer requirements around inclusion of pregnant people and the research that we fund. And then from there, I think that researchers and industry follow and in that order.

Manju Chatani-Gada: A lot of moving pieces, a lot people in different roles who have a job to do. And a great unmet need— to bring HIV prevention to people at a point in their lives, during pregnancy or when they are lactating, when they are especially at risk. Dr. Sola as a public health official speaking out on this, how do we capture what matters most to improve the health of this population.

Dr. Sola: What we have noted is that sometimes we can end up missing the point in terms of, yes, we may have the regulatory authorities looking at the research, whether they think the research would be safe for pregnant and lactating persons, and the ethics behind that research. But you also find that sometimes then you can also have the voices of the pregnant and lactating persons themselves muted in the conversations. The key takeaway from even from this discourse will be: in everything that we be doing, we seek to place pregnant and lactating women at the center of all health care, whether it's research or whether it's direct delivery of the products.

Manju Chatani-Gada: It's clear that up to now, too many people have been left out of the discussion and out of the research. Pregnant and lactating people for one and, importantly activists and civil society too. Regulators are in a critical position, as are donors, policymakers, civil society and affected communities— among them all, there are champions on the issue standing ready to help push the research enterprise in the right direction.

Centering these voices in the HIV prevention research agenda is not just an ethical obligation; it is a strategic necessity for reproductive justice…
and to end the epidemic.

For anyone interested in learning more, read the AVAC/PHASES 2022 Think Tank Report—an action agenda for advocacy—calling for multiple stakeholders to act in moving the needle forward. This report is your essential guide, but the journey doesn't end here. In the coming months, expect key resources from AVAC, PHASES, and another key partner, HAVEG from South Africa. We're sharing user-friendly training and materials for ethics & review boards on global guidance for the inclusion of pregnant and lactating people in research. AVAC's CASPR project will also launch a literacy campaign, equipping advocates to find allies, educate communities, and engage with national governments. Because success comes from working together. You've been listening to PxPulse.