Transcript: World of Prevention, Vaccines and More

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At the 15th Conference on Retroviruses and Opportunistic Infections (CROI) in Boston, Regan Hofmann talks with Susan Buchbinder, MD, of the San Francisco Department of Public Health about new data on circumcision, vaccines, microbicides and other possible HIV prevention tools.

Regan Hofmann: This is Regan Hofmann, editor-in-chief at POZ, and I'm here with Dr. Susan Buchbinder, who is a professor at UCSF, and she is also with the San Francisco Department of Health, and an expert on HIV of course. Thank you for coming and talking with us this morning. The first thing I wanted to touch base with you about was circumcision. There's some new information, some new findings at CROI; in particular one study that showed that men who were circumcised actually had an increased risk of transmitting HIV to their partners. So I was wondering if you could talk a little bit about that.

Susan Buchbinder, MD: I'd be happy to. There have been three randomized trials that have looked at the ability of circumcision to protect HIV-negative men, and they all showed substantial protection for those men; probably a two-thirds, sixty percent reduction in the rate of HIV infection. What was presented here were data in HIV-positive men; if you circumcise them, can you prevent transmission to their HIV-negative female partners. Unfortunately, they didn't find any protection; they found a trend toward an increased risk of infection, particularly in those men who resumed sexual activity before the wound had healed.

RH: And that's been a point of discussion. Getting circumcised is one thing, but waiting until you're healed before engaging is sex is very important.

SB: That's right.

RH: Obviously not so much of an issue in the United States, it's primarily an issue in the developing world. But it has implications.

SB: I think what we don't know is—we have three studies in Africa that, in men who were having sex with women, circumcision is protective if you're HIV-negative. What we don't have is information about what the role of circumcision is in men who have sex with men, and we don't know about other regions of the world. Because one of the other studies that was presented here about circumcision that was very exciting was that circumcision decreased the risk of other sexually transmitted diseases in the men and in their female partners. So that's very exciting because it has implications for HIV since they may help to decrease the cycle of HIV transmission. But also helps to prevent other kinds of sexually transmitted infections that some of which are

treatable and some of which aren't, like herpes. So if you can reduce the risk of herpes, that's a great thing. Because the rates of other sexually transmitted infections, including herpes, are different in different parts of the world, we don't necessarily know how those are going to translate to other areas of the world. But it's very promising that we now have an abundance of data that suggests that circumcision may be preventive, particularly if people wait until they heal before resuming sexual activity--unprotected sexual activity.

RH: So we'll keep looking for studies to come out on that one.

SB: Yes.

RH: Vaccines. Your big study, the STEP study. Basically, it was shown that the vaccine was largely ineffective, but what were their other findings, looking at the data, that could lead to new ideas or further studies?

SB: We set out to ask a question about whether or not this particular vaccine, this approach to vaccines, could actually provide protection. The fortunate thing is that the study was very well conducted and we have these amazing volunteers who followed the protocol very closely and we got a very definitive answer that the vaccine didn't provide protection. We were looking to see if it could provide protection either against infection or, if people were later exposed to HIV and became infected, if they could control the amount of virus in their blood. Unfortunately, the vaccine didn't do either of those things. There was this trend going in the wrong direction, towards an increased risk of infection, so we've been exploring that and I can talk a little bit about that. But I think that even if we just look at this question of, "Gee, the vaccine didn't work, does that mean that it's a failure?" and in fact, the vaccine trial's going to be remarkably important in moving forward with other vaccines of this type as well as other approaches. Because we now have a bar over which we need to exceed. And we're really looking in very in depth ways in the laboratory of why this vaccine didn't work. And I think that this is going to give us enormous insight into what we need for a successful vaccine.

RH: Right. And there was some data, some insights that came out of the study about circumcised people versus uncircumcised people. Could you talk a little bit about that?

SB: We had three questions that we wanted to ask. We saw this trend toward an increased number of infections, and the question was, was it real or not? Was it true for everyone or just a subgroup? And was it durable or was it just a transient effect around the time of the vaccination? We found that even after we controlled for other differences in the different groups that this trend still held. So we don't know if it's real or not, but it is consistent; we haven't been able to make it go away. We're not trying to make it go away, but we don't want to be saying that there's an association if there really isn't one, if it's just because of an imbalance in the groups. But we did want to know if this applied to the entire group who were vaccinated or if it was just different subgroups. What we found was that it seemed to be particularly in the men who were uncircumcised and in the men who had preexisting antibodies to the type of virus that we used as part of the vaccine; it's not an HIV virus, it's a cold virus called Adenovirus type five. So that generates a couple of different hypotheses about how, if this vaccine did increase the risk of infection, how might that have happened? We're very certain that the vaccine didn't infect anyone. There isn't any live HIV, there's no way that the vaccine can cause infection. But what it could do is stimulate a part of the

immune system that then makes it easier for HIV to enter that part of the immune system and cause infection. So the two hypotheses are, is it possible that, there's something about it you've already been exposed to this type of cold virus that once you get the vaccine, it makes another part of the immune system more susceptible to HIV. We've done a whole variety of studies and so far we haven't seen that that's the case, though we're still continuing to look. The second question is, could it be that, in the uncircumcised men, is it possible that it's taking something that would normally be a lower-risk practice like being the insertive partner, having unprotected insertive anal sex, could it make that a riskier practice? We have a little bit of data that suggests that it was particularly the men who were having unprotected insertive anal sex who seemed to be at greater risk. But we have a lot more analyses to do. And then the third question about the durability, the reason that we're continuing to follow the study volunteers, we're telling everyone, whether they got vaccine or placebo, we're asking them to stay in follow up, because it's very important to see whether this trend toward an increased number of infections in the vaccine group remains over time or if it goes away.

RH: Right. So we'll keep waiting for results. But in the meantime, microbicides; as a woman living with HIV I'm asked all the time, why don't we know, when will we have them, please, please please. I think one of the issues that translates around the world is gender empowerment for women and the ability to negotiate safer sex. I've been giving lectures at the University of Pennsylvania, the sorority systems and I hear the same things from those women as I do from sex workers in Vietnam or women in sub-Saharan Africa. So frankly, tell us some good news about microbicides.

SB: I think that there's tremendous progress that's being made with microbicides. Unfortunately, we've had some setbacks in the past with different microbicides that were not successful. And what we have now is a full range of research happening on microbicides. First of all we have some of the models to try and help us understand before we move the microbicides into clinical trials; whether they have the potential to cause harm or whether they look protective. We also have a whole range of new delivery systems that are being tested because the issue is, will it be difficult for a woman to use the microbicides right at the time that they're having sex, or could you have, for instance, vaginal rings—

RH: Time released.

SB: Exactly. So it doesn't have to be used at each episode. And then the third thing is that we've got now a rand of different products that we think might be remarkably more successful; we're looking at variety of antiretrovirals, anti-HIV medicine that's being given topically, vaginally in HIV-negative women. So we're studying that both as pre-exposure prophylactics vaginally as well as orally to see if that might protect against infection. And in the animal studies that have been done so far, they look remarkably protective. So we're now in clinical trials testing this in HIV-negative women and men to see if we can--in terms of the oral formulations we're looking in men and women, and in the vaginal we're getting ready to launch trials, looking at these products to protect women, vaginally.

RH: And we're talking always about microbicides for use in women, but what about in men?

SB: Yes, it's an area that really needs a lot of work. First of all, men and women both have anal

sex, so we need to know both the safety and the efficacy for anal sex. And then we do need to know for men who have sex with men, where we still have a huge epidemic going on throughout really all of the world, we need more protective strategies for them as well. So we do need topical, rectal microbicides for both women and men.

RH: And they are being studied?

SB: They are being studied, but they're a little bit further behind in development. I think it's because, well, two reasons: one is that the biology's that much more challenging; at least in the vaginal studies we can look at, are we getting the product where it needs to go, how much are we coating the area that needs to be coated; in the rectum, it's daunting, because it's looks like we don't actually know the whole region that needs to be covered with the microbicide and whether or not that's going to be feasible. I also think that there are political reasons why it's more challenging to do the rectal studies than the vaginal studies. We are trying to move forward with the rectal studies as well, they're just lagging a little behind the vaginal studies.

RH: Well hopefully if it proves to be efficacious as a great prevention tool, it will open their eyes and its power will be considered that way.

SB: Absolutely.

RH: So let's talk a little bit about PrEP. Most of our viewers will probably know what it means, but, Pre-exposure Prophylaxis—could you maybe give us a little overview in your own words?

SB: Sure. Well people know about PEP, which is taking an antiretroviral after you've had an exposure, to try to prevent HIV infection from happening. But pre-exposure prophylaxis means taking the antiretrovirals before you're even exposed. And that really grew out of some studies with animals in the mid 1990s that suggest that Tenofovir in particular, if given to animal, and then they were [exposed] to a virus that's close to HIV that infects monkeys, then you could actually prevent infection even after you exposed them. But the closer to the time of infection that you gave the drugs, the more effective they were. And if you gave them before you actually exposed the monkeys, they were most effective. So there's this idea that, could you use fewer drugs and would it be more effective if you gave HIV-negative people who are at risk of HIV infection these drugs to take, probably on a daily basis. Now what we don't know right now is whether or not it will work. We've seen this approach be remarkably effective in non-human primate studies, in monkey studies, and we're testing them in humans. But the way that we're testing them right now is to give a continuous, daily dose of the pill over a long period of time for people who may be at risk for a long period of time.

RH: Like a sex worker?

SB: Or anyone who's engaging in risk activities. I think one of the challenges that we've found in our study so far is that, for instance, in particular men who have sex with men who have become infected, is that people don't always recognize when it was that they got infected or which particular practice might have put them at risk. So if you could take some individuals who may be at some risk over a prolonged period of time and give them a daily dose of this medication, could you help prevent HIV infection?

RH: Right. You know, one of the things I found interesting that was discussed at the conference

was the issue of risk, and that if you have unprotected sex even once with someone who's status you don't know—or you think you know, but don't have proof of—it's a risky activity. And I think people tend to try to say, "Well, I'm not involved in high-risk." And I think that's a big mistake, even in terms of how we attack prevention; it's maybe reeducating people about what risk is. You are putting yourself at risk if you have unprotected sex even once with a partner of an unknown status.

SB: Yeah, this is such a challenge because what we're trying to do in the scientific community is to get people the information so that they can make their own choices about what they want to do and what they don't want to do. But what we see, for instance, is, for men who have sex with men, that they unprotected, receptive anal sex with people who they believed were negative, that that's also an independent risk factor for infection—because sometimes, people don't have the accurate information about their partner's serostatus. But also recognizing that we're all sexual beings, and that people need to make decisions about what makes sense in their own lives. If at least they know what the relative risk is of a variety of different strategies, then they can try to reduce their risk of HIV infection.

RH: With PrEP, is there any thought that maybe some day you could take it just prior to having sex? The same day? Only each time you have sex?

SB: I think that we don't know the answer to that yet. Just like post-exposure prophylaxis (PEP) is not a morning-after pill; you actually have to take it for a full month, and we don't actually even know if it works. But that's how it seemed to work in monkeys and that's how we give it in people. We don't yet have an evening-before pill. We would hope that we could get to that point, and we're also looking at—are there any kinds of longer acting products that could be used in the same way that we're talking about for vaginal administration—

RH: That would linger.

SB: Exactly. That would provide protection for a longer period of time. We don't have anything like that yet that we know of; we don't know whether any of these approaches will work. So what we're trying to do in these tests is give it the best opportunity to work, which is to give people a daily pill over a prolonged period of time. If that's successful, then we'd see if we can back off on it, and how long would people really need to take this for.

RH: In summary, [is there] anything you want to tell the community about what's happening on the bio-medical prevention front? Anything we haven't touched on?

SB: Well, I think what I'd say is, this is a time of great challenge but also a time of great promise. We've had some setbacks; the herpes suppression trial did not provide protection for HIV-negative men and women who were given acyclovir to try to prevent their herpes infection and try to prevent them from becoming infected. But there's a sister trial going on, giving herpes suppression to HIV positive people to see if you can their risk of transmitting HIV to their negative partner. So that approach still has a lot of promise. We have this pre-exposure prophylaxis approach. There were some other data on non-biomedical approaches to prevention; serosorting (choosing to have unprotected sex only with partners of the same HIV status), other things people might be able to do to help reduce their risk of HIV infection. So I think that there's actually a full range of approaches—a lot are being tried simultaneously—and I think we need all of them to try

to bring down the epidemic.

RH: My favorite was the Hot Sex Calculator; online models for people—in the case of the Hot Sex Calendar it was for MSMs—but they were vehicles for people to try, techniques of navigating, discussions about safer sex. There was one where they were suggesting you assume an avatar on a cruise ship, it was great. So there's a lot to explore in terms of how people talk to one another about safer sex and prevention issues.

SB: And I do just have one last comment about the Swiss coming out with a recommendation; did you talk with someone about that already?

RH: We interviewed Bernard Hirschel. But please, I'd love to hear your thoughts on it.

SB: Well I think that what's challenging about this—at least my feeling about it is that the community has the right to know what information we have and what we don't have, and then they can make their own decisions. I think we don't have the information that men or women who are HIV-positive, who have undetectable viral load in the blood, are not ever infectious to their HIV-negative partners. As long as people understand that that is a recommendation based on an assumption about data and that we don't actually have data. And I did see a poster here that was presented which suggested that you still can detect HIV in seminal fluid, even in people who have undetectable levels of virus in the blood. Now the per contact risk may be exceedingly low, but I wouldn't want people to be mislead into thinking that it can't cause HIV infection—it may be less likely to cause HIV infection. And they need to make their own decisions.

RH: Thank you very much.

SB: Thank you.

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