Transcript: Antiretroviral Highlights from CROI

May 11, 2009

At the 16th Conference on Retroviruses and Opportunistic Infections (CROI) in Montreal, David Evans talks with Tony Mills, MD, a private practice physician and researcher at the University of California in Los Angeles, about the latest in antiretroviral research. Dr. Mills gives his take on the surprising results of an Isentress (Raltegravir) clinical trial, the latest news from Gilead about their four-in-one pill, and the promise of viral eradication. To view the video click here.

David Evans: Hi, this is David Evans from AIDS Meds and POZ.com. I'm here with Dr. Tony Mills, he is a physician in private practice and is a researcher on faculty at UCLA. Welcome. (Makes a welcoming gesture to Dr. Mills.)

Tony Mills: Thank you for having me.

DE: Sure. I wanted to talk with you today about integrase inhibitors. A couple of things; First, let's talk about the Merck integrase inhibitor Isentress, also known as raltegrevir. There were data presented at the conference I believe yesterday. Can you talk a little bit about that? You were involved in the study, is that right?

TM: Yes, yes, we were investigators in the trial that Joe Eron presented yesterday, the Switchmark Study, which looked at people who are stable on a Kaletra (lopinavir and ritonavir)-based regimen and whether or not it was a good thing to switch them to an integrase inhibitor. These were patients who were being switched not because of some sort of toxicity but just had stable good viralogic suppression and no bad lipid problem and whether or not it's a good idea to switch people over to the new class of agent.

DE: Okay. And how treatment-experienced were these patients in general, or was it a mix?

TM: Well, that was the really interesting thing about the trial, and we really didn't appreciate that at the beginning of the trial, and we really came to see that as we started to analyze the data, that there was a wide variety of experience in the trial. So some people came in suppressed on their first regimen, and other people came in suppressed on their tenth or eleventh regimen, with lots of underlying drug resistance. And we didn't really appreciate this at the beginning of the study.

DE: And did the majority of the people, I forget if you said this, did they come in with problems

with their cholesterol?

TM: No, no, in fact they had to come in on a non-lipid-lowering agent, so these people came in doing well on lopinavir/ritonavir.

DE: Okay, okay, fantastic. And then you switched some of them to start receiving Isentress?

TM: Yes, and we randomized them because all the data on the integrase inhibitors, particularly raltegravir, had been so exciting that we were looking at whether that was a strategy that was going to be helpful to us, to switch these people over maybe before they had complications from the protease use, and whether we could maintain good viralogic suppression and keep them healthy and well.

DE: Okay. And what was the outcome of this study, what did we learn?

TM: Well, the vast majority of the patients did fine with the switch, but the way the study was designed was that it was trying to show that raltegravir was non-inferior to lopinavir, and as we know, all the studies we've designed over the last few years have been shown to prove non-inferiority to lopinavir because it's such a great drug, and unfortunately we weren't able to demonstrate non-inferiority as far as that goes to lopinavir. We had a few more patients on the raltegravir that failed than on the lopinavir and again as we looked at that more closely those tended to be patients where they were probably being suppressed based solely on the power of the lopinavir and they did not have any extra boost they were getting from the nucleosides they were on so then when we switched them to the raltegravir we didn't have that same level of potency unfortunately. The nice thing was that patients tolerated it well; the side effect profile was really good, the immune response was good, but we just didn't in some patients maintain that same level of viralogic suppression that we wanted.

DE: Which on the one hand was a little bit unexpected because of how stellar Isentress had performed in the heavily treatment-experienced population, right?

TM: Yeah, and that was really the perspective we came from when we put the study together, you know, we had looked at the BENCHMRK study where we had taken patients who had GSS and PSS of zero, who looked like they really didn't have any other active agents in their background, and sixty percent of those patients went undetectable and stayed undetectable. So we came from this place of not knowing, wow, how potent is this drug? Maybe this is going to be the only drug that we're gonna need. It was just a little bit of an eye-opening experience to tell us we still had some stuff to learn about this. I certainly still think the raltegravir is an amazing compound and I think everyone who's been involved in the development of it really still feels the same way. But we also have known that lopinovir has been an amazing compound, there's lots of people who are alive today because of lopinavir, and so this really just sort of emphasizes the strength and the power of the protease class as well.

DE: Right. Okay. On a similar, but not exactly the same topic; so, Gilead also has a integrase

inhibitor in studies, elvitegravir, they didn't present data on that drug but they did announce just before the conference that they are planning to do a four-in-one pill that will include their new integrase but also has a boosting agent, something akin to Norvir, called GS9350. That data was presented here, on that boosting agent. What can you tell me about that?

TM: We've known that Gilead has had this integrase inhibitor elvitegravir in development for the past few years, and we haven't seen a lot of data on it, but certainly we know again with raltegravir that it's a potent class and that we are very excited about it. The early information about it said that it was going to be once a day, which was an improvement, but that it had to be boosted with ritonavir in order to achieve good levels, and so what Gilead has opted to do was to try and develop their own boosting agent so it doesn't actually have to be combined with ritonavir. And then Gilead is actually not right now testing that booster with other agents, but just testing it with their integrase inhibitor. So that was what they presented yesterday: the data on the boosting agent and its effect on boosting elvitegravir levels. And it was extremely exciting. During the course of the presentation, the presenter, who was a representative from Gilead, mentioned the Quad pill, that was going to be smaller than the Atripla tablet, and there was this gasp from the audience that was sort of fun because a lot of people didn't know that there was a quad pill in development. And so it was sort of one of those fun, you know, Ah Ha! moments…I'm glad I'm at Retrovirus because this is a fun moment!

DE: Sure! Sure. That's amazing. And is this going to be sort of McSame, the same as ritonavir, or is there a chance that it might be different than ritonavir in some important ways?

TM: You know we're all hoping that it's going to be different from ritonavir, we're hoping that it's going to be much more gentle on the system, and have a better side effect profile, and that it will be equally good at boosting up the other agents and will be much better tolerated, and so it will give us a really important agent in our armamentarium really to take forward.

DE: Okay, fantastic. Just kind of closing remarks. Any other impressions about antiretroviral drug development, any take-home messages from the conference?

TM: I think this has really been a great conference. It's been a very exciting meeting. And I think there's some really exciting stuff still to be presented. I think we're all increasingly optimistic about treatments that we have available for HIV. New ways of combining those treatments. New possibilities for the future. I think that while the vaccine research in the past hasn't been very optimistic, certainly the treatment research has been. And so I think Bob Siliciano as kick-off of the meeting kind of talking about the possibility of viral eradication is very exciting. We have an abstract that is being presented today on looking at IVIG in combination with therapy to mobilize the latent reservoir and if we can actually move towards eradication. Those things are very exciting. Certainly for all of us living with HIV it's a very exciting thing to think that we might one day be able to live drug-free.

DE: That would be amazing. Thank you so much, Dr. Mills.

TM: Great!