Transcript: What's New? Update on Experimental Agents

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PETER STALEY: This is Peter Staley with AIDSmeds.com and we're here with Dr. Calvin Cohen, research director of the HIV-focused Community Research Initiative of New England. We're talking about some of the exciting data presented at the 14th Conference on Retroviruses and Opportunistic Infections, otherwise known as CROI 2007, and involving several experimental drugs in the pipeline. Welcome Dr. Cohen, it's good to speak with you

DR. CALVIN COHEN: Thanks very much, it's a pleasure to be here.

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STALEY: First off, we heard some very exciting news about the new class of drugs called integrase inhibitors, and they're very useful especially for patients with drug-resistant HIV who have limited available options to choose from. Let's start with the really exciting news of the 16 week results from the Phase III clinical trials of a drug called Isentress, which is Merck's new integrase inhibitor that everybody's been buzzing about. Can you tell us a little bit about the study and what the results were?

COHEN: You bet. So the design of the study is a pretty familiar one. People who had triple-class resistant virus who were not suppressed virologically on their current regimen were entered into a study to see how well this drug worked and what it contributes to the new regimen. So the design was a simple randomization in which people were asked to create the best possible regimen they could with available approved drugs, including darunavir, or Prezista, and enfuvirtide or T-20 [Fuzeon], if they wanted to do so. The randomization was the best possible regimen or the best possible regimen plus raltegravir or Isentress. That's a design that we've used for years to figure out, "what does this drug contribute to whatever the best possible regimen is." and the design showed exactly what most of these designs show, which is that the addition of one more fully

active drug doubles your chance of getting virologic control in as little as 16 weeks. So for example, on the background regimen, about 40% on average people were able to get their viral load to less than 400 copies in 16 weeks, it was 80% with the addition of one more drug, this drug called raltegravir, the integrase inhibitor. And that robust finding was there no matter how the data got sliced, that drug was contributing.

STALEY: So even for those who weren't adding Fuzeon and Prezista, there was still a substantial result.

COHEN: So you point out a very important thing, which is, "what was the contribution of the rest of the regimen?" And there were some very interesting analyses presented about that. But you're right. The punch line is that no matter how good or how compromised the background regimen was, there was still evidence that raltegravir made the regimen that much more successful.

STALEY: That's great news. What about side effects?

COHEN: Well that's the stunning part of it. Now of course we have to acknowledge we had 16-week experience in this trial and it sometimes takes a year two before we see long-term toxicities. But the short-term toxicity looked really not much different than placebo. Meaning, in this study, and there were two international trials going on simultaneously, there was no single side effect that was higher on raltegravir than placebo in both trials. So, for example, if there were people who had increased liver function tests in one study, in the other study they didn't. So, so far this looks like an extraordinarily safe drug in the short-term.

STALEY: What was the total number of patients studied between the two groups in the international studies?

COHEN: I think in total we have somewhere close to 700 people in all of these trials.

STALEY: So, big trials.

COHEN: Yeah, we think we've got a pretty good substantive look. And this by the way is only one of two sets of studies. We also have treatment inexperienced patients who are undergoing a study, so we'll have a lot more data on this drug in all stages of therapy later this year.

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STALEY: And it is expected that this integrase inhibitor will be the first one to market and probably come to market this year. Let's move on, there was another integrase inhibitor that made news with some Phase II clinical trial, that's Gilead's integrase inhibitor called elvitegravir. Any gut reactions to those results?

COHEN: So this study was much more of a ghost finding trial, which contrasts with what Merck did, since their design was already to confirm the activity of the drug once they knew the dose. The design of this therefore is much more exploratory. It's also a much smaller trial. And because of some drug-drug interaction issues, because elvitegravir is also ritonavir boosted, at the time the

study was done, we didn't understand enough about how to combine elvitegravir with protease inhibitors. So the design was a particularly challenging one, which was elvitegravir versus the best boosted PI we could pick from prescribable drugs. Despite that design, despite it being kind of a comparison of elvitegravir without PIs versus a PI, what we saw was that at the highest of the three doses tested, elvitegravir was actually statistically more potent than even the boosted PIs that we might choose.

STALEY: Between these two integrase inhibitors are we seeing any cross-resistance yet? Or is there a potential for that?

COHEN: Unfortunately there is the potential for it. We don't have the clinical experience yet of people going from one to another, at least not available, but what we do have are the in vitro, or test tube-based findings, looking at resistance mutations and unfortunately there is the possibility, based on these test tube studies, that some mutations may arise as a result of either drug and that phenotypically we can see the potential for cross-resistance from one to the other. That doesn't mean there will always be cross-resistance, but at least the potential exists to not assume we have two chances at the integrase bat. We may have one swing at this bat for now.

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STALEY: Moving on to the next class of drugs that looks like it's going to have a first approval this year by the FDA, and that is the CCR5 inhibitors. Pfizer's maraviroc is the first along in the pipeline and it also had a good showing at the conference. Can you tell us a little bit about this drug and what the study demonstrated?

COHEN: Sure. Maraviroc, as you say, is a CCR5 inhibitor. And it turns out that we've learned about five to 10 years ago that HIV gets in our cells by first binding to the CD4 receptor and then binding to a second, or coreceptor. AND CCR5 is the name of the most common receptor that HIV uses. One of the issues that we already face and understand is that it isn't the only coreceptor that HIV uses. And so this trial focused on people who had a screening test done to show that their virus population exclusively used the CCR5 pathway. So in those patients who have a CCR5-tropic, or focused, virus, and who then get a CCR5 blocker, maraviroc does exactly what you'd expect. It doubled the chance of getting virologic suppression compared to a background regimen that doesn't include maraviroc.

STALEY: Any side effects with this yet?

COHEN: Well, once again we only have 24 week data. And like with the Merck compound there were two international trials going simultaneously with exactly the same design. And once again, there does not appear to be any single side effect that was consistently increased in frequency in both trials. Meaning that if there were more people with, let's say, abdominal pain in one study, in the other study there was less abdominal pain on maraviroc versus placebo. So right now, we have very reassuring 24-week data with regards to safety, at least clinical toxicity and side effects. The one thing that people are still looking for, partly because of another drug study that was done with another CCR5 inhibitor, is some of the complications of using these drugs and thoughts of

increased risk of malignancies or opportunistic infections. And fortunately, we don't see yet any sign that there's any worrisome development of diseases in people who've taken R5 inhibitor. Again, our experiences are short, we have 24-week experiences with these studies, but so far we have good news.

STALEY: And it is one that's a little scary for people because unlike most of the antivirals we've been using, the CCR5 inhibitors or inhibiting something in your body. They're not really inhibiting the virus directly and so we don't know whether there might be some possible positive uses for your CCR5 in your body that's being blocked. But thus far the trials are showing that we seem to be okay on that front.

COHEN: And partly the reason that we have a CCR5 inhibitor class is that it turns out that there are a small percent of people who genetically are born without a CCR5 receptor, and they seem to be perfectly healthy as far as we can tell and live a normal, healthy lifespan without increased risks of diseases and malignancies. And so we are reassured by that genetic experiment, if you will, that people don't seem to need their CCR5 receptor pathway to have a good, healthy life.

STALEY: So with the likely approval of maraviroc at some point this year, we're all going to be hearing about a new laboratory test, you mentioned it briefly, called tropism assays. Could you briefly explain how these tests work and why they're going to be so important?

COHEN: So, you're right. What we learned about 10 years ago is that most people with HIV start out with a virus that uses the CCR5 pathway, or CCR5 receptor, to get in our cells. First it finds CD4 in everybody, and then it finds the second receptor. And most people start out with a virus that looks for that CCR5 receptor. Unfortunately, over time, the virus can change and, as the CD4 counts drop, the virus seems to then start to use another receptor called the X4 receptor. And so, the reason we have this tropism assay, is that when we use a CCR5 blocker in people who have a CCR5-tropic virus, we do a good job. But when we use a CCR5 blocker to people who have a virus that uses a different pathway [CXCR4], we see much reduced activity. The virus is just ignoring the drug because it has another way to get in our cells. And the studies have shown very little activity of the CCR5 blocker in that circumstance. And so, it's not surprising that we have a tropism assay to know when should we use the drug and when is the drug going to have minimal benefits.

STALEY: And just to clarify for our listeners, what CCR5 kind of really is, is an exterior part of our CD4 cells where HIV latches onto to get in. And it has a couple of ways it can get in, but this is one of the main ones.

COHEN: You got it.

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STALEY: Okay. Finally, last question, I'd like to discuss the early clinical trial results for TMC-278 [rilpivirine], which is Tibotec's second experimental non-nucleoside reverse transcriptase inhibitor, following on the heels of the company's leading non-nuke, etraverine. The study presented at CROI involved patients new to treatment. At 48 weeks, TMC 278 seemed comparable to Sustiva.

Any thoughts on this study?

COHEN: Well, you said it well. It's one pill, once a day, just like Sustiva. And it went head-to-head against Sustiva in people who were given two nucleosides, either Combivir or Truvada. As a result of this comparative study, we have some data already to suggest that 278 appears to be perhaps as good a drug as Sustiva in terms of virologic suppression rate. And importantly, it has a different side-effect profile and perhaps less of a problem of side-effects. Sustiva has well-known side-effects in the field, mostly the risk of having vivid dreams and feeling a little bit vertiginous or a little bit hung over the next morning for at least a week in people who start it. This drug didn't seem to have any of that. There are some limitations to the study that make it hard to be totally confident that that is the case, but nevertheless, it certainly suggests that if we can find a drug as potent as Sustiva with reduced toxicities, we have an important drug on our hands. And this study suggests that rilpivirine might be such a drug.

STALEY: Do you have any idea what we might expect from this drug in patients who have developed resistance to the current non-nukes, like Sustiva or Viramune?

COHEN: Well, so right now Tibotec has done most of the work in treatment-experienced patients in terms of non-nuke resistance with the other drug you mentioned, etravirine, or TMC-125. It turns out that, at least in test tubes, 278 might have some activity in that population but we don't have any good clinical experience yet to understand how well this drug compares to 125. So for now, and because 125 or etravirine is pretty near approval, most of us are thinking that etravirine would be the drug that we might use for non-nuke resistance until we have some experience that 278 is as good or maybe even better.

STALEY: Well thank you very much Dr. Cohen for spending time with us. It definitely sounds as if the drug development pipeline is alive and well in a lot of compounds that will be extremely useful to people living with HIV/AIDS. So thank you for joining us. To learn more about this and other drugs in development we encourage listeners to check out all the news that we've reported on from CROI and the various drug pages we have on AIDSmeds.com. Thanks, Dr. Cohen.

COHEN: Thanks very much for having me.
