Transcript: Pipeline Preview: All The New AIDS Drugs Coming Soon

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Peter Staley reviews all the new experimental AIDS drugs with Dr. Joe Eron, Professor of Medicine at the University of North Carolina at Chapel Hill. He discusses two experimental non-nukes, and two completely new classes of drugs: CCR5 inhibitors and integrase inhibitors. Below is the transcript. To see the video click here.

Good morning from Sydney. This is Peter Staley from AIDSmeds.com and I'm here this morning with Dr. Joe Eron from the University of North Carolina. Joe, you spoke eloquently yesterday at the morning plenary session with a talk titled "New Kids on the Block" and you gave a great overview of all the experimental HIV/AIDS agents that are in the pipeline now that people with HIV and patients needing second-line therapy or even some first-line opportunities can look forward to. Welcome.

Well, thank you. Thanks for inviting me here.

Let's start with Celsentri, which is probably going to be the first one approved. It's called maraviroc and it's Pfizer's new CCR5 inhibitor. This would be the first one in this new class of entry inhibitors. At the retrovirus conference in February, we saw encouraging data from the MOTIVATE studies looking at the safety and effectiveness of the drug in treatment-experienced patients. Data from these studies are being reported here as well. Anything new to report?

Well I think that for the treatment-experienced patients we're just getting a little bit more detail. I think what we're learning is, just like with other new drugs, maraviroc works best when it's paired with other active agents. There's actually a very nice poster being presented showing that—that no matter what the other active agent is, whether it's enfuvirtide or a protease inhibitor, if that drug is active then the pair work much better. Also, there's some information here about once daily versus twice daily and I think, at least for the treatment-experienced patients, we're going to be seeing twice daily therapy—probably what will end up being approved by the FDA. I think they're still discussing the details of the approval but, like you said, I think it's imminent.

Okay. Another maraviroc study, the MERIT study, is looking at the drug in patients starting therapy for the first time. What can you tell us about the 48-week follow-up data presented here on that?

Right. So that actually is being presented today by Michael Saag. If we look at the abstract, which

is the data that we have so far, it looks like maraviroc compared to efavirenz are pretty similar looking at the less than 400 copy level, but it appears that there might be some differences in the less than 50 copy data, where perhaps the efavirenz-based therapy was a little bit better.

Efavirenz is Sustiva.

Sustiva, right. Right, exactly. So it's Celsentri or maraviroc compared with nucleosides compared to Sustiva, or efavirenz, with nucleosides. And while the 400 data, I think, in the abstract, looked very similar, the less than 50 data are not quite as similar. So, we'll have to see how that gets interpreted.

Another drug, Schering-Plough's CCR5 inhibitor, vicriviroc. It's being presented here as well. I understand there are a few snags in the study, including a report of five cancers. What can you tell us about the study and the cancer alarm that went off?

Well, vicriviroc, this is a much smaller study than MOTIVATE. So there's really only thirty patients per treatment arm and about thirty patients in the control arm. And the good news is they showed forty-eight week activity data and it looks like there's persistent activity of this class of drug. So that's the good news. The news that we're not quite as certain about is there were now eight malignancies in the study—six in the vicriviroc arm and two in the placebo arm. And while it's a small study, they were most lymphomas so they are malignancies you see in HIV patients. I think we're just not sure what that means. I think it's important to point out that in the MOTIVATE studies—the studies of Celsentri or maraviroc—there really was no difference in malignancies. There really was no association with malignancies, so this vicriviroc thing—I think we just need more information.

But it brings up a continuing issue with this new class of drugs—that there's fear because it's blocking something in the body that we haven't been dealing much with before, that it might be causing trouble in other areas.

Yeah, I think that's a concern, but really if we look at the big data set, which is the Celsentri or maraviroc data set, we really don't see any malignancy signal at all and, in fact, the MOTIVATE data that you mentioned really there were absolutely no clinically important differences between maraviroc and placebo. That was a placebo-controlled trial, both with optimized backgrounds. So I agree with you. Everybody's a little bit anxious about blocking this human receptor. But so far, I don't think there's been a strong signal, but I think that's going to temper people's enthusiasm a little bit, plus you actually have to get a test, a tropism test, before we can really use these drugs. So we'll see. I'm curious to see how people will use them and how excited people will be about them. But really, with the larger data set, we don't really see a signal of toxicity yet.

Back to the one that's further along. Celsentri, or maraviroc, it got an approvable letter from the FDA, so it's like we thought we'd have it by now and we don't quite. What's your guess on this?

Yeah, well it's just a guess, I don't really know. But Celsentri or maraviroc has some fairly complicated pharmacokinetics, there are probably several different doses, depending on which other drugs are combined with Celsentri. Plus, the issue of needing a certain test to define the patients who will benefit from treatment, I imagine there's just a lot of discussion between the FDA

and the people at Pfizer, so I think the approvable thing is good. It would have been great if it was approved already, but I think it's coming. I think they're just discussing the exact wording of what they call the label, of that package insert that comes with your drugs.

The test you mentioned will be the Trofile test. It will really test everyone for what kind of virus they have to see whether this drug will work or not.

Exactly right. So the point is that patients have two flavors of virus. One are the R5 tropic, they use a certain receptor. And then the other flavor are what people are calling, duel-mix. They can kind of use a second receptor. And really in those duel mixed patients, maraviroc or vicriviroc just doesn't have activity, doesn't have antiviral activity. So, you know, it just becomes a little bit more complicated.

Yeah. It's going to be a challenging new class of drugs, but much needed.Let's talk a bit about Tibotec's etravirine, also known as TMC-125. It's now being reviewed by the FDA. Results from two phase-III studies, called the DUET trials, were recently reported in The Lancet. I understand the data are also being presented here. Can you tell us a little about the studies and what this non-nucleoside analogue might offer people with HIV resistance to the current non-nukes, like Sustiva and Viramune? Quite a few people out there have resistance to that class. This is exciting news.

Yeah, I think that we've always been saying that, well, once you're resistant to non-nukes, you can't use them anymore. And I think the DUET studies, which looked at highly treatment-experienced patients, all of them had to have some evidence of non-nuke resistance. It really shows, pretty clearly, that etravirine adds additional benefit in that setting so it is a drug that's beneficial for people that have non-nuke resistance. And, like I said, I think the top line is that's really good news to have another agent that's useful in people that have resistant viruses.

How is it looking on the potency front? Is it a strong antiviral?

Well that's a really good question. The published studies, that have been published for years now, if you actually look at TMC-125 against wild-type virus, it's an *extremely* potent drug. I think against resistant virus, it has a little bit less potency, but again, in this trial, it depends on—there were actually two kind of mirrored trials—but about 60% of the patients, highly treatment-experienced patients, got less than 50 at 24 weeks. Its really very, very good news.

Are they testing it in treatment-naïve patients?

Well, there's a second Tibotec compound called 278 or rilpivirine, which is a once-a-day drug and I think, though I don't have an inside into the company, I think that they're focusing on their treatment-naïve evaluation for that drug because it's a once-daily drug.

So yeah, they're putting their marbles in that bag. That was my second question. What are we hearing about late-stage studies on TMC-278?

Yeah, TMC-278, or rilpivirine. We didn't see any more antiviral data. It looks similar to Sustiva with nucleosides in treatment-naïve patients. But a smaller study, not a big phase 3 study, but a smaller study. But what we saw here is that perhaps it will have less of those CNS side effects that we see with Sustiva. And clearly it doesn't seem to have much in the way of negative impact on

lipids—cholesterol doesn't go up, triglycerides go up very modestly. So it's looks like it's going to be very, what people like to say, lipid-friendly. But it's a ways off. The bigger studies, the phase-three studies are really just starting.

I forgot to ask you on toxicities about TMC-125, etravirine, the one that we first talked about from Tibotec.

So, again, in the DUET studies that have been published, really the major toxicity was a rash and it's typically a mild rash. Like all non-nukes, like Sustiva, Viramune, there is a risk of a rash, but if you look at other things like CNS side effects in the DUET studies there really was no difference from placebos. So it looks like it will be a pretty well tolerated type of drug, but we'll have to watch out for rash, just like we do with the others.

Let's end with what's probably the most exciting drug everybody's talking about. Merck's new integrase inhibitor, first in a class, raltegravir. At the retrovirus conference, we saw some great results from a study involving treatment-experienced patients. Now we've got some relatively long-term data from a study involving patients starting HIV treatment for the first time with raltegravir. How's it looking as a first-line treatment option?

Well, these data were presented by Marty Markowitz yesterday and so it's forty-eight week data. Again, that's what we call a phase-II study so smaller numbers of patients. So it's hard to make really robust conclusions, but basically, compared to Sustiva in treatment-naïve patients, it was really very similar. I mean, the results were pretty much overlapping, with a very high percentage, 80% or more, were less than 50 copies at 48 weeks, so that's really as good as we can do, I think. So that looked very promising and the tolerability of raltegravir, in this study and in the treatment-experienced studies were really very, very good.

They're not finding side effects for this drug.

Basically, I think we need to be cautious about it.

Yeah, especially long-term.

We've only followed patients for shorter periods of time. But I think that interpretation is pretty much correct. In the treatment-experienced trials, again, there really were no real differences from placebo, and in the treatment-naïve trial that Marty Markowitz presented, it really just looked very well tolerated. It also doesn't appear to have a negative impact on lipids—total cholesterol doesn't go up, triglycerides don't go up—but it is twice daily and I think that's something that you can get missed in all the kind of excitement. It is a twice-daily drug and therefore it's not going to get co-formulated with Truvada. That's just probably not going to happen.

A lot of people with HIV are getting kind of spoiled, thankfully, on once a day these days.

Right. Once a day, one pill. So it won't be quite like that. On the other hand, maybe many people would be willing to take a medication twice a day and not have some of the side effects that we see with other medications. So patients and physicians and caregivers can have choice, which is what we want.

Are we learning about its resistance profile? Like, you know, it's a strong drug, but Sustiva, you only need like one mutation and you're shot. Does this have a high threshold? Do you need a lot of mutations?

Yeah, it's a little bit—you can't really say it's like this or like that. I think the take-home message is that if you have virologic rebound on raltegravir, you're likely to develop resistance. So, on the other hand, you don't see a single mutation, like you see with Sustiva or with Viramune. Typically, there's kind of a complex set of mutations. So, is that a low barrier, a high barrier? Basically, if you virologic rebound, you will see some level of resistance, I think, in most patients. In the treatment-naïve study they only have five virologic failures, two out of the five had evidence of raltegravir resistance. In the treatment-experienced studies where they've had more virologic failures, because the patients are harder to treat and there were more numbers, about 90% of those who fail—a small number of patients fail—but 90% of those who fail end up with resistance.

Wouldn't it be great if we could finally find a drug that had no resistance?

It would be good. On the other hand, you know, resistance really gives you evidence that that drug is really working. Basically.

Well thank you very much for joining us and good luck at the rest of the conference and congratulations on the great talk yesterday.

Thank you.
