Transcript: New Menu of Antiviral Options

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At the European AIDS Conference in Madrid, Dr. José Gatell talks with David Evans about the latest treatment news on Selzentry, rilpivirine (TMC278) and the continued interest in Kaletra monotherapy. To see the video click here.

David Evans: Hello, I'm David Evans with AIDSmeds.com, and we're here in Madrid at the European AIDS Conference. With me today is Dr. José Gatell, who is the head of Infectious Diseases and AIDS Unit at the Hospital Clinic in Barcelona. He's also the professor of medicine at the University of Barcelona and the current President of the European AIDS Clinical Society and this year's co-chair of the conference. Thank you so much, it's a great conference, and for extending such a warm welcome to us this year.

José Gatell: Thank you. It's a pleasure to be here with you.

DE: Thank you. So, at the conference so far, we've had presentations on new ways to use existing antivirals and new data on experimental and recently approved drugs. Let's start off with an old drug. There was a presentation of a study using Kaletra, all by itself, with no nucleosides, as monotherapy. It was the OK04 study. And people who were stable on a triple combination including Kaletra stopped using their nucleoside backbone. Can you tell us a little bit about that study and what was found?

JG: I think this study was the long-term follow-up of the OK04 study that was presented for the first time, if I remember well, in Toronto about one year ago. So now I think it's the two years' follow-up. And essentially, I think this study proves two things. One is that what is important to sustain an undetectable viral load is not the number of drugs but the genetic barrier to develop resistance. And so three is not a magic number; so we can do the same job with two drugs and sometimes with one drug as long as these two drugs or this one drug have enough genetic barrier. Then when we move specifically to that study, what we saw was that switching from triple therapy to monotherapy with a boosted PI in general and specifically in this study with Kaletra, what happened is that the vast majority of patients remained suppressed but there was a small number of patients who developed a virological rebound. It was a small virological rebound—somewhere between 50 copies and 500 copies that then these patients were re-suppressed by switching again to triple therapy. And it probably was a problem of compliance, because the majority of these patients didn't develop resistance. And so, essentially, I think this is not a strategy we're going to

use in routine clinical practice; however, it might well be a few selected patients that, for whatever reasons, they would be better to be treated or to be maintained with monotherapy as opposed with double or triple therapy. And so this study proves that in selected cases, this strategy can work.

DE: And in that particularly study, the people who discontinued due to side-effects, there were zero discontinuations with people on monotherapy and about eight with the people who stayed on triple therapy. Is that right?

JG: I think that's right, I don't remember exactly the figures, but I remember that the discontinuation due to side effects was higher in the triple [therapy arm]. Which probably makes sense, because despite several of the drugs we are using today are pretty well tolerated, it makes sense that three drugs would be worse tolerated than one drug. So that's something that's not surprising in this study. Despite the patients who were included in the study, they were suppressed and tolerating well the drugs they were already receiving. However, during the period of two years, always something happens.

DE: Now we're going to talk about the new entry inhibitor, Selzentry [maraviroc]. There were 48-week data presented on the MOTIVATE 2 study. Can you describe those results?

JG: Well, essentially, the MOTIVATE 1, the 48-week data of the MOTIVATE 1 that was recently presented at ICAAC just a month and a half ago, and now, here, the 48-week results of the MOTIVATE 2. Both trials are the classic salvage therapy trials that were designed following, if you wish, the rules that were predefined in the development of enfuvirtide just five years ago.

DE: Fuzeon...

JG: Fuzeon. That is just randomizing—advanced, failing patients were randomized to an optimized background therapy in one arm and to optimized background therapy plus an active drug that in this case was [Selzentry], and to see if there was a difference after 24 weeks or after 48 weeks follow-up. And essentially these study, both MOTIVATE 1 and MOTIVATE 2, were able to demonstrate that there was an improvement in the active arm as compared with the control arm. That's good news. The not-so-good news is—and even better news would be that in the future, this drug would be able to be combined with other drugs that were not used in the optimized background, because this was an experimental design, so for example, let's say a drug like the integrase inhibitor, raltegravir [Isentress], was not allowed, neither in the control arm, nor in the active arm. And so one may guess that in the near future—when in the near future means now—this drug might be able to be combined with all available agents after taking care of the following interactions, then the response would be even better. The only drawback for MOTIVATE in advanced patients, as you know very well, is that MOTIVATE is a blocker of the CCR5 receptor. And in advanced patients, no more than roughly fifty percent of the patients have a virus that predominantly uses [the] CCR5 [receptor]. The rest of the patients have a mixed tropic virus or X4 tropic virus. So this drug in this situation would be feasible to be used just in about half of the patients.

DE: Now let's talk about an experimental drug by Tibotec. It's called TMC-278. This is a second-generation non-nucleoside that was designed to be active against virus that has become resistant to the older non-nukes, Sustiva and Viramune. But in this study, they actually compared different

doses of TMC-278 against Sustiva in people who had never been on treatment. What was the result of that study.

JG: The TMC-278—I don't remember the generic name—it's a very strange pronunciation.

DE: Rilpivirine.

JG: Yes, it's rilpivirine, right. Tibotec has been developing two second-generation non-nucleosides. The first one is TMC-125, the name is etravirine. That is now in advanced stages of development. And then the second one is rilpivirine. That is in the earliest stages of development, and I think the first date that has been presented with rilpivirine is this naïve study comparing [it] with efavirenz [Sustiva]. The advantage of rilpivirine over etravirine is that this is a once-a-day drug and as a consequence of this study, also, the dose to move forward has been selected. The advantage of this drug—the results of the study essentially was that at 48 weeks, the outcome was pretty similar to the outcome of efavirenz. And the potential advantage in this specific study, that would be a very good advantage if confirmed in future studies, is that this drug, at least in these specific studies, did not have central nervous system side effects. The prevalence of skin rash was lower, and potentially this drug may well be safer if used in pregnant women, as opposed to efavirenz, that, as you know is teratogenic in experimental animals, and is contraindicated in pregnant women or in women who would like to become pregnant. So that if the results of these studies are confirmed in the future, I think we will have a drug that will be a strong competitor with efavirenz because it may be as active as efavirenz and have some advantages in the field of side effects, although all these things will need to be confirmed in further studies with a bigger sample size.

DE: Just to wrap up, the European treatment guidelines recently changed, and I'm wondering if you could tell us and perhaps how they compare to the US treatment guidelines.

JG: Well, in 2007, all the guidelines are essentially evidence-based medicine plus the opinion of a group of experts when there is no clear-cut evidence available in the literature. So, you cannot expect strong or big differences in the European guidelines as compared with the British guidelines, or the International AIDS Society (IAS) guidelines, or the DHHS guidelines. What we have done is just try to go through all the available European guidelines, trying to reach a consensus and then also trying to incorporate a couple of new findings. The first is that the recommendation to initiate antiretroviral therapy is probably now a little bit less conservative or a little bit more aggressive than it was just half a year or one year ago.

DE: They recommend starting a little bit earlier, is that right?

JG: We are recommending starting a little bit earlier, so that as opposed to less than 200 CD4s, that was the recommendation of several guidelines since very recently, we are recommending to start below 350 CD4s. And to consider the possibility of starting earlier, at least to discuss that situation with the doctors and the patients, and maybe in some circumstances, we can start earlier. And also, we make the point that antiretroviral therapy is never contraindicated, irrespective of the situation of the patient. We may decide to start or not to start, or we may decide to wait a little bit more or a little bit less, but if the patient is ready to start, if he discusses that with a doctor. Even in a patient who has 500 CD4s and 30,000 copies of the virus, antiretroviral therapy is not contraindicated at all, if the doctor and the patient weigh all the circumstances and they make a positive decision. This is one point. The second point is that it's

been—in the last few months, there have been some advances, both for backbone nucleosides and also for salvage antiretroviral therapy. And for backbone nucleosides, it's more and more clear that the thymidine analogs should not be recommended as first-line antiretroviral therapy. We have now at least a couple of very good combinations, abacavir plus 3TC, or tenofovir plus FTC, and we do not need at all to initiate antiretroviral therapy with a thymidine analog combination.

DE: So we won't use things like Zerit or Retrovir, and instead use things like Viread or…

JG: At least as a first-line recommendation. The combination of AZT plus 3TC—the classic Combivir: it's a good one, it's been used successfully for years. It's nothing that needs to be prescribed. Probably there is not need today to use a timing analog like ATC as first-line therapy. Then if something happens with the recommendation for first-line therapy then you can easily and safely switch to an alternative. Then, in the field of salvage therapy: here, it's due to the availability of new drugs. After looking to the results of the studies with integrase inhibitor, with maraviroc, with etravirine, now I think it should be very clearly stated that the goal for salvage therapy is undetectable, is less than 50 copies, and we should try to get in salvage therapy more or less the same results as in—the expectation for deep salvage therapy should be to get pretty much comparable results as the results we get in antiretroviral naïve patients.

DE: Well thank you so much for that explanation and for sharing this time with us, and I really appreciate your work on the conference.

JG: Thank you. It's a pleasure.
