Transcript Details

This is a transcript of a continuing medical education (CME) activity accessible on the ReachMD network. Additional media formats for the activity and full activity details (including sponsor and supporter, disclosures, and instructions for claiming credit) are available by visiting: https://reachmd.com/programs/cme/clinical-and-practical-advances-management-hiv/12020/

Released: 12/09/2020
Valid until: 12/09/2021
Time needed to complete: 15 minutes

ReachMD
www.reachmd.com
info@reachmd.com
(866) 423-7849

Clinical and Practical Advances in the Management of HIV

Announcer:
Welcome to CME on ReachMD. This activity, entitled, “Clinical and Practical Advances in the Management of HIV” is provided by PROVA EDUCATION and is supported by an independent educational grant from Merck.

Prior to beginning the activity, please be sure to review the faculty and commercial support disclosure statements as well as the Learning Objectives.

Here is your host, Dr. David Wohl.

Dr. Wohl:
It’s now going to be almost the 25th anniversary from when the first non-nucleoside reverse transcriptase inhibitor, or NNRTI, was approved by the FDA [US Food and Drug Administration] in the United States. So 25 years later, I think it’s fundamental to ask, where do NNRTIs fit? Where do they fit in in our management of HIV? So with that in mind, today on Clinical Countdown, I’ll be discussing advances in HIV management with Dr. Sorana Segal-Maurer. We’ll look specifically and closely at who, what, when, and the whys of non-nucleoside reverse transcriptase inhibitors and their place in the current and emergent management of HIV.

Dr. Segal-Maurer, welcome to the program.

Dr. Segal-Maurer:
Thank you, Dr. Wohl. We certainly have seen a shift in the non-nucs, with the introduction of newer agents. The real advantage of the newer non-nucs is that they can be paired with other high barrier to resistance agents, such as the combination rilpivirine-dolutegravir, or rilpivirine-cabotegravir. The injectable combination currently in studies awaiting regulatory review gives us a different option in terms of administration. What we’ve seen with the newer non-nucs is the increased activity in the setting of resistance, such as etravirine, doravirine, rilpivirine, some flexibility around food intake, which I think is very important with some patients, and also a neutral impact on lipids and weight gain in the small number of studies to date.

Dr. Wohl:
Well, I think you make a good case for why NNRTIs have been around for so long and some of their durability and their features. But I do wonder, really, when you think about it, how relevant are they?

Dr. Segal-Maurer:
Yeah, and I think you’re absolutely right, and as I said, I’m wondering where we will have that injectable option, as it undergoes regulatory review, if that will bring back some of our use of the NNRTIs as paired in that setting.

Dr. Wohl:
Yeah, I agree. But on the other hand, I do think that there are some newer agents, as you mentioned, like doravirine, which may be metabolically more inert. So, again, I think it’s – I’m always looking for where to prescribe a medication like doravirine, and the opportunities, when they present themselves, are fairly obvious, but they’re not an everyday occurrence in my practice.

So, let’s move on to a different class. It sounds almost like, NNRTIs, but this is the nucleoside reverse transcriptase translocation

inhibitor, and that's islatravir. Islatravir is not available right now, but it's in development. It's a novel agent, and there are data to support its use in clinical practice once it becomes available, based upon some early data. So can you walk us through some of that?

Dr. Segal-Maurer:
I'm very glad you brought up this new class – very exciting. It's one of a couple of new classes of antiretrovirals that is being explored in some early studies and some studies that are continuing in extended phases. So the NRTTIs have a dual mode of action, and I'm going to beg forgiveness, because it really speaks to the biochemistry major in me – actually, organic chemistry. The 4 prime ethynyl group functions to block primer translocation, and together with the 3 prime hydroxyl group, achieve chain termination by changing viral DNA structure and preventing nucleotide incorporation. Now, there's the presence of a 2-fluoro group – the reason why that is important is that is part of the molecules – part of the ability to inhibit the molecule's metabolism, and directly contributing to the long half-life that we have seen. So depending if you're looking at intracellular half-life or different body tissues, anywhere between 120 to 177 hours, so pretty long half-life. The 3 prime hydroxyl group exhibits very high binding affinity for the reverse transcriptase enzyme, and the potency is magnitudes greater than existing NRTIs, depending on which in vitro study we're looking at. So, very impressive.

We've also seen a marked effect on replication capacity. Remember, replication capacity – we don't really talk about it as much, but, it's certainly worth taking that into the efficacy package – and difficult to develop resistance. The last upside is that very, very small dosages have very long-lasting effects.

If I can take another second, you mentioned some data. The recent 96-week data for a small study that was presented with a combination of islatravir with doravirine demonstrated very good efficacy and tolerability. High viral loads in the small study did not impact efficacy, so we'll see as the studies progress.

To me, major advantage of the class is the long half-life, the potency, the small doses. And I'll open up the small disadvantage, which is really lack of knowledge disadvantage. The other disadvantage, which I think comes, again, from our lack of knowledge – this is a very long half-life agent. How do we pair agents? Do we pair with other long half-life? What if somebody wants to stop?

Dr. Wohl:
Yeah, I think that there's a lot of buzz, as you mentioned, about islatravir, and to play devil's advocate for the purpose of the Clinical Countdown, so here is a potent agent, got a novel mechanism of action, as you described, it looks really good. Yet, you know, it's been a couple of years now, and we have a small phase 2 study that is getting squeezed to 96 weeks to try to get us as much data as we can out of this very small cohort. I just wonder again, what do we not know about this particular agent? So at the same time that this is a hopeful and novel therapy, on the other hand, I just feel like I wish there were more data available about it for the things that you mentioned and in combination with other types of antiretrovirals.

Which gets us to our third topic. So we've discussed islatravir a bit in combination with an NNRTI, with doravirine, specifically. For the third topic in our Cinical Countdown, I want to pose the question, as far as this class goes, is this it? Is this where we're going to see this NRTTI end up in the future, combined with doravirine, or do you see there being a future where we can use this in other creative ways?

Dr. Segal-Maurer:
So you can't help but think, where is this going to go? That long half-life is a real stimulating idea to me. It makes me think of drug-eluting formulations, injectable preparations, sort of all these different ways of delivery. Also, the question is will we use this in pre-exposure prophylaxis [PrEP], right? Again, that long half-life makes it very interesting. The difficulty to develop resistance is also interesting. There was some simian studies with PrEP. One dose protected them from a rectal SIV [simian immunodeficiency virus] challenge, but what does that mean? I don't know, but it certainly is making me think.

I do want to ask you, because one of the other things that's sort of niggling the back of my head – should we rethink monotherapy? I know that that is a huge taboo in the field of HIV, but at some point with these newer agents, is that something we should think about?

Dr. Wohl:
Yeah, we've seen this incrementalism, if you will, where we went from 3 or 4 active agents, or antiretroviral agents, to now 2, including 3TC or FTC, which most of us think of sort of like a half antiretroviral, cherry-on-top antiretroviral. And so something like dolutegravir plus 3TC, just having the potency that it does, the barrier to resistance, all the things we like in a combination, usually of more drugs, is really sort of tantalizing. So what if we had a particular agent like you described, like islatravir, that has a couple of modes of action, a high barrier to resistance, real potency. You know, it is interesting to think about, especially maybe for maintenance, but we're a long way off. As we talked about, we just have phase 2 data from a pretty small number of participants in that study. I think we need larger trials of the drug in a more standard sort of application, and then I think we can start to be a little bit more creative, as people were with dual therapy.

Dr. Segal-Maurer:
Yeah, that's right, and I'm just wondering if that is a possibility for the future. Certainly, I think our patients would absolutely love that one injection – come back in six months or administer it to yourself in six months.

Dr. Wohl:
Agreed, and that's the thing I really do like about islatravir is that you can imagine it being an oral therapy, like we're doing now in the studies, or it could even be given not just every day, but maybe once a week or, as you mentioned, could be implantable or injectable. So I think there's a lot of flexibility with this particular agent, so you're going to hear a lot more about islatravir.

Great. We're going to move on now, to the lightning round. We're going to be very succinct in our answers, try to keep it under a minute. You're going to be up first. So the first thing is – it's a heavy issue, so you have to think fast – the psychosocial and health status impact of therapeutic choices for patients with HIV. So just discuss the impact of the whole package – the psychosocial issues, the health issues – on how you choose a therapeutic agent for your patients with HIV, not just their viral load and CD4 cell count. Go!

Dr. Segal-Maurer:
Quickly, two things, right off the top of my head. Neurocognitive disease, number one, hasn't gone away with new classes or with potent antiretroviral therapy, so I think about it a lot when I choose treatment. Weight gain – another real buzzword for me and my patients in clinic. Multifactorial, but there are increasing reports around women, women of color, and those over the age of 50. There is some data around relationship with particular antiretroviral classes. We're still waiting for more data, more studies to come in, but I do think about these things, and they do have an impact on how I choose antiretrovirals or at least discuss them with my patients.

I know you talk a lot about interdisciplinary management, so I hope this is up your alley. We know it's crucial when it comes to HIV management and prevention. Now we've had, and continue to have, a current pandemic that we are grappling with. How do you think this has impacted interdisciplinary management?

Dr. Wohl:
Well, the COVID pandemic clearly has changed life for all of us in many ways, including the management of people living with HIV in our clinics. On the one hand, there has clearly been stress and a challenge in delivering that care. We don't have people coming into our clinics anymore, and like your clinic and my clinic, when people come in, they don't just see me, they see our social worker; they see our adherence counselor; they see our financial counselor; they fill out paperwork. That's all now disjointed, and it's now virtual. And that really challenges people, and I'm getting messages from my patients saying, "I've been trying to get in touch with you." And I do think that there's evidence that we're not getting as many labs as we used to. There's pretty good data, too, that PrEP has kind of fallen by the wayside, and we've not been able to really start PrEP or continue PrEP the way that we used to. So there's real major challenges.

On the other hand, I've been really impressed by how many people have responded positively to virtual visits, and they're not having to schlepp into clinic. They like the efficiency of me talking to them and then maybe going to a local commercial lab or a hospital lab – in and out, get their bloodwork done. So as we emerge from this, as this new normal sets in or as it changes, I do think the way we deliver clinical care to people living with HIV and even PrEP is going to change, largely because of what we learned during this pandemic.

Well, this has been great, but before we wrap up, can you just share with our audience maybe one take-home message?

Dr. Segal-Maurer:
I think with the introduction of the new classes, there will be a strong potential for personally tailored therapies. Can I do one more?

Dr. Wohl:
You got it!

Dr. Segal-Maurer:
I think that older treatments have not completely lost their role in management, I really do. I think, you know, maybe for the 90% or the 95%, you could maybe choose one path, but there's always going to be a small number of patients, and depending on practices there could more of those small number of patients. I think we need to be very open to still using things that are not sort of the cookie-cutter approach.

Dr. Wohl:
I'll take two take-home messages, as well, to match yours. One is I think we're seeing that we have great HIV therapies, but less is more. Less medicines in a pill, less pills to take, or maybe even less frequent administration of antiretrovirals, including byinjectables. And now we are talking on the realm of can we give something not just every month or every two months, but every six months, and that's where we're headed. Less is more when it comes to antiretroviral therapy. That's what people want, and I think that's what we're

going to see.

The other take-home message is more is more. And in that sense, as we age and get more years under our belts, there's more challenges. That just happens to everyone, but I think for people living with HIV, there is added challenges because it's the concentrated problems or syndromes of aging, poverty, discrimination, frailty, depression, isolation. These things, I think, conspire to make it really difficult for a lot of people who are growing old with HIV. And I don't think we have great systems in place to help those people. So I think those are going to be two very dueling issues that we're going to be dealing with over the next few years.

Unfortunately, that's all the time we have today, so I want to thank our audience for listening in and thank you, Sorana, for joining me, for sharing your insights, for being a good sport, and it was great, really, to talk to you today.

Dr. Segal-Maurer:
And thank you so much, David, for having me today, and thank you to our audience for spending time with us.

Announcer:
You have been listening to CME on ReachMD. This activity is provided by PROVA EDUCATION and is supported by an independent educational grant from Merck.

To receive your free CME credit, or to download this activity, go to ReachMD.com/Prova. Thank you for listening.