Today and Tomorrow: Managing Resistance in Heavily ART-Experienced People with HIV

CMEO Podcast Transcript

David Wohl:

Hello. I'm Dr. David Wohl, and on behalf of CME Outfitters, I'd like to welcome you today to today's educational activity titled Today and Tomorrow: Managing Resistance and Heavily ART-Experienced People with HIV. So, today's activity is brought to you by CME Outfitters, an award-winning, jointly accredited provider of continuing education for clinicians worldwide. It's supported by an educational grant from Gilead Sciences and ViiV Healthcare. So, I'm really happy to be joined today by Dr. Sorana Segal-Maurer. She is the director of the Dr. James Rahal Jr Division of Infectious Diseases in New York at Presbyterian Queens. She's a professor of clinical medicine at the Weill College of Medicine at Cornell University in New York. I'm Dr. David Wohl, as I mentioned, I am at the University of North Carolina in Chapel Hill, and together we're going to be working through some of the major issues, thinking about heavily treatment-experienced patients. And as we'll talk about, there are a lot of different things we have to consider, and the learning objectives cover this, and they're there for you to see.

So, Dr. Segal-Maurer there... You and I have been doing this for a long time, and we certainly understand that the way that we thought about resistance before and how we're thinking about resistance in the current context of really great drugs, and certainly therapies that are first line, and extremely effective at keeping people from developing resistance. But we still have patients that we are managing who are veterans, if you will, of the ART arms race and have cultivated resistance. And of course, some people do continue to have virologic failure, sometimes with resistance. So, can you give us a little bit more context, and maybe explain to our audience a little bit about how you think about resistance and the etiology of drug resistance?

Sorana Segal-Maurer:

Sure, absolutely. Thank you David and it's a pleasure to join you today. You and I have had many conversations in the past, so I feel comfortable this is a continuation. I think people who may come to this program may say, "Oh, I don't have these patients. I don't really need to hear about this, there really is no resistance. I don't see it, I don't think it affects my practice," and I just wanted to take a step back. I think that we have some terrific options for our treatment-naive patients, and I think people who are newer to HIV, people who either just starting out or switching careers, and entering and joining us in caring for our patients may not have encountered some of these more challenging cases. Sometimes they also concentrate themselves in people who've been dealing with HIV for decades, so maybe some people in general practice may not be seeing them. But in spite of all of these wonderful regimens for our treatment-naive patients...

You talked about some of our patients who really made it through the long haul with a lot of very challenging regimens for decades, who are now in a different place. But we'll get into a little bit, I think, as we talk about how resistance happens and transmission, but we'll talk a little bit about that. What I wanted to put in perspective is that treaters, providers like you and I, resistance is part of our makeup when it comes to taking care of HIV patients. We think about this, we worry about it, we may choose regimens based on our concerns, and I think that's what's important for us to share today. Even though the majority of the patients don't have these

challenges, I think it's very important to hear about it, because we don't want to end up where we were by not being very mindful. So, I think that's how I think about it.

David Wohl:

There is resistance that people cultivate while they're on therapeutics, less and less nowadays, but some people have cultivated this over time on agents that have a lower barrier to resistance, but then also people can get infected with virus that is resistant. So, I think that that's an important concept for people to understand, that there's, “wild type virus” out there that doesn't have inherent resistance to medications. But then there are viruses that we either breed, and ask, with selective pressure, to become resistant. And in the era of COVID, I think we're understanding this all of us more and more, but there's also people who are unfortunately, and not a very, very small number of them, are acquiring resistance because they were infected with a virus that already was inherently resistant to some of our medications, right?

Sorana Segal-Maurer:

That's exactly right. And I think many times providers think, "Oh, my patient is resistant to medicines because they're just not taking them. So, it's an issue, they're not telling me." And I think sometimes that is correct, patients may not be able to take their medicines on time, and I think that's very complex why that happens. Is it their social stressors? Is it adverse events that we're not identifying and they're not sharing with us? So yes, difficulty taking medications is a driver to selecting for resistant mutations. However, one thing that I think is happening more and more, and you mentioned COVID and we're talking about people as they get older, there's polypharmacy, and also people who want to be in great health, and start taking supplements and vitamins, and mega doses of other things that they don't share with us. There's a fair amount of drug-drug interactions that we never hear about, the patients do not think are relevant to their medication, because these are natural medicines, so how could it possibly be an issue? So that is also a significant component.

The last thing I wanted to say, because we're so focused on nutrition and all of that, we have to be very wary about what requires food, what doesn't require food, what kind of food, all of that, because absorption matters. So, they could be taking their medicines on time every day, they get frustrated, but there are other things that are happening that we need to ask about.

David Wohl:

Absolutely, so that's really helpful. So key messages when we think globally about HIV drug resistance, people can acquire it through no fault of their own, this happens very commonly. And for different agents, different proportions of people newly diagnosed, will have virus that's resistant. Fortunately, as we'll get into a little bit more about the classes, integrase resistance being transmitted is very, very rare, which is great because it's a workhorse class for us. But to NRTIs, older medicines, drugs with lower barrier to resistance, and certainly mutations that don't confer much of a hit to the viral fitness. So, we know NNRTI resistance, that that wild type virus that acquires that can replicate happily without much of an evolutionary detriment, or hit, or deficit. Then the other thing, of course, is that there could be medications that people are on that don’t have as high barrier to resistance that could be interfered with through medication interactions or absorption issues, in addition to certainly suboptimal adherence.

And again, we've moved more recently to more bulletproof, if you will, agents that can, you can take them 70% of the time and there is no problem. You don't need 95% adherence like we used to, namely the newer integrase inhibitors, just to call it out as we'll talk about it. But NNRTI regimens are still used, they have a lower barrier to resistance, and some older integrase inhibitors as we'll talk about also. It's interesting because in certain cohorts, we look at, well, what proportion of people are highly treatment-experienced? And we'll get into some of the numbers, but there's also characteristics, as you mentioned, of people who do have multi-class resistance. And again, this is rare, but it does happen. It's rarer than it used to be, but these are generally, like you said, people who are older, who've been diagnosed a longer period of time, reflecting maybe sequential therapy, including monotherapy, or dual therapy, and then lower barrier to resistance drugs. Unboosted PIs, whatever. So, these are people who are older, they've been around longer, they've been previously treated with some of those.

And I know OPERA cohort, which is a nice cohort that represents lots and lots of people living with HIV. The CNICS cohort, and we're a CNICS site, so these are a bunch of clinics across the United States that are representational of people living with HIV. They've really identified basically the phenotype of people who are more likely to be highly treatment-experienced. Very hard to find a 23-year-old who's highly treatment-experienced, unless, and this is key, they were born with HIV, right? So perinatal infection leads to people being infected long-term, and they definitely have had some of these issues too.

Sorana Segal-Maurer:

Those are really good points, because I think we think about who are these people living with HIV that we're talking about. I want to draw a distinction between treatment-experienced, where you might have possibly one mutation or two mutations, and you really have options for a new regimen. The heavily treatment-experienced patients are people who have cycled through multiple regimens. As we just said, selecting for resistance, we're now putting a regimen together, can be a little bit more challenging. The other thing, which is really one of those catch-22s, is as their virus is more multi-drug resistant, and our regimens are really trying, as we'll talk about the guidelines soon, we're really trying to put together things to maximally suppress them. They end up on more complex regimens. So, if they were struggling with what they were already on, which might have been simpler to take, they're really going to have challenges now, and I think that's where, just speaking from my clinical practice, you know when they come in and they say, "I read about that one pill, can I have that one pill?"

And you just really, internally, without sounding dramatic, I want to start weeping because, "No, you cannot have that one pill, which I love to give to as many people as I can, because you are infected with a virus that is so challenging to us." And David, I feel like, again without being dramatic, these poor patients are really looking over the fence at everyone else who's taking very simple regiments and I feel that we're just not there to make their life as easy as can be. So, I find this population very challenging, as you just mentioned, from these cohorts. The numbers are small, but they are not very, very small, so we all have some of these people living with HIV who are very challenging. I want to add one more thing to that, which I think is very important, because everything now we try to be as financially and as cost aware of our medical care delivery. These people living with HIV who are heavily treatment-experienced, they use up a significant amount of healthcare resources. They are seen more frequently at visits, because they're not suppressed. They may have more comorbid conditions that required more attention, because of that inflammatory background that we're not able to control. So, to me, this is why I think it's important that we talk about this today.

David Wohl:

Absolutely. Great, this is great. So, like you mentioned Sorana, I think good news is the number of people who are heavily treatment-experienced, again, has somewhat gone, without treatment options has gone down, even though there's certainly a lot of folks who are heavily treatment-experienced, so the proportion that don't have many options left has gone down as we've had newer therapies come along. You mentioned really helpfully about the issues that feed into this. One thing we should also talk about is, how do we even determine who is, has resistance? And a lot of my folks, like you mentioned, who are on mega heart, so they're on complicated regimens, they're not on one pill a day, they're actually, their viral load is suppressed. So, we know that they've had resistance, because we've been following it for years, and they do have that inverse pyramid of HIV therapy. "I was on AZT, I was on AZT 3TC, I was on DBI d4T, then Indinavir." So, they have this inverse pyramid where they get more and more drugs to the top of the list.

So, one thing is, I think most folks are aware that there is HIV resistance testing, of course. So, you can do genotype, and we do this at baseline now, although that's something we can talk about too. With new therapies, we may not need to do it as much, but right now if you're following guidelines and standard practice, we get a baseline genotype that helps us understand if there is transmitted resistance that we can detect that's a majority population. HIV genotype testing, and all resistance testing, is really like polling. And in this election season, I think we all understand about polling and sampling. You can't poll all 180 million voters in the United States, so you poll 1,000 and extrapolate from that. Same sort of thing happens when we do resistance testing in the blood, we look for a virus that's there, and we can get what's the majority, extrapolate it from that drop of blood. But we're going to miss minority opinions, we're going to miss minority variants, so that's important.

There are other ways that we think about testing though, and it could be during virologic failure, right? So, the virus starts to pop up all of a sudden. In my clinic, of course, when I get the genotype, it's almost always showing wild type, and it's because the person just stopped their medicine. Insurance fell through, their job changed, something happened, so that is where we use it as well. But sometimes, especially for those low-barrier to resistant drugs, we could see, "Oh, a mutation occurred, it was cultivated." All of a sudden we now see that the pins have been knocked down by the balling ball, we're not going to have as much effect. So, genotype is really helpful at baseline for understanding is there transmitted resistance that we could detect? If it's not there, it doesn't mean it's not there, but if we detect it, it is. And if there's virologic failure or rebound, we can look at the virus and say, "Hmm, is this because the person stopped taking the medicine, or if something's interfering with the absorption of the medicine, and/or have they cultivated resistance?"

So those are really key things, I think, for people to understand how to use the tools that are available. Switching therapy, I generally don't check for resistance, although there is a way to do that looking at DNA. So not the RNA of the virus, but looking at human DNA, in some of our cells, to see if there's integrated viral DNA from way back when, right? It's an archeological dig to look to see, are there the fingerprints of a previously resistant virus that may have integrated into our cells years ago? It's a funky test, I think it's an interesting test. I don't know about you, I don't use it very often, and I usually take a good history, figure out what people are exposed to, and then make judgements about that. But that's a little bit about resistance testing, and maybe get your thoughts about maybe how to use the DNA archive test that I just mentioned.

Sorana Segal-Maurer:

Yeah, I think we're pretty much in agreement about that, and I want to underscore the optimal time to do resistance testing is while the patient is either on medications and not virally suppressed, or just off medications, because that active drug pressure that we're talking about will force the virus. Again, I'm being a very cartoon-like here, but will force the virus to maintain mutation, so that's the optimal time for us to really see what the virus is doing in terms of subpopulation resistance. Once a patient is off medications for some time, and you get your resistance testing, I want to underscore the fact that just because it's not there, you have to be careful, because you have to use your medication history to aid you into thinking, again, I want to underscore what you said much earlier, what mutations might have been selected for, because mutations where the virus takes what we call a replication capacity hit, which means, keeping that mutation, it is not fully able to replicate in a very successful healthy way for the virus.

Once you take a hit in that replication capacity, the second those medications go away, more or less, the virus will archive that mutation, and I think many times M184V is usually the classic example for that, but there are other mutations that fit. The classic mutation that you talked about, the NNRTI, the K103, the virus does not take a hit. So, one mutation 10 years ago, you may see it continually through, because it doesn't affect the virus. So, it matters a lot when we do our resistance testing, and then I think as much as we can do, put it side by side with a medication history. The transmitted drug resistance I think is also very tricky because again, it depends what mutations were transmitted, are they then archived? And then following a patient, let's say six weeks or so, after starting treatment, if they're not virally suppressed at that point, that could be a time to consider repeating a resistance test, because again, medication pressure might have forced those mutations to come back out.

We could talk about resistance forever. Luckily, we don't have to for our patient's sake, but there's a lot of considerations I think.

David Wohl:

Absolutely. There's also data, and I think that helps me a lot when I look at this. So given that there is complexity, I think the good news is we now have agents that are really potent, that are easier to take, and have a higher barrier to assistance. So, people who have virologic suppression on somewhat older regimens, we have data now that when we switch them to newer regimens with an anchor drug that has a high barrier to resistance, that therefore, they should not have resistance mutant-virus that is not susceptible to these agents. Vis-a-vis bictegravir, dolutegravir, and boosted darunavir. These are agents that, if you're on something else, two nukes, and you name it, and you switch to two nukes and any one of those three, chances are very high that you'll maintain suppression. So, this is conceptual, as well as it is individual to these drugs. The idea is if you have a drug that's very high barrier to resistance, thus ergo, you don't have resistance mutations, then you're going to be effective on that regimen that contains that if you're already successful on, a “lesser regimen” or a more vulnerable regimen.

And we've got that from a number of different studies, and that's been a very important concept. And it's also important, because we even know from the BRAAVE study, you could even have that 184V that you talked about. So we think of three active drugs, but we really understand now, it takes basically two active drugs as long as the two active drugs have certain characteristics. Not just any two, but that there be one of them at least that has a

super high barrier to resistance, like the drugs we've mentioned, boosted PIs, especially darunavir, I think we have better data on that than others, and it's more user-friendly. And dolutegravir and bictegravir, not older integration inhibitors that have a lower barrier to resistance, not NNRTIs, right, so this is key. And even with 184V, that doesn't seem to make a difference, and we've got more and more data that shows that, that's been incredibly important. In the BRAAVE study, not only 184V, but even NRTI resistance in people going to an NRTI-based regimen, plus one of those three drugs, in this case, it was bictegravir, maintained virologic suppression, it didn't matter.

So, we really have high quality drugs now that can protect people who are virologically suppressed, and getting someone suppressed is different than keeping them suppressed. So, I think the data really are showing that we have good results there. And in fact, longer term data, from a number of different studies, that show these new drugs are really revolutionizing. So, I'll tell you, there's that inverse pyramid, but I have a bunch of people where it's starting to go back towards a tippy top point, where they were on three, four different agents, maybe more than three pills a day, and we've been able to switch these suppressed people back to, even sometimes, one pill a day.

Sorana Segal-Maurer:

No, you're absolutely right, and I think we like to use the term simplification, and it's not just for people starting a new regimen, and within a number of months you can simplify, but we're approaching a lot of our more treatment-experienced patients and thinking, "Can we go into a switch consideration?" I like to do that proactively, I don't like for patients to come in and tell me they'd like to switch, because by that point, they've already been thinking about it, they're frustrated. So, I like to, with every visit, take an opportunity, quickly look and see if these could be options, and then introduce them. They are a little frightened, because many of them have been so focused on full adherence, they're very anxious whenever you destabilize their ship. But I have to say, no one's gone back once we've been able to successfully go to something potent yet simpler. Those are incredible concepts. The other thing, without getting into really the weeds of resistance, keeping a combination nucleoside NRTI regimen is very important, because depending on what prior mutations they had, it helps keep that pressure on and decrease that replication capacity.

So, I do soul-searching when I simplify, if I do it to three drugs or two, and I'll say that in these cases, I'll keep it to three drug combinations, because the last thing I want is to talk a patient into trying to take something simpler and then have virologic breakthrough. So, a lot of our most successful switches, simplifications, have been to a three drug combination, as you just discussed, a dolutegravir, bictegravir, or boosted darunavir with two nukes. Hopefully some of the more complex patients, really keeping that balance of those mutations that reduce also the viral replication capacity.

David Wohl:

Right, because all these studies, as you point out, did keep the nukes going on, including drugs that can put pressure to keep the 184 mutation. There's some really good guidance, I think, in the Department of Health and Human Services, guidelines that can help people walk through this, an algorithm that you can look at. It's very rare to have boosted PI, and dolutegravir or bictegravir resistance, so that fortunately is not as much a problem. We'll talk in a second about newer agents that may be helpful for those folks, hopefully in the future, not too far

from now future, but also for those who have some susceptibility, of course, to the newer integrase and retain PI susceptibility. There definitely are those options of using them, again, with maintaining those nukes. So, let's do talk about newer generation, novel ARTs that are here now and that are coming down the pike, because this has helped the folks for whom, maybe there has been a chink in the armor for integrase. And of course, again, this is a hard thing to get.

It's usually because of exposure to elvitegravir, or raltegravir previously. They have a lower barrier to resistance than the newer integrases, so unfortunately some people develop that, and then maybe we'll see in the future too, people who fail with resistance to cabotegravir, either for prep or for treatment. So, it's interesting in the Department of Health and Human Services guidelines, people who've been on cabotegravir for prep. Darunavir ritonavir is listed as the preferred regimen, not an integrase inhibitor, and so they snuck that recently in italic. So, we have to think about those folks too as cabotegravir's used more and more for prevention and treatment. So maybe it's important to talk about some of the agents that are here right now that people may or may not know about. So ibalizumab, so wonderful that we can have this. It's wonderful that we've had it long enough that I could learn how to pronounce it pretty easily, flows off the tongue now, didn't begin with, as so many things. So, this is a really interesting drug.

This is a CD4-directed attachment inhibitor. And I have to admit, I do have a patient on this, and a colleague has a couple of patients on it, so we have about three or four people in our clinic. This is infused, like monoclonal antibodies are, and it's a novel mechanism of action, so no one should have de novo resistance to this. And I have to say, as part of a salvage regimen for whom a newer integrase, and a boosted PI are not expected to be very, very helpful for, this has been useful for me, and I'm sure you as well have had some experience with this.

Sorana Segal-Maurer:

So yes, absolutely. And I just say "iba," just to keep it short and keep myself honest, but your pronunciation is remarkable. I think what's important about this infusible drug, which does have challenges, we have a big infusion unit, so for us it's absolutely fine. What's important about this new medication is that it is active, either against CCR5 tropic viruses or CXCR4. So, for example, if any one of our patients had been on maraviroc in the past, and ended up selecting for CXCR4 virus, you can now have this as an option. The other thing that was very interesting at a recent conference, is that there is potentially the ability to use this as a subcutaneous injection, so hopefully we'll hear more about that. Again, it was at a scientific meeting, and it got me certainly thinking that maybe going forward, we can explore if this as an option.

David Wohl:

Absolutely, so I think that's right. So, this may be, and again, just like we're talking about for monoclonals for COVID, if we don't have to infuse it and we can give it, and this is a drug that could be given by IV push, hopefully, like you said, we could see subcutaneous administration, which would make it much more accessible. But, you know, there are people who have rheumatological conditions, autoimmune conditions, IBD, who unfortunately, or fortunately, go in and get an infusion. This is every two weeks, which makes it a little bit of a downer. But I think for somebody who really needs this, it could be a lifesaver. So really important drug, I think that's great. Another one, because you don't want to use it alone of course, is fostemsavir. So fostemsavir is available right now, it's an oral agent, we have data that shows that this does have antiviral activity that's pretty good. So again,

this is another drug, it's a GP120 attachment inhibitor, people should not be resistant to this because of prior exposures.

So, you can imagine that some of our ibalizumab patients are on fostemsavir at the same time, so all hope is not lost. And this is a twice a day drug, okay. But again, we're trying to save people's lives. And so, this is another thing that I think we can bring to the table for some of our very highly treatment-experienced patients who may be on cumbersome regimens, regimens that are hurting them one way or another, because some of our older regimens can hurt people, or people who are not getting virologically suppressed. You could cobble together a regimen, including with fostemsavir, which again we've had some use for.

Sorana Segal-Maurer:

Yeah, absolutely, it definitely gives you a good option. It is twice a day, and I think when we engaged in the conversation with ibalizumab, we entered discussing the long-acting era, fostemsavir keeps us on the daily concept. But, for these people who have really challenging regimens that you can't really put together full activity, I think it's an option. The 24-week data has been presented at conferences, and it really gives some hope for some of these very challenging patients. Eighty percent of the 60% that remain suppressed continue to be suppressed at 240 weeks, which is remarkable. I know it doesn't sound like big numbers, because I think we're so accustomed to hearing about treatment-naive successes, but for these patients who have not been virologically suppressed in years, to be able, at 240 weeks, to at least half of them be suppressed is certainly a huge benefit.

I do want to add a tiny downside. There are amino acid substitutions that can occur, that make the virus already resistant to this. And I think we'll learn a little bit more if and when we really go into more mainstream use fostemsavir, how that impacts our regimens.

David Wohl:

Yeah, absolutely, really important. So, thinking about that future use of it again. Yeah, I want to make sure we also talk about things that are coming down the pike, especially one I think is near and dear to your heart, given your role in advancing this particular agent moving forward, because you mentioned long acting. So lenacapavir is a very interesting drug that I think is going to be the next big thing when we talk about treatment for HIV infection. And it's a capsid inhibitor, so this works at a couple of different points of the HIV life cycle, which has some advantages, and has been studied in heavily treatment-experienced patients in the Capella study, and you've published on this recently in The New England Journal. And I think this is a drug that has a lot of flexibility. It could be given as a long-acting sub-q, it could be given as PO, and it's been studied in both. So maybe just getting your take on lenacapavir and understanding how you're thinking about maybe the use in the heavily treatment-experienced space.

Sorana Segal-Maurer:

Sure, absolutely. So very exciting to have been part of the study, and where I see it is really partnering with other long-acting agents. When and if it receives approval, it received approval in the European Union, and hopefully it'll undergo review in the United States shortly. The results were remarkable. Again, the population was very similar to the other two agents that we discussed when we're looking at studies, very challenging. The majority

were multi-drug, multi-class resistant, hadn't been suppressed in years. And at the end of 26 and then 52 weeks, significant suppression for the majority of them. Even the patients who had zero, no active agents, well over two-thirds of them at a year, were viral loads less than 50 pretty much on monotherapy. Do not do monotherapy, I do not support monotherapy, but for these patients, they had already lost ibalizumab, they lost fostemsavir, they lost everything. It was pretty much lenacapavir monotherapy. When there are more than one or two active agents, the efficacy reached over 90%, so you're talking about really high numbers if you are able to partner with other agents.

You touched on a couple of things that are super important about this medication. Its flexibility, sub-q every six months, oral once a week. There are a number of studies right now looking at various partners, some of them incredibly exciting, which are found on clinicaltrials.gov, partnering with other injectables in a much longer-term type of administration. So, I'm really, really, really excited about entering an era where it could be possible to just see our patients once or twice a year for one little injection, or they give themselves one little injection, maybe a patch. I don't know, some delivery system, and remain suppressed, and really free them up to really enjoy their life, and not think about HIV day in and day out.

David Wohl:

Absolutely, it is exciting. I will say one thing, again, I'm very excited about this drug. I think it does need some dance partners, so that we could have a truly long-acting regimen to offer people, whether they're suppressed and highly treatment-experienced, or maybe not. I think this is going to be something that people are interested in, even if they don't have resistance in the group we're talking about. I will point out, of course, there has been resistance cultivated to lenacapavir in this study and other, so the barrier to resistance may be pretty low. It's been forced, as you mentioned, there are people who enter the study with very limited active agents predicted. So even though they were on other therapeutics when they were taking lenacapavir, they weren't expected to have much antiviral activity. They may have had replication capacity impact, like you mentioned, but some of this was explained by non-adherence, especially to the oral therapy, so I think that's what we've seen before with some of these types of things.

So, I think the barrier to resistance is there, it's not like bictegravir or dolutegravir, where we really hardly ever see, or boosted darunavir, hardly ever see resistance. This will have some resistance, so we just have to be aware of that. It's low proportion, but it does happen, especially when there isn't a good companion there, or when adherence is not as good to the, especially oral. But I think it is really exciting.

Well, this has been really a great conversation. I think that it helps me understand a little bit more contextually where we're going, some of the big topics that we're dealing with historically, and also moving forward, what do we have to start thinking about? What do we have now? What should we be doing? Using tools, whether they be laboratory tools, like we talked about resistance testing, our clinical suspicion, which is the most important tool, and doing a little sleuthing to put things together. And then looking at what's coming down the pike that offers help.

And again, that curve where we show the proportion of people with highly treatment-experienced patients who don't have options, that is going lower, and lower, and lower. And so, with new regimens, I think we're getting

there. And thanks to you for your work, and your service both clinically and in advancing the science, and for talking with me today.

Sorana Segal-Maurer:

Oh, it was my pleasure. Always wonderful to have a conversation with you.

David Wohl:

Thank you so much. Thank you all for listening. Certainly visit the Infectious Disease Hub. The URL is down there for more resources and education that are available to help you and your patients. Also remember to complete your post-test and evaluation for your CME credit.

