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Treating Patients With Drug-Resistant HIV: What's the Approach?

Dr. Turck:
For most patients living with HIV, antiretroviral therapy is extremely effective. However, HIV mutates with frequency, allowing it to become resistant to antiviral medication. So how can we effectively treat patients who have become resistant to therapies and help them live longer, healthier lives?

Welcome to *Clinician's Roundtable* on ReachMD. I'm your host, Dr. Charles Turck, and joining me today is Dr. Sorana Segal-Maurer, who is the Director of Infectious Diseases at New York-Presbyterian Queens and Professor of Clinical Medicine at Weill Cornell Medicine.

Dr. Segal-Maurer, thanks for joining me today.

Dr. Segal-Maurer:
Thank you so much, Dr. Turck. It's my pleasure.

Dr. Turck:
So to get us started, Dr. Segal-Maurer, why are we even talking about drug resistance in HIV? I mean, we've gotten to the point where we're able to give a number of patients a single pill a day with considerable efficacy, haven't we?

Dr. Segal-Maurer:
Yeah, you're absolutely right. For the most part, we're incredibly successful at controlling HIV once we get people into care. However, multidrug-resistant HIV is still an important topic, and how HIV becomes resistant to antiretrovirals is also very important. The reason for us talking about it is that there are people who are newer providers to HIV-infected persons. They have not really gone through the history—for me, it's going to be 40 years in a few years—of all of the early days of HIV. And one of the other reasons we still should talk about it is that we have new treatments for prevention, and some of those can lead to some breakthrough HIV infection with drug-resistant mutations, and treating them can be a little bit more challenging. The guidelines have recently addressed that. So for many of these reasons, we really still need to talk about resistance.

Dr. Turck:
And how did we define treatment resistance in HIV? And how does geography factor into resistance considerations?

Dr. Segal-Maurer:
With geography we do, for the most part, focus on very large urban areas where the transmission rates can be high, as well as transmission of drug-resistant HIV, so geography can make a difference, but more I think when it comes to other comorbid conditions.

Coming back to HIV resistance, there's two major factors that we think about. We think about transmitted drug-resistant mutations, and we also think about treatment-emergent mutations. So how are those different? So the first is—again, going back to large urban areas

—we have a pretty good sense of how many resistant mutations we're seeing, what the prevalence is, what the incidence is. So somebody who acquires a new HIV infection—maybe they were not on PrEP—and presents to care, we always have to do a baseline resistance test to make sure they're not one of those people who may already have some baseline mutations, even though they have never been on treatment. And then, of course, we need to address that differently, maybe change our antiretroviral choices.

For treatment-emergent mutations, those are a little bit different. Those are people already HIV-positive, already on antiretroviral therapy, and for various reasons have mutations. So how does that happen? One of the factors that most people are familiar with is adherence. So if somebody is incompletely adherent with antiretroviral therapy, we know that in time—it could be weeks; it could be months, depending on the antiretroviral—they'll end up with resistance.

Now with adherence, it is a very complex topic, as I think you'll know, Dr. Turck. There could be mental health issues. There could be substance use. There could be insecurity housing, lack of access to food. It could just simply be somebody not fully comprehending what adherence means and lack of adherence or completely out of their control. Other than that adherence, which again, is very multifactorial adverse events. Antiretrovirals are not well tolerated. Drug-drug interactions, that is more on us as providers. Either we're not asking the right questions when we ask about medications that have significant impact on the antiretroviral metabolism, bioavailability, and therefore, eventually, its efficacy.

So these are the topline factors that go into treatment-emergent mutations in somebody who's already been on treatment.

Dr. Turck:
So taking resistance into account, how effective are current antiretroviral therapies?

Dr. Segal-Maurer:
Our current antiretroviral therapies for the most part are relatively good when it comes to some minor transmitted drug-resistant mutations. So as you know, we have moved for quite a few years now towards rapid treatment initiation. It has different names depending where we are in the United States. It could be early treatment initiation. It could be test and treat, but really, the bottom line is once somebody is diagnosed, being HIV infected, the key is to enter care within hours of a diagnosis, begin antiretroviral therapy in order to really engage that person in the future care.

So of course, you realize we don't have access to resistance testing within hours—it takes a few weeks, so our choices now have to take that into account. So for the most part, for that rapid treatment initiation, we do choose something, which as per guidelines is very commonly elvitegravir, emtricitabine, and tenofovir alafenamide. BFTAF is much higher barrier to resistance. And I have to say that there are a couple of studies, one that came out of New York City, and one that came out of New York State that were presented over the last few years, and one of the questions other than the engagement in efficacy and all that was how many times—if you start somebody on BFTAF—how many times do you actually need to adjust it because you now discover there's resistance two, three weeks down the line? And that is actually less than one percent of the time. So it's important that we think about this when we start somebody so rapidly when we don't have all our results back.

The other common high barrier to resistance choice is boosted darunavir single tablet, so it would be boosted darunavir with cobicistat, emtricitabine, and tenofovir alafenamide, so that also comes as a single tablet. So some areas in the United States do choose that, again, really based on that barrier to resistance.

Dr. Turck:
For those just tuning in, you're listening to *Clinician's Roundtable* on ReachMD. I'm Dr. Charles Turck, and I'm speaking with Dr. Sorana Segal-Maurer about drug-resistant HIV.

Now according to current guidelines, Dr. Segal-Maurer, how do we approach treating patients living with HIV who experience multidrug resistance?

Dr. Segal-Maurer:
So unfortunately, as successful as we have been treating treatment-naive patients, we have been successful in keeping many of our older patients alive and healthy. However, because we did not have the extensive tolerable antiretrovirals that we have now back then —20 years ago, 25 years ago, possibly more—these patients have come along and unfortunately, at this point have multidrug-resistant

HIV, and they're struggling. They're struggling because their current regimen is very complex. It may not be very successful in suppressing their HIV, and we know that when HIV is not fully suppressed, there's actually quite a bit of inflammation in that background, and we know from many other disciplines of medicine having inflammation is not a good thing. We know that from cardiovascular disease, malignancy, and various other comorbid conditions, so the goal is always to have suppression.

The guidelines are very helpful because they help give a background to why it's important, and second of all, it's strategy. How do you get somebody who has multidrug-resistant HIV suppressed? There's a couple of major factors to consider. One is you really need to have combination regimen, and that is almost always based on resistance testing. And sometimes you may not have one fully active agent. You may have half activity for this, for that, and you end up with four or five antiretrovirals that together add up maybe to two or three fully active agents.

Number one is looking to see if you have access to a new antiretroviral with a new mechanism of activity. That is key because if you have multiple integrase inhibitor mutations, adding that integrase inhibitor on may just give you maybe 10, 20 percent activity, and it's just not going to be enough for you, but adding a new agent, such as fostemsavir, ibalizumab, lenacapavir, which has been recently approved is incredibly helpful. The virus is not resistant, there's no cross-resistance, and therefore, you now can maybe do a full regimen of fostemsavir, ibalizumab, and lenacapavir and really get somebody suppressed.

Dr. Turck:
And are there any other challenges associated with treating these patients that you could share?

Dr. Segal-Maurer:
Yeah. I think the other thing that until you have a patient sitting in front of you, we don't really appreciate is our patients know what's happening. They know that most people take one pill, and they're doing fine, and they don't come to see us more than once or twice a year. They may have friends like that, and it's psychologically, a great burden to them to know that they're not like their friends, that they're taking complex regimens. And there's burnout, there's depression, there's frustration, and I just want all of us as providers to understand that getting them suppressed is not just medically a very good goal, but it gives them hope. It gives them the ability to look forward to having a good life just like their friends maybe who are taking that one pill.

The last piece that I wanted to add to that is that we have a number of long-acting treatments now that may be used in combination for some of our patients with multidrug-resistant HIV, the newest one again being lenacapavir, which is subcutaneous injection twice a year. I think that we need to look towards improving their current regimens. Maybe something needs to get swapped out if the regimen is too complex, even though they're virally suppressed. So there's a lot of opportunity in taking care of these folks living with HIV.

Dr. Turck:
Well, this has been such an enlightening discussion on a very important topic, and I want to thank my guest, Dr. Sorana Segal-Maurer, for joining me today to share her insights on drug resistant HIV.

Dr. Segal-Maurer, it was a pleasure speaking with you today.

Dr. Segal-Maurer:
And it was a pleasure speaking with you. Thank you for the opportunity.

Dr. Turck:
For ReachMD, I'm Dr. Charles Turck. To access this and other episodes in our series, visit ReachMD.com/CliniciansRoundtable where you can Be Part of the Knowledge. Thanks for listening.