Transcript: Aiming Low: ’Undetectable’ Not Just for Treatment Newbies

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At the 11th European AIDS Conference in Madrid, Dr. Jonathan Schapiro tells Peter Staley that an undetectable viral load is almost always an obtainable goal, even for highly treatment-experienced patients with drug-resistant HIV. To see the video click here.

Peter Staley: Welcome, this is Peter Staley with our first interview in Madrid at the European AIDS Conference. We’re here with Dr. Jonathan Schapiro. You have a couple of titles: you’re director for HIV/AIDS at the National Hemophilia Center in Tel Aviv, Israel. But you’re also the adjunct clinical assistant professor at Stanford University School of Medicine. Do you…commute?

Jonathan Schapiro: Well, my work is primarily in Israel today, but I work with Bob Schaefer at Stanford on his database. So most of my clinical work now is focused in Israel. The research is more international.

PS: Very good. You gave a fascinating talk yesterday. It was titled “Multi-Drug Resistant Virus: Achieving and Attaining Virologic Suppression.” Let’s describe the folks we’re talking about here: highly treatment experienced, people who have been on therapy for a decade or more, probably started on monotherapy or dual therapy, they got resistant to various classes. How many people are we talking about these days.

JS: Well, as you said, I think you describe them well. Most of these patients are indeed folks who started treatment either before the HAART era or in the very early HAART era, so as you said it’s either folks who started with mono or dual therapy. Or some of the folks who started just as we were beginning to use the un-boosted PIs, when we probably didn’t quite know what we were doing, or weren’t able to do what we really needed to do which was to get enough drugs on board. I might also mention that some of this was also clinicians not realizing how important adherence was. So it’s not rare to actually find patients who had started treatment officially in the HAART era, but with maybe not having clinicians understand how important adherence is, and therefore I think early to mid-90s, most of these patients began. I would also mention that we still do have smaller populations of patients who did start in the HAART era and received what we would call today our standard therapies. This would be, again, un-boosted PIs, maybe followed by an NRTI, and also started down this pathway. And I think what characterize is they have extensive NRTI resistance.

PS: The low-level viremia that some people—you challenged clinicians and patients in your talk yesterday.

JS: And myself.

PS: And yourself, basically saying that people are being lackadaisical out there. A lot of clinicians are kind of accepting the fact that they've got some of their patients who are highly treatment-experienced, some of them have low-level viremia or even high-level viremia that's kind of persistent over the years, and it can be a very slow path, but we've seen data now that if you have even low-level viremia for a long period of time, you can continue to develop resistance mutations, and that increases your chance of death, basically. What are these trials?

JS: And as you say, Peter—lackadaisical's probably not fair, so it's very challenging to be the patient who has to come to the clinic, and it's challenging to be the doctor who has ten minutes to see your patient, but from my experience, I think there was a point four or five years ago where we had these patients accumulating and we simply did not have the tools to get them undetectable. But we did realize that if we could keep their viral load low, we could at least keep a stable CD4 [count] and keep our patients not only alive, but living well. And that's the best we could do. So our focus really was not necessarily to get these patients undetectable, because we couldn't, but to do everything we could to keep the viral load down. Now, in the short term, that was fine. So as clinicians, you had your patients treated as best you could, the viral load was low, and when you saw them the next visit, they were doing fine. And this sort of lulled us into feeling, "That's okay." And some of these studies that I mentioned, the study from Denmark, which looks longitudinally and says, "Okay, but what's going to happen eventually." And now, with these nice cohorts and longitudinal data, we know that when you do look at a perspective of years, resistance eventually catches up, and that's going to affect the CD4, and eventually, it's going to give bad clinical results. And that's what's new in these studies. You can actually see in the study, for example, from Denmark, mortality. That if you look five years later, the patients do die. And now we actually have multiple studies, good data from Italy and others that show this link which tells us, if you *can* do better, you *need* to do better, and what's new today is we can do better. And I think that's the change.

PS: We were dealing with a long period there in the late 90s—with HAART—but we were dealing with a period there when you had these failing regimens, you didn't have a lot of options, you kind of had to stick with them. But let's also differentiate here: we're talking about persistent viremia, not people who have the occasional blips.

JS: Good point, yes, I think that's very important—you know, how we define blips, there are various definitions, but that's a very important point, Peter. Patients who are undetectable all the time—they can have every now and then a little burst of viremia that can be detected. And if that is a low level of viremia, maybe in the hundreds, and then afterward we again see undetectable, that's definitely not a patient who is at risk of clinical progression. If this continues to happen and we see multiple viral loads being detectable, we have to figure out what's happened, but that's a very good point. We're talking about patients who have a persistently detectable viral load above fifty, and oftentimes it's actually above 500, above 1,000.

PS: So what are the new strategies? We've got three new drugs on the market in the past year: Prezista, a strong new protease inhibitor; maraviroc—Selzentry—which is Pfizer's new first in class CCR5 antagonist, an entry inhibitor; and just released in the US a little over a week ago, Isentress, the brand new integrase inhibitor. So we've got all these new options—how do clinicians figure this

out? What do we do with this group of patients?

JS: In fairness, enfuvirtide, T-20 was also an important agent.

PS: Fuzeon.

JS: Fuzeon. So it's hard for patients to take, but that drug did save a lot of lives. And, you know, I think we should give it credit. It's no fun to take, there's a lot of logistics, but we definitely had patients who, with the help of Kaletra, lopinavir/ritonivir, and T-20 were able to get their virus undetectable. At least get it down for a long time. So I think that was the first new one, but as you said, the challenges of injecting it twice a day were the real issue. Aside from that it's a very good drug. If we could just take a pill twice a day, I think enfuvirtide would be an excellent tool. Tipranavir [Aptivus] should also be mentioned. Although it has more toxicity than others, tipranavir also in the RESIST study

PS: Another protease inhibitor.

JS: Yes. It came actually, it was approved before darunavir [Prezista], and tipranavir is also sort of this next generation of protease inhibitors, which can be effective even if patients have failed others. So as you mentioned, today, darunavir, Prezista, and maraviroc [Selzentry], the CCR5 antagonist, and raltegravir [Isentress], the Integrase inhibitor; all exciting drugs, all showing great results. I might also mention that there's a drug which is now submitted to the FDA for approval, which is also by Tibotec, TMC-125, or etravirine, which also seems to be attractive for these patients because despite being an NNRTI, it's different from the other NNRTIs. Even if you have some degree of NNRTI resistance—in fact, if you have the most common resistance mutation, the K103N, it actually works very well. And so if you combined, and you know, it's not yet FDA approved, but there's an expanded access program, so many of us have been using it, this is one more tool. And so we have an NNRTI, which hopefully will be approved soon, and will have activity in many of these patients. As you mention, protease inhibitors, that despite failing drugs like Kaletra, still have activity. Darunavir and tipranavir, and drugs which everyone should be able to benefit from, like an integrase inhibitor, raltegravir, and maraviroc, patients who are found not to use X4, but only R5, can use it as well. And of course, we have a limited number of studies showing wonderful results. Some of these we know can be combined well. We know that the integrase and darunavir have been combined with very big success, that darunavir and TMC-125 have been combined with very good success, and maybe we can do additional. We have studies starting, for example, using darunavir and TMC-125 and raltegravir…

PS: So the important thing is, though, if you're on a failing regimen, don't add just one of these drugs. If you're resistant to everything you're currently on. Make sure you've got at least two active agents.

JS: That's a very good point, but I think we're going even beyond that today. The key number of two is probably sort of old-fashioned thinking. It may be that it depends—you know, some drugs have what we call a large genetic barrier to resistance, like darunavir/ritonavir. Probably, if you take that drug every day and you have no PI mutations, it's enough. That's what we're sort of finding. Where other drugs, maybe like the NRTI and 3TC, two would not be enough. So it's important for us to start realizing that how to combine wisely is going to be something we still have to discover. But definitely, what these studies have shown us is that using two new drugs

together is far better. One point I'd like to make—I think in concept what's changing—you know, all these studies, we've been so excited about seeing these high number of patients. We see 50, 60 percent being below 50 at 24 weeks. We're really jumping out of our socks. We're just delighted. Probably today we should start looking at those who don't. We should today be in a situation where we almost have to go to court on every patient that we *can't* now get below 50. With all these tools, with all these drugs, with all that we know about adherence. I might just mention also that drugs/drug interactions. Today, when a drug gets approved by the FDA, we know much more than we knew six or seven years ago. So we know about adherence, we know about drug interactions, we have these new drugs, we know about resistance. So every patient that we can't get undetectable, we should sit down and figure out why is that? What's wrong here, what are we doing wrong? The medical staff, the patients should get together and say, with all these good tools, all this knowledge, every single patient we should be able to get undetectable, and if not, we should figure out why.

PS: That's a great challenge for all the clinicians out there. And to push your clinician, if you're not undetectable, there are all these amazing options. You've got to really look hard, but it can be done now.

JS: Yes. Obviously, there will be patients, and there are patients, and after you do that whole process, there are patients where we're going to have to raise our head and look forward to the next group of drugs. And they'll come. And we're going to have to keep them alive until they do come. But the process now should be that until we decide that that patient cannot reach undetectable, we've done a process, and the burden is really going that way as opposed to saying, "Well, you know, it's very hard to get those patients undetectable."

PS: In Chicago, we interviewed a long-term survivor and AIDS activist, Matt Sharp from Chicago. And he had never gotten to undetectable in his whole life until very recently, because of Isentress and a new combination. So the options are exciting. And I really appreciate your spending time with us today. It's chilly out here, so let's end this interview. And good luck with the rest of the conference.

JS: Thank you very much.

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