Transcript: The Plot Thickens: HIV Treatment Challenges

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- part I about Kaletra's possible lipoatrophy advantage to Sustiva
- part II about the CDC's new data showing a rise of HIV drug resistance in the newly infected
- part III about HIVers dying more from non-AIDS-related cancers

PETER STALEY: This is Peter Staley with AIDSmeds.com and I'm talking once again with Dr. Calvin Cohen, an HIV specialist and the research director at the Community Research Initiative of New England in Boston. Dr. Cohen attended the 14th Conference on Retroviruses and Opportunistic Infections, CROI 2007 it's called, held at the end of February in Los Angeles. There are a number of key presentations involving patients on their first treatment regimens and patients not even yet on therapy. Research that continues to shape expert opinion on when to begin therapy and what to begin with, and it's that area that we'd like to discuss today with Dr. Cohen. Welcome and thank you for joining us.

DR. CALVIN COHEN: Thanks for having me.

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STALEY: We'd like to begin with spending some time talking about two very popular treatment options for HIV-positive people starting therapy for the first time: Kaletra and Sustiva. Kaletra, being a protease inhibitor, and Sustiva being the leading non-nucleoside reverse transcriptase inhibitor, or non-nuke. At the International AIDS Conference in Toronto, we got a glimpse of data from ACTG 5142, a study comparing Sustiva plus two nucleoside analogs to Kaletra plus two nucleoside analogs along with a comparison of both groups to a third group taking Sustiva plus Kaletra without the nucleoside analogs. In Toronto, we learned that Sustiva might have a slight virologic benefit that specifically, the time to virologic failure, meaning a viral load that increased above 200 after being below this point during the study, was shorter in the Kaletra group than in the Sustiva group. But in Los Angeles, we learned that Kaletra might have an important advantage over Sustiva. Can you tell us about that?

COHEN: Sure thing. So most of us entering this conference would not have predicted the results we saw, which is that we certainly have known for many years the safety of Truvada [plus] Sustiva, which was one of the choices that people could make on these regimens, was we had a choice of that third nucleoside, and about a third of the participants added tenofovir [Viread] to

the 3TC [Epivir] plus either Sustiva or Kaletra. And most of us have been using tenofovir, 3TC, Sustiva because it was amongst our safest, meaning the least amount of lipoatrophy. What none of us would have predicted is that when we look now at the rate of lipoatrophy on tenofovir, 3TC, and Kaletra, there was actually less lipoatrophy in those people who were taking Kaletra instead of Sustiva. Now the results are not huge, it's about a 6 percent advantage for Kaletra, it's 6 percent with lipoatrophy versus 12 percent on Sustiva, so both regimens are doing well for most people. Nevertheless, we certainly learned something very interesting by suggesting that Kaletra and perhaps even other ritanovir-boosted PIs may not contribute to lipoatrophy as much as we had been thinking.

STALEY: There's a bit of controversy on looking at the backbones in this study. What about the selection of the nukes? Everyone knows that certain nukes are more likely to be associated with lipoatrophy than others. Was this the case here as well, and could this possibly explain the higher rate of lipoatrophy in the Sustiva group compared to the Kaletra group?

COHEN: You're right that people had a choice between either d4T [Zerit], AZT [Retrovir], or tenofovir, and this study does confirm exactly what we would have expected to see, which is that d4T had the most lipoatrophy, AZT had kind of a medium amount, and those on tenofovir had the least lipoatrophy. Those results were confirming exactly what we had learned from previous studies and we're not at all surprised. However, within each group, whether it was with Kaletra or Sustiva as a backbone, we were able to see that still, those on Kaletra had less lipoatrophy than Sustiva. Regardless of the nucleosides, Sustiva had about twice the risk of lipoatrophy versus Kaletra – regardless of which of the three nucleosides. And that was the amazing result. Even for those on tenofovir, this relationship held up.

STALEY: I'm just looking here at the stats for Zerit, which of course has got kind of the worst record for lipoatrophy. And among those combining Sustiva with Zerit, lipoatrophy was documented in 51 percent of the cases, compared to 33 percent among those combining Kaletra with Zerit. So it didn't look like it was just the Zerit. It's a very surprising finding.

COHEN: Yeah, most of us are still trying to puzzle it out, because the whole story doesn't entirely fit either of what we would expect. And even within the study, there are a couple of ways to look at it in which it's hard to totally make a storyline out of it. For example, there was one group who got no nucleosides. They got Kaletra plus Sustiva, and in fact they had about the least lipoatrophy.

STALEY: Yeah, like 8 percent, very low.

COHEN: Exactly.

STALEY: And so Sustiva on its own, or with Kaletra, doesn't seem to be doing this.

COHEN: Exactly. There's something about the combination of Sustiva and two nucleosides that seems to contribute a little bit more to lipoatrophy. And again, thankfully most people are not having it. I mean, even at the most, we're talking about 88 percent of people are not having any degree of lipoatrophy that we can detect here. Nevertheless, it does certainly give us some insight and I think some options, because before this conference, if somebody was dealing with lipoatrophy, most people would not recommend a boosted PI as a way to see if we could lessen it. And now we've learned something that may give us another option to improve people's

appearance and make them feel better as well as controlling the virus.

STALEY: Any difference in lipid levels in these groups?

COHEN: Yeah sure. Of course, what we saw. But once again, what is a major surprise, is that both Sustiva and Kaletra have a very similar overlapping increase in the lipids, particularly the total cholesterol. There's a little bit more triglyceride elevation on Kaletra versus Sustiva, that's not too surprising. And the magnitude of the average difference is reasonably small, and it's not really clear that it much matters in terms of people's health. But again, the surprise was that Kaletra and Sustiva had a similar impact on total cholesterol. Now again, it's important to remind ourselves that these are the averages. There is no doubt going to be some people who, when they take Kaletra, have profoundly elevated cholesterol and triglycerides. And it may be that that group does better on Sustiva than the average data would suggest. So it's important to distinguish between average responses and then what happens at the edges, at the extremes. But nevertheless, these data are reassuring that both Kaletra and Sustiva have a similar and pretty minimal impact on total cholesterol.

STALEY: As far as the difference with lipoatrophy, do we have any theories boiling to the top to explain these rather surprising results? Or are we just going to have to do some further study to figure this out?

COHEN: Well, it's fair to say that we are in the guessing mode. And probably amongst the guesses would include the possibility that within the cell and within the mitochondria there may be some interaction between Sustiva as a non-nucleoside and tenofovir and 3TC as nucleosides, that while each one alone has very minimal if any impact on mitochondrial function, that perhaps when we put three of these together we see a little bit more lipoatrophy than what happens if there's just two of these drugs present. And it may be something as subtle and as simple as that.

STALEY: So there might be some synergies going on there.

COHEN: Yeah, within the nucleoside family. There may be some impact of these drugs, in terms of the numbers of them and how much stress we're putting on the mitochondria in terms of our fat cells.

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STALEY: Very good. Let's move on to another subject. The CDC came out with some depressing news. They've been looking at those who were newly infected in this country, following hundreds of individuals who just got their HIV test and they found now that 1 in 10 who are being diagnosed with HIV in recent years have HIV strains that are resistant to at least one available antiretroviral. And that's up from about 5 percent in the 1990s. As a doctor, what do these results say to you, and what do they mean for the treatment of HIV?

COHEN: We've been watching this issue for a decade, ever since Mike Kozal presented something at the retrovirus conference about eight years ago, a presentation about the incidence of resistance in "rural Iowa," as he described it. I'm not entirely clear where "rural" Iowa is, but nevertheless, even in "rural" Iowa, new infections were sometimes associated with resistant virus. And for years, the storyline has been pretty stable, which is; number one, resistant viruses are transmitted; number 2, it typically seems to be a little bit more common for non-nucleoside

resistance to be transmitted than other classes; and number 3, the rates vary and typically, at least in some cohorts, have been increasing rather than declining for at least the non-nucleosides.

Now, some of this of course reflects the popularity of non-nucleoside regimens, and if they don't result in complete suppression, there is the likelihood of non-nucleoside resistance and unfortunately the likelihood of non-nucleoside resistance transmission. The problem is that we've also learned at these conferences that it matters. Meaning that if someone with a non-nuke resistant virus then goes on a non-nucleoside based regimen as their first regimen, it won't work. We see more failures explained by this pre-existing resistance. So we see a problem here in which some of our better and simplest regimens, certainly the non-nucleoside plus two nucleoside approach is now a single tablet. And for 10, maybe even 20 percent based on some adolescent presentations about a year ago, 20 percent of adolescents won't have that simple, non-nucleoside option because of the resistant virus they acquired.

STALEY: Does this steer you in what you do before you put a patient on therapy for the first time? Are more doctors running resistance tests first before starting therapy?

COHEN: It should be standard of care that a resistance test is done before starting therapy. Indeed, a resistance test should be done the first time somebody with HIV is tested positive. Because we want the best chance to see resistance if it's present. And the best chance to see it is as soon as possible after infection. Over time, what happens is that HIV starts to become closer and closer to its wild type, and those resistant strains sometimes are hidden below the surface. So the state-of-the-art care for people with HIV is if you're diagnosed, that's the time to get a resistance test to see what that virus population looks like.

STALEY: I guess there was a silver lining they stated, in that the number of individuals who were multi-drug resistant still is relatively low, a little under 2 percent.

COHEN: Yeah that number has been pretty stable also for a few years. And that was part of the controversy of last year at the CROI meeting when we had the discussion of the so-called " New York case," and all the controversy around whether we were going overboard in our attention. And thankfully, people who are acquiring that highly highly treatment resistant virus remain at 1 to 2 percent. But still, 1 to 2 percent are being diagnosed with a virus that's very tough to treat. Obviously a pretty worrisome statistic even if it's just 1 percent.

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STALEY: Finally, I wanted to touch upon a somewhat disturbing report from the DAD study, which stands for the Data Collection on Adverse Events of Antiretroviral Drugs,

indicating for what appears to be for the first time that HIV-positive people seem to be at a higher rate of dying from non-AIDS-related cancers than from AIDS-related cancers for the first time. The international study demonstrated that cases of KS and non-Hodgkin's lymphoma are down but that cases of lung cancer, liver cancer, leukemia, Hodgkin's disease, and cervical cancer are on the up. It seems as if we're really entering an area where general preventative healthcare, not just HIV care, is becoming really important for people living with the virus. Your thoughts?

COHEN: Well, you said it well. What we're doing here is seeing the silver lining of controlling HIV. As we control HIV, we control the cancers associated with HIV such as KS and non-Hodgkin's

lymphoma. But unfortunately, we also know that a pretty high percent of people with HIV still smoke, and so it doesn't surprise us that we're going to see lung cancer. We do see coinfection with hepatitis B and C, and so the liver cancers aren't a surprise. And one of the PE studies that I think hopefully will again increases the attention on it is anal cancer. Anal cancer was associated with 20 of the deaths reported here. And anal cancer is amongst perhaps the least attended to, in part because of not entirely understanding what to do if we find some of the precursors of anal cancer and how do we eradicate it, as we do with women and Pap smears. Nevertheless, this study puts a lens to say that people are dying of anal cancer, it is there and it's real, and it is possible to at least find it before it becomes cancerous. So this study really put a lens on what the challenges are of reducing risks for all cancers.

STALEY: And the other two non-AIDS-related cancers that we can do some preventative work on is obviously the biggest one which is lung cancer. We definitely should be encouraging all people living with HIV to stop smoking if they're smoking. Because lung cancer is now a reality for people living with HIV. And then for the liver cancers, we need to really diagnose and prevent and treat chronic hep B infection. Which is a rising concern for people with HIV.

COHEN: You're right, and the good news at least with hep B is that we've got some very effective antivirals that control not just hepatitis B virus but also HIV at the same time. We've got a subset of our antivirals that do a very good job for both. And it's entirely likely that we can make the cancers associated with hepatitis B part of the fading past of this disease.

STALEY: Well thank you Dr. Cohen once again for your incredibly thoughtful explanations and comments and thanks for joining us.

COHEN: My pleasure, Peter, as always.

STALEY: And for our listeners, check out our more detailed reviews of these and other conference presentations on AIDSmeds.com.
