Transcript: The Latest on Lipo: Advances & Setbacks

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Peter Staley interviews lipo expert Dr. Donald Kotler at the International AIDS Society Conference in Sydney, where he discusses the latest news, both good and bad, on lipodystrophy treatment and cardiovascular risk in people with HIV. Below is the transcript. To see the video click here.

This is Peter Staley with AIDSmeds.com and we got Sydney in the background here at the International AIDS Convention in Sydney, Australia. And today we're with Dr. Donald Kotler who we have interviewed many times at conferences over the last year. He is the chief of the division of gastroenterology and liver disease at St. Luke's Roosevelt in New York. Welcome, Dr. Kotler.

Hi Peter. Hi Everybody.

There was a workshop prior to this conference—the International Workshop on Adverse Drug Reactions and Lipodystrophy in HIV—the 9th annual. Can you tell us what the big highlights on lipodystrophy out of that conference were?

Well, I don't know if there really are big highlights. I can think back to the first meeting back in San Diego—9 years ago—when the big highlight of that meeting was that nucleosides may be causing toxicity rather than protease inhibitors which was widely believed to be the cause of lipodystrophy at the time.

With "Crix gut"?

Right and Ritonavir and I must say that as time has gone on we now believe more and more and we now see more and more that it is the nucleosides that really bare the brunt of the toxicity at least the metabolic toxicity. Perhaps, much more than the protease inhibitors. And as we see various studies, and there are many studies now, it seems to be that the problems related to protease inhibitors are rather mild compared to the problems related to nucleosides especially stavudine and zidovudine. F or those who don't know those names: AZT and Zerit.

d4T.

d4T—right—and AZT.

We moved away, mostly, from d4T. We're using safer nukes now. Right?

Yes, and with those safer nucleosides t here is much less in the way of adverse events. I won't say

that none occur, and more and more those that occur seem to be interacting with aging. And I see looking ahead that in the next 5 to 10 years we are going to be talking more about non-HIV related phenomenon. You know, not— for example for oncology—not Kaposi's sarcoma or lymphoma but rather lung cancer, skin cancer, other cancers—that we're not really seeing to be HIV-related yet seem to occur with more frequency in the HIV infected population than in non-HIV related population, surprisingly enough.

Were there any surprises about cardiovascular risk and HAART?

Only one, and maybe it was a little bit hard to describe. People know of atherosclerosis—hardening of the arteries. Before you can actually see the thickening of the arteries, there is a dysfunction of arteries, in terms of contracting and relaxing, and that's well known to occur. And certainly untreated patients who are HIV-infected do have endothelial dysfunction, and a number of studies early on looked to see if the protease inhibitors specifically caused endothelial dysfunction and, sure enough, Crixivan seemed to do so. In the lipodystrophy meeting, Judy Currier presenting for Dr. Torriani in an ATCG study showed that it's not really the protease inhibitors at all. That looked at a study—5142—which is an interesting study—it's called a class sparing study. People either took HAART that did not have nucleosides or HAART that did not have protease inhibitors or HAART that did not have NNRTIs and then looked at endothelial function and showed that it improved no matter what regimen was taken. Some of those regimens had AZT or d4T. And when they looked to find what was it that was common among all of those treatments that might have explained the improvement of endothelial function, it turned out to be a fall of HIV RNA. The fall in viral load was what seemed to cause the improvement in endothelial function or arterial function or, if you will, the precursor to atherosclerosis which was really unexpected and yet perhaps if shouldn't be. Certainly, there have been a number of studies saying that long-term HAART therapy increases cardiovascular risk. You may know of the DAD study, which shows it with the largest number of patients.

HAART therapy in the sense of antiviral therapy?

Antiviral therapy. Excuse me. But there was one study—the one outlier study—was the study from the Veterans Administration Hospital published about four or five years ago in *The New England Journal of Medicine*, in which there was no effect of HAART therapy—antiviral therapy—in terms of worsening cardiovascular risk. In fact, what they saw starting from prior to the HAART era was actually a marked improvement in cardiovascular outcomes—a more decrease in heart attacks and strokes among the veterans—HIV-infected veterans—who started antiviral therapy even before HAART, even starting in 1992 and 1993. What it probably represents is the fact that inflammation is a cardiovascular risk and that's why people who have rheumatoid arthritis or lupus also have an increase in cardiovascular risk. HIV just represents an infection leading to that inflammation and reversing that inflammation is probably providing the improvement.

This is a big theme we're hearing at this conference about non-AIDS defining events as being an increasing concern as we're living longer. And I find this fascinating because it's a real reversal of what people with HIV have been hearing for many years—that the drugs are probably hurting us from a cardiovascular standpoint—and now it might actually be somewhat the opposite because HIV was hurting us more on a cardiovascular front and the drugs—they might be having some cardiovascular

damage—but they have a… but by lowering viral load there was a net benefit.

Right. Exactly right. But the idea… it does not exonerate the medications but certainly from the very start people have said even though there was cardiovascular risk it is nowhere near the risk of being untreated with HIV infection. And certainly… how can I put it… In the population, the base line cardiovascular risk—it's not zero. In fact, there's more cardiovascular disease in the general population than any other disease, perhaps. And the optimal cardiovascular risk is zero. So, not only in the general population but in HIV, we have to take a look at the individual patient and try to lower that cardiovascular risk to zero.

Did we hear any news about any therapies last week, specifically Theratechnologies' TH 9507 which sparks natural growth hormone production. I know we have been looking at Serostim for a while but this is a new experimental drug. What was the latest we heard?

Okay. This was a follow-up study to one that was presented at CROI, which is actually the second of the studies of the Theratechnologies product. It's true the growth hormone comes from the pituitary gland, and Serostim just supersedes the pituitary gland because you're giving it externally. The Theratechnologies product—the growth hormone releasing factor—actually stimulates the pituitary to release growth hormone. It is as they say more physiologic because it is still bound by physiology. There could be feed back, in addition. It is probably less prone to abuse because you don't get as much of an effect. Serostim, when it was used for wasting, was used in doses as high as six milligrams. That's fairly toxic, especially in lipodystrophy . But growth hormone has what's called dose responsiveness—the more you give the better the benefit. Unfortunately, the more you give the greater the toxicity. The Theratechnologies product appears to be the equivalent of about one and a half milligrams of Serostim—not six. And probably at that level is really not so different than growth hormone, in terms of what you see in a patient. They claim, and it's possible, that it's a bit of a better safety profile. But in terms of the efficacy—the amount of weigh that's lost, the amount of fat that's lost off the belly—it's probably about the same, and sort of, I guess, in our terms, it's about an inch off the waistline.

And what we're talking about, for our audience here, all these drugs are basically dealing with the fat accumulation that can occur in some people with HIV. With this drug, were they seeing any…there's always a risk if you're reducing fat in the gut that you might also take even more fat out of the face and the arms. Does that happen?

No. They did not see in this study any lipoatrophy. Although, at the equivalent doses of Serostim, you really don't see that either. What was presented was actually six-month information rather than the just three-month information. And the six-month data suggest that most of the effect that you see is there by three months, so that there is a fall and then a leveling off. In addition—and this is quite important, when the people in power have to decide if this drug is to be approved or not—the worse people are at the beginning, the more excess fat that you have in your belly, the better the response. Unfortunately, for clinical trials you try to get, or for sales you try to get everybody in… as many people as possible. And in fact, I would probably qualify for the Thera product. You know, and if I was HIV infected and etcetera.

(Pointing to his jacket) This is very slimming.

(They laugh) Yeah, I understand, I understand. It is very slimming.

But I would expect that most people would say “that drug is not for me or people like me.” It really is I believe is for those much more affected, much more paralyzed by the effects. Another poster—not an oral presentation—talked about the quality of life, and specifically, not so much the quality of life but the stress—and people who have fat accumulation really are distressed by it—more distressed than depressed—more distressed than unable to function. And the drug or the effect of the drug really does reduce the distress. It doesn’t reduce the stress of facial lipodystrophy. It doesn’t reduce the distress of skinny legs and no butt. But the distress caused by the size of the belly and how it causes pressure, how it causes bloating, how it keeps people from taking a deep breath easily, and the distress of looking in the mirror. That does get better.

And eliminating that distress… the furthest drug along in the investigational process for doing that was Serostim, and this weekend AIDSmeds.com actually got kind of a scoop, because very quietly the FDA turned down Serostim’s application for using the drug for reducing lipodystrophy. And this is rather shocking. It looks like they did the studies the way the FDA wanted them to do them. What happened here?

What the FDA… Alright. Both Serono and Thera had consulted with the FDA to find out what the FDA wanted to see and, for example, the quality of life, the stress, was really done at the behest of the FDA. The endpoints were those that were agreed upon with the FDA and, in fact, both Serono and Thera, their studies seem to have met the endpoints, so it’s really unclear the reasons why the FDA declined to approve the drugs. In fact—not even allowing the information to go to an advisory committee to get the opinion of the respected advisors that the FDA calls together—they denied the application before that even took place.

Well, activists are already complaining loudly. We quoted Marty Delaney from Project Inform saying, you know, yes, there might be toxicities with this drug but this is a very condition for some people. It really affects their lives, and just give the patients the information about the pros and cons of this—and there are pros—and let them make the decision about whether they want to deal with the diabetes risk, the lipoatrophy risk, the stiffness, whatever.

As I was saying before, there are people with lipodystrophy and then there are people with lipodystrophy. One of the problems in the whole field is one of definition: who is abnormal and who is so bothered by what’s going on or so affected by what’s going on that their life is intolerable without it. And it really may be that whereas about a third of HIV-infected patients on highly active antiretroviral therapy developed fat accumulation in the belly, and maybe 10% or 15 % develop a buffalo hump or a lot of fat around the back of the neck or even the front of the neck, there’s a small subset, there’s a small group of people that are terribly affected. And if we knew a way to identify those people in an objective way, that might really be helpful. And I hope that this is not the last word. And I hope that the activists and the government don’t just fight it out and either leave it the way it is or open it up to absolutely everyone. I hope that people really take a step back and take a closer look and say really what’s the problem that we have and how do we get around it. How do we find those people in whom the therapy is really indicated, not on the basis of having a belt size or a pants size that’s more than 36 inches, which is a huge number of people, but those who are truly damaged by the lipodystrophy.

But you think the FDA got this wrong?

Yeah.

Alright, well, we'll have to fight for this one. And thank you for joining us again, and we hope to see you at the next AIDS conference.

Thank you very much. Thank you everybody.

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