Transcript: Which HIV Meds Cause Lipoatrophy?

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Peter Staley interviews Dr. Eric Daar at the International AIDS Society Conference in Sydney, asking him which nukes, non-nukes, and protease inhibitors might cause fat loss, and which ones probably won't. To see the video, click here.

Peter Staley: This is Peter Staley with AIDSmeds.com. And tonight we're speaking with Dr. Eric Daar, who is with the David Geffen School of Medicine at UCLA. Dr. Daar, you spoke tonight at the Abbott satellite meeting on lipoatrophy, which I know from personal experience and from speaking to many people who were newly infected, many friends over the years. It is probably the thing that scares the most about starting HIV treatment. It's the fear of fat loss in their face and their arms, possibly their buttocks. And you spoke, pretty much summarizing what we know to date on how all the various antivirals react with the body and create body changes.

First let's start with the nukes. Can you tell us what we know to date on how different they are and why they cause lipoatrophy.

Eric Daar, MD: Sure, and first of all I completely agree with you. It is sort of a devastating complication of HIV and/or therapy, and it's been a high priority over the last ten years to better understand it so that we can try to prevent it and manage it when it happens. And that's led to a lot of studies looking, over time, at people randomized in control trials to one regimen versus another, and then looking in a very careful, objective way, using things like DEXA scan or CT, at how changes in subcutaneous fat occur. And it's clear that d4T seems to be the biggest contributor to lipoatrophy, and AZT also contributes, probably to a lesser extent. The merging data would suggest that abacavir and tenofovir, the non-thymidine analogs, contribute the least, and maybe not at all. As we use less of those drugs, I think we'll see whether this continues to be a problem.

PS: d4T isn't used much anymore because of its (probably accurate) bad reputation on lipoatrophy. But there is still a fair amount of use of Videx, which is known as ddI. Does that cause lipoatrophy as well?

ED: You know, we have a lot less data. Most of the data we have with ddI is in combination with d4T, so it's really difficult to sort that out. I would assume that it might, based at least on the hypothesis that a lot of this is driven by changes in mitochondrial DNA. And looking at how these drugs interact with this DNA polymerase gamma, ddI probably does so more than abacavir and tenofovir. So it may very well contribute.

PS: And then you spoke about the clinical trials that have been done on the backbones, which most people start with either an NNRTI or a non-nuke protease inhibitor. And the two that have had the longest record of being on the NIH's list of preferred regimens for starting therapy, although now that list is more crowded. The first two were Sustiva and Kaletra. And there have been a couple of trials comparing those, and how they can create body changes. And what were the results of those?

ED: Yeah, so there was this study called ACTG 5142 that was presented earlier this year where they did a head-to-head comparison, it was the first one, of those two first-line options using nucleosides, any one of a variety of them, with either efavirenz or lopinavir/ritanovir. And part of that study, and I think it illustrates how important it is to the investigators to define this issue, was to do DEXA scans to quantitate the amount of subcutaneous fat in the entire population of 750 patients for up to 2 years. And the surprise in that study was that people who received nukes with efavirenz had greater loss of subcutaneous fat…

PS: Efavirenz is Sustiva…

ED: Sustiva, and a higher frequency of what they defined as lipoatrophy than the people who received similar nukes with lopinavir and ritanovir.

PS: Which is Kaletra.

ED: Which is Kaletra.

PS: A lot of patients are more familiar with the brand names these days. But there was kind of a tradeoff, because didn't the same trial show a slight viral load advantage for the Sustiva group?

ED: That's exactly right. So the primary endpoint really was looking at safety and efficacy comparing these first-line regimens and the reality is that both groups did extremely well, but statistically, the results favored the Sustiva group.

PS: For viral load?

ED: For viral load.

PS: But not for lipoatrophy?

ED: Not for lipoatrophy. But the other important observation is that the nucleosides are still contributing a great deal to what we see. And when they broke the analysis down based on whether you were receiving d4t with either of those drugs, AZT with either of those drugs or tenofovir, you could see that there was always a relationship that efavirenz had more lipoatrophy than lopinovir/ritanovir, Kaletra, but it was a much bigger effect in association with the nucleosides. And when you got down to tenofovir, the nucleoside that seems to have the least effect on subcutaneous fat, the number of individuals in the proportion that developed lipoatrophy in both groups was very small, even though it was higher in the efavirenz group.

PS: So most patients who were started on the most common Sustiva regimen now, which would be the once-a-day Atripla, they probably have very little to worry about on the lipoatrophy front because of the nucleoside backbone that's built in.

ED: I think that's right. I think overall the risks are very low and the majority of people probably won't suffer the consequences from that. And there's very nice data, including another presentation at this meeting, following people for up to three years, and one of the pivotal trials for tenofovir, the 934 study, showing a continued increase in the overall population of subcutaneous fat, in people who are on tenofovir and efavirenz. I think for people who aren't on tenofovir, these kinds of decisions and differences may be more important. And there may be a subset of individuals who are on tenofovir and efavirenz who may be developing lipoatrophy despite that. Where they may want to look at this kind of data to help guide decision-making in the future.

PS: Right. And was there any difference in the ACTG 5142 as far as… the people who got lipoatrophy, was there a relationship with their baseline CD4 count when they started the trial, or a CD4 nadir?

ED: Great question, because other cohort studies have suggested that there may be a relationship. I'm not aware of that analysis having been done.

PS: Finally, somebody asked a question afterwards, and there was some new data I guess, on some posters here. Is there any data yet comparing the various PIs, Kaletra, against other protease inhibitors, when it comes to lipoatrophy. Because now that NIH list is a little more crowded for what you can start with.

ED: Right. So there was one data set that was actually published late last year that looked at non-boosted atazanavir versus efavirenz.

PS: Reyataz…

ED: Reyataz. And showed no real difference as far as subcutaneous fat. It was 48 weeks of data. There's data here comparing Kaletra, lopinovir/ritanovir, and tipranavir/ritanovir, or Aptivus, showing that there was no difference. That both of them had an increase in the amount of subcutaneous fat and that there was no difference between the two groups. Again at 48 weeks. So I think there's reason to be optimistic that these effects may be consistent with other boosted protease inhibitors as well. I think the caveat is 48 weeks is a little bit early, because the observation is that everybody, no matter what they're on, first increases the amount of subcutaneous fat and then over time it gradually decreases. So it may be 48 weeks is a little bit early, but it's reassuring that this may extend to other drugs.

PS: We know the mechanism of why d4T and some of the other nukes cause lipoatrophy or we're pretty sure. Do we know why Sustiva had that effect?

ED: I think pretty sure is probably the best way to put it, because I don't think we know definitively. The mitochondrial hypothesis is certainly favored and more and more data supports it. I don't think we have a clue as to how or why NNRTIs may either interact with nucleosides or, in and of themselves, cause increases in subcutaneous fat loss. And that may be a new area for exploration.

PS: It was a real surprise and it obviously is gonna take more research. Finally, you probably prepared long for the discussion tonight, it was a great speech, but it was quite delayed. You had a front row seat to a little demonstration on the stage, which delayed tonight's talks, by some AIDS

activists obviously upset with Abbott, over, I guess, some access issues with Abbott's drugs in Thailand. You had a front row seat, what's your cut and dry opinion on that demonstration tonight.

ED: Well, I mean, I clearly don't know anything about the underlying issues, so I can't comment on that. But I must say that the activists were extremely professional. They were given some specific time at the beginning of the presentation to make a statement, they did so in an orderly fashion, they got to make their point to the audience when it was at its highest number and I think that we all appreciated that they then allowed the conference to go on.

PS: It was good that they allowed it to continue. I'm from the old-school ACT UP days, and sometimes we didn't do that. So it was great that everybody got a say tonight. And thank you for presenting your data.

ED: Thank you.

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