Transcript: HIV & Your Heart-Part I

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At the 15th Conference on Retroviruses and Opportunistic Infections (CROI) in Boston, David Evans talks with St. Luke's Roosevelt's Donald Kotler, MD about the role of inflammation in heart disease and surprising research on Ziagen and heart attacks. To see the video click here.

David Evans: Hi, I'm David Evans with POZ magazine and Aidsmeds.com at the 2008 Conference on Retroviruses and Opportunistic Infections in Boston Massachusetts. With me today is Dr. Donald Kotler who is the chief of gastroenterology at St. Luke's Roosevelt Hospital in New York City. And Dr. Kotler, I want to start off by talking about…in the SMART study, which we got the results from last year, roughly, we learned that people who stayed on therapy did better than people who went off and took treatment interruptions, particularly in terms of their heart health. There was some additional data presented more recently that talked about the role that inflammation may be playing. I'm wondering if you could tell us a little more about that; what are we learning about inflammation in people living with HIV and their heart?

Donald Kotler, MD: Thanks, good morning. Well, that's a very interesting question. Inflammation has been known for a long time to be related to cardiovascular (heart) disease. Taken at the most basic, people with autoimmune diseases like Rheumatoid arthritis or systemic lupus erythematosus, which are autoimmune diseases, inflammatory diseases, are associated with increased cardiovascular risk—even though there is no infectious agent, even though there is nothing other than inflammation. Well infections also lead to inflammation, so the idea that an infectious disease, over the long term, might be associated with cardiovascular risk, shouldn't be terribly surprising. More and more information, not just from the SMART study, does actually demonstrate inflammation increases cardiovascular risk. Exactly how it occurs is uncertain, but inflammation does increase the likelihood of blood to clot; it's call procoagulate activity. And clotting in a vessel is the mechanism by which you can clog a vessel and cause a heart attack or a stroke. That's related to but different from hardening of the arteries or build up of artherosclerotic plaque (artery clogging fat and calcium build-up). Now a number of studies on HIV have actually demonstrated increases in markers of both coagulation as well as markers o inflammation within the vessels. Even more, several studies at this meeting have shown that when people start antiviral therapy, those markers tend to diminish, the inflammation tends to diminish, and the markers of procoagulate activity tends to diminish as do markers of inflammatory activity. And it appears—not actually at this meeting, in Sydney over the summer there was an analysis of I believe it was 5142, or a sub study, of 5142, which looked at multiple different kinds of regimens; nucleoside-sparing, NNRTI-sparing, protease-sparing, and it appeared that no matter what

regimen you started, the markers of vascular disease and inflammation tended to diminish. It was not related to any specific antiviral; it was mostly related to a fall of viral load. So it's a generalized phenomenon: treating HIV with antivirals decreases viral load, decreases inflammation, and that may be related to cardio protection. To take it back to the SMART study, either staying on therapy or starting and stopping therapy, two things that happen when people stop therapy is that viral load comes back, inflammation comes back, and with it comes vascular, blood vessel changes that might lead to coagulation, clotting within the vessel, and in addition, the inflammation that occurs also lowers HDL level, which is the good cholesterol level, and that may also contribute to cardiovascular disease. So it appears that there's real science behind this, and what is new at least over the past year is that the role of inflammation seems to actually be detectable when you study it, and possibly even something that can be manipulated. To take one more second, in Sydney there was an abstract from Indiana University in which an anti-inflammatory agent was given to I believe treatment naive subjects (first time on antiretrovirals) subjects and led to an improvement in what's called flow-mediated dilatation, or vascular flow. At this meeting, the same group--Michael Dubé's group, Sumir Gupta's group--from Indiana University gave the drug pentoxifiline, a TNF (tumor necrosis factor) inhibitor, and anti-inflammatory agent; it was tried for other reasons in HIV and failed, a while ago, but was given in an experimental way and shown to improve vascular flow. It acts as an anti-inflammatory, and an anti-inflammatory itself might then have some kind of cardio protective effect.

DE: Going from HIV itself to the drugs we use to treat HIV, there were data presented at the conference that are leaving some people sort of surprise, puzzled, and sort of scratching their heads. And that was the finding out of the D:A:D study that people taking abacavir (Ziagen) of ddI (didanosine, Videx), may be at some increased risk of a heart attack. One of the things that is not necessarily being talked about as much is the difference between someone's actual risk of a heart attack and their relative risk in this particular study. Could you elaborate on that a little?

DK: Well I would have an easier time elaborating on relative versus absolute risk than I would trying to explain why abacavir and ddI seem to be bad for you. We've spent the last ten years thinking that it was Zerit (stavudine) and maybe zizovudine or AZT (Retrovir) that's bad for you, yet this study didn't find that; they found two other villains. The absolute risk of having a heart attack is just what is says: what's your chance of actually developing a heart attack. The relative risk is really a comparative risk; it's how much you're likely to have a heart attack compared to someone else, whether or not the risk is high or low. For example, the first time this came up in relationship to cardiovascular disease was in a paper that was authored by Judith Currier, from UCLA, who looked at the MediCal database and looked to see if there was an increased risk of having a myocardial infarction (heart attack) in HIV positives versus HIV negatives. A number of those studies came out between 2001 and 2005, and she did find evidence that there was some increased risk. But what she really found was that the relative increased risk occurred mostly in young women. Well young women hardly ever get heart attacks; so if you hardly ever get a heart attack, anyone that you see looks like a lot. Right?

DE: Right. One plus one equaling two is very different from fifty and fifty equaling one hundred.

DK: Give me a dollar and I'll be really happy with you, give Bill Gates a hundred dollars and he'll not even blink. So the relative risk is a comparative, whereas your actually risk just tells you what

your chances actually are. Like I said, the relative risk is often higher where the absolute risks are low. So now we have a study of D:A:D, which follows thirty or so thousand people, has been doing it for many years now, they have what they say is one hundred and sixty thousand patient years of follow up. So that's a lot of numbers to look at. And they've been looking at people in terms of all of their risk factors as well as the drugs—which drugs, how long, cumulatively, taking them now, not taking them now. And then they look for heart attacks. They found that abacavir almost doubled the risk of having a heart attack, and that ddI increased it by about fifty percent. Less of an increase, I should say, than smoking cigarettes, versus not smoking cigarettes. But sort of more than you'd really like to see. On the other hand, the number of heart attacks that they've seen, which is a little over five hundred, of this one hundred and sixty thousand years of patient follow up, comes out to about three per thousand years. Which is really what the general population has. So it's not high; relatively speaking, it sounds bad, but absolutely, it's not so very high. So the real question is, what do you do with that information? They were not able to show that there's a risk from Zerit, but I don't think anybody would say, "Better stop your abacavir and go back to taking Zerit." I mean that would be stupid. But I can't deny the data, because there were really smart people who looked very carefully and found it, and yet I really can't understand it, and I really can't explain why it would have occurred. The effect was seen for heart attack, but it wasn't seen for stroke. They presented heart attacks, but they didn't present who died. I mean, having a heart attack's not bad; having a heart attack and surviving it is okay. I had a heart attack and I survived it. And other than being humbled, I'm okay. You know, makes me work harder. So if they said that the death rate went up, that would be something I'd really be concerned about. If abacavir seems to cause some increased risk, it's concerning; somebody better figure out why, because they couldn't explain it—it wasn't because they had more diabetes, it wasn't because they had higher bad cholesterol or lower good cholesterol, or any of those other factors, and they couldn't find any reason to explain it. Yet it was there.
