PROJECT inform
Information, Inspiration and Advocacy for People Living with HIV/AIDS

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Mitochondrial Toxicity and Lactic Acidosis

Mitochondrial Toxicity

Mitochondrial toxicity and one of its symptoms called *lactic acidosis* have been highlighted recently as a previously undiagnosed side effect of anti-HIV drugs. Some researchers believe that *mitochondrial toxicity* contributes to the fat redistribution (lipodystrophy) associated with anti-HIV therapy. Although much more research is needed to fully understand this issue, this article explores the current thoughts about the connections among *mitochondrial toxicity*, *lactic acidosis* and lipodystrophy.

What Are Mitochondria?

Mitochondria are tiny rods found inside all human cells. Essentially, they are the cell's "power plants" and are also involved in the formation of protein and the processing of fat in cells.

Several things can affect how well mitochondria work. As people age, get an infection or take certain anti-HIV drugs, changes can occur in mitochondria. These changes, or mutations, may damage the mitochondria and either disrupt the normal function of the cells or cause them to stop working altogether.

Mitochondrial toxicity is a general term that refers to these changes. Perhaps more accurately, it is mitochondrial *damage*. It can cause different symptoms in the heart, nerves, muscles, pancreas, kidney, and liver (or perhaps anywhere it occurs), and it can also cause changes in lab tests.

How Anti-HIV Drugs Affect Mitochondria

Mitochondria need an enzyme called *polymerase gamma* to reproduce. Almost all nucleoside analogue drugs (NARTIs) such as 3TC (lamivudine, Epivir), AZT (zidovudine, Retrovir), abacavir (Ziagen), d4T (stavudine, Zerit), ddC (zalcitibine, HIVID), and ddI (didanosine, Videx) interfere with polymerase gamma to some degree. As a result, the NARTI class of drugs can block the production of new mitochondria, which then results in lower numbers of mitochondria and interference with their ability to function normally.

Among the nucleoside analogues, lab studies suggest ddC and ddI interfere the most with *polymerase gamma* followed by d4T. Lab studies also suggest that ddC and d4T are the strongest blockers of making new mitochondria (ddI wasn't studied). However, lab studies may not accurately predict what happens in the body. The other three nucleoside analogues are rather weak in this regard. It's not known whether using nucleoside analogues together interferes with this enzyme synergistically (where 1+1 = more than 2). At least one group of researchers claims d4T is most commonly related to mitochondrial toxicity in people, though others do not accept this finding.

What Are Common Results of Mitochondrial Toxicity?

Anti-HIV drug side effects linked to mitochondrial toxicity have been around for years. It has been brought into the limelight recently because of its growing incidence and its possible role in lipodystrophy. The reason for the higher rate may be due to people taking anti-HIV drugs longer. As a result, some once rare side effects are now more common. It is also possible that mitochondrial toxicity has always been present but was poorly diagnosed. Previous analysis, for example, may have focused only on the symptoms or conditions which resulted from mitochondrial toxicity.

Other more common conditions related to mitochondrial toxicity include myopathy (muscle cell destruction and weakness), peripheral neuropathy (numbness and tingling in fingers and toes) and pancreatitis (inflammation of the pancreas). Many common blood abnormalities are also thought to be related to this condition. These include thrombocytopenia (low levels of platelets), anemia (low levels of red blood cells) and neutropenia (low levels of neutrophils). All these problems have been seen since the earliest use of nucleoside analogue drugs for HIV.

All these conditions are reversible if diagnosed early and the offending therapy is stopped or the dose is reduced when appropriate. However, in some cases, especially when the condition is improperly diagnosed and not managed well, the condition might become irreversible.

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Mitochondrial Toxicity and Lactic Acidosis

Healthy cells normally produce *lactate*, a natural by-product when mitochondria process glucose and fat. The body routinely clears itself of lactate through normal body functions. However, mitochondrial toxicity can create abnormally high levels of lactate in the cells. This, in turn, can lead to *lactic acidosis*, a life-threatening condition caused by too much lactate.

In early stages of lactic acidosis, people experience shortness of breath, nausea, vomiting and pain in the gut. At later stages (lactate levels over 5mmol/liter), it can lead to widespread loss of energy in the cells and cause organ failure and a high risk of death. In the past, such conditions may have simply been attributed to AIDS.

What Is Fatty Liver?

One of the more serious conditions linked to mitochondrial toxicity is "fatty liver," or *hepatic steatosis*. This build-up of fat around the liver can affect the way it processes fats. *Hepatic steatosis* often also leads to *lactic acidosis*, as described earlier.

People who weigh over 70kgs or about 150 pounds—especially women—may be more at risk for developing *hepatic steatosis* and, as a result, *lactic acidosis*. It is currently not a part of standard of care to measure lactate levels so this condition may go unnoticed. To further complicate matters, lactate breaks down rapidly when not stored properly, and only certain labs can accurately measure these levels.

Mitochondrial Toxicity and Lipodystrophy

Contrary to early reports that only protease inhibitors were associated with changes in body composition, there are now many reports showing that people taking only nucleoside analogue drugs develop lipodystrophy (read Project Inform's *Lipodystrophy Discussion Paper*). Until recently, research may have overlooked the fact that protease inhibitor use almost always includes use of nucleoside analogue drugs.

Moreover, different patterns of fat redistribution consistent with symptoms of mitochondrial toxicity have been seen among people only on nucleoside analogue drugs compared to people on protease inhibitors along with nucleoside analogue drugs. There are very little data available about people who use protease inhibitors without nucleoside analogue drugs. These theories and questions are being actively investigated and more information should be available soon.

Reducing the Risk of Mitochondrial Toxicity?

The best thing you can do is to recognize the potential of the drugs you take to contribute to this condition. Also, pay attention to your body for these side effects. Talk to your doctor about getting accurate lab tests to check changes in your lactate levels. Again, since these tests are not part of standard of care, they may be difficult to get or have covered by health insurance.

Beyond that, the only tested approach is to reduce the dose or stop using nucleoside analogue therapy. However, this is usually done after mitochondrial toxicity occurs and symptoms develop. Research needs to be quickly started to test combination drug regimens that don't include using nucleoside analogue drugs or use versions that cause less mitochondrial toxicity. To date, the only such combination tested to a significant degree is ritonavir + saquinavir.

Other approaches need to be tested to correct mitochondrial toxicity. At least one researcher has suggested testing the supplements coenzyme Q10, L-carnitine and riboflavin. Furthermore, lab studies suggest that some nucleoside analogue drugs in development, like Fd4C, may be less likely to cause mitochondrial toxicity. They may actually prevent it from developing when used with other nucleoside analogue drugs.