Mitochondrial toxicity and lactic acidosis

*Mitochondrial toxicity* and one of its symptoms called *lactic acidosis* can become an unwanted side effect of some HIV drugs. Some researchers believe that mitochondrial toxicity contributes to how your body processes fats, which may lead to other conditions including *lipodystrophy*. Much of the study on this condition was done in the 1990s on older HIV drugs, and may not apply to the same degree as more recently developed drugs. This publication explores the connections among these 3 conditions.

**What are mitochondria?**
Mitochondria are tiny rods found inside all human cells. Essentially, they’re the cell’s “power plants” and also help form proteins and process fats inside cells.

Several things can affect how well mitochondria work. As people age, get an infection or take certain 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). It can also cause changes in lab tests.

**How HIV drugs affect mitochondria**
Mitochondria need an enzyme called *polymerase gamma* to reproduce. Almost all nucleoside analog drugs (NRTIs) interfere with this enzyme to some degree. As a result, NRTIs can block the production of new mitochondria, which results in fewer mitochondria and how well they function.

Among the NRTIs, lab studies suggest Videx (didanosine, ddl) interferes the most with the enzyme, followed by Zerit (stavudine, d4T). Lab studies also suggest that stavudine is the strongest blocker of making new mitochondria.

However, lab studies may not accurately predict what happens in the body. Most of the other NRTIs are rather weak in this regard. It’s also not known whether using NRTIs together interferes with this enzyme *synergistically* (where 1+1 = more than 2).

Early results from a small study show in the mid-90s that people on NRTIs have fewer mitochondria in cells compared to HIV-positive people not taking NRTIs or HIV-negative people. Fewer mitochondria were only seen among people taking stavudine and not among people on other NRTIs. The average number of mitochondria decreased by 44%. One interesting but unexplained observation was that people with fat loss in the face, arms or legs (*lipodystrophy*) had fewer mitochondria while people who developed a buffalo hump had an increased number.

Another study also looked at the number of mitochondria in cells. Forty people participated, 10 with fat wasting (group A), 10 without signs of body fat changes (B), 10 never on HIV therapy (C) and 10 HIV-negative people (D). The number of mitochondria was looked at from tissue samples from the back of the neck, abdomen and mid-thigh.

The study found that people in group A had fewer than those in group B who, in turn, had fewer mitochondria than groups C or D. No differ-
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In the number of mitochondria were found in cells between groups C or D. This study suggests that fewer mitochondria result from HIV therapy and not HIV disease itself.

What are the common results of mitochondrial toxicity?

HIV drug side effects linked to this condition have been around for years. Its incidence is likely due to people taking certain classes of HIV drugs and taking them over time.

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

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 may be irreversible.

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

In its early stages, people experience shortness of breath, nausea, vomiting and pain in the gut. At later stages (lactate levels over 5mmol/liter), it can lead to organ failure and a high risk of death.

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. The condition often also leads to lactic acidosis, as described earlier.

People who weigh about 150 pounds (over 70kgs)—especially women—may be more at risk for developing hepatic steatosis. However, routine tests to check lactate levels can help prevent this and other conditions.

Mitochondrial toxicity and lipodystrophy

Contrary to early reports that only protease inhibitors were linked to body shape changes, reports now show that people taking only NRTIs develop lipodystrophy. Research may have overlooked the fact that many protease inhibitor regimens also included NRTIs. Very little are data available about people who use protease inhibitors without NRTIs. These theories and questions are being investigated.

Lowering your 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 symptoms. Talk to your doctor about getting accurate lab tests to check lactate levels. Beyond that, changing your HIV meds to ones that are less likely to cause mitochondrial toxicity may also help.

Other publications that may help

Dealing with Drug Side Effects

www.projectinform.org/publications/sideeffects/