

# Mitochondrial Dysfunction: Patient Monitoring and Toxicity Management

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**Summary:** Mitochondrial toxicity has been implicated in the development of a variety of nucleoside reverse transcriptase inhibitor-associated syndromes. Mitochondrial damage and decreases in mitochondrial DNA levels have been demonstrated in various tissues of patients treated with NRTIs, especially in conjunction with exposure to stavudine. Clinical syndromes that may be mediated by mitochondrial toxicity include hyperlactatemia and lactic acidosis, hepatic steatosis, lipoatrophy, peripheral neuropathy, HIV-associated neuromuscular weakness syndrome, pancreatitis, skeletal myopathies, and cardiomyopathy. Early recognition of these syndromes in their mild forms involves close monitoring and a high index of suspicion. This may allow prompt discontinuation of the causative agent(s) and initiation of appropriate therapeutic measures, thereby increasing the chances of reversibility of the syndrome.

**Key Words:** mitochondrial toxicity, NRTIs, antiretroviral safety, drug tolerability

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## BACKGROUND

The first reports of mitochondrial dysfunction appeared in the early 1990s, with the observation of lactic acidosis and hepatic steatosis in patients treated with zidovudine (ZDV), didanosine (ddI), and stavudine (d4T).<sup>1–3</sup> In 1995, a phase 2 clinical study of the nucleoside analogue fialuridine, being tested by the National Institutes of Health for treatment of hepatitis B, was prematurely terminated because of high rates of fatal lactic acidosis and hepatic steatosis in patients exposed to the agent.<sup>4</sup> Further study during the late 1990s and 2000 increased the appreciation of the wide spectrum of symptoms associated with hyperlactatemia, including a milder syndrome of symptomatic hyperlactatemia as well as compensated asymptomatic disease.

Proposed clinical manifestations of mitochondrial toxicity associated with different NRTIs are listed in Table 1. In

addition to hyperlactatemia and lactic acidosis, these include body habitus changes such as lipoatrophy, peripheral neuropathy, HIV-associated neuromuscular weakness syndrome (HANWS), pancreatitis, hepatic steatosis, skeletal myopathies, cardiomyopathies, and adverse effects on maternal and fetal health.

Mitochondria are the energy powerhouses of the cell. These organelles contain their own DNA. Dysfunctional mitochondria produce insufficient amounts of ATP, leading to tissue and organ dysfunction and increased lactate levels. Nucleoside reverse transcriptase inhibitors (NRTIs) have been shown to inhibit mitochondrial DNA (mtDNA) polymerase gamma, an enzyme important to the synthesis of mtDNA.<sup>3,5</sup> Thus, NRTIs as a class inhibit mtDNA synthesis but to variable extents. A hierarchy has been noted with respect to the in vitro inhibition of mtDNA polymerase gamma, with zalcitabine (ddC) exhibiting the greatest degree of inhibition, followed in decreasing order by ddI, d4T, ZDV, and finally lamivudine (3TC), abacavir (ABC), emtricitabine (FTC), and tenofovir DF (TDF), which appear to exert minimal inhibition of mtDNA polymerase gamma.

Exposure of skeletal muscle cells to different NRTIs in vitro has been shown to produce varying effects on mtDNA.<sup>3</sup> As indicated in Figure 1, TDF, ABC, and 3TC had very little impact on mtDNA. In contrast, ddC and ddI had the greatest effects on mtDNA. Although the amount of mtDNA toxicity shown with d4T in this in vitro experiment does not provide sufficient evidence to link it to clinical mitochondrial toxicity, d4T has been associated with clinical manifestations of mitochondrial toxicity in numerous studies. ZDV did not appear to affect mtDNA in the same experiment, although it was associated with concentration-dependent increases in lactate production.<sup>3</sup> These observations leave open the possibility that NRTIs may produce mitochondrial toxicity through mechanisms other than depletion of mtDNA, an idea that has been suggested in other studies.<sup>6,7</sup>

Investigators have also assessed mtDNA in peripheral blood as a noninvasive marker of mitochondrial toxicity. Côté et al.<sup>8</sup> noted that HIV-negative subjects have a higher ratio of mtDNA to nuclear DNA in peripheral blood mononuclear cells (PBMCs) than HIV-positive patients never exposed to antiretroviral therapy (ART). In this study, the ratio was further de-

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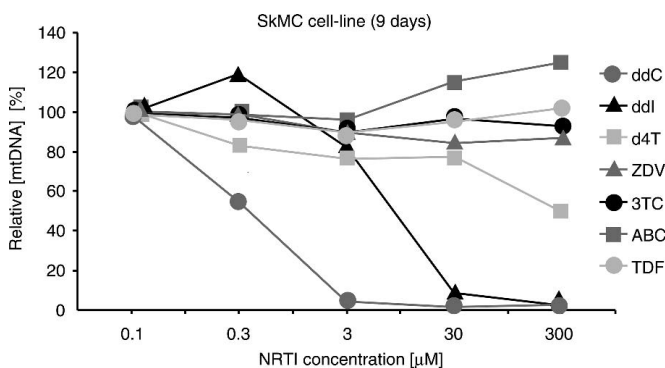
**TABLE 1.** Proposed Clinical Manifestations of Mitochondrial Toxicity

|  |   |
|--|---|
| • Hyperlactatemia/lactic acidosis: d4T > ddl > ZDV > other NRTIs | • Pancreatitis: ddl > d4T                             |
| • Lipoatrophy: d4T > ZDV > other NRTIs                           | • Hepatic steatosis: d4T > other NRTIs                |
| • Peripheral neuropathy: ddC > d4T > ddl                         | • Skeletal myopathy/cardiomyopathy: ZDV               |
| • HANWS: ?d4T > other NRTIs                                      | • Adverse effects on maternal/fetal health: d4T + ddl |

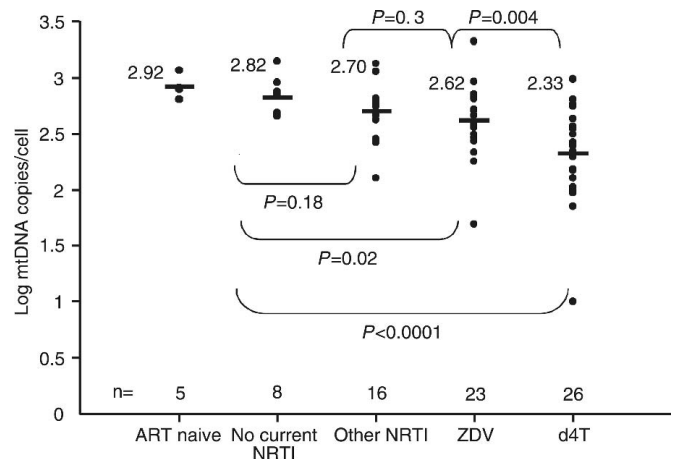
creased in HIV-positive patients on ART. Those who interrupted treatment had ratios comparable to HIV-infected ART-naive individuals. Cherry et al.<sup>9</sup> also assessed mtDNA content in the PBMCs of ART-naive patients, those treated with NRTIs in the past, and those currently receiving treatment with d4T, ZDV, or other NRTIs. They found no significant depletion of PBMC mtDNA in any of the treatment groups. However, when mtDNA content in limb fat was analyzed, a significant depletion was seen in patients treated with d4T (Fig. 2). A lesser, but statistically significant, depletion was observed in patients receiving ZDV treatment. It is important to note that d4T-treated subjects had statistically significant mtDNA depletion compared with ZDV-treated patients.

**ADIPOSE TISSUE EFFECTS AND LIPOATROPHY**

Evidence suggests that the lipoatrophy seen in HIV-infected patients on ART is at least partly due to mitochondrial toxicity. Several studies have reported data pointing toward apoptosis as the main mechanism mediating lipoatrophy.<sup>10-13</sup> Histopathologic analysis revealed adipocyte loss in association with lipogranulomata as well as increased variability in



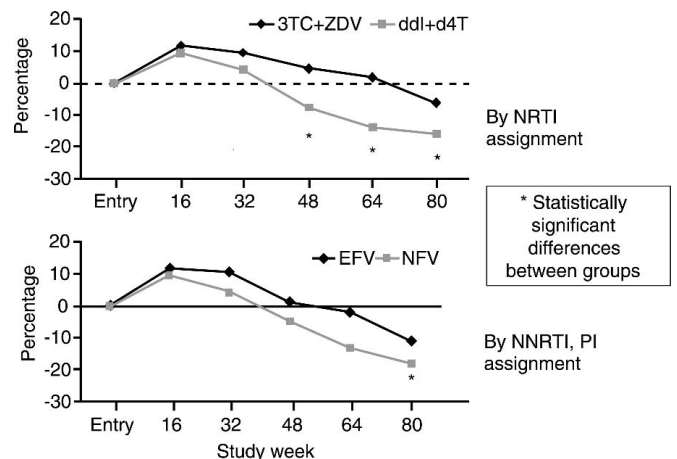
**FIGURE 1.** Mitochondrial toxicity in human cells.<sup>3</sup> Adapted with permission. SkMC, skeletal muscle cells; ZDV, zidovudine; 3TC, lamivudine; ABC, abacavir.



**FIGURE 2.** mtDNA levels in limb fat by NRTI treatment.<sup>9</sup>

adipocyte size in patients with lipoatrophy. Identical features were observed in the presence or absence of protease inhibitor (PI) therapy, suggesting that PIs may not affect this parameter. In fact, in one study of patients with lipoatrophy, no significant difference in apoptotic indices was found between those continuing treatment with PI-based therapy involving indinavir and those who switched to a non-NRTI (NNRTI)-based treatment with nevirapine.<sup>12</sup> In contrast, switching from d4T to either ZDV or ABC is associated with an improvement in adipose tissue cell apoptosis.<sup>13</sup>

In a trend also noted in other studies, a metabolic sub-study of the AIDS Clinical Trials Group (ACTG) 384 trial found that HIV-infected patients who begin ART, regardless of the regimen, initially gain limb fat in the upper and lower extremities.<sup>14</sup> The ACTG 384 study compared the nucleoside backbones of 3TC/ZDV and d4T + ddI plus efavirenz (EFV),

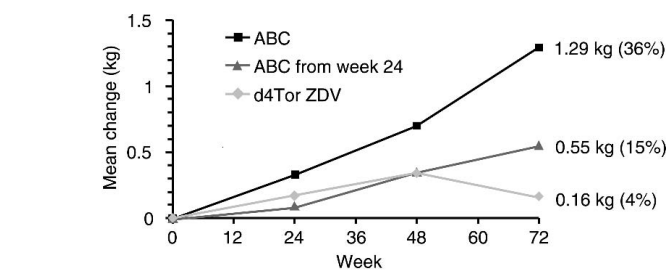


**FIGURE 3.** Median percentage change in limb fat by NRTI and PI assignment in the ACTG 384 metabolic substudy, 5005s.<sup>14</sup>

nelfinavir (NFV), or both. Increases in limb fat were observed in the first 16 weeks of therapy in both arms. Patients treated with d4T + ddI manifested a greater degree of limb fat loss at weeks 48–60 than patients treated with 3TC/ZDV (Fig. 3). Patients on NFV also had a significantly greater decrease in limb fat compared with those on EFV. Similar reports of more deleterious fat loss associated with the combination of d4T + ddI were found using skinfold measurements in a metabolic substudy of the Flexible Initial Retrovirus Suppressive Therapies (FIRST) Study, CPCRA058.<sup>15</sup> In this study, investigators used anthropometric measurements such as skinfolds and body circumferences to gauge the effects of treatment with a first antiretroviral regimen containing d4T + ddI or ABC + 3TC. At long-term follow-up (32 months), peripheral and central subcutaneous fat loss were significantly greater in patients treated with d4T + ddI than with ABC + 3TC. There was no evidence of subcutaneous fat loss in the ABC + 3TC group compared with baseline values.

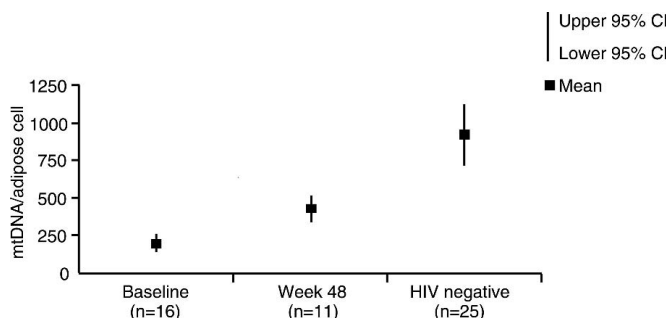
Mallon et al.<sup>16</sup> reported the results of a study investigating the effect of NRTIs on adipocyte tissue in a group of healthy volunteers. In this study, expression of peroxisome proliferator activated receptor (PPAR) gamma and 3 mitochondrial function genes were significantly decreased after 2 weeks of NRTI therapy. This study indicates a significant and acute effect of NRTIs on adipose tissue, even without the possible confounding effect of HIV infection.

Hammond et al.<sup>17</sup> have observed an association between mtDNA depletion and altered adipocyte function. The investigators assessed mitochondrial enzyme activity in the adipocytes of 7 patients starting treatment with NRTI-containing regimens. Within 6–12 months of beginning treatment, the patients demonstrated a reduction in mtDNA content and evidence of cellular toxicity. In addition, the amount of mitochondrial enzyme cytochrome c oxidase (COX) activity was significantly reduced compared with baseline values. This decrease in COX activity correlated positively with mtDNA levels. Moreover, 3 of the patients in this study had reduced expression of COX subunit I.



|    |             |    |    |    |    |
|----|-------------|----|----|----|----|
| n= | ABC         | 47 | 42 | 35 | 33 |
|    | ABC week 24 | 23 | 19 | 15 | 13 |
|    | d4T or ZDV  | 29 | 25 | 22 | 19 |

**FIGURE 4.** Changes in limb fat over 18 months in the MITOX (mitochondrial toxicity) study.<sup>18</sup>



**FIGURE 5.** Change in mtDNA in the adipose tissue of subjects with lipoatrophy after switching from d4T to ABC or ZDV.<sup>19</sup>

In contrast to the lack of improvement associated with discontinuation of PIs, several studies have demonstrated improvement in lipoatrophy with NRTI switches. Limb fat improved at week 72 following a switch from d4T or ZDV to ABC in patients with evidence of lipoatrophy in the MITOX (mitochondrial toxicity) study.<sup>18</sup> An analysis at 24 weeks found a modest increase in limb fat in patients who switched from thymidine analogue treatment to ABC, although this difference was not clinically apparent. However, improvement in lipoatrophy continued 2 years after the switch (Fig. 4).

Clinical improvement in fat loss was also demonstrated at 48 weeks in a subset of the ESS40010 study that involved 16 patients with lipoatrophy on d4T-containing regimens who switched to ABC or ZDV.<sup>19</sup> In addition to improvements in dual-energy x-ray absorptiometry (DEXA) scores, fat biopsies of these patients demonstrated a significant increase in fat mtDNA that correlated with the clinical improvement in fat loss (Fig. 5). At baseline, mtDNA levels were lower in the study patients than in HIV-negative controls. At 48 weeks, mtDNA levels in the patients remained below the level observed in HIV-negative controls, suggesting either an effect of HIV itself or that 48 weeks may not be a sufficient duration to reverse mtDNA depletion completely. The improvements in body fat, mtDNA, and adipocyte apoptosis 48 weeks after patients switched from d4T to ABC or ZDV did not appear to be dependent on cellular cytokine mRNA levels in fat.<sup>20</sup> Despite the improvements in arm, leg, and trunk fat, there was little or no change in intracellular levels of cytokine mRNA. These findings suggest that the NRTI effects on peripheral fat are unrelated to cytokine dysregulation. Adipocyte apoptosis declined in the 10 patients analyzed for this parameter following discontinuation of d4T. In fact, at 48 weeks, there was no significant difference in fat apoptosis between these patients and HIV-negative controls. Anthropometric measurements did not correlate with changes in DEXA and CT scan findings following the switch, indicating that anthropometric measurements may not be sensitive enough to detect and quantify changes in fat in lipoatrophic patients. Elevated lactate levels also improved in ESS40010 study patients following the switch from d4T to ABC or ZDV.<sup>21</sup>

**PERIPHERAL NEUROPATHY**

Peripheral neuropathy associated with NRTI use may also involve mitochondrial toxicity. Patients initially randomly allocated to receive d4T + ddI in the ACTG 384 study demonstrated a greater rate of peripheral neuropathy (20%) compared with patients randomly allocated to 3TC/ZDV (<5%).<sup>22,23</sup>

Moore et al.<sup>24</sup> analyzed >1100 patients from the Johns Hopkins AIDS Service to identify risk factors for peripheral neuropathy. The risk of neuropathy was found to be additive and possibly even synergistic for the combination of d4T + ddI + hydroxyurea (HU) compared with ddI alone, d4T alone, and d4T + ddI in combination. The relative risk of peripheral neuropathy was approximately 3.5-fold higher for the d4T + ddI combination than for ddI alone (Table 2). Non-drug-related factors also found to be associated with an increased risk of peripheral neuropathy were a lower baseline CD4 cell count, a history of non-drug-associated peripheral neuropathy, and age >40 years.

When a patient presents with peripheral neuropathy, it is important to exclude other possible causes or contributing factors, such as cytomegalovirus infection, syphilis, vitamin B<sub>12</sub> deficiency, thyroid dysfunction, diabetes mellitus, alcoholism, and use of other neurotoxic agents. HIV disease itself may also cause peripheral neuropathy. Once other causes are ruled out, management of NRTI-associated peripheral neuropathy may involve discontinuation or dose reduction of the responsible agent, although there is a lack of data on the efficacy of the latter management strategy. Even after the drug is stopped, a substantial proportion of patients may continue to experience chronic pain. Treatment of symptomatic peripheral neuropathy may include the use of ibuprofen, acetaminophen, tricyclic antidepressants such as nortriptyline and amitriptyline, anti-convulsants such as lamotrigine and gabapentin, topical lidocaine and capsaicin, narcotics for refractory pain, acupuncture, and nerve growth factors.

**HIV-ASSOCIATED NEUROMUSCULAR WEAKNESS SYNDROME**

Another neurologic condition that may be caused by NRTI-associated mitochondrial toxicity is HANWS. This syn-

drome presents with rapidly progressive severe neuromuscular weakness associated in most cases with hyperlactatemia. It has been described in 69 patients receiving NRTIs, 61 of whom were on d4T-containing regimens.<sup>25</sup> Neurologic features observed in these patients included ascending paresis in 100%, sensory symptoms in 32%, areflexia in 17%, and bulbar symptoms in 12%. Outcomes reported for 44 of these patients indicated that 16 recovered, 19 had residual weakness requiring the use of a wheelchair after 6 months, and 9 died, generally as a result of lactic acidosis and multiorgan failure. For many of the patients who died, a causal connection to NRTIs was not recognized and the NRTIs had not been stopped.

**HYPERLACTATEMIA**

Hyperlactatemia observed in NRTI-treated patients ranges from an asymptomatic condition to severe lactic acidosis. The clinical significance of asymptomatic hyperlactatemia is unclear. When lactate is collected properly, up to 8% of patients may have elevated levels without manifesting symptoms. In contrast, lactic acidosis is rare, rapidly progressive, and life threatening. Risk factors for the development of hyperlactatemia are female sex, obesity, hepatitis C virus infection, pregnancy, low CD4 nadir, renal insufficiency, and intercurrent illness.<sup>26,27</sup>

A study assessing the natural history of sustained hyperlactatemia in 396 HIV-infected patients revealed that 22 of 385 patients (6%) had elevated baseline levels of lactate.<sup>28</sup> A total of 299 patients underwent serial lactate testing with a median of 4 lactate measurements per patient over 24 months. Baseline cholesterol and current d4T use were the only predictors of elevated lactate. Lactate levels were not found to correlate with lipotrophy. Of 16 patients who demonstrated sustained hyperlactatemia during the study, 12 remained asymptomatic for a median of 210 days, and 4 developed symptoms consistent with lactic acidosis syndrome. One of these 4 subjects had normal lactate levels within 2 months of the onset of symptoms. Based on these findings, the investigators concluded that lactate levels should not be drawn routinely in asymptomatic patients on NRTI therapy. In addition, it is not necessary to discontinue or switch NRTIs in patients who have asymptomatic hyperlactatemia.

In another study, lactate levels improved after the switch in therapy in patients with lipotrophy whose plasma HIV RNA was undetectable at the time of the switch.<sup>29</sup> In this study 30 patients switched from d4T to TDF; all other drugs in the regimen remained unchanged. Following the switch, venous lactate levels progressively decreased, with the most substantial drop occurring in patients with elevated baseline lactate readings. Fasting cholesterol and fasting triglycerides decreased significantly (*P* < 0.05), with the greatest reduction seen in the first month following the switch. Levels of mtDNA in PBMCs rose at 12 weeks and decreased somewhat at 24 weeks but remained above baseline values. There were no dis-

**TABLE 2.** NARTI Combinations and Peripheral Neuropathy<sup>24</sup>  
Adjusted Hazard Ratios

| Variable                 | Hazard Ratio | 95% CI     | P value |
|--------------------------|--------------|------------|---------|
| ddI (n = 410)            | 1.0          | —          | —       |
| d4T (n = 699)            | 1.39         | 0.84, 2.32 | 0.20    |
| ddI + HU (n = 89)        | 2.35         | 0.69, 8.07 | 0.18    |
| ddI + d4T (n = 166)      | 3.50         | 1.81, 6.77 | 0.001   |
| ddI + d4T + HU (n = 128) | 7.80         | 3.92, 15.5 | 0.0001  |

continuations due to adverse events, and 1 patient on TDF + ABC + 3TC experienced virologic failure.

The majority of patients who have symptomatic hyperlactatemia initially manifest nonspecific symptoms, making diagnosis challenging. Common symptoms include fatigue; gastrointestinal effects such as nausea, vomiting, abdominal pain, anorexia, and weight loss; and neurologic effects such as myalgia, arthralgia, and paresthesia.<sup>30,31</sup> Dyspnea is usually a late compensatory manifestation reflecting the presence of metabolic acidosis. Patients with symptomatic hyperlactatemia typically have hepatic steatosis with mildly elevated liver transaminases. Although elevated, lactate levels are generally <5 mM, and there are no or mild acid-base abnormalities. The timing of symptom onset can sometimes help differentiate symptomatic hyperlactatemia from other drug-related side effects: Patients typically present after several months of therapy, following resolution of the initial side effects associated with antiretroviral therapy.

Treatment of symptomatic hyperlactatemia and lactic acidosis involves immediate discontinuation of ART. Patients who are more severely ill may require supportive care in the intensive care unit and hemodialysis to replace bicarbonate and improve acidosis. Patients often develop respiratory failure due to the severe acidosis and require ventilation. In addition, treatment with agents such as L-carnitine, thiamine, riboflavin, coenzyme Q10, and antioxidants has been advocated. However, these agents have not been proven effective in clinical trials.<sup>30</sup> Even after discontinuation of NRTIs, resolution of hyperlactatemia may take 3–6 months.

Following recovery from symptomatic hyperlactatemia, rechallenge with an NRTI-sparing regimen remains the safest option. However, results of a recent study of 12 patients rechallenged with an alternative NRTI-containing regimen after NRTI-related symptomatic hyperlactatemia or lactic acidosis showed promise.<sup>32</sup> Nucleosides at the time of symptomatic hyperlactatemia/lactic acidosis diagnosis included d4T + 3TC in 6 patients, d4T + ddI in 4 patients, and d4T + ABC in 2 patients. The median peak lactate level in patients on these regimens was 5.4 mM. After an extended period with no ART, new regimens were initiated. The new regimens included ABC + 3TC in 5 patients, 3TC/ZDV in 2 patients, and ABC/3TC/ZDV in 5 patients. The median lactate level following rechallenge with the new regimens was 1.9 mM. Symptoms recurred in only 1 patient, who was rechallenged with triple-NRTI therapy. Thus, for patients who developed symptomatic hyperlactatemia or lactic acidosis on a regimen containing d4T with or without ddI, and who may not have the option of using an NRTI-sparing regimen, an alternative approach that may prove effective is rechallenge with an NRTI-containing regimen that avoids d4T, ddI, and possibly ZDV. For patients with mild symptomatic hyperlactatemia, a switch in NRTIs without a treatment interruption may be possible.

## CONCLUSIONS

NRTIs can cause various highly tissue-specific syndromes linked to mitochondrial toxicity. Clinical syndromes mediated by mitochondrial toxicity include hyperlactatemia and lactic acidosis, lipoatrophy, peripheral nephropathy, HANWS, and hepatic steatosis. Noninvasive methods for longitudinal monitoring, including lactate and blood mtDNA levels, have not proven useful. Close monitoring for these syndromes requires a tissue-specific approach. Early recognition of mild or subclinical disease phenotypes, especially neuropathy and lipoatrophy, increases the likelihood that these syndromes will be reversible with appropriate management, which includes discontinuation of the offending agents.

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