

METABOLIC DISTURBANCES ASSOCIATED WITH ANTIRETROVIRAL THERAPY AND HIV INFECTION

Des Martin, MB ChB, MMed, FCPATH, DTM&H, DPH
Toga Laboratories, and University of the Witwatersrand

With the increasing use of antiretroviral (ARV) drugs, some of the long-term effects of the use of these agents are now being recognised. Whereas in the first instance ARVs were blamed for the causation of these abnormalities, it is to be noted that similar abnormalities have been reported in patients who have not used ARVs at all.

The pathogenesis of these metabolic disturbances is ill understood and probably represents a complex interaction between HIV infection itself, use of antiretroviral therapy (ART) and the immune reconstitution effects consequent upon ART. Another factor that has impacted on the confusion relating to metabolic disturbances is the absence of universally accepted and clear-cut definitions of these disturbances.

When metabolic disturbances were first reported the protease inhibitors (PIs) appeared to be associated co-factors, but recent experience has shown that these disorders have been reported with nucleoside reverse transcriptase inhibitors (NRTIs).

There has been an attempt to classify metabolic disturbances in the developed world, but no such attempt has been made in the African setting.

The major metabolic abnormalities that have been reported are:

- serum lipid abnormalities
- maldistribution of body fat
- disturbances of glucose metabolism
- lactic acidemia
- reductions in bone mineral density.

LIPODYSTROPHY SYNDROME

Clinical features:

- Peripheral lipotrophy
 - more common in men
 - distribution: face, arms, legs and buttocks.
- Central fat accumulation
 - more common in women

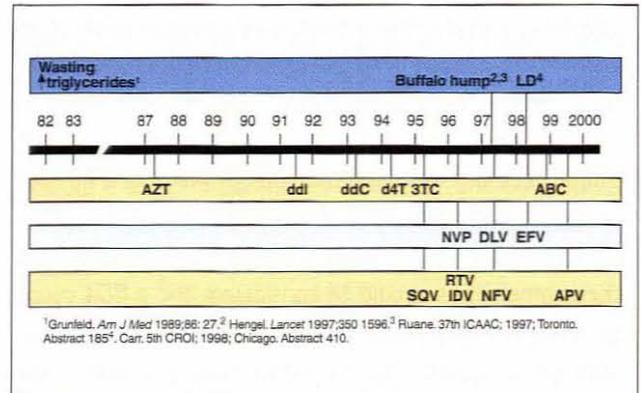


Fig. 1. History of ARV usage and initial reports of lipodystrophy.

- distribution: intra-abdominal, dorsocervical spine, breasts and lipomas.

Metabolic features:

Lipid abnormalities

- hypertriglyceridaemia
- hypercholesterolaemia.

Insulin resistance

- Increased insulin, C-peptide
- Impaired glucose tolerance and type 2 diabetes mellitus.

Lactic acidemia.

Parameters for measuring clinical lipodystrophy:

- clinical examination
- patient reporting
- laboratory tests
- anthropometric measures
- dual energy x-ray absorptometry (DEXA) scan
- CT scans for visceral fat and mid-thigh measures.

THERAPY FOR LIPODYSTROPHY

Therapy has been largely unsatisfactory to date, but includes:

- Lifestyle changes
 - exercise
 - diet.
- Lipid-lowering agents

statins
fibrates.

- Drugs
growth hormone
anabolic steroids
dietary supplements
L-carnitine.
- Hypoglycaemic agents
metformin.
- Surgery
liposuction
plastic surgery.
- Switching ART.

Studies have been performed to investigate the merits of switching therapies, but reports generally show some biochemical improvement but very little morphological change in established lipodystrophy. For example, substituting nevirapine for a PI results in improvement of cholesterol and triglyceride but no significant improvement in body shape.

REDUCED BONE MINERAL DENSITY

The osteopenia associated with PI therapy, of which there is increasing evidence, is thought to be due to increased bone turnover and subsequent decreased bone density. Bone mineral density reduction is also associated with, and may result from, lactic acidosis. Low-density lipoprotein (LDL) oxidation has been shown to impair osteoblastic function. In addition, PIs inhibit alpha-hydroxylase which impairs bioactivation of vitamin D 25 OH.

It is important to note that osteopenia is also found in untreated HIV infection, although this has not as yet been well documented.

In a study of a group of 72 HIV-infected patients (mean CD4+ count 375, mean viral load 3.6 log) who had DEXA scans, 64% were found to have a reduced bone mineral density T score and 50% a reduced Z score. Eight per cent were found to have osteoporotic lumbar spines. The most likely risk factor associated with osteoporosis was identified as prior antiretroviral use.

LACTIC ACIDOSIS

Lactic acidosis is one of the most severe and life-threatening side-effects of NRTI therapy, and several cases have been reported in the last few years.^{1,2} To date this condition has been shown to occur in patients receiving AZT, ddI or d4T. In 1997 Dr Kees Brinkman described the condition in an Ethiopian patient who had been treated with NRTIs. Despite intensive care, the patient died and Brinkman concluded that only mitochondrial dysfunction

could have accounted for the patient's biochemical parameters.³

The incidence is reported to be approximately 1.3 per 1 000 person-years.⁴

Symptoms include:

- episodes of malaise
- nausea and vomiting with abdominal pain, and
- hyperventilation due to the acidosis.

The symptoms are accompanied by:

- lactic acidemia
- increased ratios of lactate/pyruvate
- β -hydroxybutyrate/acetoacetate.

MITOCHONDRIAL MALFUNCTION

ROLE OF NRTIs

There have been few reported cases of hereditary mitochondrial diseases in HIV-infected patients. A number of manifestations of hereditary mitochondrial diseases overlap with classic side-effects of nucleoside analogues, particularly the following neurological disorders:

- peripheral neuropathy and dementia
- muscular complications including hypotonia
- myopathy and cardiomyopathy
- hepatocellular manifestations such as steatosis and lactic acidosis
- pancreatitis
- pancytopenias
- renal problems.

ROLE OF DNA POLYMERASE

Human cellular DNA contains polymerase- γ . HIV contains its own polymerase known as reverse transcriptase.

NRTIs are triphosphorylated intracellularly to nucleotides. They are then preferentially incorporated into the growing DNA chain by HIV reverse transcriptase. As they lack the hydroxyl group needed for further chain growth, the NRTIs inhibit DNA elongation. These nucleotides can be mistaken for natural substrates by polymerase- γ and in turn may irreparably damage mtDNA during replication. Other cellular DNA polymerases involved in nuclear DNA replication are not inhibited by NRTIs.

NRTIs vary in their specificity for polymerase- γ . DdC > d4T > ddI = AZT = 3TC (based on an examination of drug concentrations needed to inhibit mtDNA synthesis by 50% in cell cultures). This variation of potency of NRTIs against mitochondrial DNA was demonstrated in a Burroughs Wellcome study published in 1994.

NRTI-related lactic acidosis begins with disturbances in the

polymerase- γ and mtDNA synthesis. These changes are accompanied by impairment of the oxidative phosphorylation system together with a shift in the redox state (increased NADH/NAD⁺ ratio). This results in a shift in the Krebs cycle, particularly the pyruvate/lactate equilibrium, whereby excess lactic acid is generated and accumulates within the cell, along with a build-up of triglycerides and fatty acids.

Note that *NNRTI agents* do not bind to DNA pol- γ .

ORGAN-SPECIFIC MITOCHONDRIAL DISEASES

A number of organ-specific mitochondrial disorders have been associated with specific antiretrovirals (see table below).

SELECTED *IN VIVO* MANIFESTATIONS OF NRTI MITOCHONDRIAL TOXICITIES*

Antiretroviral drugs	Organ tissue	Toxic feature
AZT, ddC, ddl	Bone marrow	Cytopenia
AZT	Muscle	Myopathy
D4T, ddC, ddl	Peripheral neuropathy	Neuropathy
All NRTIs	Liver	Hepatic steatosis/lactic acidosis

MUSCLE

- Mitochondrial damage in muscle is associated with fatigue, myalgias, proximal wasting, and raised plasma creatine phosphokinase (CPK).
- Muscle biopsy shows ragged red fibres and disrupted mitochondrial cristae.
- Reported incidence in studies: up to 17%. Most commonly associated with AZT use. (There appears to be a population-based difference in plasma CPK levels.)

HEART

- Mitochondrial damage has most commonly been thought to result in dilated cardiomyopathy.
- Myocardial biopsy shows ragged red fibres and disrupted mitochondrial cristae.
- Reported incidence in studies: rare. The most commonly associated drug is AZT.

NERVE TISSUE

- Patients with low CD4 counts and previous neuropathy are at risk.
- Distal pain with numbing, paraesthesiae and reduced reflexes has been associated with mitochondrial deficiency in neuronal tissue.
- Nerve conduction studies are nonspecific with axonal degeneration.

- Reported incidence in studies: 10 - 30% (ddC = d4T > ddl > 3TC).

Treatment:

Tricyclic antidepressants and sodium valproate are used for symptomatic relief. Neuronal growth hormone and gammapentone have also been used.

INH, vitamin B₁₂ deficiency or vinca alkaloids and alcohol may worsen the problem.

Stopping the drug results in improvement in 80% of patients by 3 - 5 months.

LIVER

- Most often occurs in treatment of > 6 months' duration with reports of dyspepsia after 4 months of therapy.
- Mitochondrial malfunction may result in liver damage with: hepatomegaly, nausea, ascites, oedema and finally hepatic encephalopathy.
- Liver enzymes are increased with lactic acidemia, increased anion gap and lowered bicarbonate.
- The transaminase enzymes, AST and ALT and amylase are at least grade 2 toxicity and bicarbonate is typically less than 15. Plasma bilirubin may or may not be raised, and in testing for lactate elevation, arterial lactate is recommended since venous lactate may give false-positive results.
- Reported incidence in studies: rare (< 1%). Associated with all nucleoside analogues except 3TC and abacavir.

Treatment:

Patients are usually very ill by the time the process is well underway and require careful intensive care support for recovery.

Riboflavin and other antioxidants have been used in therapy but a high risk of mortality exists and rechallenge with NRTI is not recommended.

FAT

- Mitochondrial dysfunction may be one of the possible mechanisms by which NRTI-induced mitochondrial damage contributes to body habitus changes and metabolic abnormalities. Mitochondrial disorder in fat is associated with lipotrophy and lipodystrophy.
- The increase in visceral fat associated with lipodystrophy might result from mitochondrial damage of brown fat tissue, ultimately showing lipolysis and a build-up of fat mass.
- Peripheral fat loss is believed to be the result of mutations or deletions of mtDNA which can lead to the release of apoptosis-inducing factor and caspase-C. Caspase-C are two mitochondrial membrane proteins responsible for cell breakdown that lead to premature

death of adipocytes.⁵ Lipoatrophy and lipodystrophy in this case often occurs with lactic acidemia.

- Reported incidence in studies: fairly common (up to 50% of patients to some degree) particularly in association with d4T usage.

PANCREAS

- Pancreatic damage has been recognised for some time as a toxic effect of nucleoside analogues. It occurs as a result of mitochondrial abnormalities and is characterised by abdominal pain, together with:
 - increased pancreatic amylase and lipase.

- Reported incidence in studies: uncommon (1 - 6%) and most commonly described with ddI > 3TC or ddC.

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