

# HIV/AIDS

## *Antiretroviral*

### Newsletter



World Health Organization  
Regional Office for the  
Western Pacific

*The aim of this biannual newsletter is to provide health workers in the Region with a brief, up-to-date summary of the latest developments in antiretroviral therapies.*

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## **SPECIAL FOCUS: COMPLICATIONS OF ANTI-RETROVIRAL THERAPY**

### **Introduction**

Recognized complications associated with antiretroviral (ARV) therapy now include a diverse group of abnormalities, which include bone marrow suppression, hepatic, renal and pancreatic inflammation, body-composition changes (lipodystrophy), skin and nail abnormalities diabetes hypersensitivity reactions, hyperlipidaemia, osteopenia, avascular bone necrosis, hypertension, atherosclerosis, hypothyroidism, hypogonadism and gout.

Increasingly, decisions concerning the timing of the introduction of ARV are balanced between the clearly demonstrated benefit of therapy and the potential for numerous, sometimes life threatening, side effects. The safe use of antiretroviral therapy requires careful clinical and laboratory monitoring.

The focus of this newsletter is on the complications of ARV, in particular lipodystrophy, and recent developments in the understanding of mitochondrial toxicity.

### **Class Specific Toxicities**

Nucleoside reverse transcriptase inhibitors	mitochondrial DNA toxicity
Nucleotide reverse transcriptase inhibitors	proximal renal tubular dysfunction
Non-nucleoside reverse transcriptase inhibitors	hypersensitivity reactions
Protease inhibitors	multiple metabolic disorders

### **Drug Specific Toxicities**

	anaemia, leucopenia, skin hyperpigmentation, gastro-intestinal intolerance, headache, myopathy, alopecia
Didanosine	pancreatitis, gastro-intestinal intolerance
Zalcitabine	mouth ulcers
Abacavir	hypersensitivity reaction (can be severe or fatal if rechallenged)
Efavirenz	CNS toxicity (drowsiness, dizziness, confusion, abnormal dreaming)
Ritonavir	peri-oral paraesthesiae, taste perversion, gastro-intestinal intolerance
Indinavir	renal calculi and crystaluria, hyperbilirubinaemia, alopecia
Nelfinavir	diarrhoea
Amprenavir	rash

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# Lipodystrophy

No generally accepted case definition exists for lipodystrophy. However, researchers attending The First International Workshop on Adverse Drug Reactions and Lipodystrophy in HIV (San Diego, June 1999) produced a working definition that included increased waist size, increased breast size, 'buffalo hump' (fat accumulation around the neck and upper back), fat accumulation around the neck and jaw ('moon face'), fat deposits in other locations, facial wasting, especially of the cheeks, wasting of the buttocks, thinning of arms and legs, and prominent leg veins.

The syndrome of lipodystrophy is also associated with insulin resistance and hyperlipidaemia.

## Pathogenesis

Lipodystrophy is no longer regarded as a direct consequence of protease inhibitors (PIs) alone. The causes of body fat changes are multi-factorial and more complex than first thought. Despite a number of emerging theories, the exact mechanisms that result in body fat and metabolic changes in patients taking ARV have not been identified.

Rare forms of genetically inherited lipodystrophy have been identified and acquired forms of lipodystrophy, which resemble those reported in HIV, have also been reported in uninfected individuals. The syndrome has also been reported in HIV-negative people taking ARV as post-exposure prophylaxis. Recently, it has become clear that both nucleoside reverse transcriptase inhibitors (NRTIs) and protease inhibitors play a role in the development of body fat and metabolic changes perhaps via different mechanisms

One theory is that protease inhibitors interfere with two human proteins involved in fat metabolism, the low-density lipoprotein-receptor-related protein (LRP) and the cytoplasmic retinoic-acid binding protein type 1 (CRABP-1). Researchers have found that the active site of HIV protease bears a close resemblance to a string of amino acids on the low-density lipoprotein receptor-related protein (LRP). A further theory suggests that body fat and metabolic disorders may result from PI-induced disruption of steroid hormone production. In one French study, serum cortisol levels were reported to be significantly higher in 37 patients taking highly active antiretroviral therapy (HAART) compared to 20 HIV-negative controls. In the same study, patients with lipodystrophy had lower levels of DHEA (which plays a role in regulating cortisol, lipid and insulin levels). Higher cortisol/DHEA ratios were associated with lipodystrophy.

The mechanism of nucleoside analogue-induced body fat changes is thought to relate to the mitochondrial toxicity caused by this class of ARV. The role of mitochondrial dysfunction in the pathogenesis of many of the complications seen in association with ARV is discussed later.

## Prevalence

Estimates of the prevalence of lipodystrophy in patients taking protease inhibitors vary widely. Australian researchers reported that 83% of the PI treated patients experienced some symptoms of lipodystrophy after 21 months of therapy, while 11% experienced severe body fat changes.

Other studies have reported a lower incidence of between 5%-30%. Spanish and French studies have also reported that a majority of patients experienced lipodystrophy after two years of treatment. A review of 624 French patients who had been taking at least one PI for an average of 18 months found that 85% had experienced at least one physical change during that time. In the Spanish study, of 158 patients treated with protease inhibitors for more than six months, 22% showed signs of lipodystrophy. Statistical analysis performed as part of this study suggested a 75% chance of developing lipodystrophy after two years of treatment.

## Risk factors for the development of lipodystrophy

Increasing patient age (especially >40 years)
Duration and type of PI therapy (ritonavir reported as more likely)
Duration and type of NRTI therapy (d4T reported as more likely)
Advanced HIV disease

## Diagnosis and monitoring

The diagnosis of lipodystrophy/lipo-atrophy can be made clinically with the typical body composition changes clearly visible to the physician and patient. Attempts have been made to quantify these changes using DEXA and CT scanning, BIA (bio-impedance assay) anthropometry and measurement of hip/waist ratio. Abnormal liver enzymes, serum lactate and anion gap are associated with mitochondrial toxicity. Protease inhibitors may cause elevated serum lipids and glucose and glycosuria.

## Management

Rational decision making in the management of lipodystrophy, lipo-atrophy, hyperlipidaemia and insulin resistance is difficult, in the absence of a known aetiology. There is no known treatment for the body composition changes. Stopping and/or switching therapy have produced variable results in clinical studies. Therefore, it is essential the patients are fully informed about lipodystrophy and that the changes may be permanent even if ARV is ceased. It is uncertain whether there will be clinical benefits from drug therapy for hyperlipidaemia and insulin resistance. The clinical options include the following:

?? doing nothing

?? switching the PI

- ?? switching the NRTI(s)
- ?? prescribing diet or exercise
- ?? treating specific abnormalities with medications

Switching from a PI to non-PI regimen has not demonstrated significant improvement in lipodystrophy in studies to date. The use of efavirenz may itself be associated with hyperlipidemia.

Researchers report that diet and exercise may reduce triglyceride levels by 20%. There are drug-interaction issues with the use of lipid-lowering drugs because all of the statins except pravastatin are metabolised by cytochrome P450. The fibrates are indicated for the treatment of hypertriglyceridemia and are reasonably effective.

Treatment of hyperglycaemia is more difficult. Sulfonylureas may lead to hepatic or renal toxicity. Metformin is contraindicated in the presence of renal or liver dysfunction. Insulin may be the safest therapy for symptomatic hyperglycemia.

## Mitochondrial dysfunction

Mitochondria generate cellular energy by the process of oxidative phosphorylation. Most cells contain hundreds of mitochondria that perform multiple cellular functions. They contain their own extra-chromosomal DNA. The enzyme DNA polymerase is responsible for mitochondria DNA replication.

Genetic mutations that disrupt mitochondrial oxidative phosphorylation occur naturally in humans. Such disruption results in a reduced cellular energy capacity and signs and symptoms of disease covering a wide clinical spectrum may appear.

### Clinical presentations of nucleoside reverse transcriptase inhibitor mitochondrial

	progressive weight loss, fatigue, elevated serum lactate, elevated anion gap
	myopathy, myalgia, muscle wasting, weakness, fatigue, elevated CPK
Heart	cardiomyopathy
	pain, parasthesiae, sensory loss, areflexia, muscle weakness
	hepatomegaly, elevated liver enzymes, lactic acidosis
Pancreas	pancreatitis, elevated serum amylase
Adipose tissue	lipoatrophy (typically peripheral)

Recently, nucleoside analogue reverse transcriptase inhibitors have been recognised as causing mitochondrial disruption, particularly following long-term therapy. Nucleoside analogues inhibit DNA polymerase resulting in decreased mitochondria DNA synthesis and increased mitochondrial DNA mutation. They also inhibit oxidative metabolism as the final common pathway. Whether NRTI-induced

mitochondrial toxicity is reversible, at least in part, after cessation of the drug is unknown. The role of supplementation with thiamine, riboflavin and co-enzyme Q (all involved in the process of oxidative phosphorylation) is being investigated.

## Mitochondrial toxicity of perinatally administered zidovudine

In February, 1999, French clinical investigators reported two cases of severe, fatal mitochondrial neurological disease in neonates born to 7 HIV-infected mothers who had been exposed perinatally to ZDV plus 3TC. The children were not HIV-infected. Theoretically, the mechanisms of NNRTI-induced mitochondrial toxicity could result in damage, which could persist after cessation of the drugs. Following the reported deaths, 6 further infants were discovered with mitochondrial metabolic abnormalities measured in muscle biopsy tissue.

In a review of five large databases at the National Institutes of Health and CDC, covering over 20,000 HIV-infected women, 227 deaths in HIV-uninfected or indeterminate children were analysed retrospectively. While none of these children died of illnesses resembling the two fatal cases in France, three had symptoms or signs that were suggestive of mitochondrial disease. However, none of these three children had known perinatal exposure to NRTIs. An extensive review of living, HIV-uninfected children is being conducted. At this stage there is insufficient evidence concerning mitochondrial toxicity in NRTI-exposed neonates to warrant a change in recommendations for perinatal prophylaxis.

## Proximal renal tubular dysfunction

Adefovir, which belongs to the nucleotide reverse transcriptase inhibitor class of ARV drugs, was recently withdrawn from clinical development due to the high incidence of proximal renal tubular dysfunction in clinical studies to date. This syndrome presents with reversible elevation of creatinine, associated with glycosuria, proteinuria, decrease serum bicarbonate and (variably) hypophosphataemia. Onset of the syndrome is typically after 20 weeks of adefovir therapy.

The aetiology may relate to mitochondrial toxicity and/or inhibition of organic anion transport protein by adefovir in proximal tubule cells.

## Hypersensitivity reactions

Drug hypersensitivity reactions are 100 times more common in HIV infected patients. Typically, such reactions are seen following therapy with non-nucleoside RTIs (nevirapine, efavirenz, delavirdine), cotrimoxazole,

abacavir and amprenavir. Clinical features include rash, hepatitis, mucosal inflammation, and constitutional symptoms such as fever and malaise. Non-nucleoside RTI hypersensitivity reactions are often self-limiting and may be managed with a 'treat through' approach, involving frequent clinical review of the patient and antihistamines. The incidence of nevirapine-induced rash is reduced by the recommended introduction of a reduced initial dose (200mg/day) escalating to 400mg/day after two weeks. Severe reactions may necessitate withdrawal of the drug. The special case of abacavir is discussed below in more detail.

## Abacavir hypersensitivity

Approximately 3% of patients treated with abacavir develop an idiosyncratic hypersensitivity reaction that resolves on discontinuation, but returns with greater severity of symptoms on reintroduction of abacavir. The median time to onset of the hypersensitivity is 11 days, with 94% of cases occurring within 6 weeks of initiation of abacavir therapy. The most frequent symptoms are fever (80%), rash (70%), gastrointestinal symptoms (50%), and malaise (40%). Respiratory symptoms have been reported in approximately 20% of patients and include dyspnoea, pharyngitis and cough. Wheezing is infrequently reported. Approximately half of patients have 3 or 4 symptoms, and an additional 20% have fever and rash. Fever and/or rash are present in 98% of cases. An important clue to the diagnosis is the evolution of the symptoms (over several days) and evidence for multi-organ system involvement. The rash can be mild. Gastrointestinal symptoms without either fever or rash are more likely to indicate common adverse events to antiretroviral therapy and not hypersensitivity.

Laboratory abnormalities reported in association with abacavir hypersensitivity reaction included lymphopenia, thrombocytopenia, elevated ALT and CPK.

If abacavir is re-introduced, the resultant reaction may develop within hours and is more severe. Rechallenge with abacavir following initial hypersensitivity reaction has been associated with death and should never be undertaken. Death has also been reported from the acute respiratory symptoms associated with an abacavir hypersensitivity reaction. The diagnosis of abacavir hypersensitivity must always be considered in patients presenting with acute respiratory symptoms in addition to other symptoms associated with abacavir hypersensitivity and the drug must be ceased immediately.

## Bone mineral density

Two abstracts presented at the 7<sup>th</sup> Conference on Retroviruses and Opportunistic Infections reported small studies of bone mineral density (BMD) in HIV-infected subjects with lipodystrophy who were receiving HAART. Both studies showed that a substantial proportion of subjects taking PIs had decreased bone mineral density, which led to diagnoses of osteopenia or osteoporosis; this was 21% of 64 persons taking a PI in

one study, and 28% of 74 patients in the other study. Men receiving protease inhibitors have been reported as having a higher incidence of osteopenia and/or osteoporosis compared to women.

Osteopenia and osteoporosis are unique metabolic complications associated with protease inhibitor containing potent antiretroviral regimens that appear to be independent of adipose tissue maldistribution.

## References and further reading

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Many review articles

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Many review articles



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