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REVIEW

Antiretroviral therapy in HIV patients: aspects of metabolic complications and mitochondrial toxicity

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INTRODUCTION

Since the introduction of highly active antiretroviral therapy (HAART) in HIV-infected patients, morbidity and mortality due to HIV infection have dramatically decreased.[1] Although resistance to antiretroviral therapy is an important issue, toxicity is becoming an even more important problem. In the ATHENA cohort (a cohort of around 3000 HIV patients in the Netherlands), the main reason to switch antiretroviral therapy is toxicity: this is 44 to 58% in patients on their first regimen and 56% on subsequent regimens.[2] Since HIV cannot be cured, chronic therapy is needed to suppress HIV replication; therefore the risk for adverse events may increase. The benefits of HAART have led to a great number of HIV patients receiving antiretroviral therapy.[3-5]

In this review we will discuss two major groups of antiretroviral therapy-related toxicity: the lipodystrophy/lipoatrophy syndrome with metabolic changes and mitochondrial toxicity.[6,7]

LIPODYSTROPHY SYNDROME

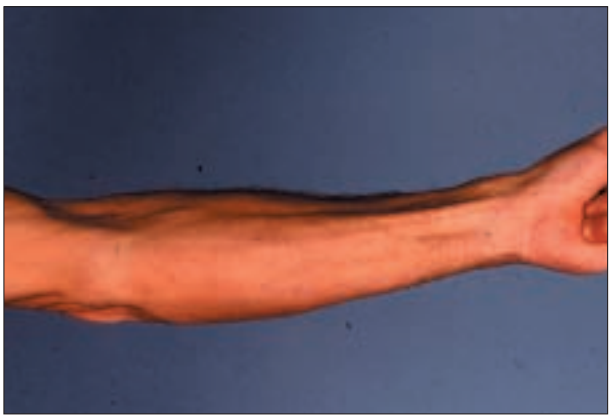
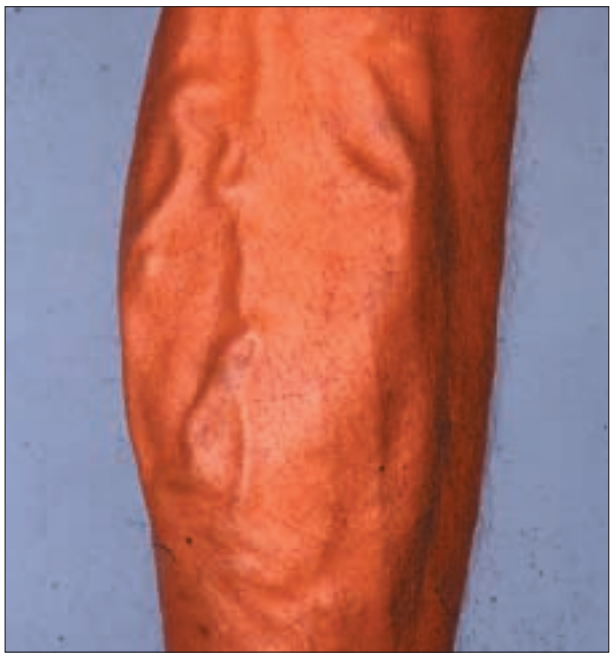
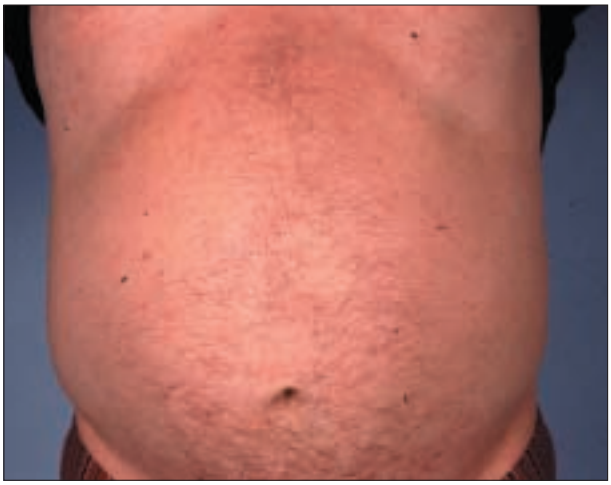
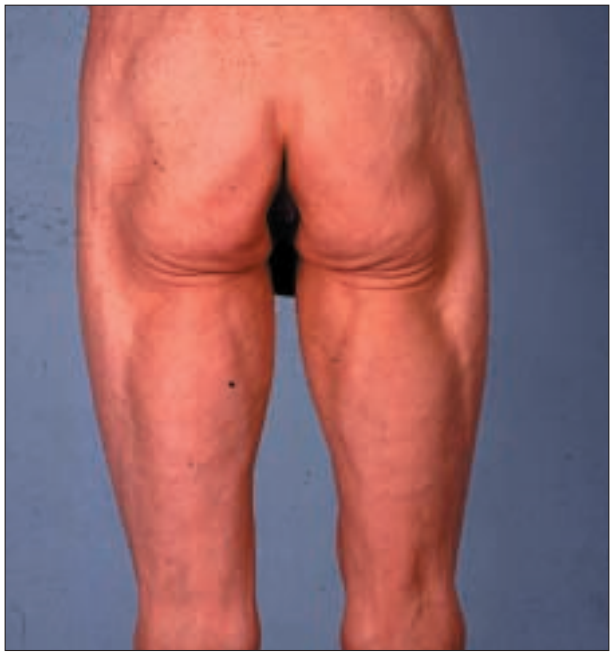
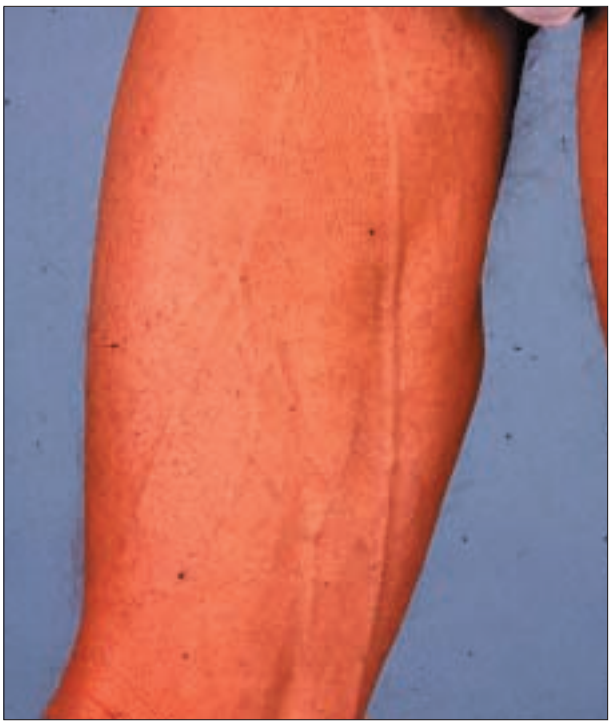
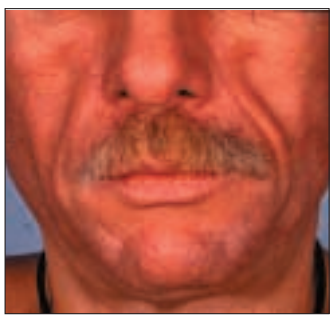
Symptoms

Exposure to antiretroviral drugs has been associated with the development of significant metabolic adverse effects, such as hyperlipidaemia, hyperglycaemia and insulin resistance with diabetes mellitus, peripheral fat wasting (lipoatrophy) and central adiposity. Fat loss on the extremities, buttocks and in the face together with localised deposits of fat, particularly in the abdomen, breasts or neck region (Buffalo hump), is very stigmatising for patients on HAART (*figures 1-6*).[8-13] This syndrome is called the lipodystrophy syndrome.

Epidemiology and predisposing factors

There are no exact data on the prevalence but in the literature it is estimated that it may occur in up to 80% of the patients on long-term therapy. A prospective cohort study from 1996 to 1999 found the following incidences: any lipodystrophy 11.7, lipodystrophy with subcutaneous lipoatrophy 9.2 and lipodystrophy with central obesity 7.7 per 100 patient years.[14] Data from the Dutch ATHENA cohort, including 1952 patients, demonstrated 261 patients who developed lipodystrophy/lipoatrophy. The incidence rate was 6.2 per 100 person years with a four-year cumulative incidence of 25%.[15] However, most lipodystrophy studies included HIV-positive Caucasian men. The incidence of lipodystrophy in subjects other than Caucasians has not been studied well. One study showed that lipodystrophy was only seen in 3.5% of a cohort of Koreans.[16]

Three major patterns are distinguished: the lipoatrophy syndrome (fat depletion), a mixed or fat redistribution syndrome and a subcutaneous fat accumulation syndrome, often due to diet prescriptions when using some types of protease inhibitors (PIs).[17] Lipodystrophy with peripheral lipoatrophy is mostly seen in HIV-infected patients receiving HAART and therefore not likely to be associated with HIV infection itself. Furthermore, the occurrence and severity of the syndrome is independent of HIV load. Recent reports highlight the fact that the fat depletion component (lipoatrophy) is primarily linked to nucleoside reverse transcriptase inhibitor (NRTI) therapy, while fat accumulation with dyslipidaemia and insulin resistance

Figures 1- 6
Patients with lipodystrophy/atrophy

are more readily associated with PI therapy. Current studies often distinguish the syndromes of fat depletion (lipoatrophy) and fat accumulation, in contrast to previous studies which use the term lipodystrophy for both components of fat changes. It is often difficult to make a clear distinction between the two components because they often appear as a mixed syndrome and the majority of the patients are treated with a combination of NRTIs and PIs. Although risk factors for these fat redistribution syndromes are not exactly known, the following factors have been suggested to play a role: low body weight before the start of HAART, elevation of C-peptide and fasting triglyceride concentrations early in therapy, female gender, age >40 years, baseline viral load >100,000 copies/ml, white ethnicity, duration of HAART and the use of a HAART regimen containing stavudine and combinations of PIs (especially saquinavir and ritonavir).[14,17-20] Lipoatrophy occurs frequently in regimens including NRTIs and is rare in NRTI-sparing regimens. Several studies confirmed the observation that the use of NRTIs contributes to the development of lipoatrophy, especially in patients on stavudine.[6,9,10,21,22] The risk of developing lipodystrophy was assessed in a study with 158 HIV-infected patients, 113 of whom received a PI-containing regimen and 45 were never treated with a PI. Predictors of subsequent lipodystrophy severity included weight before PI therapy, duration of therapy and fasting triglyceride and C-peptide concentrations on therapy. Lipodystrophy was very common and even progressive in most cases after two years of HAART with a PI.[18] This is in contrast to a prospective cohort study following almost 500 patients for 18 months, in which the risk factors for developing lipoatrophy/dystrophy were multifactorial and overlapping and could not be ascribed to the duration of exposure to a particular antiretroviral drug.[14]

Hypothesis on the pathogenesis

Changes in adipose tissue

Different aspects of adipose tissue disturbances have been postulated in the development of lipodystrophy/lipoatrophy. One of the hypotheses of this syndrome is that it occurs due to inhibition of lipid and adipocyte regulatory proteins, which have partial homology to the catalytic site of HIV-1 protease, to which all PIs bind. PIs are suggested to inhibit cellular retinoic acid-binding protein (CRABP)-1-modified and cytochrome P450-3A-mediated synthesis of cis-9-retinoic acid and peroxisome proliferator-activated receptor type gamma (PPAR-γ) heterodimer.[23] The inhibition increases the rate of apoptosis of adipocytes and reduces the rate at which pre-adipocytes differentiate into adipocytes, reducing triglyceride storage and increasing lipid release. PI binding to low-density lipoprotein receptor-related protein would impair hepatic chylomicron uptake and endothelial triglyceride clearance, resulting in hyperlipidaemia and insulin resistance.[6,18,24] Another factor suggested to play a role in lipodystrophy is the transcription protein sterol-regulatory-element-binding-protein-1 (SREBP1). SREBP1 is necessary for adipocyte differentiation. *In vivo* investigation of fat tissue in HIV patients with lipoatrophy versus HIV-negative healthy controls demonstrated a higher proportion of small adipocytes and a reduced expression of SREBP1 in patients with lipoatrophy.[25] Recent investigations show the role of the autonomic nervous system in regulation of adipose tissue. Parasympathetic stimulation of adipose tissue results in glucose and free fatty acid (FFA) uptake, resulting in an increase in adipose tissue. Autonomic neurons in the brainstem or the spine are able to innervate abdominal and subcutaneous fat tissue. A misbalance in the autonomic nervous system could lead to a different distribution of fat tissue intra-abdominally and subcutaneously, leading to central fat accumulation and peripheral fat loss as seen in the lipodystrophy/lipoatrophy syndrome in HIV-infected patients.[26]

Changes in adipocyte cell and glucose metabolism

In addition, endocrine changes have been revealed in lipodystrophy. The natural course of HIV-1 infection is associated with an increase in whole body lipolysis and an increase in resting energy expenditure (REE) without an increase in catecholamines (normally stimulators of these processes). However, in patients with lipodystrophy, plasma concentrations of norepinephrine have been found to be increased, indicating increased sympathetic activity. In the same study, lipodystrophy patients had a lower REE compared with HIV patients without lipodystrophy. HAART-associated lipodystrophy is therefore suggested to have only minor effects on lipolysis induced by HIV infection itself, as a result of concomitant sympathetic stimulation of adipose tissue.[27] Also, an imbalance between peripheral lipolysis and lipogenesis, both regulated by cortisol and dehydro-epiandrosterone, has been found to play a role in lipodystrophy. Furthermore, subcutaneous adipocyte apoptosis has been found in lipoatrophic areas of HIV-patients treated with PIs.[28,29]

Insulin resistance in antiretroviral therapy-associated lipodystrophy has been attributed to impaired glucose transport and phosphorylation. PIs interfere with glucose metabolism in muscle and adipocyte cells, leading to an increase of basal lipolysis. PIs have also been found to directly inhibit the activity of GLUT4, an important cellular glucose transporter, which is generally thought to be the major contributor to insulin-stimulated glucose uptake in adipocytes and skeletal muscle. GLUT4 inhibition by PIs thereby leads to a decrease in insulin-stimulated glucose uptake.[30-32]

NRTI-associated mitochondrial toxicity has also been postulated to play a role in antiretroviral therapy-related

lipodystrophy.[21,22,33] The fat redistribution as seen in HIV patients treated with antiretroviral therapy resembles the body composition of patients with Madelung's disease. Mitochondrial impairment has been found in patients with benign or multiple symmetrical lipomatosis (Madelung's disease). Investigation of muscle mitochondria in HIV patients with lipodystrophy has shown abnormalities in mitochondrial respiratory chain complexes, mitochondrial DNA (mtDNA) and mitochondrial morphology suggestive of mitochondrial dysfunction.[34] Adipocyte mitochondria have been studied in HIV-infected patients on NRTIs, therapy-naive patients and healthy controls, revealing mtDNA depletion and mitochondrial proliferation in adipocytes in the first group.[35,36]

Cardiovascular risk of antiretroviral therapy

The occurrence of metabolic changes, such as hyperlipidaemia and insulin resistance, with the use of antiretroviral therapy may affect the risk of cardiovascular disease in HIV-infected patients. Even after short-term therapy with antiretroviral drugs, metabolic changes have been observed. In a recent study in which healthy volunteers were treated with indinavir, insulin resistance was already found after four weeks of drug use.[37]

Prior to the availability of protease inhibitor therapy, endothelial dysfunction, hypercoagulability, hypertriglyceridaemia and abnormal coronary artery pathology were associated with HIV infection. This was even seen in children and young adults. Autopsy reports showed major atherosclerotic lesions in HIV subjects in the absence of traditional cardiovascular risk factors. A cohort of over 5000 HIV patients in the USA, followed between 1993 and 2002, showed an increase in myocardial infarctions after the introduction of protease inhibitors in 1996.[38] In contrast, a retrospective analysis of a cohort of 36,000 HIV-infected patients between 1993 and 2001 demonstrated a decline in the rate of admissions for cardiovascular or cerebrovascular disease from 1.7 to 0.9 per 100 patient-years. The authors did not find a relation between the use of NRTIs, NNRTIs or PIs and the cardiovascular and cerebrovascular events. Antiretroviral therapy was associated with an overall decrease in death from any cause.[39] The DAD study assessed the risk of cardiovascular disease in HAART-treated patients in a prospective multinational cohort study including around 17,000 subjects. Data from this study indicate that NNRTIs and PIs (and especially in combination) are associated with a lipid profile known to increase the risk of coronary heart disease. This was particularly seen in older patients with normalised CD4 counts and suppressed HIV replication.[40]

Plasma markers that play a role in endothelial function have been shown to be significantly elevated in HIV patients (von Willebrand factor, tissue plasminogen activator, β_2-microglobulin and soluble thrombomodulin). Levels of these markers have been found to be related to the stage of HIV disease and may be proportional to the viral load. The course of vascular disease may be accelerated in HIV-infected patients because of atherogenesis stimulated by HIV-infected monocyte macrophages, possibly via altered leucocyte adhesion or arteritis. In recent literature, a relation between chronic inflammation and atherosclerosis has been postulated. In this light, chronic HIV infection with the occurrence of co-infections (opportunistic or not) makes subjects prone to atherogenic disturbances. In addition, insulin resistance, hypercholesterolaemia and the fat redistribution syndrome (increase of visceral fat) associated with HIV therapy may exacerbate these HIV-associated atherosclerotic risk factors.[41-44] Especially protease inhibitors are known to interfere with lipid and glucose metabolism resulting in insulin resistance with hyperglycaemia, hypertriglyceridaemia and elevated total cholesterol (HDL cholesterol is often reduced).[38,45] However, lipid changes have also been seen in patients on efavirenz. Moreover, NRTIs may play a significant role in a synergistic effect on these metabolic changes.

Overall, there are conflicting data on cardiovascular effects of HAART. The growing concern that the metabolic complications associated with HIV and antiretroviral therapy may lead to accelerated coronary artery disease is being evaluated in large prospective trials with long-term follow-up. Until the results are available, monitoring the traditional cardiovascular risk factors and risk factors associated with HAART such as dyslipidaemia, glucose levels and visceral fat accumulation in HIV patients is justified (*table 1*).[38,39,44,46-48]

Table 1
Risk factors for atherosclerosis in HIV patients on HAART

Increased triglycerides
Increased total cholesterol
Increased LDL cholesterol
Decreased HDL cholesterol
Insulin resistance
Increased visceral fat
Increased plasminogen-activator inhibitor type I
Increased apolipoprotein B

Diagnosis

The diagnosis of this syndrome is difficult and is based on objective and subjective parameters such as physical examination with measurement of hip/waist ratio, presence of fat disposition/loss and visible veins on the extremities together with the patient's report of a changed body com-

position. The HIV Lipodystrophy Case Definition Study Group evaluated a model to diagnose lipodystrophy. This model included a scoring system for age, sex, duration of HIV infection, HIV disease stage, waist/hip ratio, anion gap, serum HDL cholesterol concentration, trunk/peripheral fat ratio, percentage of leg fat and intra-abdominal/extra-abdominal fat ratio. By using this score the diagnosis lipodystrophy had a sensitivity of 79% and a specificity of 80%, which is far more than with scores using only clinical or metabolic variables.[49]

Lipoatrophy/dystrophy with lipid and glucose disturbances has been studied by means of blood measurements, CT scans, DEXA scans and body impedance amplitude (BIA) in combination with weight and measurement of subcutaneous fat. A problem with this syndrome is the subjective part of it; changes in body composition experienced by the patients cannot always be evaluated by standard tests.[50,51] Changes in fat distribution have been objectively confirmed by dual energy X-ray absorption (DEXA) and computed tomography. However, DEXA and CT scanning cannot demonstrate a change in all aspects related to the lipoatrophy/lipodystrophy syndrome. Facial lipoatrophy, one of the most distressing features of the syndrome, cannot be measured in this way.[53] In addition, sonography can be considered as an additional tool to quantify regional fat distribution. The measurement of subcutaneous facial and arm fat seems to be simpler, less variable and more discriminative for diagnosing abnormal regional fat distribution than that of intra-abdominal fat.[54]

Treatment

HAART-receiving patients with hyperlipidaemia and diabetes are currently treated with lipid-lowering agents and oral antidiabetic drugs or even subcutaneous insulin. Thiazolidinediones, such as rosiglitazone, have shown to improve insulin sensitivity and promote adipocyte differentiation *in vitro*. Small studies with metformin and thiazolidinediones in HIV patients with impaired insulin sensitivity and diabetes during HAART showed amelioration of antiretroviral therapy-associated insulin resistance, improvement of body fat distribution (increase in lean body mass), a decrease in total body fat and a decline in triglycerides and VLDL cholesterol.[55-57]

Leptin therapy is suggested to be of use in lipodystrophy. A study in mice demonstrated a positive effect of leptin replacement with reduction of ritonavir-induced hypercholesterolaemia, interscapular fat mass and improvement of liver steatosis. This is in contrast to the administration of a polyunsaturated fatty acid diet, which did not alleviate PI-induced metabolic abnormalities.[58] Patients with congenital lipodystrophy have been studied while on chronic leptin therapy. An improvement in insulin-stimulated hepatic and peripheral glucose metabolism in severe insulin resistance was demonstrated with marked reduction of hepatic and muscle triglyceride content.[59,60] However, the usefulness in HIV lipodystrophy has to be proven.

Lipid disorders are treated with statins (HMG-CoA reductase inhibitors) in case of elevated cholesterol, and fibrates are used in patients with elevated triglycerides. Up until now, pravastatin has been the statin of choice since it has no potential to cause rhabdomyolysis or to interact with the other medications often used in HAART regimens (especially the PIs).[61,62] Furthermore, traditional risk factors, such as age >40 years, positive family history, male gender and smoking, should be taken into account when treating patients with abnormal lipid values and insulin resistance. Also dietary modifications and exercise are general health measures that have been proven to be beneficial in HIV-infected patients with lipodystrophy and for lipid and glucose disturbances.[8,44,48]

Switching studies have shown that metabolic disturbances due to HAART appear to be partially reversible, but improvement in fat redistribution has not been clearly demonstrated. There have been a few studies switching PIs to abacavir, efavirenz or nevirapine showing improvement in insulin resistance. Furthermore, there seems to be a favourable change in lipid concentrations, particularly after switching to nevirapine and abacavir.[46,63] One study with PI-treated patients who presented with lipoatrophy, hyperlipidaemia and insulin resistance analysed the switch from a PI-containing regimen to one containing efavirenz.[63-65] Even one year after substitution of efavirenz for PIs, the lipid profile did not improve nor did it resolve the insulin resistance or lipoatrophy. Another study, replacing ritonavir by nelfinavir or nelfinavir/saquinavir in HAART combinations, led to improvement in triglyceride levels.[66] Decrease in lipids was also seen in a randomised study in which patients were switched from a PI-containing regimen to a combination of zidovudine, lamivudine and abacavir.[67-69]

Peripheral fat loss can sometimes be treated by implantation of the patient's subcutaneous fat or synthetic material (bio-alcamid, New Fill® and botulin toxin); unfortunately the results are not always satisfactory. Cosmetic surgery with liposuction can be performed in patients with abdominal fat disposition and buffalo hump; however it is not clear if the fat accumulation will re-occur.[70]

MITOCHONDRIAL TOXICITY

Epidemiology, predisposing factors and pathogenesis

Side effects associated with NRTI therapy are (cardio)myopathy, neuropathy, pancreatitis, hepatic steatosis and lactic acidosis (*table 2*). These events generally occur after at least three to four months of NRTI treatment. The clinical symptoms resemble symptoms that occur in paediatric patients with congenital mitochondrial diseases.

Table 2
Adverse events in NRTIs/NtRTI associated with mitochondrial toxicity

	AZT	3TC	d4T	ddI	ddC	ABV	TFV*
Anaemia	+	-	-	-	-	-	-
(Cardio)myopathy	+	-	-	-	-	-	-
Neuropathy	-	-	+	+	+	-	-
Pancreatitis	-	+/-	-	+	-	-	-
Hepatic steatosis	+	-	+	+	+	-	-
Lactic acidosis	+	-	+	+	+	-	-

*AZT = zidovudine, 3TC = lamivudine, d4T = stavudine, ddI = didanosine, ddC = zalcitabine, ABV = abacavir, TFV = tenofovir. *NtRTI.*

Therefore, it is supposed that the pathogenic pathway of these side effects can be explained by NRTI-induced mitochondrial damage. NRTIs interfere with an enzyme (polymerase γ), which is essential for the synthesis of mitochondrial DNA strands. The triphosphate compounds of the nucleoside analogues inhibit polymerase γ. By interference with this enzyme, NRTIs are built into a new mitochondrial DNA strand instead of the normal nucleosides, resulting in chain termination and thereby impaired mtDNA synthesis (*figure 7*). Direct proof for NRTI-induced mitochondrial toxicity has been demonstrated in zidovudine-related myopathy in humans, showing ragged-red fibres and moderate lipid droplet accumulation and myofilamentous loss without inflammatory infiltration.[71-74]
Incidences are not well known and vary depending on the analysis, such as neuropathy 12 to 46%, myopathy 17% and pancreatitis 0.5 to 7%. The most life-threatening NRTI-related toxic event reported is lactic acidosis with hepatic failure. It has been described for zidovudine, didanosine and stavudine. The incidence is estimated around 1.3 per 1000 person-years, found retrospectively in a cohort of antiretroviral drug users.[5,71-81] This number fits reasonably well with our own experience, when we found four fatal cases within one year in the Netherlands, where around 3000 patients are treated with antiretroviral combination therapy.[82] Imminent lactic acidosis should be suspected if a patient complains of malaise, nausea and vomiting, often accompanied by abdominal pain and hyperventilation, followed by rapid liver failure and uncontrollable arrhythmias.
Another striking feature of the NRTI toxicity is its apparent tissue specificity: myopathy can be caused by zidovudine, but rarely occurs with any of the other NRTIs and conversely, neuropathy and pancreatitis are common features in treatment with zalcitabine, didanosine and stavudine, but not with the other NRTIs (see also *table 2*). A possible explanation for this phenomenon of apparent tissue specificity is the so-called polymerase-γ hypothesis, which states that four factors contribute to an effective inhibition of DNA polymerase γ by a certain NRTI at a special tissue level. These factors are pharmacodynamic capability to enter the target cells, the right cellular nucleoside kinases to triphosphorylate the NRTI, inhibition of DNA polymerase γ by the triphosphorylated NRTI either by serving as a competitive (ineffective) alternate substrate or by chain termination of the nascent mtDNA strand (non-competitive) and finally metabolic reliance on oxidative phosphorylation by the target tissues.[5]
At present, the reason why some individuals suffer from mitochondrial toxicity is not clearly understood, although several factors have been identified to play a role in this mechanism of toxicity. As in congenital mitochondrial diseases, this mitochondrial impairment might have a genetic basis. Patients with suboptimal mitochondrial function due to inherited mtDNA mutations or deletions, with no symptoms yet, might be more susceptible to

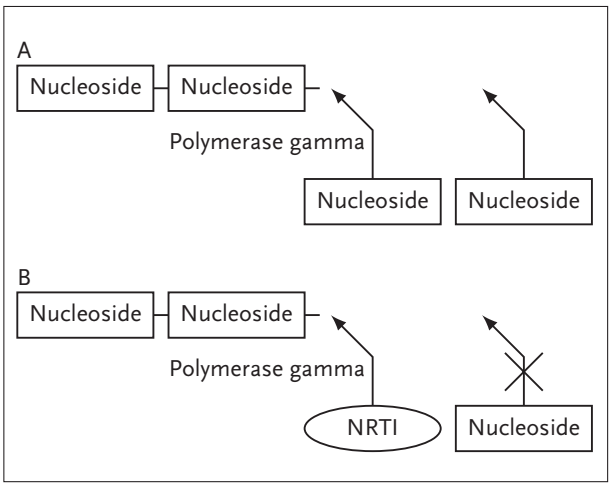


Figure 7
Synthesis of new mitochondrial DNA strand

A = Normal situation. B = Situation in NRTI use; blockage of the formation of a new strand by NRTI.

developing severe dysfunction of mitochondria on NRTI therapy. In a comparable fashion, ageing will result in increasing mitochondrial dysfunction, since mutations in mtDNA accumulate in time and repair mechanisms in mitochondrial DNA replication are limited compared with nuclear DNA replication. Older people might therefore be more susceptible than younger age groups. A certain time span appears to be necessary for the accumulation of toxic effects. Consequently, long-term exposure to antiretroviral nucleoside analogues is likely to result in symptomatic mitochondrial dysfunction. Accumulative toxicity with mitochondrial toxicity due to prior NRTI use is also seen. Another predisposing factor might be the patient's nutritional state. Biochemical reactions in mitochondria depend on a large range of vitamins, co-factors and substrates. In malnourished patients there might be a deficiency for these co-factors, in this way contributing to impaired mitochondrial function.[5,19,82]

In case of toxicity and discontinuation of medication, some tissues show a very slow recovery. Factors that determine this recuperation capacity are unknown but tissues with a low cell turnover, such as neurones, seem to recover very slowly and appear to be more vulnerable for this kind of toxicity. An example is NRTI-induced neuropathy that can last for months after NRTIs have been stopped.

Diagnosis

Histology is the only method to demonstrate mitochondrial disorders conclusively. It is an invasive examination and the biopsy site has to be targeted to the tissue affected. For instance, in muscle biopsies the difference between HIV myopathy and AZT-induced myopathy can be established. The presence of ragged-red fibres and myofilamentous is characteristic of an acquired mitochondrial-related myopathy. Damaged mitochondria can be seen with electron microscopy, showing swollen mitochondria with disruption and fragmentation of cristae, cristalline inclusions and lipid droplets. However, tissue biopsies are not useful as screening tests and not every tissue can be sampled.[5,83]

For more then a decade, specific knowledge of mitochondrial dysfunction has been obtained during zidovudine-induced myopathy by evaluating cytochrome c oxidase histochemical reaction in muscle biopsies.[84-86]

Cytochrome c oxidase (COX), is an enzyme essential in complex IV of the mitochondrial respiratory chain. Deficiency of this enzyme was found in all patients with AZT-related myopathy and in the majority of AZT-treated patients, however, without myopathy. In contrast, no deficiency was detected in patients with HIV-related myopathy. COX deficiency was found in patients with full-blown AZT myopathy as well as in myopathic tissue from asymptomatic AZT recipients with only histological changes characteristic of AZT myopathy.[87-90]

Histochemical reaction to COX could therefore be a marker of AZT-induced mitochondrial toxicity in HIV-infected patients. Disadvantages of mitochondrial function tests are the invasive character of these tests and the results do not always correlate with the clinical picture.

NRTI-induced hepatic steatosis and neuropathy are diagnoses often detected by exclusion of other possibilities. Histological examination of the liver reveals macrovesicular steatosis without necrosis, in contrast to steatosis induced by other toxic agents and diseases, which shows a microvesicular pattern with necrosis. Additional histochemistry has to be performed to exclude infectious causes.

Less invasive tests, such as blood tests, are easier to perform and therefore might be more useful. As a result of mitochondrial dysfunction, pyruvate can only be metabolised into lactate, which leads to an increased lactate and lactate/pyruvate ratio. Determination of the blood lactate/pyruvate ratio (L/P) is used as diagnostic screening method in patients with mitochondrial diseases. Chariot *et al.* performed a small pilot study in 20 HIV-infected patients with AZT-induced myopathy.[91,92] Although elevated lactate levels have been described in patients suspected of mitochondrial toxicity, not all patients with mitochondrial toxicity develop hyperlactataemia, and lactataemia does not always result in lactic acidosis. Zidovudine, didanosine and stavudine have all been described to cause lactic acidosis.[93-95] In addition, several studies found elevated lactate levels more frequently in stavudine-containing regimens. Hyperlactataemia in patients on stavudine is noticeable and not always directly related to adverse events.[96-103] Interestingly, serum lactate analysis in a group of our own patients revealed the highest lactate values in patients with presumed NRTI-related neuropathy. This is consistent with a recent study using serum lactate levels in distinguishing between HIV- and NRTI-associated neuropathy.[104] Overall, asymptomatic mild hyperlactataemia is a rather common feature of antiretroviral therapy. In recent publications the use of lactate to monitor complications of antiretroviral therapy has been discussed.[96,100,101,105-107] Routine lactate measurement is not recommended; a difference has to be made between symptomatic and asymptomatic hyperlactataemia and lactic acidosis. Mild asymptomatic hyperlactataemia (lactate levels of ≥2500 μmol/l) requires careful monitoring but no immediate action. Symptomatic hyperlactataemia and lactate levels above 5000 μmol/l are clinically relevant and need intervention. It is advisable to check lactates in patients with NRTI-related neuropathy, hepatic steatosis or elevated transaminases, myopathy and in case of extreme fatigue, unexplained nausea, vomiting, dyspnoea or abdominal pain. Patients with hyperlactataemia should be closely monitored and in case of increasing lactates or lactic acidosis, nucleoside analogues should be discontinued.[83,97,108,109]

Another option to study mitochondrial toxicity is to

measure mtDNA contents. *In vitro* studies have been performed in different cell lines showing time- and dose-dependent mtDNA depletion in cells incubated with zalcitabine, didanosine and stavudine in combination with an increase in lactate production. This effect is also seen in zidovudine-treated cells, although to a lesser extent. Lamivudine and efavirenz did not affect any of these measurements. In conclusion, NRTIs (except lamivudine) can inhibit mtDNA polymerase γ and cause termination of synthesis of growing mtDNA strands and mtDNA depletion, although the propensity to injure particular target tissues is unexplained.[5]

In patients with symptomatic hyperlactataemia, changes in mtDNA relative to nuclear DNA in peripheral blood cells were studied. The ratios of mitochondrial to nuclear DNA in HIV patients with symptomatic hyperlactataemia were 68% lower compared with non-HIV-infected subjects and 48% lower than the ratios in asymptomatic HIV patients. The decline in mtDNA resolved partially after discontinuation of antiretroviral therapy.[110] Depletion of mtDNA seems at least to be partially reversible. Patients followed longitudinally showed a decline in mtDNA that preceded the increase in lactate levels. In patients on HAART (including NRTIs) with peripheral fat wasting (lipoatrophy), mtDNA contents of subcutaneous fat tissue from the neck, abdomen and thigh were measured. The results showed a decline in mtDNA content compared with HIV patients on HAART without lipodystrophy/lipoatrophy, HIV therapy-naive patients and HIV-negative controls. Unfortunately not all studies show consistency. One study showed higher mtDNA levels in patients on antiretroviral therapy compared with HIV-infected patients without HAART. This suggests mitochondrial recovery during HAART. Apparently more mechanisms play a role in the mechanism of toxicity.[108,111-118]

Treatment

Besides the discontinuation of NRTIs, there is no real treatment for mitochondrial toxicity. Case reports have been described treating lactic acidosis due to severe HIV-induced mitochondrial damage with co-enzyme Q, thiamine, L-carnitine and riboflavin. These substrates play an important role in mitochondrial biochemical reactions; however it is not clear what effect they had in these case reports, since antiretroviral therapy was always discontinued in these cases.[102,119-123]

CONCLUSION

Human immunodeficiency virus infection can be successfully treated with HAART. However, the long-term safety of the present drugs is a major concern. The pathogenesis of the major syndromes such as lipodystrophy and the so-called mitochondrial toxicity is still unclear, while treatment options are limited. Close observation and monitoring of side effects and potential risk factors as well as studies on pathogenesis and treatment remain warranted.

REFERENCES

1. Palella FJ, Delaney KM, Moorman AC, et al. Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. N Engl J Med 1998;338:853-60.
2. Dieleman J, Jambroes M, Gijssens IC, et al., on behalf of the ATHENA Study Cohort Group. Determinants of recurrent toxicity-driven Switches of highly active antiretroviral therapy. The ATHENA Cohort. AIDS 2002;16:737-45.
3. Struble KA, Pratt RD, Gitterman SR. Toxicity of antiviral agents. Am J Med 1997;102:65-7.
4. Carr A, Cooper DA. Adverse effects of antiretroviral therapy. Lancet 2000;356:1423-30.
5. Brinkman K, Hofstede HJM ter, Burger DM, Smeitink JAM, Koopmans PP. Adverse effects of reverse transcriptase inhibitors: mitochondrial toxicity as common pathway. AIDS 1998;12:1735-44.
6. Carr A, Samaras K, Burton S, et al. A syndrome of peripheral lipodystrophy, hyperlipidemia and insulin resistance in patients receiving HIV protease inhibitors. AIDS 1998;351:867-70.
7. Carr A. HIV protease inhibitors-induced lipodystrophy syndrome. AIDS Rev 1999;1:29-36.
8. Blanco F, Carr A. Lipodystrophy syndrome: Diagnostic, clinic and therapeutic aspects. AIDS Rev 2001;3:98-105.
9. Saint-Marc T, Partisani M, Piozot-Martin I, et al. A syndrome of peripheral fat wasting (lipodystrophy) in patients receiving long-term nucleoside analogue therapy. AIDS 1999;13:1659-67.
10. Saint-Marc T, Partisani M, Piozot-Martin I, et al. Fat distribution evaluated by computed tomography and metabolic abnormalities in patients undergoing antiretroviral therapy: preliminary results of the LIPOCO study. AIDS 2000;14:37-49.
11. Carr A, Miller J, Law M, Cooper DA. A syndrome of lipoatrophy, lactic acidaemia and liver dysfunction associated with HIV nucleoside analogue therapy: contribution to protease inhibitor-related lipodystrophy syndrome. AIDS 2000;14:F25-32.
12. Carr A. HIV protease inhibitor-related lipodystrophy syndrome. Clin Infect Dis 2000;30:S135-42.
13. Carr A, Cooper DA. Images in clinical medicine. Lipodystrophy associated with an HIV-protease inhibitor. N Engl J Med 1998;339:1296.
14. Martinez E, Mocroft A, Garcia-Viejo MA, et al. Risk of lipodystrophy in HIV-1-infected patients treated with protease inhibitors: a prospective cohort study. Lancet 2001;357:592-8.
15. Dieleman J. Risk of lipodystrophy is highest after prolonged exposure to stavudine containing antiretroviral treatment. The ATHENA cohort. Thesis: Safety aspects of HIV-protease inhibitors; chapter 3.2:108-22.
16. Chang K, Kim J, Song Y, Hong S, Lee H, Lim S. Does race protect an Oriental population from developing lipodystrophy in HIV-infected individuals on HAART? J Infect 2002;44:33-8.

17. Saint-Marc T, Partisani M, Piozot-Martin I, et al. Fat distribution evaluated by computed tomography and metabolic abnormalities in patients undergoing antiretroviral therapy: preliminary results of the LIPOCO study. AIDS 2000;14:37-49.
18. Carr A, Samaras K, Thoridottir A, Kaufmann G, Chisholm DJ, Dooper DA. Diagnosis, prediction and the natural course of HIV protease inhibitor-associated lipodystrophy, hyperlipidaemia and diabetes mellitus. Lancet 1999;353:2093-9.
19. Cohen C, Shen Y, Rode R, et al. Effect of nucleoside intensification on prevalence of morphologic abnormalities at year 5 of ritonavir plus saquinavir therapy in an HIV-infected cohort [Abstract 683]. 9th CROI. Seattle 2002.
20. Bogner JR, Vielhauer V, Beckmann RA, et al. Stavudine versus zidovudine and the development of lipodystrophy. J Acquir Immune Defic Syndr 2001;27(3):237-44.
21. McComsey G. Update on mitochondrial toxicity of antiretrovirals and its link to lipodystrophy. AIDS Rev 2002;4:140-7.
22. Valk M van der, Gisolf EH, Reiss P, et al. Increased risk of lipodystrophy when nucleoside analogue reverse transcriptase inhibitors are included with protease inhibitors in the treatment of HIV-1 infection. AIDS 2001;15:847-55.
23. Carr A, Samaras K, Chisholm D, Cooper D. Pathogenesis of HIV-1-protease inhibitor-associated peripheral lipodystrophy, hyperlipidaemia and insulin resistance. Lancet 1998;351:1881-3.
24. Barbaro G, Klatt E. HIV infection and the cardiovascular system. AIDS Rev 2002;4:93-103.
25. Bastard JP, Caron M, Vidal H, et al. Association between altered expression of adipogenic factor SREBP1 in lipoatrophic adipose tissue from HIV-1-infected patients and abnormal adipocyte differentiation and insulin resistance. Lancet 2002;359(9311):1026-31.
26. Kreier F, Fliers E, Voshol P, et al. Selective parasympathetic innervation of subcutaneous and intra-abdominal fat-functional implications. J Clin Invest 2002;110(9):1243-50.
27. Valk M van der, Reiss P, Leth FC van, et al. Highly active antiretroviral therapy-induced lipodystrophy has minor effects on human immunodeficiency virus-induced changes in lipolysis, but normalizes resting energy expenditure. J Clin Endocrinol Metab 2002;87(11):5066-71.
28. Christeff N, Melchior JC, Truchis P de, Perronne C, Nunez EA, Gougeon ML. Lipodystrophy defined by a clinical score in HIV-infected men on highly active antiretroviral therapy: correlation between dyslipidaemia and steroid hormone alterations. AIDS 1999;13(16):2251-60.
29. Domingo P, Matias-Guiu X, Pujol RM, et al. Subcutaneous adipocyte apoptosis in HIV-1 protease inhibitor-associated lipodystrophy. AIDS 1999;13(16):2261-7.
30. Behrens GM, Boerner AR, Weber K, et al. Impaired glucose phosphorylation and transport in skeletal muscle cause insulin resistance in HIV-1-infected patients with lipodystrophy. Clin Invest 2002;110(9):1319-27.
31. Murata H, Hruz PW, Mueckler M. Indinavir inhibits the glucose transporter isoform Glut4 at physiologic concentrations. AIDS 2002;16(6):925-6.
32. Ben-Romano R, Rudich A, Torok D, et al. Agent and cell-type specificity in the induction of insulin resistance by HIV protease inhibitors. AIDS 2003;17(1):23-32.
33. Brinkman K, Smeitink JA, Romijn JA, Reiss P. Mitochondrial toxicity induced by nucleoside reverse transcriptase inhibitors is a key factor in the pathogenesis of antiretroviral therapy-related lipodystrophy. Lancet 1999;354:1112-5.
34. Zaera MG, Miro O, Pedrol E, et al. Mitochondrial involvement in antiretroviral therapy-related lipodystrophy. AIDS 2001;15:1643-51.
35. Nolan D, Hammond E, Martin A, et al. Mitochondrial DNA depletion and morphologic changes in adipocytes associated with nucleoside reverse transcriptase inhibitor therapy. AIDS 2003;17(9):1329-38.
36. Walker U, Bickel M, Walker UA, et al. Evidence of nucleoside analogue reverse transcriptase inhibitor-associated genetic and structural defects of mitochondria in adipose tissue of HIV-infected patients. J Acquir Immune Defic Syndr 2002;29(2):117-21.
37. Noor MA, Lo JC, Mulligan K, et al. Metabolic effects of indinavir in healthy HIV-seronegative men. AIDS 2001;15:11-8.
38. Holmberg S, Moorman A, Williamson J, et al, and the HIV Outpatient Study (HOPS) investigators. Protease inhibitors and cardiovascular outcomes in patients with HIV-1. Lancet 2002;360:1747-8.
39. Bozzette S, Ake C, Tam H, Chang S, Louis T. Cardiovascular and cerebrovascular events in patients treated for human immunodeficiency virus infection. N Engl J Med 2003;348:702-10.
40. Friis-Moller N, Weber R, Reiss P, et al, for the DAD study group. Cardiovascular disease risk factors in HIV patients - association with antiretroviral therapy: Results from the DAD study. AIDS 2003;17(8):1179-93.
41. Stein J, Klein M, Bellehumeur L, et al. Use of human immunodeficiency virus-1 protease inhibitors is associates with atherogenic lipoprotein changes and endothelial dysfunction. Circulation 2001;104:257-62.
42. Passalaris J, Sepkowitz K, Glesby M. Coronary artery disease and Human immunodeficiency virus infection. Clin Infect Dis 2000;31:787-97.
43. Acevedo M, Sprecher D, Clabrese L, et al. Pilot study of coronary atherosclerotic risk factors and plaque burden in HIV patients: 'A call for cardiovascular prevention.' Atherosclerosis 2002;163:349-54.
44. Barbaro G. HIV infection, antiretroviral therapy and cardiovascular risk. J Cardiovasc Risk 2002;9:295-300.
45. Tashima K, Bausserman L, Alt E, Flanigan T. Lipid changes in patients initiating efavirenz- and indinavir-based antiretroviral regimens. HIV Clin Trials 2003;4:29-36.
46. Valk M van der, Kastelein J, Murphy R, et al, on behalf of the Atlantic study. Nevirapine-containing antiretroviral therapy in HIV-1 infected patients results in an anti-atherogenic lipid profile. AIDS 2001;15:2407-14.
47. Safrin S, Grunfeld C. Fat distribution and metabolic changes in patients with HIV infection. AIDS 1999;13:2493-505.
48. Tsiodras S, Mantzoros C, Hammer S, Samore M. Effects of protease inhibitors on hyperglycaemia, hyperlipidaemia and lipodystrophy. Arch Intern Med 2000;160:2050-6.
49. HIV lipodystrophy case definition study group. An objective case definition of lipodystrophy in HIV-infected adults: a case-control study. Lancet 2003;361:726-35.
50. Kaul DR, Cinti SK, Carver PL, et al. HIV protease inhibitors; Advances in therapy and adverse reactions, including metabolic complications. Pharmacotherapy 1999;19(3):281-98.
51. Sluys TEMS, Ende ME van der, Swart GR, Berg JWO van der, Wilson JHP. Body composition in patients with acquired immunodeficiency syndrome: A validation study of Bioelectric Impedance Analysis. J Parenteral Enteral Nutr 1993;17:404-6.
52. Hadigan C, Rabe J, Meininger G, Aliabadi N, Breu J, Grinspoon S. Inhibition of lipolysis improves insulin sensitivity in protease inhibitor-treated HIV-infected men with fat redistribution. Am J Clin Nutr 2003;77:490-4.

53. Carr A, Law M, on behalf of the HIV Lipodystrophy Case Definition Study group. An objective lipodystrophy severity grading scale derived from the lipodystrophy case definition score. J Acquir Immune Defic Syndr 2003;33:571-6.
54. Martinez E, Bianchi L, Garcia-Viejo M, Bru C, Gatell J. Sonographic assessment of regional fat in HIV-1-infected people. Lancet 2000;356:1412-3.
55. Hadigan C, Corcoran C, Basgoz N, Davis B, Sax P, Grinspoon S. Metformin in the treatment of HIV lipodystrophy syndrome: A randomized controlled trial. JAMA 2000;284(4):472-7.
56. Gelato M, Mynarcik D, Quick J, et al. Improved insulin sensitivity and body fat distribution in HIV-infected patients treated with rosiglitazone; a pilot study. J Acquir Immune Defic Syndr 2002;31:163-70.
57. Walli R, Michl G, Mühlbayer D, Vrinkmaan L, Goebel F. Effects of roglitazone on insulin sensitivity in HIV-infected patients with protease inhibitor-associated diabetes mellitus. Res Exp Med (Berl) 2000;199(5):253-62.
58. Riddle T, Fichtenbaum C, Hui D. Leptin replacement therapy but not dietary polyunsaturated fatty acid alleviates HIV protease inhibitor-induced dyslipidemia and lipodystrophy in mice. J Acquir Immune Defic Syndr 2003;33:564-70.
59. Oral EA, Simha V, Ruiz E, et al. Leptin-replacement for lipodystrophy. N Engl J Med 2002;346:570-8.
60. Petersen K, Oral E, Dufour S, et al. Leptin reverses insulin resistance and hepatic steatosis in patients with severe lipodystrophy. J Clin Invest 2002;109(10):1345-50.
61. Manfredi R, Chiodo F. Disorders of lipid metabolism in patients with HIV disease treated with antiretroviral agents: frequency, relationship with administered drugs, and role of hypolipidaemic therapy with bezafibrate. J Infect 2001;41:181-8.
62. Moyle GJ, Lloyd M, Reynolds B, Baldwin C, Mandalia S, Gazzard BG. Dietary advice with or without pravastatin for the management of hypercholesterolaemia associated with protease inhibitors. AIDS 2001;15(12):1503-8.
63. Drechsler H, Powderly W. Switching effective antiretroviral therapy: a review. Clin Infect Dis 2002;35:1219-30.
64. Carr A, Workman C, Smith D, et al. Abacavir substitution for nucleoside analogs in patients with HIV lipodystrophy; A randomised trial. JAMA 2002;288:207-15.
65. Estrada V, Villar N de, Martinez Larrad M, Gonzalez Lopez A, Fernandez C, Serrano-Rios M. Long-term metabolic consequences of switching from protease inhibitors to efavirenz in therapy for human immunodeficiency virus-infected patients with lipodystrophy. Clin Infect Dis 2002;35:69-76.
66. Wensing A, Reedijk M, Richter C, Boucher C, Borleffs J. Replacing ritonavir by nelfinavir or nelfinavir/saquinavir as part of highly active antiretroviral therapy leads to an improvement of triglyceride levels. AIDS 2001;15:2191-3.
67. Murphy R, Smith W. Switch studies; a review. HIV Med 2002;3:146-55.
68. Opravil M, Hirshel B, Lazzarin A, et al, Swiss cohort study. A randomised trial of simplified maintenance therapy with abacavir, lamivudine, and zidovudine in human immunodeficiency virus infection. J Infect Dis 2002;185:1251-60.
69. Negredo E, Cruz L, Paredes R, et al. Virological, immunological and clinical impact of switching from protease inhibitors to nevirapine or to efavirenz in patients with human immunodeficiency virus infection and long-lasting vial suppression. Clin Infect Dis 2002;34:504-10.
70. Cheonis N. New Fill to treat facial wasting. Bull Exp Treat AIDS 2002;15(2);10-5.
71. Dalakas MC, Illa II, Pezeshkpour GH, Laukaitis JP, Cohen B, Griffin JL. Mitochondrial myopathy caused by long-term zidovudine therapy. N Eng J Med 1990;322:1098-105.
72. Swartz MN. Mitochondrial toxicity - New adverse drug effects. N Eng J Med 1995;333:1146-8.
73. Peters BS, Winer J, Landon DN, Stotter A, Pinching AJ. Mitochondrial myopathy associated with chronic zidovudine therapy in AIDS. QJM 1993;86:5-15.
74. Fortgang IS, Belitsos PC, Chaisson RE, Moore RD. Hepatomegaly and steatosis in HIV-infected patients receiving nucleoside analogue antiretroviral therapy. Am J Gastroenterol 1995;90:1433-6.
75. Moyle GJ. Toxicity of antiretroviral nucleoside and nucleotide analogues. Is mitochondrial toxicity the only mechanism? Drug Safety 2000;23:467-81.
76. Valk M van der, Gisolf EH, Reiss P, et al. Increased risk of lipodystrophy when nucleoside analogue reverse transcriptase inhibitors are included with protease inhibitors in the treatment of HIV-1 infection. AIDS 2001;15:847-55.
77. Lea AP, Faulds D. Stavudine: a review of its pharmacodynamic and pharmacokinetic properties and clinical potential in HIV infection. Drugs 1996;51:846-64.
78. Perry CM, Balfour JA. Didanosine. An update on its antiviral activity, pharmacokinetic properties and therapeutic efficacy in the management of HIV disease. Drugs 1996;52:928-62.
79. Adkins JC, Peters DH, Faulds D. Zalcitabine. An update of its pharmacodynamic and pharmacokinetic properties and clinical efficacy in the management of HIV infection. Drugs 1997;53:1054-80.
80. Hoetelmans RM, Burger DM, Meenhorst PL, Beijnen JH. Pharmacokinetic individualisation of zidovudine therapy. Current state of pharmacokinetic-pharmacodynamic relationships. Clin Pharmacokinet 1996;30:314-27.
81. Wilde MI, Langtry HD. Zidovudine. An update of its pharmacodynamic and pharmacokinetic properties, and therapeutic efficacy. Drugs 1993;46:515-78.
82. Hofstede HJM ter, Marie S de, Foudraine NA, Danner SA, Brinkman K. Clinical features and risk factors of lactic acidosis following long-term antiretroviral therapy: 4 fatal cases. Int J STD AIDS 2000;11:611-6.
83. Hofstede HJM ter, Brinkman K. Mitochondrial toxicity owing to nucleoside reverse transcriptase inhibitors: importance of clinical features and early diagnosis. Int Antiviral News 1999;7:148-51.
84. Arnaudo E, Dalakas M, Shanske S, et al. Depletion of muscle mitochondrial DNA in AIDS patients with zidovudine-induced myopathy. Lancet 1991;337:(8740):508-10.
85. Peters BS, Winer J, Landon DN, et al. Mitochondrial myopathy associated with chronic zidovudine therapy in AIDS. QJM 1993;86:(1):5-15.
86. Chariot P, Gherardi R. Myopathy and HIV infection. Curr Opin Rheumatol 1995;7(6):497-502.
87. Dalakas MC, Illa I, Pezeshkpour GH, et al. Mitochondrial myopathy caused by long-term zidovudine toxicity. N Engl J Med 1990;322:1098-105.
88. Lai KK, Gang DL, Zawacki JK, et al. Fulminant hepatic failure associated with 2'3'-dideoxyinosine (ddI). Ann Intern Med 1991;115:283-4.

89. Chariot P, Gherardi R. Partial cytochrome c oxidase deficiency and cytoplasmic bodies in patients with zidovudine myopathy. Neuromuscul Disord 1991;1:(5):357-63.
90. Chariot P, Monnet I, Gherardi R. Cytochrome c oxidase reaction improves histopathological assessment of zidovudine myopathy. Ann Neurol 1993;34(4):561-5.
91. Munnich A, Rustin P, Rötig A, et al. Clinical aspects of mitochondrial disorders. J Inherit Metab Dis 1992;15:448-55.
92. Chariot P, Monnet I, Mouchet M, et al. Determination of the blood lactate: pyruvate ratio as a non-invasive test for the diagnosis of zidovudine myopathy. Arthritis Rheum 1994;37(4):583-6.
93. Sundar K, Suarez M, Banogon PE, Shapiro JM. Zidovudine-induced fatal lactic acidosis and hepatic failure in patients with acquired immunodeficiency syndrome: report of two patients and review of the literature. Crit Care Med 1997;25:1425-30.
94. Falco V, Rodríguez D, Ribera E, et al. Severe nucleoside-associated lactic acidosis in human immunodeficiency virus-infected patients: Report of 12 cases and review of the literature. Clin Infect Dis 2002;34:838-46.
95. Lenzo NP, Garas BA, French MA. Hepatic steatosis and lactic acidosis associated with treatment in an HIV patient: a case report [Letter]. AIDS 1997;11:1294-6.
96. Lonergan TJ, Behling C, Pfander H, Hassanein TI, Mathews WC. Hyperlactataemia and hepatic abnormalities in 10 human immunodeficiency virus-infected patients receiving nucleoside analogue combination regimens. Clin Infect Dis 2000;31:162-6.
97. Mokrzycki MH, Harris C, May H, Laut J, Palmisano J. Lactic acidosis associated with stavudine administration: A report of five cases. Clin Infect Dis 2000;30:198-200.
98. Miller KD, Cameron M, Wood LV, Dalakas MC, Kovacs JA. Lactic acidosis and hepatic steatosis associated with use of stavudine: Report of four cases. Ann Intern Med 2001;133:192-6.
99. John M, Moore CB, James IR. Chronic hyperlactatemia in HIV infected patients on antiretroviral therapy. AIDS 2001;15:717-23.
100. Boubaker K, Flepp M, Sudre P, et al. Hyperlactatemia and antiretroviral therapy: The Swiss Cohort Study. Clin Infect Dis 2001;33:1931-7.
101. Gerard Y, Maulin L, Yazdanpanah Y. Symptomatic hyperlactataemia: an emerging complication of antiretroviral therapy. AIDS 2000;14:2723-30.
102. Delgado J, Harris M, Tesiorowski A, Montaner JSG. Symptomatic elevations of lactic acidosis and their response to treatment manipulation in human immunodeficiency virus-infected persons: a case series. Clin Infect Dis 2001;33:2072-4.
103. Vrouwenraets S, Treskens M, Regez RM, et al. Hyperlactatemia in HIV-infected patients: the role of NRTI treatment [Abstract 625]. 8th Conference on retroviruses and opportunistic infections. Chicago, 2001.
104. Brew B, Tisch S, Law M. Lactate concentrations distinguish between nucleoside neuropathy and HIV distal symmetrical sensory polyneuropathy [Abstract 9]. 8th Conference on Retroviruses and Opportunistic Infections. Chicago, 2001.
105. Brinkman K. Editorial response: Hyperlactatemia and hepatic steatosis as features of mitochondrial toxicity of nucleoside reverse transcriptase inhibitors. Clin Infect Dis 2000;31:167-9.
106. Brinkman K. Management of hyperlactatemia: no need for routine lactate measurements. AIDS 2001;15:795-7.
107. Boffito M, Marietti G, Audagnotto S, Raiter R, Di Perri G. Lactacidemia in asymptomatic HIV-infected subjects receiving nucleoside reverse-transcriptase inhibitors. Clin Infect Dis 2002;34:558-9.
108. Benbrik E, Chariot P, Bonavaud S, et al. Cellular and mitochondrial toxicity of zidovudine (AZT), didanosine (ddI) and zalcitabine (ddC) on cultured human muscle cells. J Neuol Sci 1997;149:19-25.
109. Bartley PB, Westacott L, Boots RJ, et al. Large hepatic mitochondrial DNA deletions associated with L-lactic acidosis and highly active antiretroviral therapy. AIDS 2001;15(3):419-20.
110. Côté HCF, Brumme ZL, Craib KJP, et al. Changes in mitochondrial DNA as marker of nucleoside toxicity in HIV-infected patients. N Engl J Med 2002;346:811-20.
111. Walker U, Setzer B, Venhoff N. Increased long-term mitochondrial toxicity in combinations of nucleoside analogue reverse transcriptase inhibitors. AIDS 2002;16:2165-73.
112. Vittecoq D, Jardel C, Barthelemy C, et al. Mitochondrial damage associated with long-term antiretroviral treatment; associated alteration or causal disorder? J Acquir Immune Defic Syndr 2002;31:299-308.
113. Cossarizza A, Troiano L, Mussini C. Mitochondria and HIV infection; the first decade. J Biol Regul Homeost Agents 2002;16:18-24.
114. Dalakas M, Semino-Mora C, Leon-Monzon M. Mitochondrial alterations with mitochondrial DNA depletion in the nerves of AIDS patients with peripheral neuropathy induced by 2'3'-dideoxycytidine (ddC). Lab Invest 2001;81:1537-44.
115. Shikuma C, Hu N, Milne C, et al. Mitochondrial DNA decrease in subcutaneous adipose tissue of HIV-infected individuals with peripheral lipoatrophy. AIDS 2001;15:1801-9.
116. Casademont J, Barrientos A, Grau J, et al. The effect of zidovudine on skeletal muscle mtDNA in HIV-1 infected patients with mild or no muscle dysfunction. Brain 1996;119:1357-64.
117. Tsai C, Doong S, Johns D, Driscoll J, Cheng Y. Effect of anti-HIV 2'-beta-fluoro-2',3'-dideoxynucleoside analogs on the cellular content of mitochondrial DNA and on lactate production. Biochem Pharmacol 1994;48:1477-81.
118. Arnaudo E, Dalakas M, Shanske S, Moreas C, DiMauro S, Schon E. Depletion of muscle DNA in AIDS patients with zidovudine-induced myopathy. Lancet 1991;337:508-10.
119. Fouty B, Frerman F, Reves R. Riboflavin to treat nucleoside analogue induced lactic acidosis. Lancet 1998,;352: 291-2.
120. Luzatti R, Del Bravo P, Di Perri G, Luzzani A, Concia E. Riboflavin and severe lactic acidosis. Lancet 1999;353:901-2.
121. Przyrembel H. Therapy of mitochondrial disorders. J Inherit Metab Dis 1987;10(suppl 1):129-46.
122. Walker UA, Byrne E. The therapy of respiratory chain encephalomyopathy: a critical review of the past and current perspective. Acta Neurol Scand 1995;92:273-80.
123. Semino Mora MC, Leon Monzon ME, Dalakas MC. Effect of L-carnitine on the zidovudine-induced destruction of human myotubes. Part I: L-carnitine prevents the myotoxicity of AZT in vitro. Lab Invest 1994;71:102-12.