HAART AND THE MITOCHONDRIA

Links:

In Vitro Cytotoxicity and Mitochondrial Toxicity of Tenofovir Alone and in Combination with Other Antiretrovirals in Human Renal Proximal Tubule Cells_

http://aac.highwire.org/cgi/reprint/50/11/3824

Impact of nucleoside reverse transcriptase inhibitors on mitochondrial DNA and RNA in human skeletal muscle cells.

http://www.pubmedcentral.nih.gov/picrender.fcgi?artid=2493104&blobtype=pdf

Impact of nucleoside reverse transcriptase inhibitors on mitochondria in human immunodeficiency virus type 1-infected children receiving highly active antiretroviral therapy.

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Zidovudine inhibits thymidine phosphorylation in the isolated perfused rat heart.

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Oxidative stress and toxicity induced by the nucleoside reverse transcriptase inhibitor (NRTI)--2',3'-dideoxycytidine (ddC): relevance to HIV-dementia.

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Pathogenesis of osteopenia/osteoporosis induced by highly active anti-retroviral therapy for AIDS.

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Hyperlactatemia in human immunodeficiency virus-uninfected infants who are exposed to antiretrovirals.

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Phosphorylation of thymidine and AZT in heart mitochondria: elucidation of a novel mechanism of AZT cardiotoxicity.

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Mitochondrial membrane hyperpolarization hijacks activated T lymphocytes toward the apoptotic-prone phenotype: homeostatic mechanisms of HIV protease inhibitors.

http://www.jimmunol.org/cgi/reprint/170/12/6006

Nucleoside analogues and HIV: the combined cost to mitochondria.

http://jac.oxfordjournals.org/cgi/reprint/51/5/1091

Mitochondrial disruption and apoptosis in lymphocytes of an HIV infected patient affected by lactic acidosis after treatment with highly active antiretroviral therapy

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Mitochondrial toxicity and HIV therapy.

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Use of anti-retrovirals in pediatric HIV-infection

http://www.ijdvl.com/article.asp?issn=0378-6323;year=2008;volume=74;issue=3;spage=208;epage=214;aulast=Gaur

Acute Respiratory Failure following HAART

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AIDS and the lung in a changing world

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Dyslipidemia and Cardiovascular Disease Risk with HAART

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Adverse effects of antiretroviral treatment

http://www.ijdvl.com/article.asp?issn=0378-6323;year=2008;volume=74;issue=3;spage=234;epage=237;aulast=Sharma

Inflammatory Reactions in HIV-1 infected persons after Initiation of HAART

http://www.annals.org/cgi/reprint/133/6/447.pdf

Targeted Transgenic Overexpression of Mitochondrial Thymidine Kinase (TK2) Alters Mitochondrial DNA (mtDNA) and Mitochondrial Polypeptide Abundance

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Cardiac-Targeted Transgenic Mutant Mitochondrial Enzymes: mtDNA Defects, Antiretroviral Toxicity and Cardiomyopathy

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Tenofovir renal toxicity targets mitochondria of renal proximal tubules

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Mitochondrial DNA Impairment in NRTIs-Associated Cardiomyopathy

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Highly active antiretroviral Therapy and the Kidney

http://cjasn.asnjournals.org/cgi/reprint/1/1/117

Suboptimal CD4 gains in HIV-infected patients receiving didanosine plus tenofovir

http://jac.oxfordjournals.org/cgi/reprint/57/5/806

Hepatotoxicity in HIV-infected children and adolscents on antiretroviral therapy

http://www.scielo.br/pdf/spmj/v125n4/v125n4a02.pdf

Impact of Nucleoside Reverse Transcriptase Inhibitors on mitochondrial DNA and RNA in human skeletal muscle cells

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Impact of Nucleoside Reverse Transcriptase Inhibitors on Mitochondria in HIV-1 infected children receiving HAART

http://www.pubmedcentral.nih.gov/picrender.fcgi?artid=2167993&blobtype=pdf

Abstracts:

Environ Mol Mutagen. 2007 Apr-May;48(3-4):166-72. Links

A brief overview of mechanisms of mitochondrial toxicity from NRTIs.

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Nucleoside reverse transcriptase inhibitors (NRTIs) in combinations with other antiretrovirals (highly active antiretroviral therapy, HAART) are the cornerstones of AIDS therapy, turning HIV infection into a manageable clinical entity. Despite the initial positive impact of NRTIs, therapeutic experience revealed serious side effects that appeared to originate in the mitochondria and which ultimately manifested as dysfunction of that organelle. It may be reasonable to consider that as the AIDS epidemic continues and as survival with HIV infection is prolonged by treatment with HAART, long-term side effects of NRTIs may become increasingly common. This consideration may be underscored in children who are born to HIV-infected mothers who received NRTI therapy in utero during gestation. The long-term effect of that NRTI exposure in utero is not clear yet. This review examines some proposed mechanisms of NRTI mitochondrial toxicity, including genetic predisposition, defects in mitochondria DNA replication, the encompassing "DNA pol-gamma hypothesis," the relationship between mitochondrial nucleotide and NRTI pools, mitochondrial DNA mutation and dysfunction, and oxidative stresses related to HIV infection and NRTIs. Mechanisms of mitochondrial toxicity are reviewed with respect to key cell biological, pathological, and pharmacological events. (c) 2006 Wiley-Liss, Inc.

1: Am J Pathol. 2007 Mar;170(3):865-74.
Links

Targeted transgenic overexpression of mitochondrial thymidine kinase (TK2) alters mitochondrial DNA (mtDNA) and mitochondrial polypeptide abundance: transgenic TK2, mtDNA, and antiretrovirals.

Hosseini SH, **Kohler JJ**, **Haase CP**, **Tioleco N**, **Stuart T**, **Keebaugh E**, **Ludaway T**, **Russ R**, **Green E**, **Long R**, **Wang L**, **Eriksson S**, **Lewis W**.

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Mitochondrial toxicity limits nucleoside reverse transcriptase inhibitors (NRTIs) for acquired immune deficiency syndrome. NRTI triphosphates, the active moieties, inhibit human immunodeficiency virus reverse transcriptase and eukaryotic mitochondrial DNA polymerase pol-gamma. NRTI phosphorylation seems to correlate with mitochondrial toxicity, but experimental evidence is lacking. Transgenic mice (TGs) with cardiac overexpression of thymidine kinase isoforms (mitochondrial TK2 and cytoplasmic TK1) were used to study NRTI mitochondrial toxicity. Echocardiography and nuclear magnetic resonance imaging defined cardiac performance and structure. TK gene copy and enzyme activity, mitochondrial (mt) DNA and polypeptide abundance, succinate dehydrogenase and cytochrome oxidase histochemistry, and electron microscopy correlated with transgenesis, mitochondrial structure, and biogenesis. Antiretroviral combinations simulated therapy. Untreated hTK1 or TK2 TGs exhibited normal left ventricle mass. In TK2 TGs, cardiac TK2

gene copy doubled, activity increased 300-fold, and mtDNA abundance doubled. Abundance of the 17-kd subunit of complex I, succinate dehydrogenase histochemical activity, and cristae density increased. NRTIs increased left ventricle mass 20% in TK2 TGs. TK activity increased 3 logs in hTK1 TGs, but no cardiac phenotype resulted. NRTIs abrogated functional effects of transgenically increased TK2 activity but had no effect on TK2 mtDNA abundance. Thus, NRTI mitochondrial phosphorylation by TK2 is integral to clinical NRTI mitochondrial toxicity.

: Chem Res Toxicol. 2008 May;21(5):990-6. Epub 2008 Apr 5.

Mitochondrial DNA impairment in nucleoside reverse transcriptase inhibitor-associated cardiomyopathy.

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Acquired immune deficiency syndrome (AIDS) is a global epidemic that continues to escalate. Recent World Health Organization estimates include over 33 million people currently diagnosed with HIV/AIDS. Another 20 million HIV-infected individuals died over the past quarter century. Antiretrovirals are effective treatments that changed the outcome of HIV infection from a fatal disease to a chronic illness. Cardiomyopathy (CM) is a bona fide component of HIV/AIDS with occurrence that is higher in HIV positive individuals. CM may result from individual or combined effects of HIV, immune reactions, or toxicities of prolonged antiretrovirals. Nucleoside reverse transcriptase inhibitors (NRTIs) are the cornerstone of antiretroviral therapy. Despite pharmacological benefits of NRTIs, NRTI side effects include increased risk for CM. Clinical observations and in vitro and in vivo studies support various mechanisms of CM. This perspective highlights some of the hypotheses and focuses on mitochondrial-associated pathways of NRTI- related CM.

Cardiovasc Toxicol. 2008 Summer;8(2):57-69. Epub 2008 Apr 30.

Cardiac-targeted transgenic mutant mitochondrial enzymes: mtDNA defects, antiretroviral toxicity and cardiomyopathy.

Kohler JJ, **Hosseini SH**, **Green E**, **Hoying-Brandt A**, **Cucoranu I**, **Haase CP**, **Russ R**, **Srivastava J**, **Ivey K**, **Ludaway T**, **Kapoor V**, **Abuin A**, **Shapoval A**, **Santoianni R**, **Saada A**, **Elpeleg O**, **Lewis W**.

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Mitochondrial (mt) DNA biogenesis is critical to cardiac contractility. DNA polymerase gamma (Pol gamma) replicates mtDNA, whereas thymidine kinase 2 (TK2) monophosphorylates pyrimidines intramitochondrially. Point mutations in POLG and TK2 result in clinical diseases associated with mtDNA depletion and organ dysfunction. Pyrimidine analogs (NRTIs) inhibit Pol gamma and mtDNA replication. Cardiac "dominant negative" murine transgenes (TGs; Pol gamma Y955C, and TK2 H121N or I212N) defined the role of each in the heart. mtDNA abundance, histopathological features, histochemistry, mitochondrial protein abundance, morphometry, and echocardiography were determined for TGs in "2 x 2" studies with or without pyrimidine analogs. Cardiac mtDNA abundance decreased in Y955C TGs (approximately 50%) but increased in H121N and I212N TGs (20-70%). Succinate dehydrogenase (SDH) increased in hearts of all mutants. Ultrastructural changes occurred in Y955C and H121N TGs. Histopathology demonstrated hypertrophy in H121N, LV dilation in I212N, and both hypertrophy and dilation in Y955C TGs. Antiretrovirals increased LV mass (approximately 50%) for all three TGs which combined with dilation indicates cardiomyopathy. Taken together, these studies demonstrate three manifestations of cardiac dysfunction that depend on the nature of the specific mutation and antiretroviral treatment. Mutations in genes for mtDNA biogenesis increase risk for defective mtDNA replication, leading to LV hypertrophy.

1: Lab Invest. 2009 May;89(5):513-9. Epub 2009 Mar 9.

Tenofovir renal toxicity targets mitochondria of renal proximal tubules.

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Tenofovir disoproxil fumarate (TDF) is an analog of adenosine monophosphate that inhibits HIV reverse transcriptase in HIV/AIDS. Despite its therapeutic success, renal tubular side effects are reported. The mechanisms and targets of tenofovir toxicity were determined using '2 x 2' factorial protocols, and HIV transgenic (TG) and wild-type (WT) littermate mice with or without TDF (5 weeks). A parallel study used didanosine (ddI) instead of TDF. At termination, heart, kidney, and liver samples were retrieved. Mitochondrial DNA (mtDNA) abundance, and histo- and ultrastructural pathology were analyzed. Laser-capture microdissection (LCM) was used to isolate renal proximal tubules for molecular analyses. Tenofovir increased mtDNA abundance in TG whole kidneys, but not in their hearts or livers. In contrast, ddI decreased mtDNA abundance in the livers of WTs and TGs, but had no effect on their hearts or kidneys. Histological analyses of kidneys showed no disruption of glomeruli

or proximal tubules with TDF or ddI treatments. Ultrastructural changes in renal proximal tubules from TDF-treated TGs included an increased number and irregular shape of mitochondria with sparse fragmented cristae. LCM-captured renal proximal tubules from TGs showed decreased mtDNA abundance with tenofovir. The results indicate that tenofovir targets mitochondrial toxicity on the renal proximal tubule in an AIDS model.

Mitochondrial function, morphology and metabolic parameters improve after switching from stavudine to a tenofovir-containing regimen

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Received 3 December 2008; returned 19 January 2009; revised 24 February 2009; accepted 26 February 2009

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Objectives: HIV-associated lipoatrophy has been associated with **mitochondria**l dysfunction induced by nucleoside reverse transcriptase inhibitor therapy. We hypothesize that lipid profiles **and** markers of **mitochondria**l function will improve in HIV-lipoatrophic patients switched to the nucleotide analogue tenofovir.

Methods: Ten patients receiving stavudine, lamivudine **and** lopinavir/ritonavir (Kaletra®) for over 6 years were switched from stavudine to tenofovir for 48 weeks. Subcutaneous fat tissue biopsies, fasting metabolic tests, HIV RNA, CD4 cell count **and** whole body dual energy X-ray absorptiometry (DEXA) scans were obtained at study entry **and** week 48. **Mitochondria**l DNA (mtDNA) copies/cell **and mitochondria**l morphology were assessed in adipose tissue biopsies, mtDNA 8-oxo-deoxyguanine in peripheral blood mononuclear cells, **and** glutathione (GSH) **and** F2-isoprostane in plasma.

Results: There was no change in limb fat mass by DEXA; however, trunk fat mass increased by 18.9% ($P = 0.01$). Fasting total cholesterol decreased by 33 mg/dL ($P = 0.005$) **and** serum glucose decreased by 4 mg/dL ($P = 0.039$). mtDNA copies/cell increased from 386 to 1537 ($P < 0.001$). Transmission electron microscopy showed that **mitochondria**l cristae were lacking or poorly defined at study entry, whereas **mitochondria**l inner structures were more well defined **and** outer membranes were intact at 48 weeks. Oxidative damage decreased in 8/10 patients, GSH increased **and** F2-isoprostane decreased.

Conclusions: The results from this study demonstrate that systemic **and** peripheral fat **mitochondria** improve in patients switched to tenofovir following long-term exposure to stavudine, while continuing protease inhibitor therapy.

Keywords: adipose , HIV , lipodystrophy , metabolic , **mitochondria**

1: J Acquir Immune Defic Syndr. 2008 Aug 1;48(4):381-8. Links

Lymphocyte mitochondrial depolarization and apoptosis in HIV-1-infected HAART patients.

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BACKGROUND: Efavirenz (EFV) and nevirapine (NVP), unlike nucleoside reverse transcriptase inhibitor drugs, do not inhibit mitochondrial (mt) polymerase gamma (Pol-gamma), although EFV has been shown to induce mt depolarization (Deltapsim) in vitro at supratherapeutic concentrations. However, the capacity of nonnucleoside reverse transcriptase inhibitor drugs to induce mt toxicity in vivo remains undetermined. OBJECTIVE: To determine the influence of EFV and NVP on peripheral lymphocyte mt transmembrane potential (Deltapsim) and apoptosis in HIV-1-infected patients treated with these nonnucleoside reverse transcriptase inhibitors. METHODS: Thirty-two HIV-1-infected patients on highly active antiretroviral therapy (HAART) between 4 and 24 months (12 on EFV, 20 on NVP) and 16 HAART-naive HIV-1-infected patients were enrolled into this study. All participants were black South African patients. Spontaneous peripheral lymphocyte apoptosis and Deltapsim were measured ex vivo by flow cytometry for all patients. RESULTS:: CD4 T-helper apoptosis for the EFV and NVP cohorts was 19.38% +/- 2.62% and 23.35% +/- 1.51% (mean +/- SEM), respectively, whereas total lymphocyte Deltapsim was 27.25% +/- 5.05% and 17.04% +/- 2.98%, respectively. Both parameters for each cohort were significantly lower ($P < 0.05$) than that of the HAART-naive patients. The NVP cohort exhibited both a significant time-dependent increase in peripheral lymphocyte Deltapsim ($P = 0.038$) and correlation between T-helper apoptosis and Deltapsim ($P = 0.0005$). These trends were not observed in the EFV cohort. CONCLUSIONS: This study provides evidence that both EFV and NVP induce peripheral lymphocyte Deltapsim in HIV-1-infected patients on nonnucleoside reverse transcriptase inhibitor-based HAART, which in the case of NVP is sufficient to induce the apoptosis cascade.

1: Antimicrob Agents Chemother. 2008 Aug;52(8):2825-30. Epub 2008 Jun 9.
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Impact of nucleoside reverse transcriptase inhibitors on mitochondrial DNA and RNA in human skeletal muscle cells.

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We previously reported that 2',3'-dideoxyinosine (didanosine, or ddI) significantly altered mitochondrial DNA (mtDNA) in peripheral blood mononuclear cells in human immunodeficiency virus type 1 (HIV-1)-infected children who had undetectable plasma HIV-1 RNA for more than 2 years while receiving highly active antiretroviral therapy. This research examines the in vitro effects of nucleoside reverse transcriptase inhibitors (NRTIs) on mitochondria of human skeletal muscle cells (HSMCs), including myoblasts and differentiated myotubes. mtDNA, mitochondrial RNA (mtRNA), and mRNA levels for nuclear mitochondrial regulatory factors were quantified in vitro using HSMCs, including myoblasts and differentiated myotubes, treated with NRTIs singly and in combination. After 5 days of treatment, mtDNA was significantly decreased in myoblasts and myotubes treated with ddI ($P < 0.001$ and $P = 0.01$, respectively) and ddI-containing regimens ($P < 0.001$ and $P < 0.001$, respectively) compared to levels in untreated cells. mtRNA (MTCYB) was also significantly decreased in the myoblasts and myotubes treated with ddI ($P = 0.004$) and ddI-containing regimens ($P < 0.001$). Regardless of the NRTI regimens examined, NRTI combinations significantly decreased mtRNA (MTCO3) in myoblasts and myotubes ($P = 0.02$ and $P = 0.01$, respectively). No significant differences were observed for nuclear mitochondrial regulatory factor mRNA in myoblasts or myotubes when treated with NRTIs ($P > 0.07$). ddI and ddI-containing regimens significantly decrease mtDNA and mtRNA in HSMCs, most notably in myoblasts. These findings may be of particular importance in developing countries, where ddI is widely used for first-line treatment of HIV-infected children.

1: Pharmacology. 2008;82(2):83-8. Epub 2008 May 27. KARGER Full Text Links

Mechanisms of zidovudine-induced mitochondrial toxicity and myopathy.

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Zidovudine (3-azido-3'-deoxythymidine), also referred to as azidothymidine (AZT), has become an integral component in highly active antiretroviral therapy, and has also been used in the treatment of cancer. The clinical effectiveness of AZT is constrained due to its association with increased adverse effects, such as myopathy. There are numerous potential mechanisms that may contribute to AZT-induced myopathy. The first hypothesized mechanism to explain AZT-induced toxicity was mtDNA depletion due to inhibition of DNA polymerase gamma. Although mtDNA depletion is present

in patients with myopathy, current data suggests that alternative mechanisms may play a more direct role in the myotoxicity. These mechanisms include AZT-induced oxidative stress, direct inhibition of mitochondrial bioenergetic machinery, and mitochondrial depletion of L-carnitine. Furthermore, we hypothesize that apoptosis may play a role in AZT-induced myopathy. Copyright 2008 S. Karger AG, Base

1: Curr Med Res Opin. 2008 Mar;24(3):609-24. Links

HIV lipodystrophy and its metabolic consequences: implications for clinical practice.

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BACKGROUND: The introduction of highly active antiretroviral therapy (HAART) around 1996 markedly reduced mortality and morbidity from human immunodeficiency virus (HIV) infection. As life expectancy has improved, the chronic complications of HIV and HAART have become increasingly relevant. SCOPE: This article provides an overview of the HIV-associated lipodystrophy, its pathogenesis and its clinical consequences (based on a search strategy in PubMed including literature published to November 2007). FINDINGS: Lipodystrophy syndrome is characterized by abnormal fat distribution syndrome associated with metabolic disturbances and includes insulin resistance, deranged glucose and lipid metabolism. It is associated with increased risks of progression to type 2 diabetes and cardiovascular disease. Robust diagnostic criteria are required for lipodystrophy, and subsequent prospective cohort studies and randomized controlled trials are then required to determine the etiology and prognosis of lipodystrophy, and to evaluate therapeutic interventions for this consequence of HAART. Therapies to improve insulin resistance have been tried but they are frequently ineffective, and are limited by potential toxicity in this population. Hence, current management options for HIV associated lipodystrophy are limited and are mostly based on avoidance of risk factors and switching of antiretroviral drugs. CONCLUSION: As the '3 by 5 strategy' of providing HIV drugs to the developing world is implemented worldwide, the numbers of patients adhering to antiretroviral medicines is dramatically increasing. One must be aware that in reducing the burden of acute retroviral disease, the treatments proposed might lead to significant rates of metabolic complications and further exacerbation of the epidemic of diabetes and cardiovascular disease.

1: Pediatr Infect Dis J. 2008 Jan;27(1):17-21. Links

Effects of the change from Stavudine to tenofovir in human immunodeficiency virus-infected children treated with highly active antiretroviral therapy: studies on mitochondrial toxicity and thymic function.

Rosso R, **Nasi M**, **Di Biagio A**, **Repetto E**, **Dentone C**, **Pinti M**, **Nemes E**, **Ferraresi R**, **Mussini C**, **Esposito R**, **Viscoli C**, **Cossarizza A**.

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BACKGROUND:Changing from drugs that have significant mitochondrial toxicity to less toxic compounds may be of benefit in human immunodeficiency virus (HIV)-positive patients who receive highly active antiretroviral therapy. Few data on mitochondrial toxicity of antiviral drugs are available in HIV-positive children. METHODS: Eighteen HIV-positive children (median age, 10.9 years) receiving a stavudine-containing regimen were randomized to maintain stavudine (arm A) or change to tenofovir (arm B), while preserving the remaining drugs. Glucose, lipidic, and viro-immunologic factors were assessed at months 0, 1, 3, 6, 12, and 18. Thymic output and mtDNA content were measured in peripheral blood mononuclear cells at 0 and 6 months, mtDNA in isolated CD4+ and CD8+ T cells after 18 months. RESULTS: From baseline to month 6, arms A and B showed similar thymic output and mtDNA. After 18 months, a significant decrease in plasma HDL was observed in arm B, along with a small increase in blood glucose; mtDNA showed no difference. In the 2 arms other factors did not show significant differences from the baseline and from the previous values at 18 months. CONCLUSIONS: Changing from stavudine to tenofovir was well-tolerated, and viro-immunologic success was maintained.

Curr Opin Clin Nutr Metab Care. 2007 Nov;10(6):693-7.

Lessons that can be learned from patients with diabetogenic mutations in mitochondrial DNA: implications for common type 2 diabetes.

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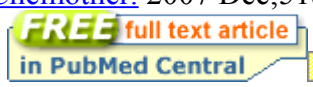
PURPOSE OF REVIEW: To discuss the role of mitochondria in the development of type 2 diabetes. RECENT FINDINGS: Some mutations in mitochondrial DNA are diabetogenic due to a gradual decline in insulin secretion by the pancreas. These mutations also result in abnormalities in lipid metabolism. A similar situation is seen in patients treated with nucleoside analogues as part of highly active antiretroviral therapy to suppress human immunodeficiency virus infection. These drugs induce a 30-50% reduction in mitochondrial DNA copy number in multiple tissues. Treated individuals develop a redistribution of body fat with concomitant development of markers of the metabolic syndrome and an elevated risk of developing type 2 diabetes. Studies have also shown the presence of reduced mitochondrial activity in muscle and adipose tissue in individuals with type 2 diabetes. SUMMARY: These observations suggest a pathogenic model for obesity-associated type 2 diabetes, in which mitochondrial activity in peripheral adipocytes is essential to keep triacylglycerol stored within these cells. Mitochondria protect the organism against fatty acid-induced insulin resistance and lipotoxicity to the pancreas. In adipocytes, mitochondria may remove fatty acids through uncoupled beta oxidation, whereas in muscle fatty acids,

removal is largely driven by adenosine diphosphate production through physical activity.

1: Antimicrob Agents Chemother. 2007 Dec;51(12):4236-42. Epub 2007 Sep 24.



Links

Impact of nucleoside reverse transcriptase inhibitors on mitochondria in human immunodeficiency virus type 1-infected children receiving highly active antiretroviral therapy.

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Mitochondrial toxicity induced by nucleoside reverse transcriptase inhibitors (NRTIs) has been reported to be responsible for various adverse effects. The relative impact of NRTIs on the mitochondria of human immunodeficiency virus (HIV) type 1 (HIV-1)-infected children receiving highly active antiretroviral therapy (HAART) is unknown. Mitochondrial DNA (mtDNA) levels were quantified longitudinally from peripheral blood mononuclear cells (PBMCs) in 31 HIV-1-infected children from Pediatric AIDS Clinical Trial Group Study 382 who were receiving HAART, including nelfinavir, efavirenz, and different NRTIs, and who had had undetectable plasma HIV-1 RNA levels for >2 years. The median mtDNA levels in PBMCs increased from 137 copies/cell at the baseline to 179 copies/cell at week 48 ($P = 0.01$) and 198 copies/cell at week 104 ($P < 0.001$). Before the initiation of HAART, children who received regimens containing didanosine had mtDNA levels persistently lower than those in children not receiving didanosine (106 versus 140 copies/cell; $P = 0.008$). During HAART, the median increase in the mtDNA level from the baseline to week 104 was the lowest in children who received regimens containing didanosine (+26 copies/cell) compared to those in children who received other regimens (+79 copies/cell) ($P = 0.02$). A multivariate analysis also demonstrated that didanosine, as part of HAART, was the only NRTI associated with the change in mtDNA levels ($P = 0.007$). Children receiving didanosine-containing antiretroviral regimens have the lowest mtDNA levels in PBMCs and may be at greater risk for long-term adverse effects due to mitochondrial toxicity. This may be of particular importance in resource-limited countries where didanosine is widely used for the treatment of HIV-infected children.

1: Antivir Ther. 2007;12(5):769-78. Links

The influence of HIV infection and antiretroviral therapy on the mitochondrial membrane potential of peripheral mononuclear cells.

Sternfeld T, **Schmid M**, **Tischleder A**, **Mudra S**, **Schlamp A**, **Kost BP**, **Gruber R**, **Youle M**, **Bogner JR**, **Goebel FD**.

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OBJECTIVES: Clinical disorders occurring in HIV-infected patients on antiretroviral therapy (ART) have been linked to mitochondrial dysfunction, for example, lactic acidosis and lipodystrophy. Mitochondrial membrane potential (delta psi m) is the most direct measure of the state of energization of the mitochondria. We analysed delta psi m, of peripheral blood mononuclear cells (PBMCs) in HIV-negative, healthy subjects (n=8), HIV-infected, treatment-naive patients (n=30), and HIV-infected patients on ART (n=58). The influence of ART was analysed in six patients who started their first regimen. METHODS: The delta psi m of PBMC was measured by flow cytometry using the dye JC-1. RESULTS: The delta psi m was significantly lower in HIV-infected patients than in HIV-negative controls. This difference was detected in both treated (P = 0.0001) and untreated patients (P = 0.001). The delta psi m of PBMCs was highly correlated with CD4+ T-cell count in therapy-naive patients (P = 0.002, r = 0.546) and in treated patients (P = 0.028, r = 0.288). The delta psi m increased significantly in therapy-naive patients after starting ART (P = 0.001). Patients with lipoatrophy had significantly lower delta psi m than patients without lipodystrophy or with lipohypertrophy (P = 0.023). CONCLUSIONS: In HIV-infected persons delta psi m is significantly reduced. Patients with lipoatrophy have significantly reduced delta psi m. This is the first study showing that the delta psi m of PBMCs is highly correlated with CD4+ T-cell count in HIV infection.

Pharmacogenomics J. 2008 Feb;8(1):71-7. Epub 2007 Aug 7.  Links

The mitochondrial pharmacogenomics of haplogroup T: MTND2*LHON4917G and antiretroviral therapy-associated peripheral neuropathy.

Canter JA, **Haas DW**, **Kallianpur AR**, **Ritchie MD**, **Robbins GK**, **Shafer RW**, **Clifford DB**, **Murdock DG**, **Hulgan T**.

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Peripheral neuropathy (PN) due to mitochondrial injury complicates HIV therapy with some nucleoside reverse transcriptase inhibitors (NRTIs). Variation in the mitochondrial genome may influence susceptibility to NRTI toxicities. Two non-synonymous mitochondrial DNA polymorphisms, MTND1*LHON4216C (4216C) and MTND2*LHON4917G (4917G) were characterized in HIV-infected participants exposed to NRTIs in a randomized clinical trial. Among 250 self-identified white, non-Hispanic participants, symptomatic PN (> or = grade 1) developed in 70 (28%). Both 4216C (odds ratio (OR)=1.98 (95% confidence interval (CI) 1.05-3.75); P=0.04) and 4917G (OR=2.93 (95% CI 1.25-6.89); P=0.01) were more frequent in PN cases. These two polymorphisms remained independently associated with PN after adjusting for age, baseline CD4 count, plasma HIV RNA level, and NRTI randomization arm; 4216C (OR=2.0 (95% CI 1.1-4.0) P=0.04) and 4917G (OR=5.5 (95% CI 1.6-18.7) P<0.01). When 4917G individuals were excluded from the analysis, the association

with 4216C was no longer seen. The mitochondrial 4917G polymorphism may increase susceptibility to NRTI-associated PN.

: Curr Pharm Des. 2007;13(21):2208-13. Links

Visceral fat as target of highly active antiretroviral therapy-associated metabolic syndrome.

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HIV-associated lipodystrophy or lipoatrophy, unreported before the introduction of highly active antiretroviral therapy (HAART), was first described in 1998, and has a prevalence ranging from 18% to 83%. As in genetic lipodystrophy syndromes, fat redistribution may precede the development of metabolic complications (dyslipidemia, insulin resistance) in HIV-infected patients receiving HAART. The pathogenesis of HAART-associated lipodystrophy and metabolic syndrome is complex and a number of factors are involved, including direct effects of HAART on lipid metabolism, endothelial and adipocyte cell function, and mitochondria.Protease inhibitors are responsible for a decrease in cytoplasmic retinoic-acid protein-1, in low density lipoprotein-receptor-related protein and in peroxisome proliferator activated receptor type-gamma. Nucleoside reverse transcriptase inhibitors, and thymidine analogues, are responsible for mitochondrial dysfunction as demonstrated by a decrease in subcutaneous adipose tissue mitochondrial DNA content. Both phenomena are responsible for a decreased differentiation of adipocytes, increased levels of free fatty acids and lipoatrophy. The increased levels of proinflammatory cytokines, such as tumor necrosis factor (TNF)-alpha and interleukin-6 may further contribute in development of lipodystrophy. TNF-alfa activates 11-beta-hydroxysteroid dehydrogenase type-1, which converts inactive cortisone to active cortisol, resulting in increased lipid accumulation in adipocytes and insulin resistance. HAART drugs and inflammatory cytokines are associated with a decrease in adiponectin. The levels of adiponectin and adiponectin-to-leptin ratio correlate positively with insulin resistance in HIV-infected patients with lipodystrophy. HAART-associated metabolic syndrome is an increasingly recognized clinical entity. The atherogenic profile of this syndrome may increase the risk of cardiovascular disease even in young HIV-infected patients. A better understanding of the molecular mechanisms responsible for this syndrome will lead to the discovery of new drugs that will reduce the incidence of lipodystrophy and related metabolic complications in HIV-infected patients receiving HAART.

Med Clin (Barc). 2007 Mar 3;128(8):311-6. Links

[Antiretroviral therapy and mitochondrial toxicity]

[Article in Spanish]

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The introduction of highly active antiretroviral therapy for the treatment of human immunodeficiency virus (HIV) infection has led to substantial reduction in morbidity and near-complete suppression of HIV-1 replication. This progress has been tempered by a growing number of new adverse effects. Mitochondrial toxicity is one aspect of these long-term toxicities of antiretroviral drugs, with the role of nucleoside analogs being particularly underlined. Some cases of impaired mitochondrial function have been clearly identified, such as pancreatitis, neuropathy, miopathy and lactic acidosis. Beyond the inhibition of DNA polymerase-g using nucleoside analogs, it appears that several physiopathologic mechanisms interact to explain the observed toxicity. At present there is no reliable method to detect subclinical mitochondrial toxicity. There is no proven effective therapy for antiretroviral therapy-associated mitochondrial toxicity other than ceasing the implicated agent, and even with this strategy, resolution of symptoms may be incomplete. Therefore, investigation of mitochondrial toxicity of new compounds or new combinations is of growing interest for the clinical application of antiretroviral agents.

: Antimicrob Agents Chemother. 2007 Apr;51(4):1142-9. Epub 2007 Jan 12.

Zidovudine inhibits thymidine phosphorylation in the isolated perfused rat heart.

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Zidovudine (AZT; 3'-azido-3'-deoxythymidine), a thymidine analog, has been a staple of highly active antiretroviral therapy. It is phosphorylated in the host to the triphosphate and functions by inhibiting the viral reverse transcriptase. However, long-term use of AZT is linked to various tissue toxicities, including cardiomyopathy. These toxicities are associated with mitochondrial DNA depletion, which is hypothesized to be caused by AZT triphosphate inhibition of mitochondrial DNA polymerase gamma. In previous work with isolated heart mitochondria, we demonstrated that AZT phosphorylation beyond the monophosphate was not detected and that AZT itself was a potent inhibitor of thymidine phosphorylation. This suggests an alternative hypothesis in which depletion of the TTP pool may limit mitochondrial DNA replication. The present work extends these studies to the whole cell by investigating the metabolism of thymidine and AZT in the intact isolated perfused rat heart. [3H]thymidine is converted to [3H]TTP in a time- and concentration-dependent manner. The level of [3H]TMP is low, suggesting that the reaction catalyzed by thymidine kinase is the rate-limiting step in phosphorylation. [3H]AZT is converted in a time- and concentration-dependent manner to AZT monophosphate, the only phosphorylated product detected after 3 h of perfusion. Both compounds display negative cooperativity, similar to the observations with cloned and purified mitochondrial thymidine kinase 2. The presence of AZT in the perfusate inhibits the phosphorylation of [3H]thymidine with a 50% inhibitory concentration of 24+/-4

microM. These data support the hypothesis that AZT-induced mitochondrial cardiotoxicity may be caused by a limiting pool of TTP that lowers mitochondrial DNA replication.

1: Exp Neurol. 2007 Mar;204(1):29-38. Epub 2006 Oct 25.

Oxidative stress and toxicity induced by the nucleoside reverse transcriptase inhibitor (NRTI)--2',3'-dideoxycytidine (ddC): relevance to HIV-dementia.

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Human immunodeficiency virus dementia (HIVD) is the most common form of dementia occurring among young adults. In HIVD, neuronal cell loss occurs in the absence of neuronal infection. With the advent of highly active anti-retroviral therapy (HAART), the incidence of HIVD has drastically reduced, though prevalence of milder forms of HIVD continues to rise. Though these agents have been used successfully in suppressing viral production, they have also been associated with a number of side effects. Here we examine the possible role of NRTIs, in particular 2',3'-dideoxycytidine (ddC), in the neuropathology of HIVD. Synaptosomes and isolated mitochondria treated and incubated for 6 h with CSF-achievable concentrations of ddC, i.e., 6-11 ng/ml, were found to show a significant increase in oxidative stress with 40 nM ddC as measured by protein carbonyls and 3-nitrotyrosine (3NT), effects that were not observed in the more tolerable NRTI, 3TC. Protection against protein oxidation induced by ddC was observed when brain mitochondria were isolated from gerbils 1 h after injection i.p. with the brain accessible antioxidant and glutathione mimetic, tricyclodecan-9-yl-xanthogenate (D609). In addition, there is a significant reduction in the levels of anti-apoptotic protein Bcl-2 and a significant increase in cytochrome c release and also a significant increase in the expression of pro-apoptotic protein caspase-3 after mitochondria were treated with 40 nM ddC. The results reported here show that ddC at 40 nM can induce oxidative stress, cause the release of cytochrome c, and in addition, reduce the levels of anti-apoptotic proteins, increase the levels of pro-apoptotic proteins, thereby increasing the possibility for induction of apoptosis. These findings are consistent with the notion of a possible role of the NRTIs, and in particular, ddC, in the mechanisms involved in HIVD.

1: Antivir Ther. 2006;11(5):625-30.

Short communication metabolic and mitochondrial effects of switching antiretroviral-experienced

patients to enfuvirtide, tenofovir and saquinavir/ritonavir.

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OBJECTIVE: Investigate the metabolic and mitochondrial effects of switching a highly active antiretroviral therapy (HAART) regimen with a high mitochondrial toxicity profile to a HAART with a theoretically low mitochondrial toxicity. PATIENTS AND METHODS: Six consecutive HAART-experienced patients receiving at least one dideoxy-nucleoside reverse transcriptase inhibitor (NRTI) switched to enfuvirtide plus tenofovir plus saquinavir/ritonavir (T20+TDF+SQV/r). Blood samples were collected at baseline, 12 and 24 weeks after the switch, and viral load (VL) and lymphocyte CD4+ T-cell count were determined. Metabolic parameters consisted of fasting serum triglycerides, cholesterol (total and fractions), glucose, insulin, C-peptide and lactate. Mitochondrial assessment consisted on mitochondrial DNA (mtDNA) quantification, COX-II mitochondrial protein expression rate, mitochondrial respiratory chain complex III and IV activities, and oxygen consumption in peripheral blood mononuclear cells. For baseline mitochondrial comparisons, we included six HIV-infected patients naive for ART. RESULTS: Switched patients exhibited a mean increase of 26 CD4+ T-cells/mm3 and a mean decrease of 1.1 log in VL (P = NS for both). Lactate, lipids and glycaemia remained stable during the study; only insulin levels increased significantly ($P < 0.05$). Switched patients exhibited, at baseline, low mitochondrial measurements, being significant only for complex III and IV activities with respect to naive patients ($P < 0.05$ for both). MtDNA content did not rise significantly during the study. However, we observed increases in COX-II mitochondrial protein synthesis (124%, $P < 0.05$), complex III activity (127%, $P < 0.05$), complex IV activity (86%, $P = 0.37$) and oxygen consumption (194%, $P < 0.05$). CONCLUSION: Switching a HAART-containing dideoxy-NRTI to T20+TDF+SQV/r minimally alters metabolic parameters and exerts beneficial effects on mitochondrial function at 24 weeks. Mitochondrial improvement should be considered as an additional advantage of this rescue therapy.

1: Ann N Y Acad Sci. 2006 Apr;1068:297-308.

Pathogenesis of osteopenia/osteoporosis induced by highly active anti-retroviral therapy for AIDS.

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The advent of highly active anti-retroviral therapy (HAART) has dramatically decreased the rate of AIDS-related mortality and significantly extended the life span of patients with AIDS. A variety of metabolic side effects are associated with these therapies, one of which is metabolic bone disease. A higher prevalence of osteopenia and osteoporosis in HIV-infected patients receiving anti-retroviral therapy than in patients not on therapy has now been reported in several studies. Several factors have been demonstrated to influence HIV-associated decreases in bone mineral density (BMD), including administration of nucleoside reverse transcriptase inhibitors (NRTIs). In this article, discussion will focus on the molecular pathogenesis and treatment of HAART-associated osteopenia and osteoporosis.

Infez Med. 2006 Mar;14(1):33-6. Links

[Hyperlactacidemia during antiretroviral therapy: frequency and clinical-therapeutic correlations]

[Article in Italian]

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While asymptomatic hyperlactacidemia is quite a frequent phenomenon among HIV-infected patients treated with highly active antiretroviral therapy (HAART), lactic acidosis is a rare, but potentially life-threatening occurrence. Epidemiology, clinical and laboratory presentation, evolution, and outcome of this phenomenon are currently under intensive investigation, and the most likely pathogenetic pathways seem to involve mitochondrial toxicity prompted by the administration of nucleoside reverse transcriptase inhibitors. Our case-control study on an extensive, single centre population treated for HIV infection provides novel insights on these emerging issues, reported and discussed on the basis of the most recently published findings.

Infez Med. 2006 Mar;14(1):5-12. Links

[Effect of anti-retroviral therapy on body composition changes: a literature review]

[Article in Italian]

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Protein-energetic malnutrition, characterized by both lean mass and fat depletion, was common in the pre-HAART era, and was associated with shortened survival and diminished quality of life. The pathogenesis of protein-energy malnutrition was

multifactorial, and nutritional treatments were largely ineffective in the absence of disease stabilization. The introduction of HAART brought markedly improved outcomes, including a decrease in the incidence of malnutrition. However, other nutritional and metabolic alterations were noticed, and included changes in body shape, both lipoatrophy and lipohypertrophy, as well as changes in metabolism, notably hyperlipidemia and insulin resistance. These conditions, though sometimes occurring together, may occur independently, suggesting a complex, multifactorial cause. Several mechanisms have been hypothesized, including impairment to adipocyte differentiation and adipokine regulation, production of proinflammatory cytokines and mitochondrial toxicity. The role of the single drug class is still unclear, because both PI and NRTI have been associated with the syndrome, and the therapeutic protocols include both groups. Most of the medical therapies proposed for lipodystrophy are ineffective, and even if surgery remains an alternative, it is not associated with long lasting outcomes.

1: J Acquir Immune Defic Syndr. 2006 May;42(1):19-28. Wolters Kluwer Lippincott Williams & Wilkins Links

Adverse effects of antiretroviral drugs on HIV-1-infected and -uninfected human monocyte-derived macrophages.

Azzam R, **Lal L**, **Goh SL**, **Kedzierska K**, **Jaworowski A**, **Naim E**, **Cherry CL**, **Wesselingh SL**, **Mills J**, **Crowe SM**.

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Antiretroviral drugs approved for treatment of HIV-1 infection include nucleoside reverse transcriptase inhibitors (NRTIs) and protease inhibitors (PIs). Use of these drugs in combinations (highly active antiretroviral therapy) has delayed disease progression. However, long-term therapy is associated with potentially serious adverse effects. NRTIs are thought to contribute to these adverse effects via depletion of mtDNA. Inasmuch as macrophages (major targets for HIV-1) are highly metabolically active with large numbers of mitochondria, we investigated the effects of NRTIs (didanosine, stavudine, lamivudine, and zidovudine) on the viability and function of HIV-1-infected and -uninfected human monocyte-derived macrophages (MDMs). We demonstrate that the combinations didanosine/stavudine and lamivudine/zidovudine decrease mtDNA content in MDMs, with HIV-1-infected MDMs displaying a greater reduction than uninfected cells. This decrease correlated with decreased complement-mediated phagocytosis (C'MP) by MDMs, a process dependent on mitochondrial function. Inasmuch as PIs have previously been reported to interact with cellular proteases and given that cellular proteases are involved in the phagocytic process, we investigated the effects of the PI indinavir on C'MP. We demonstrate that indinavir augments C'MP by uninfected MDMs, but not HIV-1-infected MDMs. This study provides additional understanding on the effects of commonly used antiretroviral drugs on cellular immune function.

: J Antimicrob Chemother. 2006 May;57(5):806-9. Epub 2006 Mar 10.

Links

Comment in:
J Antimicrob Chemother. 2006 Jul;58(1):220-1.

Suboptimal CD4 gains in HIV-infected patients receiving didanosine plus tenofovir.

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The combination of nucleos(t)ide analogues (NAs) is essential for the design of effective antiretroviral regimens. Although there are currently many options for the selection of such drug backbones, not all combinations display optimal results. As the number of these compounds has increased, it has become clear that the concomitant administration of certain NAs should be avoided due to high rates of toxicity and/or greater risk of virological failure. As an example, the combination of didanosine and tenofovir has recently been associated with a paradoxical depletion of CD4+ T cells in the face of complete viral suppression. Interference between the pathways leading to the intracellular activation of didanosine and tenofovir, and their blocking of the purine nucleoside phosphorylase, seems to explain this phenomenon.

J Peripher Nerv Syst. 2006 Mar;11(1):72-6. 

Links

Acetyl-l-carnitine in the treatment of painful antiretroviral toxic neuropathy in human immunodeficiency virus patients: an open label study.

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Antiretroviral toxic neuropathy causes morbidity in human immunodeficiency virus (HIV) patients under dideoxynucleoside therapy, benefits only partially from medical therapy, and often leads to drug discontinuation. Proposed pathogeneses include a disorder of mitochondrial oxidative metabolism, eventually related to a reduction of mitochondrial DNA content, and interference with nerve growth factor activity. Carnitine is a substrate of energy production reactions in mitochondria and is involved in many anabolic reactions. Acetyl carnitine treatment promotes peripheral nerve regeneration and has neuroprotective properties and a direct analgesic role related to glutamatergic and cholinergic modulation. The aim of this study was to evaluate acetyl-l-carnitine in the treatment of painful antiretroviral toxic neuropathy in HIV patients. Twenty subjects affected by painful antiretroviral toxic neuropathy were treated with oral acetyl-l-carnitine at a dose of 2,000 mg/day for a 4-week period. Efficacy was evaluated by means of the modified Short Form McGill Pain

Questionnaire with each item rated on an 11-point intensity scale at weekly intervals and by electromyography at baseline and final visit. Mean pain intensity score was significantly reduced during the study, changing from 7.35 +/- 1.98 (mean +/- SD) at baseline to 5.80 +/- 2.63 at week 4 (p = 0.0001). Electrophysiological parameters did not significantly change between baseline and week 4. In this study, acetyl-l-carnitine was effective and well tolerated in symptomatic treatment of painful neuropathy associated with antiretroviral toxicity. On the contrary, no effect was noted on neurophysiological parameters.

Antivir Ther. 2006;11(1):79-86. Links

Exploring mitochondrial nephrotoxicity as a potential mechanism of kidney dysfunction among HIV-infected patients on highly active antiretroviral therapy.

Côté HC, **Magil AB**, **Harris M**, **Scarth BJ**, **Gadawski I**, **Wang N**, **Yu E**, **Yip B**, **Zalunardo N**, **Werb R**, **Hogg R**, **Harrigan PR**, **Montaner JS**.

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BACKGROUND: Tenofovir (TDF) exposure has been associated with renal dysfunction. Mitochondrial nephrotoxicity was investigated as an underlying mechanism. Given the interaction between TDF and didanosine (ddl), their concurrent use was also investigated. DESIGN: Relative kidney biopsy mitochondrial DNA (mtDNA) to nuclear DNA ratios were measured retrospectively. HIV+ individuals on TDF within 6 months preceeding the biopsy (HIV+/TDF+, n=21) were compared to HIV+ individuals who never received TDF (HIV+/TDF-, n=10) and to HIV uninfected controls (HIV-,n=22). Twelve of the HIV+/TDF+ individuals received concurrent ddl, 10 of those once at unadjusted ddl dosage. Tubular mitochondria morphology was also examined by electron microscopy. Statistical analyses were done on log-transformed mtDNA/nDNA, using non-parametric tests. RESULTS: Kidney mtDNA levels were different among the three groups (P=0.046). mtDNA ratios were lower in HIV+/TDF+ subjects (7.5 [2.0-12.1]) than in HIV- ones (14.3 [6.0-16.5], P=0.014), but not lower than HIV+/TDF- controls (6.4 [2.8-11.9], P=0.82). Among HIV+ subjects, there was a difference between TDF-, TDF+/ddl- and TDF+/ddl+ (P=0.005), with concurrent TDF/ddl use associated with lower mtDNA (2.1 [1.9-5.5], n=12) than TDF+/ddl- (13.8 [7.5-16.4], n=9, P=0.003). No TDF-/ddl+ biopsies were available. In regression analyses, only HIV infection (P=0.03), and TDF/ddl use (P=0.003) were associated with lower mtDNA. At the ultrastructural level, abnormal tubular mitochondria was more prevalent in HIV+/TDF+ biopsies than HIV+/TDF- and HIV- ones together (P<0.001) but not more so in TDF+/ddl+ biopsies than TDF+/ddl- ones (P=0.67). CONCLUSIONS: Renal dysfunction in this population may be mediated through mitochondrial nephrotoxicity that involves more than one drug and/or pathogenesis. Kidney mtDNA depletion was associated with HIV infection and concurrent TDF/ddl therapy but not TDF use alone, while kidney ultrastructural mitochondrial abnormalities were seen with TDF use. The interaction between TDF and ddl may be relevant in the kidney where both drugs are cleared. The clinical

relevance of our findings needs to be evaluated given the current recommendation for reduced doses of ddl when used in conjunction with TDF.

1: Rev Neurol (Paris). 2006 Jan;162(1):62-70.  Links

[Mitochondrial cytopathies associated with HIV infection]

[Article in French]

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The tremendous progress achieved during the last few years with the use of highly active antiretroviral therapy in suppressing HIV replication together with improvements in immunity have been tempered by a growing number of new adverse effects. Mitochondrial toxicity is one aspect of these long-term toxicities of antiretroviral drugs, with the role of nucleoside analogs particularly underlined. Some cases of impaired mitochondrial function have been clearly identified, such as pancreatitis due to didanosine, neuropathy due to zalcitabine, myopathy due to zidovudine, and lactic acidosis due to stavudine. These mitochondrial toxicities can affect several organs, presenting different patterns of symptoms: from asymptomatic to states with few symptoms despite huge metabolic abnormalities whose prognosis is immediately life-threatening. Beyond the inhibition of DNA polymerase gamma using nucleoside analogs, responsible for decreasing mitochondrial DNA in certain targeted organs, it appears that several physiopathologic mechanisms interact to explain this observed toxicity, HIV itself plays a role, and the underlying genetic pool needs to be better identified. Such cases mean that, it is imperative to avoid cumulated toxicities caused by associated treatments. With serious cases, or persistent symptoms despite discontinuing the nucleoside analogs responsible for such toxicity, one must propose vitamins, mitochondrial co-factors, or anti-oxidants. However, the future lies in the use of potent, less toxic nucleoside analogs, and in developing compounds belonging to other classes of antiretrovirals.

AIDS Res Hum Retroviruses. 2006 Jan;22(1):33-9. Links

Longitudinal study on mitochondrial effects of didanosine-tenofovir combination.

López S, **Negredo E**, **Garrabou G**, **Puig J**, **Ruiz L**, **Sanjurjo E**, **Ramos X**, **Infante AB**, **Casademont J**, **Cardellach F**, **Clotet B**, **Miró O**.

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Tenofovir disoproxil fumarate (TDF) has been reported to be free of adverse effects on mitochondria. We evaluate the effects of the introduction of TDF in a didanosine (ddI)-based highly active antiretroviral therapy (HAART) on mitochondrial DNA (mtDNA) content, mitochondrial mass (MM), and cytochrome c oxidase (COX) activity of the oxidative phosphorylation (OXPHOS) system over a 12-month period. Forty-four asymptomatic HIV patients with undetectable viral load receiving a ddI-based HAART were recruited and switched to ddI plus TDF (ddI + TDF) and nevirapine (n = 22) or maintained with the same baseline ddIbased HAART scheme (n = 22). Peripheral blood mononuclear cells were obtained at 0, 6, and 12 months. COX activity and MM were determined by spectrophotometry and the mtDNA content by quantitative realtime PCR. The mtDNA content showed a progressive decrease over the 12-month period of the study for the two groups with respect to baseline, with such a decrease statistically significant only in the ddI + TDF group (55% decrease, $p < 0.001$). In addition, the decrease of mtDNA content over time was statistically different between both groups ($p < 0.001$). Consistently, MM and COX activity decreased significantly at 12 months with respect to baseline only in the ddI < TDF group (28% decrease for MM, $p < 0.05$; 47% decrease for COX activity, $p < 0.001$). We conclude that switching to a HAART regimen containing ddI + TDF is associated with evolutive mitochondrial damage expressed as mtDNA depletion, loss of MM, and decrease in COX efficiency. The particular relevance of either ddI, TDF, or any interaction between them in such a mitochondrial dysfunction remains to be established.

1: Antivir Ther. 2005;10(8):945-51. Links

In vivo effects of highly active antiretroviral therapies containing the protease inhibitor nelfinavir on mitochondrially driven apoptosis.

Miró O, **Villarroya J**, **Garrabou G**, **López S**, **Rodríguez de la Concepción M**, **Pedrol E**, **Martínez E**, **Giralt M**, **Gatell JM**, **Cardellach F**, **Casademont J**, **Villarroya F**.

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BACKGROUND: In vitro studies have reported controversial effects of protease inhibitors (PIs) on mitochondrially driven apoptosis. Additionally, since PIs in the clinical setting are almost always given in combination with nucleoside analogues, which may have negative effects on mitochondrial DNA (mtDNA), the impact of PI-containing highly active antiretroviral therapy (HAART) on apoptosis and mtDNA content is unclear. PATIENTS AND METHODS: A cross-sectional study was performed including 20 HIV-negative (HIV-) patients, 16 HIV-positive, antiretroviral-naive (HIV+) patients and 17 HIV-positive patients receiving the PI nelfinavir (NFV) plus zidovudine and lamivudine (AZT+3TC) or didanosine and stavudine (ddI+d4T)--collectively known as HIV+PI--as first-line antiretroviral treatment for at least 12 months. Peripheral blood mononuclear cells (PBMCs) were isolated. BCL2 expression (anti-apoptotic) and the levels of the cleaved, active form of caspase-9 (pro-apoptotic) were determined by western blot. An index of mitochondrially driven apoptotic activation was estimated calculating the ratio caspase-9:BCL2. Mitochorldrial DNA

content was measured by real-time PCR. RESULTS: BCL2 expression was lower in HIV+ than in HIV-patients ($P < 0.01$), whereas levels of caspase-9 were higher ($P = 0.001$). The caspase-9:BCL2 ratio was significantly increased in HIV+ compared with HIV-individuals ($P < 0.001$). Mitochondrial DNA content was also decreased in HIV+ compared with HIV-patients ($P < 0.001$). The HIV+PI group exhibited a trend to normalization for BCL2 expression and caspase-9 compared with the HIV+ group, whereas the caspase-9:BCL2 ratio significantly improved (decreased, $P < 0.05$ compared with HIV+ group). The mtDNA content in the HIV+PI group was similar to that of the HIV+ group, although the results of mtDNA content differed depending on whether NFV was combined with AZT+3TC (preserved) or with ddl+d4T (depleted). Conversely, no differences were found in apoptotic markers between the two subgroups of HIV+PI. CONCLUSIONS: NFV-based PI-containing HAART regimens may exert some beneficial effects counteracting the increased mitochondrially driven apoptosis present in HIV-infected people.

Assessment of adipokine expression and mitochondrial toxicity in HIV patients with lipoatrophy on stavudine- and zidovudine-containing regimens.

Jones SP, **Qazi N**, **Morelese J**, **Lebrecht D**, **Sutinen J**, **Yki-Järvinen H**, **Back DJ**, **Pirmohamed M**, **Gazzard BG**, **Walker UA**, **Moyle GJ**.

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OBJECTIVES: Despite evidence for the role of adipokines such as adiponectin in the metabolic toxicities of protease inhibitor (PI)-treated patients, little is known about their role in nucleoside reverse transcriptase inhibitor (NRTI)-induced lipoatrophy (LA). We analyzed the relations between mitochondrial toxicity, adipokine expression, and clinical LA in peripheral blood mononuclear cells (PBMCs) and adipose samples from individuals treated with stavudine (d4T) or zidovudine (ZDV) in comparison to patients undergoing highly active antiretroviral therapy (HAART) as well as HIV-negative individuals. METHODS: In this cross-sectional analysis, we studied 18 PI-naive HIV-infected patients with LA treated with d4T (d4T+LA+ [n = 12]) or zidovudine (ZDV+LA+ [n = 6]) in comparison to HAART-treated patients with (HAART+LA+ [n = 8]) and without (HAART+LA- [n = 8]) LA as well as HIV-negative controls (n = 12). Adipose samples were assessed for protein and/or messenger RNA (mRNA) levels of adiponectin, tumor necrosis factor-alpha (TNFalpha), interleukin (IL)-6, and sterol regulatory element-binding protein (SREBP) 1a/c in all groups, whereas adipose and PBMC samples from the d4T+LA+, ZDV+LA+, and HIV-negative subgroups were assessed for mitochondrial DNA (mtDNA) depletion and cytochrome c-oxidase (COX) II/COX IV ratios. RESULTS: There was no change in mtDNA levels in adipose or PBMC samples in NRTI-treated patients with LA, although patients treated with d4T had reduced COX II/COX IV ratios in adipose and PBMC samples. Adipose tissue adiponectin mRNA and plasma levels were reduced in the d4T- and ZDV-treated patients regardless of the use of PIs.

Tissue SREBP1c mRNA levels were also significantly reduced in both NRTI groups when compared with the HIV-negative controls. Significant reductions in SREBP1c levels were also evident with the HAART+LA+ group when compared with HAART+LA- controls. CONCLUSIONS: Patients with LA on d4T-based regimens show evidence of mitochondrial respiratory chain dysfunction, whereas the d4T- and ZDV-based regimens also demonstrated reduced SREBP1c and adiponectin levels, findings that have previously been shown with PIs.

AIDS. 2005 Oct 14;19(15):1627-33. Wolters Kluwer | Lippincott Williams & Wilkins Links

Effect of treatment interruption monitored by CD4 cell count on mitochondrial DNA content in HIV-infected patients: a prospective study.

Mussini C, **Pinti M**, **Bugarini R**, **Borghi V**, **Nasi M**, **Nemes E**, **Troiano L**, **Guaraldi G**, **Bedini A**, **Sabin C**, **Esposito R**, **Cossarizza A**.

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BACKGROUND: HIV infection per se and HAART can alter mitochondrial functionality, leading to a decrease in mitochondrial DNA content. OBJECTIVE: To evaluate whether treatment interruption monitored by CD4 cell count can restore mitochondrial DNA content in peripheral blood lymphocytes. METHODS: Mitochondrial DNA content was measured in platelet-free CD4 and CD8 T cells by real-time polymerase chain reaction; flow cytometry was used to identify and quantify activated CD4 and CD8 T lymphocytes. RESULTS: The 30 patients had been treated for a mean of 107 months (range, 27-197). Median CD4 cell count at discontinuation was 702 cells/microl (range, 547-798). Median observational time from HAART discontinuation was 11.3 months (range, 4-26). Discontinuation of treatment provoked significant increases in mitochondrial DNA in CD8 T cells, which started only 6 months after therapy discontinuation [5.12 copies/cell per month from 0 to 6 months ($P = 0.37$) and 26.96 copies/cell per month from 6 to 12 months ($P < 0.0001$)]. CONCLUSIONS: This study is the first showing that mitochondrial DNA content can increase in peripheral blood lymphocytes during treatment interruption, but only after at least 6 months of interruption. Consequently, interruptions of shorter periods, whether by clinician or patient decision, are unlikely to allow restoration of mitochondrial DNA and so decrease HAART-related toxicity.

1: Mitochondrion. 2002 Oct;1(6):511-8. ELSEVIER FULL-TEXT ARTICLE Links

In vitro evidence of inhibition of mitochondrial protease processing by HIV-1 protease inhibitors in yeast: a possible contribution to lipodystrophy syndrome.

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Highly active antiretroviral therapy has been associated with the emergence of lipodystrophy syndromes that have clinical features commonly seen in patients with mitochondrial dysfunction. The effect of therapeutic protease inhibitors (PIs) on mitochondrial function is unknown. Mitochondrial matrix space proteins possess an amino-terminal leader peptide that is removed by the mitochondrial processing protease (MPP). Lack of cleavage could result in non- or dysfunctional mitochondrial proteins. The effects of different PIs on protease processing using pure MPP or yeast mitochondria, recognized models for mammalian counterparts, were examined in vitro. Multiple PIs were found to inhibit MPP, evidenced by accumulation of immature pALDH and decreased levels of processed ALDH. Both indinavir and amprenavir at 5.0 mg/ml resulted in significant inhibition of MPP. Although inhibition of MPP was also observed with ritonavir and saquinavir, the inhibition was difficult to quantify due to background inhibition of MPP by DMSO that was required to solubilize the drugs for the in vitro studies. Indinavir was also shown to inhibit MPP within yeast mitochondria. Lack of processing may impair mitochondrial function and contribute to the observed mitochondrial dysfunctions in patients receiving HAART and implicated in antiretroviral-associated lipodystrophy.

1: Drug Saf. 2005;28(1):53-66. Links

Hepatotoxicity of antiretrovirals: incidence, mechanisms and management.

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Hepatotoxicity is a relevant adverse effect derived from the use of antiretrovirals that may increase the morbidity and mortality among treated HIV-infected patients and challenges the treatment of HIV infection. Although several antiretrovirals have been reported to cause fatal acute hepatitis, they most often cause an asymptomatic elevation of transaminase levels. In addition to ruling out a variety of processes not related to the use of antiretrovirals or to the HIV infection, for appropriate management of the complication it is necessary to deduce the possible pathogenic mechanisms of the hepatotoxicity. Among these mechanisms, direct drug toxicity, immune reconstitution in the presence of hepatitis C virus (HCV) and/or hepatitis B virus (HBV) co-infections, hypersensitivity reactions with liver involvement and mitochondrial toxicity play a major role, although several other pathogenic pathways may be involved. Liver toxicity is more frequent among subjects with chronic HCV and/or HCB co-infections and alcohol users. Complex immune changes that alter the response against hepatitis virus antigens might be involved in the elevation of transaminase levels after suppression of the HIV replication by highly active antiretroviral therapy (HAART) in patients co-infected with HCV/HBV. The contribution of each particular drug to the development of hepatotoxicity in a HAART regimen is difficult to determine. The incidence of liver toxicity is not well known for most of the antiretrovirals. Although it is most often mild, fatal cases of acute hepatitis linked to the use of HAART have been reported across all families of antiretrovirals.

Acute hepatitis is related to hypersensitivity reactions in the case of non-nucleosides and to mitochondrial toxicity in the case of nucleoside analogues. Alcohol intake and use of other drugs are other co-factors that increase the incidence of transaminase level elevation among HIV-infected patients. The management of liver toxicity is based mainly on its clinical impact, severity and pathogenic mechanism. Although low-grade HAART-related hepatotoxicity most often spontaneously resolves, severe grades may require discontinuation of the antiretrovirals, for example when there is liver decompensation, hypersensitivity reaction or lactic acidosis.

1: Cardiovasc Toxicol. 2004;4(4):327-37. Links

HAART drugs induce mitochondrial damage and intercellular gaps and gp120 causes apoptosis.

Fiala M, **Murphy T**, **MacDougall J**, **Yang W**, **Luque A**, **Iruela-Arispe L**, **Cashman J**, **Buga G**, **Byrns RE**, **Barbaro G**, **Arthos J**.

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HIV-1 infection is associated with serious cardiovascular complications, but the roles of HIV-1, viral proteins, and highly active antiretroviral therapy (HAART) drugs are not understood. HAART decreases the overall risk of heart disease but leads to metabolic disturbances and possibly coronary artery disease. We investigated toxicities of HIV-1, HIV-1 glycoprotein 120 (gp120), and HAART drugs for human coronary artery endothelial cells (CAECs), brain microvascular endothelial cells, and neonatal rat ventricular myocytes (NRVMs). HIV-1 and gp120, but not azidothymidine (AZT), induced apoptosis of NRVMs and CAECs. Ethylisothiourea, an inhibitor of nitric oxide synthase, inhibited apoptosis induction by gp120. AZT, HIV-1, and gp120 all damaged mitochondria of cardiomyocytes. HAART drugs, AZT, and indinavir, but not HIV-1, produced intercellular gaps between confluent endothelial cells and decreased transendothelial electrical resistance. In conclusion, HIV-1 and gp120 induce toxicity through induction of cardiomyocyte and endothelial cell apoptosis. HAART drugs disrupt endothelial cell junctions and mitochondria and could cause vascular damage.

Pediatrics. 2004 Nov;114(5):e598-603. Epub 2004 Oct 18. PEDIATRICS FREE FINAL VERSION Links

Hyperlactatemia in human immunodeficiency virus-uninfected infants who are exposed to antiretrovirals.

Noguera A, **Fortuny C**, **Muñoz-Almagro C**, **Sanchez E**, **Vilaseca MA**, **Artuch R**, **Pou J**, **Jimenez R**.

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OBJECTIVE: Exposure to nucleoside analogues in fetal or early life has been associated with rare clinically significant mitochondrial toxic effects, mainly neurologic symptoms. Lactate (LA) measurements have been used to monitor nucleoside-related mitochondrial toxicity. Our aim was to determine the prevalence, clinical evolution, and risk factors for hyperlactatemia in our cohort of human immunodeficiency virus (HIV)-uninfected children who were exposed to antiretrovirals. METHODS: We conducted a prospective observational study of 127 HIV-uninfected infants who were born to HIV-infected women. Clinical symptoms suggesting mitochondrial dysfunction were analyzed in routine follow-up, and LA and alanine plasma levels were obtained at 6 weeks, 3 months, 6 months, and 12 months in all patients. Elevated alanine levels, together with hyperlactatemia, suggest chronic mitochondrial injury. RESULTS: Most (85%) women received highly active antiretroviral therapy (HAART) during pregnancy (mean duration: 31 weeks) and zidovudine during labor (93%). Most (96%) children received zidovudine alone. Hyperlactatemia with hyperalaninemia was detected in 63 children in at least 1 of the measurements. Mean LA levels were significantly higher in children who were exposed to nucleoside analogue reverse transcriptase inhibitors than in control subjects (2.88 vs 1.61 at 6 weeks, 2.78 vs 1.49 at 3 months, 1.89 vs 1.39 at 6 months, and 1.71 vs 1.24 at 12 months; peak levels: 8.06, 10.1, 7.28, and 4.48 mmol/L, respectively). In 44 patients, LA levels progressed spontaneously to normality within the first year of life. Three girls presented a slight and self-limited delay in psychomotor development, with LA peak levels of 7.3, 4.0, and 4.6 mmol/L. Only the gestational use of didanosine was associated with a higher risk of hyperlactatemia. CONCLUSIONS: In our series, almost half of the children (63 of 127) who were exposed to nucleoside analogues developed benign and self-limited hyperlactatemia. When symptomatic, nucleoside analogue-induced toxicity affected neurologic development.

1: Cardiovasc Toxicol. 2004;4(2):155-67. Links

Phosphorylation of thymidine and AZT in heart mitochondria: elucidation of a novel mechanism of AZT cardiotoxicity.

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Antiretroviral nucleoside analogs used in highly active antiretroviral therapy (HAART) are associated with cardiovascular and other tissue toxicity associated with mitochondrial DNA depletion, suggesting a block in mitochondrial (mt)-DNA replication. Because the triphosphate forms of these analogs variably inhibit mt-DNA polymerase, this enzyme has been promoted as the major target of toxicity associated with HAART. We have used isolated mitochondria from rat heart to study the mitochondrial transport and phosphorylation of thymidine and AZT (azidothymidine, or zidovudine), a component used in HAART. We demonstrate that isolated mitochondria readily transport thymidine and phosphorylate it to thymidine 5'-triphosphate (TTP) within the matrix. Under identical conditions, AZT is phosphorylated only to AZT-5'-monophosphate (AZT-MP). The kinetics of thymidine

and AZT suggest negative cooperativity of substrate interaction with the enzyme, consistent with work by others on mitochondrial thymidine kinase 2. Results show that TMP and AZT-MP are not transported across the inner membrane, suggesting that AZT-MP may accumulate with time in the matrix. Given the lack of AZT-5'-triphosphate (AZT-TP), it seems unlikely that the toxicity of AZT in the heart is mediated by AZT-TP inhibition of DNA polymerase gamma. Rather, our work shows that AZT is a potent inhibitor of thymidine phosphorylation in heart mitochondria, having an inhibitory concentration (IC)(50) of 7.0 +/- 0.9 microM. Thus, the toxicity of AZT in some tissues may be mediated by disrupting the substrate supply of TTP for mt-DNA replication.

1: Cardiovasc Toxicol. 2004;4(2):117-31. Links

Effects of HIV drug combinations on endothelin-1 and vascular cell proliferation.

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Pulmonary arterial hypertension (PAH) is a progressive disease of the pulmonary vasculature involving endothelial and vascular smooth muscle cell (VSMC) proliferation, vasoconstriction, right ventricular hypertrophy, and eventually, right heart failure and death. PAH occurs 1000-fold more frequently in HIV patients than in the general population. Although conventional HIV therapy with nucleoside reverse transcriptase inhibitors (NRTIs) leads to regression of PAH, highly active antiretroviral therapy (HAART; two NRTI plus a protease inhibitor) increases the incidence of HIV-associated PAH as much as twofold. Although there are relatively few models for PAH, previous reports indicate the disease can be initiated by endothelial injury and release of the mitogen endothelin-1 (ET-1). ET-1, in turn, stimulates VSMC proliferation. To determine whether HAART induces endothelial injury and release of cytokines like ET-1, we treated human umbilical vein endothelial cells with micromolar amounts of AZT (3'-azido-3'-deoxythymidine), the protease inhibitor indinavir, or AZT plus indinavir, and measured cell viability, mitochondrial function, and ET-1 release. Both AZT and indinavir induced marked decreases in cellular oxygen uptake, as well as increases in ET-1 release. Although the drugs had no apparent effect on proliferation in VSMCs alone, in cocultures of VSMCs plus endothelial cells, the drugs increased proliferation of both endothelial cells and VSMCs. Finally, when cocultures of endothelial cells and VSMCs were treated with BQ-123 and BQ-788, selective antagonists for ET(A) and ET(B) receptors, respectively, drug-induced proliferation of both VSMCs and endothelial cells was attenuated. These data thus suggest that HIV drug cocktails may exacerbate preexisting HIV-associated PAH by inducing endothelial mitochondrial dysfunction, in turn stimulating the release of ET-1, and ultimately, vascular cell proliferation.

1: Antivir Ther. 2004 Feb;9(1):133-8. Links

High rate of didanosine-related mitochondrial toxicity in HIV/HCV-coinfected patients receiving ribavirin.

Moreno A, **Quereda C**, **Moreno L**, **Perez-Elías MJ**, **Muriel A**, **Casado JL**, **Antela A**, **Dronda F**, **Navas E**, **Bárcena R**, **Moreno S**.

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BACKGROUND: Nucleoside analogues may induce mitochondrial toxicity, particularly didanosine. Ribavirin increases didanosine exposure, which might be clinically relevant when coadministered in HIV/HCV-coinfected patients. OBJECTIVE: To evaluate, among 89 patients receiving highly active antiretroviral therapy (HAART) and therapy for chronic hepatitis C, clinically relevant mitochondrial toxicity in those treated with concomitant ribavirin and didanosine (n=35, 39%). METHODS: From January 2000 to July 2002 longitudinal analysis of the incidence and clinical course of didanosine-related hyperamylasaemia, pancreatitis, hyperlactataemia/lactic acidosis or neuropathy. Risk factors were evaluated using univariate and multivariate Cox's proportional hazards model. RESULTS: Among 35 patients who received concomitant didanosine (400 mg/day in 86%) and ribavirin (> or = 10 mg/kg/day in 91%), 20 (57%) developed one or more adverse events after a mean of 87 days. Most frequent laboratory abnormalities were hyperamylasaemia (18 patients, 51%) and hyperlactataemia (eight patients, 23%). Acute pancreatitis and symptomatic hyperlactataemia developed in 10 (28%) and six (17%) patients, respectively. Two patients (6%) with pancreatitis and severe lactic acidosis died; the other patients recovered uneventfully despite continuation of anti-HCV therapy in 83% after didanosine withdrawal in 40%. In the Cox's model higher baseline amylase levels (HR: 1.04, 95% CI: 1.02-1.06, P=0.001) and three nucleoside reverse transcriptase inhibitor-based HAART (HR: 5.3, 95% CI: 1.73-16.24, P=0.003) were significantly associated to toxicity. CONCLUSIONS: The coadministration of didanosine and ribavirin should be avoided in HIV/HCV-coinfected patients, due to a high rate of clinically significant toxicity, particularly in triple nucleoside-based HAART. Amylase levels should be strictly monitored, especially if elevated at baseline.

: Antivir Ther. 2004 Feb;9(1):47-55. Links

Mitochondrial effects of antiretroviral therapies in asymptomatic patients.

López S, **Miró O**, **Martínez E**, **Pedrol E**, **Rodríguez-Santiago B**, **Milinkovic A**, **Soler A**, **García-Viejo MA**, **Nunes V**, **Casademont J**, **Gatell JM**, **Cardellach F**.

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BACKGROUND: A decrease in the mitochondrial (mt) DNA to nuclear DNA ratio has gained acceptance as a marker of mitochondrial toxicity in treated HIV-infected

patients, but the functional meaning of this alteration is unclear. METHODS: We assessed mtDNA content, mitochondrial content and function in peripheral blood mononuclear cells (PBMCs) of consecutive asymptomatic HIV-infected patients. Patients selected had been receiving a first-line highly active antiretroviral therapy (HAART) regimen for at least 6 months, consisting of zidovudine plus lamivudine or stavudine plus didanosine plus either nelfinavir or nevirapine, or were antiretroviral-naive. The mtDNA content was assessed by quantitative real-time PCR, mitochondrial content by citrate synthase activity, enzyme activity of complexes III and IV (both partially encoded by mtDNA) of the electron transport chain by spectrophotometry, oxygen consumption by polarography, and oxidative damage in cell membranes by monitoring cis-parinaric acid fluorescence. RESULTS: Mitochondrial content was significantly lower in all treated groups. Patients receiving stavudine plus didanosine had mtDNA depletion and a decrease in complex IV activity. However, oxygen consumption capacity and lipid peroxidation were unaffected in all groups. CONCLUSION: Long-term HAART may induce mitochondrial abnormalities in PBMC mitochondria, which do not necessarily translate into functional abnormalities, at least in asymptomatic patients.

AIDS Res Hum Retroviruses. 2003 Nov;19(11):1027-32.

Short communication: reversible mitochondrial respiratory chain impairment during symptomatic hyperlactatemia associated with antiretroviral therapy.

Miró O, **López S**, **Martínez E**, **Rodríguez-Santiago B**, **Blanco JL**, **Milinkovic A**, **Miró JM**, **Nunes V**, **Casademont J**, **Gatell JM**, **Cardellach F**.

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Direct evidence confirming the hypothesis that a dysfunction of the mitochondrial respiratory chain (MRC) underlies the pathogenesis of hyperlactatemia associated with highly active antiretroviral therapy (HAART) is scarce. We studied mitochondrial DNA (mtDNA) content and MRC function in the skeletal muscle of an HIV-infected patient during an episode of symptomatic hyperlactatemia. Skeletal muscle biopsy was performed during the episode when the patient was symptomatic and 3 months later when the patient was clinically recovered. Assessment of mitochondria was performed using histological, polarographic, spectrophotometrical, and Southern blot and real time PCR DNA quantification methods. The histological study disclosed extensive mitochondrial impairment in the form of ragged-red fibers or equivalents on oxidative reactions. These findings were associated with an increase in mitochondrial content and a decrease in both mitochondrial respiratory capacity and MRC enzyme activities. Mitochondrial DNA content declined to 53% of control values. Mitochondrial abnormalities had almost disappeared later when the patient became asymptomatic. Our findings support the hypothesis that MRC dysfunction stands at the basis of HAART-related hyperlactatemia.

J Acquir Immune Defic Syndr. 2003 Sep;34 Suppl 1:S85-90. Wolters Kluwer | Lippincott Williams & Wilkins Links

Mitochondrial toxicity in the era of HAART: evaluating venous lactate and peripheral blood mitochondrial DNA in HIV-infected patients taking antiretroviral therapy.

Montaner JS, **Côté HC**, **Harris M**, **Hogg RS**, **Yip B**, **Chan JW**, **Harrigan PR**, **O'Shaughnessy MV**.

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Nucleoside analogs can induce mitochondrial toxicity by inhibiting the human DNA polymerase gamma. This can lead to a wide range of clinical toxicities, from asymptomatic hyperlactatemia to death. Despite their technical and physiological variability, we propose that random venous lactate measurements can be useful to monitor the development of nucleoside-related mitochondrial toxicity. Recently, we have developed an assay that can measure changes in mitochondrial DNA levels in peripheral blood cells. Using this assay we have characterized changes in mitochondrial DNA (mtDNA) relative to nuclear DNA (nDNA) in peripheral blood cells of patients with symptomatic nucleoside-induced hyperlactatemia. Our results demonstrate that symptomatic hyperlactatemia was associated with markedly low mtDNA/nDNA ratios, which were on average 69% lower than HIV-uninfected controls and 45% lower than HIV-infected asymptomatic/antiretroviral naive controls. A statistically significant ($p = .016$) increase in mtDNA/nDNA ratio was observed following discontinuation of antiretroviral therapy. The mtDNA/nDNA ratio remained stable among selected patients who reintroduced antiretroviral therapy with stavudine (d4T)-sparing regimens. Of note, the decline in mtDNA preceded the increase in venous lactate levels. More recently we have evaluated changes in the mtDNA/nDNA ratio in relation to selected antiretroviral drug regimens in a cross-sectional study on a non-random sample of participants within the British Columbia Centre for Excellence in HIV/AIDS Drug Treatment Program. Eligible patients had continuously received saquinavir plus ritonavir with either nevirapine ($n = 20$), lamivudine ($n = 15$), d4T ($n = 53$) or lamivudine + d4T ($n = 69$), for 4 to 30 months. d4T-sparing regimens were associated with a higher median mtDNA/nDNA ratio than d4T-containing regimens ($p = .016$), despite the fact that study patients had received d4T-containing regimens for a shorter median time than patients taking d4T-sparing regimens (13 versus 25 months, $p = .002$). In summary, mtDNA levels are significantly decreased among patients who develop symptomatic, nucleoside-related hyperlactatemia, an effect reversed upon therapy discontinuation. Furthermore, mtDNA/nDNA ratios were statistically significantly lower in patients taking d4T-containing regimens than in those taking selected d4T-sparing regimens in a population setting. These results suggest that measurement of this parameter should be investigated as a potential clinical management tool.

1: Antivir Ther. 2003 Aug;8(4):333-8. Links
Comment in:

Antivir Ther. 2003 Aug;8(4):261-3.

Mitochondrial DNA depletion and respiratory chain enzyme deficiencies are present in peripheral blood mononuclear cells of HIV-infected patients with HAART-related lipodystrophy.

Miró O, **López S**, **Pedrol E**, **Rodríguez-Santiago B**, **Martínez E**, **Soler A**, **Milinkovic A**, **Casademont J**, **Nunes V**, **Gatell JM**, **Cardellach F**.

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The main objective of the present study was to ascertain if mitochondrial DNA (mtDNA) depletion as reported in HIV-infected patients with highly active antiretroviral therapy (HAART)-related lipodystrophy (LD) implies any degree of mitochondrial respiratory chain (MRC) dysfunction. For this purpose, we evaluated HIV patients on different HAART schedules with LD (group A; n=12) and on HAART but without LD (group B; n=12), and untreated HIV-infected patients as controls (group C; n=24). mtDNA content was determined on peripheral blood mononuclear cells (PBMCs) with a real-time PCR method. Complex II, III and IV activities of the MRC were simultaneously measured spectrophotometrically, as were spontaneous and stimulated oxygen consumption by PBMCs. Compared to controls (group C, 100%), patients with LD (group A) showed a decreased mtDNA content (54%, P<0.001), which was associated with a decline in complex III (62%, P<0.05) and IV activity (69%, P<0.05) (both complexes partially encoded by mtDNA), but not in complex II activity (exclusively encoded by nuclear DNA). Patients in group B showed a similar pattern of mitochondrial dysfunction but to a lesser extent and without statistical significance. Respiratory activities in both treated groups (A and B) did not differ in comparison with controls. We conclude that mtDNA depletion occurring during HAART is associated with deficiencies in MRC complexes partially encoded by mtDNA, which are detectable by PBMCs. Presented in 'Late Breakers and Hot Topics' session at 6th International Congress on Drug Therapy in HIV Infection, Glasgow, UK, 17-21 November 2002.

Antivir Ther. 2003 Aug;8(4):323-31. Links
Comment in:
Antivir Ther. 2003 Aug;8(4):261-3.

Mitochondrial proliferation, DNA depletion and adipocyte differentiation in subcutaneous adipose tissue of HIV-positive HAART recipients.

Pace CS, **Martin AM**, **Hammond EL**, **Mamotte CD**, **Nolan DA**, **Mallal SA**.

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OBJECTIVES: To examine the in vivo effects of highly active antiretroviral therapy (HAART) regimens on adipose tissue mitochondrial DNA (mtDNA) depletion, mitochondrial organellar proliferation, and markers of adipocyte differentiation and phenotype. DESIGN AND METHODS: DNA and mRNA quantification using real-time PCR methods was performed on adipose tissue samples from 31 HIV-infected individuals, of whom 11 were treatment-naive and 20 were receiving HAART. mtDNA depletion was measured as mtDNA copies/cell, and mitochondrial proliferation by quantification of mitochondrial protein mass. Regulation of mitochondrial biogenesis was assessed by NRF-1 and mtTFA mRNA. PPARgamma, UCP2 and UCP1 mRNA expression was used to assess adipocyte differentiation and phenotype. RESULTS: Stavudine-based HAART recipients (n=10) displayed significant mtDNA depletion (12.8% of control, P<0.001), mildly increased mitochondrial protein mass (2.6-fold of control, P=0.032) and decreased expression of PPARgamma (53.9% of control, P=0.021), UCP2 (62.2% of control, P=0.024) and UCP3 (51.8% of control, P=0.047) mRNA compared with controls. Zidovudine-based HAART recipients (n=7) also displayed significant mtDNA depletion (34.45% of control, P=0.031), increased mitochondrial protein mass (5.7-fold of control, P=0.009), and markedly increased UCP1 (18-fold of control, P=0.009) mRNA. Elevated UCP1 mRNA expression was found to be associated with non-stavudine (zidovudine or abacavir), protease inhibitor (PI)-containing HAART (95-fold of non-stavudine, non-PI-containing HAART, P=0.006). CONCLUSION: Differential effects of stavudine and zidovudine therapy on mtDNA depletion and expression of adipocyte differentiation markers PPARgamma and UCP2 were observed, consistent with increased adipose tissue toxicity associated with stavudine therapy. Increased UCP1 mRNA, a marker of brown adipose tissue phenotype, was associated with non-stavudine, PI-containing HAART, and may represent an adaptive response to the increased fatty acid flux associated with PI therapy, and may contribute to the increased resting energy expenditure reported in such patients.

: J Immunol. 2003 Jun 15;170(12):6006-15. 

Links

Mitochondrial membrane hyperpolarization hijacks activated T lymphocytes toward the apoptotic-prone phenotype: homeostatic mechanisms of HIV protease inhibitors.

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A decrease of mitochondrial membrane potential has been hypothesized to be a marker of apoptotic cells, including activated T lymphocytes. It was recently demonstrated that HIV protease inhibitors, independently from any viral infection, can hinder lymphocyte apoptosis by influencing mitochondrial homeostasis. To analyze the mechanisms underlying these effects, a specific study was undertaken in both resting and activated human PBL exposed to either receptor (e.g., anti-Fas)- or nonreceptor (e.g., radiation)-mediated apoptotic stimuli. T cell activation was found to be accompanied by a significant increase in mitochondrial membrane potential, or

hyperpolarization, which was undetectable in resting cells. We also detected apoptotic hindering by HIV protease inhibitors only in activated T lymphocytes. This was apparently due to the ability of these drugs to block activation-associated mitochondria hyperpolarization, which, in turn, was paralleled by an impairment of cell cycle progression. Remarkably, protease inhibitors also prevented zidovudine-mediated mitochondrial toxicity. Finally, HIV-infected cells from naive patients behaved identically to activated T cells, displaying hyperpolarized mitochondria, while lymphocytes from patients under highly active antiretroviral therapy (which included HIV protease inhibitors) seemed to react as resting cells. Altogether these results clearly indicate that the hyperpolarization state of mitochondria may represent a prerequisite for the sensitization of lymphocytes to the so-called activation-induced cell death. They also suggest that HIV protease inhibitors, by interfering with induction of the mitochondrial hyperpolarization state, can result in cell survival even independent of any viral infection.

: AIDS Read. 2003 Apr;13(4):176-84, 187. Links

Long-term complications of nucleoside reverse transcriptase inhibitor therapy.

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HAART has resulted in dramatic declines in morbidity and mortality among patients infected with HIV. Increased experience with HAART has led to the detection of drug related toxicities that may compromise adherence and necessitate discontinuation of treatment and alteration of otherwise effective regimens. This article considers the major long-term complications associated with nucleoside reverse transcriptase inhibitor (NRTI) use--hyperlactatemia and lactic acidosis/hepatic steatosis, other hepatotoxicities, pancreatitis, lipodystrophy, lipoatrophy, neuropathy, and hematologic toxicities. Mechanisms by which NRTIs may produce these effects are discussed, as are differential effects of agents in this class and management options.

1: J Antimicrob Chemother. 2003 May;51(5):1091-3. Epub 2003 Mar 28.

FREE FINAL TEXT OXFORD JOURNALS Links

Nucleoside analogues and HIV: the combined cost to mitochondria.

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PMID: 12668570 [PubMed - indexed for MEDLINE] HIV Clin Trials. 2003 Jan-Feb;4(1):11-9.  Links

First-line therapy and mitochondrial damage: different nucleosides, different findings.

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BACKGROUND: Antiretroviral therapy has been associated with the development of morphologic body-shape changes and metabolic abnormalities, including dislipemia, insulin resistance, and hyperlactatemia. Mitochondrial damage secondary to the use of nucleoside analogue reverse transcriptase inhibitors (NRTIs) has been related to some of these complications, although the role of different NRTIs in their development is not well established. OBJECTIVES: To assess the incidence of hyperlactatemia and lipodystrophy body-shape changes in drug-naïve HIV-infected patients who began highly active antiretroviral therapy (HAART) based on a backbone of two different NRTI combinations. METHOD: Prospective, longitudinal, observational study of all consecutive drug-naïve HIV-infected individuals who started HAART with zidovudine (AZT) plus lamivudine (3TC) or didanosine (ddI) plus stavudine (d4T) between June 2000 and June 2001 at one single institution. Serum lactate levels and lipodystrophy body-shape changes were monitored periodically during 12 months. RESULTS: At 1 year, mean lactate values remained <2 mmol/L in all 26 patients who received AZT+3TC, but they significantly increased (mean, 2.6 mmol/L) in 50 patients treated with ddI+d4T. The percentage of patients with hyperlactatemia (lactate >or=2 mmol/L) steadily increased in those on ddI+d4T (from 30% at 3 months to 71% at 12 months), whereas it remained below 10% in patients treated with AZT+3TC. Two patients on ddI+d4T developed lactic acidosis. Mean serum lactate dehydrogenase (LDH), gamma-glutamyltransferase (GGT), and amylase significantly increased in patients treated with ddI+d4T, whereas they remained unaltered in patients under AZT+3TC. Significant correlations were found between lactate and LDH, alkaline phosphatase (AP), and GGT. In the multivariate analysis, treatment with ddI+d4T, LDH, and AP was significantly associated with lactate levels. At 12 months, subcutaneous lipoatrophy was significantly more frequent in patients treated with ddI+d4T than in those on AZT+3TC (35% vs. 8%; p =.01). CONCLUSION: In drug-naïve HIV-infected patients who start antiretroviral therapy, ddI+d4T-based combinations produce a greater increase in serum lactate and lipoatrophy than therapies based on AZT+3TC within the first year of therapy. An increase in LDH, amylase, GGT, and AP levels may signal an increase in lactate, which may be harmful.

: J Clin Pathol. 2003 Feb;56(2):147-51.  
Links

Mitochondrial disruption and apoptosis in lymphocytes of an HIV infected patient affected by

lactic acidosis after treatment with highly active antiretroviral therapy.

Tolomeo M, **Mancuso S**, **Todaro M**, **Stassi G**, **Catalano M**, **Arista S**, **Cannizzo G**, **Barbusca E**, **Abbadessa V**.

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AIMS: Highly active antiretroviral therapy (HAART) can induce an increase in lactic acid concentrations that seems to be caused by mitochondrial dysfunction induced by the interaction of nucleoside reverse transcriptase inhibitors (NRTIs) with DNA polymerase gamma in the mitochondria. Mitochondrial alterations have been described in liver and muscle cells of NRTI treated human immunodeficiency virus (HIV) infected patients. Because lymphocytes are the main target for HIV and because mitochondria are involved in apoptosis, we studied mitochondrial morphology and apoptosis in the lymphocytes of an HIV infected patient with severe lactic acidosis after treatment with stavudine, didanosine, and indinavir. METHODS: The patient was a 39 year old woman. After two years of treatment she developed rapid weight loss with severe fat wasting, peripheral neuropathy, and hyperlacticaemia, which persisted after treatment withdrawal. The numbers and the morphology of the mitochondria were evaluated by electronic microscopy; the percentage of apoptotic cells was calculated by flow cytometry after staining with annexine V and by fluorescent microscopy after staining with ethidium bromide and acridine orange. RESULTS: The numbers of mitochondria in the lymphocytes were greatly decreased when compared with the lymphocytes of healthy individuals. The most important mitochondrial morphological alterations were swelling and the disruption of cristae and internal mitochondrial structure. These alterations were more evident during the period in which lactic acid values were very high. Moreover, a high percentage of apoptotic lymphocytes was seen. Morphological examination conducted one week after the normalisation of lacticaemia showed a pronounced increase in the number of mitochondria. The morphological alterations were no longer evident, although the size of each mitochondrion was smaller than normal. Moreover, the percentage of apoptotic cells was lower than 5%. CONCLUSIONS: This report describes important morphological alterations in lymphocyte mitochondria in an HIV infected patient during a severe phase of HAART induced hyperlacticaemia. These alterations persisted for several weeks after treatment withdrawal and were associated with an increase in lymphocyte apoptosis. Considering the important role of mitochondria in the apoptotic pathway, the increase in lymphocyte apoptosis may be a consequence of proapoptotic factors released from altered mitochondria.

1: J Acquir Immune Defic Syndr. 2002 Nov 1;31(3):299-308.
Links

Mitochondrial damage associated with long-term antiretroviral treatment: associated alteration or causal disorder?

Vittecoq D, **Jardel C**, **Barthélémy C**, **Escaut L**, **Cheminot N**, **Chapin S**, **Sternberg D**, **Maisonobe T**, **Lombès A**.

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Combination of antiretroviral drugs has dramatically improved the prognosis of human HIV infection but is also associated with many adverse effects, the mitochondrial origin of which is discussed. In this study using extensive diagnostic procedures set up for inherited mitochondrial disorders, we analyzed HIV patients under active antiretroviral therapy who complained of severe adverse symptoms unexplained by HIV. All these patients had been treated for at least 5 years. They all had significant mitochondrial damage as evidenced by the diverse combination of lactate accumulation in blood or cerebrospinal fluid, mitochondrial morphologic alterations in muscle, and biochemical defects in muscle and liver, which designated mitochondrial DNA (mtDNA) as the main target of the toxic mechanisms. Southern blot and/or polymerase chain reaction -based analyses disclosed multiple deletions of the muscle mtDNA and reduction of the muscle and/or liver mtDNA copy number in a majority of the patients. In opposition to muscle and liver, blood mononuclear cells were devoid of significant biochemical or genetic alterations. Whether the mitochondrial toxicity is directly responsible for the patients' adverse symptoms remains disputable, because the investigations were transversal. Its severity argues for its clinical relevance, however. The skewed tissue distribution of mitochondrial alterations indicates potential pitfalls in the needed future prospective studies.

: Bioessays. 2001 Nov;23(11):1070-80. Links

Mitochondria in the pathogenesis of lipodystrophy induced by anti-HIV antiretroviral drugs: actors or bystanders?

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Effective therapies are now available that can stop the progression of HIV infection and significantly delay the onset of AIDS. The "highly active antiretroviral therapy" (HAART) is a combination of potent antiretroviral drugs such as viral protease inhibitors or nucleoside-analogue reverse-transcriptase inhibitors, that has a variety of serious side effects, including lipodystrophy, a pathology characterized by accumulation of visceral fat, breast adiposity, cervical fat-pads, hyperlipidemia, insulin resistance as well as fat wasting in face and limbs. There is still an open debate that concerns the precise responsibility of HAART as well as metabolic pathways and mechanisms that are involved in the onset of lipodystrophy. The similarities with multiple symmetric lipomatosis (MSL), in which mitochondria impairment plays a crucial role, lead to the hypothesis that drug-induced damages to mitochondrial DNA are able to alter mitochondria functionality to an extent that is similar to what occurs in MSL. In addition, several evidences indicate that HAART is also linked to a deregulated production of tumour necrosis factor-alpha, which uses mitochondria as

intracellular targets. In this paper, we review data concerning the role of mitochondria in the pathogenesis of lipodystrophy, and advance a unifying hypothesis involving either direct or indirect effects of the drugs employed during HAART. Copyright 2001 John Wiley & Sons, Inc.

Sex Transm Infect. 2001 Jun;77(3):158-73.   Links

Mitochondrial toxicity and HIV therapy.

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Nucleoside reverse transcriptase inhibitors (NRTIs) remain the cornerstone of highly active antiretroviral therapy (HAART) combination regimens. However, it has been known for some time that these agents have the potential to cause varied side effects, many of which are thought to be due to their effects on mitochondria. Mitochondria, the key energy generating organelles in the cell, are unique in having their own DNA, a double stranded circular genome of about 16 000 bases. There is a separate enzyme present inside the cell that replicates mitochondrial DNA, polymerase gamma. NRTIs can affect the function of this enzyme and this may lead to depletion of mitochondrial DNA or qualitative changes. The study of inherited mitochondrial diseases has led to further understanding of the consequences of mutations or depletion in mitochondrial DNA. Key among these is the realisation that there may be substantial heteroplasmy among mitochondria within a given cell, and among cells in a particular tissue. The unpredictable nature of mitochondrial segregation during cellular replication makes it difficult to predict the likelihood of dysfunction in a given tissue. In addition, there is a threshold effect for the expression of mitochondrial dysfunction, both at the mitochondrial and cellular level. Various clinical and in vitro studies have suggested that NRTIs are associated with mitochondrial dysfunction in different tissues, although the weight of evidence is limited in many cases. The heterogeneity in the tissues affected by the different drugs raises interesting questions, and possible explanations include differential distribution or activation of these agents. This article reviews the major recognised toxicities associated with NRTI therapy and evidence for mitochondrial dysfunction in these complications. Data were identified through searching of online databases including Medline and Current Contents for relevant articles, along with abstracts and posters from recent conferences in the HIV and mitochondrial fields.

Lancet. 1999 Sep 25;354(9184):1112-5.  Links

Comment in:
Lancet. 1999 Sep 25;354(9184):1046-7.
Lancet. 2000 Mar 25;355(9209):1096.

Mitochondrial toxicity induced by nucleoside-analogue reverse-transcriptase inhibitors is a key factor in the pathogenesis of antiretroviral-therapy-related lipodystrophy.

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Highly active antiretroviral therapy (HAART) can induce a characteristic lipodystrophy syndrome of peripheral fat wasting and central adiposity. HIV-1 protease inhibitors are generally believed to be the causal agents, although the syndrome has also been observed with protease-inhibitor-sparing regimens. Here, we postulate that the mitochondrial toxicity of the nucleoside-analogue reverse-transcriptase inhibitors plays an essential part in the development of this lipodystrophy, similar to the role of mitochondrial defects in the development of multiple symmetrical lipomatosis.

1: Clin Ther. 2000 Jun;22(6):685-708. ELSEVIER FULL-TEXT ARTICLE Links

Pharmacology of nucleoside and nucleotide reverse transcriptase inhibitor-induced mitochondrial toxicity.

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OBJECTIVE: This paper reviews the function of the mitochondria and the mechanisms by which nucleoside and nucleotide reverse transcriptase inhibitors (NRTIs) cause mitochondrial toxicity. BACKGROUND: Highly active antiretroviral therapy (HAART) reduces rates of morbidity and mortality due to HIV disease. However, long-term treatment with these drugs may be associated with adverse effects. Nucleoside and nucleotide analogues are potent inhibitors of HIV reverse transcriptase and have become the cornerstone of HAART. Unfortunately, these drugs have also been shown to inhibit cellular polymerases, most notably mitochondrial DNA polymerase gamma. RESULTS: Studies of the NRTIs in enzyme assays and cell cultures demonstrate the following hierarchy of mitochondrial DNA polymerase gamma inhibition: zalcitabine > didanosine > stavudine > lamivudine > zidovudine > abacavir. In vitro investigations have also documented impairment of the mitochondrial enzymes adenylate kinase and the adenosine diphosphate/adenosine triphosphate translocator. Inhibition of DNA polymerase gamma and other mitochondrial enzymes can gradually lead to mitochondrial dysfunction and cellular toxicity. The clinical manifestations of NRTI-induced mitochondrial toxicity resemble those of inherited mitochondrial diseases (ie, hepatic steatosis, lactic acidosis,

myopathy, nephrotoxicity, peripheral neuropathy, and pancreatitis). Fat redistribution syndrome, or HIV-associated lipodystrophy, is another side effect attributed in part to NRTI therapy. The morphologic and metabolic complications of this syndrome are similar to those of the mitochondrial disorder known as multiple symmetric lipomatosis: suggesting that this too may be related to mitochondrial toxicity. The pathophysiology of less common adverse effects of nucleoside analogue therapy, such as diabetes, ototoxicity, and retinal lesions, may be related to mitochondrial dysfunction but have not been adequately studied. CONCLUSION: NRTIs can block both HIV reverse transcriptase and mitochondrial DNA polymerase gamma. Inhibition of the latter enzyme is the most likely cause of the adverse effects associated with these drugs.

AIDS. 2008 Nov 30;22(18):2429-39. Wolters Kluwer | Lippincott Williams & Wilkins Links

Mitochondrial DNA haplogroups influence AIDS progression.

Hendrickson SL, **Hutcheson HB**, **Ruiz-Pesini E**, **Poole JC**, **Lautenberger J**, **Sezgin E**, **Kingsley L**, **Goedert JJ**, **Vlahov D**, **Donfield S**, **Wallace DC**, **O'Brien SJ**.

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OBJECTIVE: Mitochondrial function plays a role in both AIDS progression and HAART toxicity; therefore, we sought to determine whether mitochondrial DNA variation revealed novel AIDS restriction genes, particularly as mitochondrial DNA single-nucleotide polymorphisms are known to influence regulation of oxidative phosphorylation, reactive oxygen species production, and apoptosis. DESIGN: This is a retrospective cohort study. METHODS: We performed an association study of mitochondrial DNA haplogroups among 1833 European American HIV-1 patients from five US cohorts: the Multicenter AIDS Cohort Study, the San Francisco City Clinic Study, Hemophilia Growth and Development Study, the Multicenter Hemophilia Cohort Study, and the AIDS Linked to Intravenous Experiences cohort to determine whether the mitochondrial DNA haplogroup correlated with AIDS progression rate. RESULTS: Mitochondrial DNA haplogroups J and U5a were elevated among HIV-1 infected people who display accelerated progression to AIDS and death. Haplogroups Uk, H3, and IWX appeared to be highly protective against AIDS progression. CONCLUSION: The associations found in our study appear to support a functional explanation by which mitochondrial DNA variation among haplogroups, influencing ATP production, reactive oxygen species generation, and apoptosis, is correlated to AIDS disease progression; however, repeating these results in cohorts with different ethnic backgrounds would be informative. These data suggest that mitochondrial genes are important indicators of AIDS disease progression in HIV-1 infected persons.