

Liver-related deaths in persons infected with the human immunodeficiency virus: the D:A:D study.

[Weber R](#), [Sabin CA](#), [Friis-Moller N](#), [Reiss P](#), [El-Sadr WM](#), [Kirk O](#), [Dabis F](#), [Law MG](#), [Pradier C](#), [De Wit S](#), [Akerlund B](#), [Calvo G](#), [Monforte A](#), [Rickenbach M](#), [Ledergerber B](#), [Phillips AN](#), [Lundgren JD](#).

Division of Infectious Diseases and Hospital Epidemiology, University Hospital, CH-809a Zurich, Switzerland. infweb@usz.unizh.ch

BACKGROUND: An increasing proportion of deaths among human immunodeficiency virus (HIV)-infected persons with access to combination antiretroviral therapy (cART) are due to complications of liver diseases. **METHODS:** We investigated the frequency of and risk factors associated with liver-related deaths in the Data Collection on Adverse Events of Anti-HIV Drugs study, which prospectively evaluated 76 893 person-years of follow-up in 23 441 HIV-infected persons. Multivariable Poisson regression analyses identified factors associated with liver-related, AIDS-related, and other causes of death. **RESULTS:** There were 1246 deaths (5.3%; 1.6 per 100 person-years); 14.5% were from liver-related causes. Of these, 16.9% had active hepatitis B virus (HBV), 66.1% had hepatitis C virus (HCV), and 7.1% had dual viral hepatitis co-infections. Predictors of liver-related deaths were latest CD4 cell count (adjusted relative rate [RR], 16.1; 95% confidence interval [CI], 8.1-31.7 for <50 vs > or =500/microL), age (RR, 1.3; 95% CI, 1.2-1.4 per 5 years older), intravenous drug use (RR, 2.0; 95% CI, 1.2-3.4), HCV infection (RR, 6.7; 95% CI, 4.0-11.2), and active HBV infection (RR, 3.7; 95% CI, 2.4-5.9). Univariable analyses showed no relationship between cumulative years patients were receiving cART and liver-related death (RR, 1.00; 95% CI, 0.93-1.07). Adjustment for the most recent CD4 cell count and patient characteristics resulted in an increased risk of liver-related mortality per year of mono or dual antiretroviral therapy before cART (RR, 1.09; 95% CI, 1.02-1.16; P = .008) and per year of cART (RR, 1.11; 95% CI, 1.02-1.21; P = .02). **CONCLUSIONS:** Liver-related death was the most frequent cause of non-AIDS-related death. We found a strong association between immunodeficiency and risk of liver-related death. Longer follow-up is required to investigate whether clinically significant treatment-associated liver-related mortality will develop.

PMID: 16908797 [PubMed - indexed for MEDLINE]

Metabolic and skeletal complications of HIV infection: the price of success.

[Morse CG](#), [Kovacs JA](#).

National Institute of Allergy and Infectious Diseases-Clinical Center HIV/AIDS Program, Critical Care Medicine Department, NIH Clinical Center, Bethesda, Md, USA.

Over the past 10 years, in conjunction with the broad availability of potent antiretroviral regimens, the care of human immunodeficiency virus (HIV)-infected patients has shifted from prevention and treatment of opportunistic infections and malignancies to management of the metabolic and related complications associated with HIV infection and its treatment. Metabolic disorders, including lipodystrophy, dyslipidemia, and insulin resistance, occur at a high rate in HIV-infected individuals receiving highly active antiretroviral therapy (HAART). These disorders are associated with increased risk of cardiovascular disease and have become an important cause of morbidity and mortality in HIV-infected patients. Herein, we present the case of a patient with HIV infection who responded well to HAART but developed multiple complications potentially related to this therapy. This article reviews the clinical characteristics of the metabolic and skeletal disturbances observed in HIV infection and discusses strategies for their management.

PMID: 16905789 [PubMed - indexed for MEDLINE]

patients 48 weeks after starting highly active antiretroviral therapy.

[Palacios R](#), [Merchante N](#), [Macias J](#), [Gonzalez M](#), [Castillo J](#), [Ruiz J](#), [Marquez M](#), [Gomez-Mateos J](#), [Pineda JA](#), [Santos J](#).

Unidad de Enfermedades Infecciosas, Hosp. Virgen de la Victoria, Malaga, Spain.

OBJECTIVES: to assess the incidence and risk factors for insulin resistance (IR) in a cohort of naive HIV-infected patients 48 weeks after starting highly active antiretroviral therapy (HAART). **DESIGN:** prospective, two centre, observational, cohort study. **METHODS:** One-hundred and thirty-seven patients who started HAART and maintained the same regimen for 48 weeks were included. IR was determined by the homeostasis model assessment (HOMA-IR) method. Individuals with a HOMA-IR value >3.8 were defined as insulin resistant. Independent associations with the development of IR at 48 weeks were evaluated. **RESULTS:** Seventeen (12.4%) individuals showed a HOMA-IR value >3.8 at baseline and were excluded for incidence analyses. Fifteen patients developed IR at 48 weeks of HAART, giving an incidence of 13%. Independent predictors of the development of IR were indinavir exposure (beta-coefficient 5.45, 95% confidence interval [CI] 1.30-22.8; P=0.02), and hepatitis C virus (HCV) antibody positivity (beta-coefficient 5.22, 95% CI 1.34-20.33; P=0.01). The appearance of IR was associated with a higher BMI (beta-coefficient 1.72 for each 2 kg/m² increase, 95% CI 1.54-1.94; P=0.02) and with the presence of lipodystrophy at 48 weeks (beta-coefficient 5.59, 95% CI 1.45-21.5; P=0.01). **CONCLUSIONS:** HAART induces the development of IR in previously naive non-insulin-resistant HIV-infected individuals, with an incidence of 13% in the first year of therapy. Indinavir exposure, and HCV coinfection are associated with an increased risk of developing IR.

PMID: 16856627 [PubMed - indexed for MEDLINE]

A patient with HIV encephalopathy presenting with parkinsonism during HAART therapy]

[Article in Japanese]

[Shimohata T](#), [Takadou Y](#), [Terajima K](#), [Tsukada H](#), [Gejo F](#), [Tanaka K](#), [Nishizawa M](#).

Department of Neurology, Brain Research Institute, Niigata University, 1-757 Asahimachi, Niigata City 951 8585, Japan.

We report the case of a 32-year-old man presenting symptoms of parkinsonism. Neurological examination revealed parkinsonism symptoms such as akinesia and postural instability, dementia and frontal lobe signs. He was diagnosed as having human immunodeficiency virus (HIV) encephalopathy. Brain MRI, 99mTc ECD-SPECT and 1H-MR spectroscopy demonstrated symmetrical cerebral white matter lesions, predominantly in the bilateral frontal lobes. Frontal lobe dysfunction could be responsible for his parkinsonism associated with HIV encephalopathy. His neurological symptoms improved transiently after the initiation of HAART but fluctuated when antiretroviral drugs were changed because of their side effects. Although HAART effectively decreased plasma HIV-RNA load and increased peripheral blood CD4 cell count, his parkinsonism and dementia eventually exacerbated. Our results suggest that a combination of antiretroviral drugs affects the therapeutic efficacy against HIV encephalopathy, and that CNS symptoms could be aggravated during HAART, even when plasma HIV-RNA load and CD4 cell count are maintained under favorable conditions.

Gender and long-term metabolic toxicities from antiretroviral therapy in HIV-1 infected persons.

[Boulassel MR](#), [Morales R](#), [Murphy T](#), [Lalonde RG](#), [Klein MB](#).

Immunodeficiency Service, Montreal Chest Institute, McGill University Health Centre, Montreal, Quebec, Canada. rachid.boulass@muhc.mcgill.ca

Gender differences in a large population-based cohort of HIV-1 infected patients (245 women and 723 men) were examined with respect to the incidence of metabolic and morphologic alterations after initiation of highly active antiretroviral therapy (HAART). Patients initiated HAART between January 1996 and December 2003. The outcome measures were the incidence of hyperglycemia, hypercholesterolemia, symptomatic lactic

acidosis, treatment-limiting lipodystrophy, and hypersensitivity reaction. Cox proportional hazards models were used to estimate the crude and adjusted hazard ratios of reaching the endpoints for exposures and covariates. Women were younger than men (35 +/- 9.8 vs. 40 +/- 8.2 years, $P < 0.001$) and more frequently from Haiti or Africa (59%), whereas 76% of men were Canadian-born. Type of initial HAART regimen did not differ between women and men. There were no gender differences in the overall incidence of hyperglycemia, hypercholesterolemia, or treatment-limiting lipodystrophy, even after adjusting for age, CD4 cell count, viral load, time since HIV diagnosis, history of AIDS-defining illness and year of HAART initiation. In contrast, women had significantly higher risk of developing lactic acidosis than men ($P = 0.0009$). Hypersensitivity reactions were also more frequent in women than men (adjusted hazard ratio = 4.4 (95% CI: 2.1-9.3)). Collectively, these data suggest that metabolic toxicities after HAART do not differ by gender but that lactic acidosis and hypersensitivity reactions are more frequent in women than men.

PMID: 16847953 [PubMed - indexed for MEDLINE]

Fat distribution in women with HIV infection.

[Study of Fat Redistribution and Metabolic Change in HIV Infection \(FRAM\).](#)

Infectious Disease Section, Veterans Affairs Medical Center, University of California, San Francisco, 94121, USA.

OBJECTIVE: Both peripheral fat loss and central fat gain have been reported in women with HIV infection. We determined the fat changes that are specific to HIV infection in women. **METHODS:** HIV-infected and control women from the study of Fat Redistribution and Metabolic Change in HIV Infection (FRAM) were compared. Lipoatrophy or lipohypertrophy was defined as concordance between participant report of fat change and clinical examination. Whole-body magnetic resonance imaging measured regional adipose tissue volumes. The relationship among different adipose tissue depots was assessed. Factors associated with individual depots were analyzed using multivariate linear regression. **RESULTS:** HIV-infected women reported more fat loss than controls in all peripheral and most central depots. Peripheral lipoatrophy was more frequent in HIV-infected women than controls (28% vs. 4%, $P < 0.001$), whereas central lipohypertrophy was similar (62% vs. 63%). Among HIV-infected women, those with central lipohypertrophy were less likely to have peripheral lipoatrophy (odds ratio, 0.39; 95% confidence interval, 0.20 to 0.75, $P = 0.006$) than those without central lipohypertrophy. On magnetic resonance imaging, HIV-infected women with clinical peripheral lipoatrophy had less subcutaneous adipose tissue (SAT) in peripheral and central sites and less visceral adipose tissue (VAT) than HIV-infected women without peripheral lipoatrophy. Compared with controls, HIV-infected women had less SAT in the legs, regardless of the presence or absence of lipoatrophy. However, those without lipoatrophy had more VAT and upper trunk SAT than controls. Use of the antiretroviral drug stavudine was associated with less leg SAT but was not associated with VAT. The use of highly active antiretroviral therapy, however, was associated with more VAT. **CONCLUSIONS:** Peripheral lipoatrophy occurs commonly in HIV-infected women but is not associated with reciprocally increased VAT or trunk fat.

PMID: 16837863 [PubMed - indexed for MEDLINE]

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

[Pan G, Yang Z, Ballinger SW, McDonald JM.](#)

Department of Pathology, The University of Alabama at Birmingham, 701 19 Street S., LHR 504 Birmingham, AL 35294, USA.

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.

[Antiretroviral treatment associated life-threatening adverse events]

[Article in Spanish]

[Moreno-Cuerda VJ](#), [Morales-Conejo M](#), [Rubio R](#).

Unidad VIH, Servicio de Medicina Interna, Hospital Universitario 12 de Octubre, Madrid, Espana. vjmorenocuerda@yahoo.es

The primary goal of the highly active antiretroviral treatment is to improve HIV-infected patient immune function through maintaining viral suppression. However, this treatment may lead to adverse events, some of them potentially serious. This article emphasizes on the antiretroviral therapy associated adverse events and their management recommendations, especially for serious or potentially life-threatening cases. Adverse events analyzed in this article include side effects derived from mitochondrial toxicity, abacavir hypersensitivity reaction, hepatotoxicity, skin rash and Stevens-Johnson syndrome, increased bleeding episodes in hemophilic patients and nephrotoxicity. In some cases, a high suspicion is needed because the onset symptoms may be unspecific.

PMID: 16759591 [PubMed - indexed for MEDLINE]

Severe liver disease associated with prolonged exposure to antiretroviral drugs.

[Maida I](#), [Nunez M](#), [Rios MJ](#), [Martin-Carbonero L](#), [Sotgiu G](#), [Toro C](#), [Rivas P](#), [Barreiro P](#), [Mura MS](#), [Babudieri S](#), [Garcia-Samaniego J](#), [Gonzalez-Lahoz J](#), [Soriano V](#).

Department of Infectious Diseases, Hospital Carlos III, Madrid. Spain.

BACKGROUND: Liver damage is frequently seen in HIV-positive subjects, often resulting from coinfection with hepatitis B and/or C viruses (HCV), alcohol abuse, etc. However, the etiology of liver disease still remains unknown for a small subset of individuals. **METHODS:** Cryptogenic liver disease (CLD) was defined as persistently elevated aminotransferases levels in the absence of hepatitis C and/or B viruses replication and of other common causes of liver disease (alcohol, medications, etc). We identified cases initially meeting this definition by examining all HIV-positive subjects attended during the year 2004 in 2 large HIV clinics in Spain. Their clinical charts were retrospectively reviewed, and their assessment completed when needed to rule out other less frequent causes of liver disease. The stage of liver fibrosis was assessed by liver biopsy and/or elastography. To assess which factors could be associated with CLD, HIV-positive controls were chosen and matched by age, gender, and CD4 status. **RESULTS:** CLD was diagnosed in 17 (0.5%) out of 3200 HIV-positive patients. Their mean age was 43 years, 82.4% were male, and 76% had acquired HIV through homosexual relationships. The mean time from HIV diagnosis was >15 years, and all patients had been exposed to antiretroviral therapy. Nevirapine, stavudine, and didanosine were the drugs more frequently used by this subset of patients. None of them had liver function test abnormalities before initiating antiretroviral therapy. Advanced liver fibrosis (F3-F4 Metavir scores) was recognized in 10 (58.8%) individuals, and 9 (52.9%) had developed symptomatic liver complications, including ascites (8), portal thrombosis (6), variceal bleeding (5), and encephalopathy (2). In the case-control analysis, prolonged didanosine exposure was the only independent predictor of developing CLD in this population. **CONCLUSIONS:** CLD is an uncommon condition in HIV-positive individuals and might be associated with prolonged didanosine exposure. It may evolve causing severe liver complications, with variceal bleeding and portal thrombosis being particularly frequent.

PMID: 16688096 [PubMed - indexed for MEDLINE]

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](#).

AIDS Pathogenesis and Clinical Research Program, Macfarlane Burnet Institute for Medical Research and Public Health, Melbourne, Australia.

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.

PMID: 16639337 [PubMed - indexed for MEDLINE]

Sensory neuropathy in human immunodeficiency virus/acquired immunodeficiency syndrome patients: protease inhibitor-mediated neurotoxicity.

[Pettersen JA](#), [Jones G](#), [Worthington C](#), [Krentz HB](#), [Keppler OT](#), [Hoke A](#), [Gill MJ](#), [Power C](#).

Department of Clinical Neurosciences, University of Calgary, Calgary, Alberta, Canada.

OBJECTIVE: Human immunodeficiency virus-associated sensory neuropathy (HIV-SN) is a common and disabling disorder, often associated with antiretroviral therapy (ART) use. We investigated the clinical features and associated pathogenic determinants of HIV-SN in a neurological cohort of HIV-infected patients, together with a novel model of HIV-SN. METHODS: HIV-infected patients with neurological disease were investigated in terms of clinical and laboratory aspects together with ART exposure focusing on symptomatic HIV-SN. Rat-derived dorsal root ganglion (DRG) cultures, transgenic for human CD4 and CCR5 treated with ARTs or HIV infected, or both, were studied with respect to quantitative neuronal injury. RESULTS: Among 221 patients assessed from 1998 to 2004, 120 had no sensory neuropathy, whereas 101 displayed HIV-SN, including 64 with distal sensory neuropathy and 37 with antiretroviral toxic neuropathy. HIV-SN patients exhibited significantly greater mean age, peak plasma viral loads, and exposure to neurotoxic dideoxynucleosides and protease inhibitors, including indinavir, saquinavir, or zidovudine. HIV-infected DRG cultures exposed to indinavir or didanosine showed significant neuronal atrophy, neurite retraction, and process loss, compared with controls. Indinavir was selectively cytotoxic to DRG macrophages compared with other ARTs. INTERPRETATION: Protease inhibitor exposure is an unrecognized risk factor for the development of HIV-SN, which may potentiate neuronal damage in HIV-infected DRGs, possibly through the loss of macrophage-derived trophic factors.

PMID: 16634006 [PubMed - indexed for MEDLINE]

Antiretroviral medications associated with elevated blood pressure among patients receiving highly active antiretroviral therapy.

[Crane HM](#), [Van Rompaey SE](#), [Kitahata MM](#).

Department of Medicine, Center for AIDS and STD Research, University of Washington, Harborview Medical Center, 325 9th Avenue, Seattle, WA 98104, USA.
hcrane@u.washington.edu

OBJECTIVE: To examine the effect of antiretroviral agents and clinical factors on the development of elevated blood pressure (BP). **METHODS:** Observational cohort study of patients initiating their first HAART regimen. We evaluated mean BP prior to HAART and while receiving HAART in relation to antiretroviral classes and individual agents, and demographic and clinical characteristics including change in body mass index (BMI) while on HAART. We used logistic regression analysis to examine factors associated with elevated BP [$>$ or $=$ 10 mmHg increase in systolic BP (SBP), diastolic BP (DBP) or new diagnosis of hypertension]. **RESULTS:** Among 444 patients who had 4592 BP readings, 95 patients developed elevated SBP ($n = 83$), elevated DBP ($n = 33$), or a new diagnosis of hypertension ($n = 11$) after initiating HAART. In multivariate analysis, patients on lopinavir/ritonavir had the highest risk of developing elevated BP [odds ratio (OR), 2.5; $P = 0.03$] compared with efavirenz-based regimens. When change in BMI was added to the model, increased BMI was significantly associated with elevated BP (OR, 1.3; $P = 0.02$), and the association between lopinavir/ritonavir and elevated BP was no longer present. Compared with lopinavir/ritonavir-based regimens, patients receiving atazanavir (OR, 0.2; $P = 0.03$), efavirenz (OR, 0.4; $P = 0.02$), nelfinavir (OR, 0.3; $P = 0.02$), or indinavir (OR, 0.3; $P = 0.01$) had significantly lower odds of developing elevated BP. **CONCLUSIONS:** Treatment with lopinavir/ritonavir is significantly associated with elevated BP, an effect that appears to be mediated through an increase in BMI. Patients receiving atazanavir were least likely to develop elevated BP. The impact of antiretroviral medications on cardiovascular disease risk factors will increasingly influence treatment decisions.

PMID: 16603854 [PubMed - indexed for MEDLINE]

Thyroid function in human immunodeficiency virus patients treated with highly active antiretroviral therapy (HAART): a longitudinal study.

[Madeddu G](#), [Spanu A](#), [Chessa F](#), [Calia GM](#), [Lovigu C](#), [Solinas P](#), [Mannazzu M](#), [Falchi A](#), [Mura MS](#), [Madeddu G](#).

Department of Infectious Diseases, Referral HIV Care Center, University of Sassari, Sassari, Italy.

OBJECTIVE: Given that few and controversial data have been reported on thyroid function in human immunodeficiency virus (HIV) patients on highly active antiretroviral therapy (HAART), we further investigated whether HAART affects thyroid hormones. **DESIGN AND PATIENTS:** Two hundred two consecutive adult HIV patients in stable clinical condition were enrolled, 182 on HAART and 20 naive; 128 were rechecked during follow-up. Body mass index (BMI), CD4 cell count, HIV RNA, hepatitis C and B virus status and infection duration were determined in all HIV patients and HAART duration in treated patients. In all patients and in 60 controls, the following were measured: FT4 and FT3 by radioimmunoassay; TSH, antithyroid peroxidase (TPO) and antithyroglobulin (TG) antibodies by immunoradiometric assay. **RESULTS:** Abnormalities in thyroid function tests were found in 23/182 (12.6%) HAART patients, but not in naive patients. Most abnormalities were subclinical hypothyroidism, with mean FT4 and TSH levels lower and higher, respectively, in HAART patients compared to naive patients and controls, FT4 levels being significantly lower than controls. TSH negatively correlated with CD4 count nadir and positively with HAART duration. During follow-up, FT4 and FT3 significantly decreased and TSH increased in patients continuing HAART, whereas CD4 counts were unmodified; subclinical hypothyroid conditions persisted and further cases occurred, whereas the only hypothyroid patient who interrupted HAART shows a normalization of thyroid tests. Patients on stavudine, included in most hypothyroid patient protocols, had significantly lower FT4 levels with prolonged treatment. **CONCLUSIONS:** HAART, particularly stavudine, is associated with a high prevalence of subclinical hypothyroidism. Hypotheses are made regarding responsible mechanisms and risk factors. Thyroid function should be tested and sequentially rechecked in HAART patients.

PMID: 16584508 [PubMed - indexed for MEDLINE]

Central nervous system immune reconstitution disease in acquired immunodeficiency syndrome patients receiving highly active antiretroviral treatment.

[Gray F](#), [Bazille C](#), [Adle-Biassette H](#), [Mikol J](#), [Moulinier A](#), [Scaravilli F](#).

Service Central d'Anatomie et de Cytologie Pathologiques, AP-HP, Hopital Lariboisiere, France. francoise.gray@lrb.aphp.fr

Highly active antiretroviral therapy (HAART)-induced immune restoration has been very beneficial for acquired immunodeficiency syndrome (AIDS) patients. In rare instances, HAART may induce a paradoxical clinical deterioration due to an immune reconstitution inflammatory syndrome (IRIS). This syndrome has been described with a wide variety of systemic infections and, in the central nervous system, with *Cryptococcus neoformans* infection, cytomegalovirus retinitis, and progressive multifocal leukoencephalopathy (PML). The authors have examined brain tissue in eight cases of IRIS: two autopsy cases and three biopsy cases of HIV encephalitis with IRIS and one autopsy case and two biopsy cases of PML with IRIS. All the patients presented with clinical deterioration following initiation of HAART and imaging showed contrast enhancement of the lesions. The symptoms regressed in four patients whereas the other four patients died. Neuropathological examination revealed severe inflammatory and demyelinating lesions with marked intraparenchymal and perivascular infiltration by macrophages and T lymphocytes. In some cases abundant viral proliferation was identified by immunocytochemistry or in situ hybridization, but in others the infectious agent could only be detected using PCR. T lymphocytes were predominantly CD8(+). In those cases with the more favorable course, inflammation was less severe with marked macrophage activation and a number of CD4(+) lymphocytes; in contrast, in the lethal cases inflammation was severe and mostly composed of CD8(+) cytotoxic lymphocytes. We conclude that HAART-induced paradoxical aggravation of HIV encephalitis or AIDS-related PML due to IRIS is reversible in most cases but may be lethal in others. In fatal cases, fulminant viral infection and/or acute perivenous leukoencephalitis may result from a dysregulation of the CD8(+)/CD4(+) T-cell balance.

PMID: 16540449 [PubMed - indexed for MEDLINE]

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

[Cote HC](#), [Magil AB](#), [Harris M](#), [Scarath BJ](#), [Gadawski I](#), [Wang N](#), [Yu E](#), [Yip B](#), [Zalunardo N](#), [Werb R](#), [Hogg R](#), [Harrigan PR](#), [Montaner JS](#).

British Columbia Centre for Excellence in HIV/AIDS, Providence Health Care, Vancouver, BC, Canada. helene.cote@ubc.ca

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 preceding 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.

PMID: 16518963 [PubMed - indexed for MEDLINE]

Adhesive capsulitis of the shoulder in human immunodeficiency virus-positive patients during highly active antiretroviral therapy.

[De Ponti A](#), [Vigano MG](#), [Taverna E](#), [Sansone V](#).

Orthopaedic Department, Vita et Salute University San Raffaele Scientific Institute, Milano, Italy. alexdeponi@hotmail.com

Many adverse events have been described in patients treated with highly active antiretroviral therapy (HAART). Recently, among these, adhesive capsulitis of the shoulder has been described in some patients using protease inhibitors. We report our experience with 6 human immunodeficiency virus-positive patients in whom adhesive capsulitis of the shoulder developed during HAART. All 6 patients were treated with the same antiretroviral drug combination (HAART) including nucleoside reverse transcriptase (stavudine and lamivudine) and protease inhibitors (indinavir). The clinical pattern of adhesive capsulitis during HAART is similar to the classical form of adhesive capsulitis. Examining our case studies, we postulate a correlation between HAART and adhesive capsulitis. Discontinuation or reduction of the dosage of protease inhibitors associated with conventional conservative treatment is effective in reducing the symptoms and resolving the disease.

PMID: 16517362 [PubMed - indexed for MEDLINE]

Antiretroviral therapy and the kidney: balancing benefit and risk in patients with HIV infection.

[Wyatt CM](#), [Klotman PE](#).

Division of Nephrology, Department of Medicine, Mount Sinai School of Medicine, New York, NY 10029, USA. christina.wyatt@mssm.edu

The widespread introduction of highly active antiretroviral therapy (HAART) has revolutionised the treatment and course of HIV infection, with complications of chronic HIV infection and HAART playing an increasingly important role in morbidity and mortality. Both HIV infection and HAART have been associated with the development of acute and chronic kidney disease. The incidence of HIV-associated nephropathy, the classic kidney disease of HIV, reached a plateau following the introduction of HAART, consistent with the pathogenic role of direct viral infection of the kidney. At the same time, antiretroviral agents and related therapies have demonstrated a range of nephrotoxic effects, including crystal-induced obstruction, lactic acidosis, tubular toxicity, interstitial nephritis and electrolyte abnormalities. This article reviews the impact of HAART on the epidemiology of HIV-related kidney disease, the potential nephrotoxicity of specific antiretroviral agents and related medications, and guidelines for monitoring kidney function in HAART-treated patients.

PMID: 16503748 [PubMed - indexed for MEDLINE]

Metabolic and cardiovascular complications of highly active antiretroviral therapy for HIV infection.

[Barbaro G.](#)

Department of Medical Pathophysiology, University La Sapienza, Rome, Italy.
g.barbaro@tin.it

Highly active antiretroviral therapy (HAART) regimens, especially those including protease inhibitors have been shown to cause, in a high proportion of HIV-infected patients, a metabolic syndrome (lipodystrophy/lipoatrophy, dyslipidemia, type 2 diabetes mellitus, insulin resistance) that may be associated with an increased risk of cardiovascular disease. A careful stratification of the cardiovascular risk of HIV-infected patients under HAART is needed according to the most recent clinical guidelines.

PMID: 16454713 [PubMed - indexed for MEDLINE]

[Cutaneous drug-reactions to nevirapine: study of risk factors in 101 HIV-infected patients]

[Article in French]

[Pitche P](#), [Drobacheff-Thiebaut C](#), [Gavignet B](#), [Mercier M](#), [Laurent R](#).

Service de Dermatologie, CHU Saint-Jacques, Besancon. ppitche@yahoo.fr

BACKGROUND: Several studies have shown a high prevalence of rash induced by nevirapine. However, there is little knowledge about the risk factors associated with nevirapine-induced rash. The aim of this study was to identify risk factors associated with the occurrence of rash during the treatment with nevirapine of HIV-infected patients. **METHODS:** A retrospective study was conducted in the dermatology department of Besancon university teaching hospital between November 1998 and September 2001. The study included all HIV-infected patients receiving HAART regimens that included nevirapine. The following data were collected: age, sex, CDC classification of HIV, CD4 and CD8 lymphocyte counts, plasma HIV RNA load, hepatitis B, C and cytomegalovirus serostatus, history of drug allergy, concomitant medication (other antiretroviral drugs, corticosteroids, antihistamines). Univariate analysis was performed using a Chi2 test or Fischer's test and Student's t test. Fischer's test and the Cox proportional hazards model were used in the multivariate analysis. **RESULTS:** During the study period, 101 HIV-infected patients (74 men and 27 women; mean age: 41.6 +/- 10.3 years) were treated with HAART regimens including nevirapine. Fourteen developed cutaneous drug-reactions attributable to nevirapine (13.86%). We observed 13 cases of maculopapular exanthema and 1 case of DRESS. In the univariate analysis, female gender ($p=0.002$), plasma HIV RNA load $> 10,000$ copies/ml ($p=0.05$), heterosexual transmission ($p=0.002$) and abacavir treatment ($p=0.05$) constituted risk factors associated with rash. In the multivariate analysis, only female gender ($p<0.0001$) and plasma HIV RNA load $> 10,000$ copies/ml ($p=0.0007$) were associated with rash. **DISCUSSION:** The results of this study confirm the high frequency of toxidermy associated with nevirapine therapy. The risk factors associated with occurrence of rash due to nevirapine therapy were female gender and plasma RNA $> 10,000$ copies/ml. Several studies showed absence of any protective effect of antihistamines and corticosteroids in preventing the cutaneous adverse reactions associated with nevirapine. The identification of risk factors closely associated with nevirapine-induced rash could help physicians determine new strategies for safer use of nevirapine in the HAART regimen.

PMID: 16446639 [PubMed - indexed for MEDLINE]

Arterial stiffness in HIV-infected patients receiving highly active antiretroviral therapy.

[Sevastianova K](#), [Sutinen J](#), [Westerbacka J](#), [Ristola M](#), [Yki-Jarvinen H](#).

Department of Medicine, Division of Diabetes, Helsinki University Central Hospital, Helsinki, Finland. ksenia.sevastianova@helsinki.fi

HIV-infected patients receiving highly active antiretroviral therapy (HAART) are at increased risk of cardiovascular events. Reported non-invasive techniques for assessment of blood pressure in this population have been limited to sphygmomanometry. The present cross-sectional study investigated the impact of antiretroviral therapy and the HAART-associated lipodystrophy on aortic blood pressure conditions and arterial stiffness in HAART-treated lipodystrophic (n=42) and non-lipodystrophic (n=17) patients. Pulse wave analysis, novel to this population, was used to evaluate measures of arterial stiffness, including the heart rate corrected augmentation index, AgI(HR). Results indicated no significant difference between the study groups in peripheral or aortic blood pressure and AgI(HR). Significant correlates of AgI(HR) included age (P = 0.003), duration of antiretroviral therapy (P = 0.020), lamivudine therapy (P = 0.015) and ritonavir therapy (P = 0.016) as well as cumulative exposure to protease inhibitors (P = 0.030). Time since HIV diagnosis, severity of immunodeficiency or presence of HAART-associated lipodystrophy bore no relationship to AgI(HR). In multivariate analysis, duration of antiretroviral therapy (P = 0.046), cumulative exposure to nucleoside reverse transcriptase inhibitors (P = 0.032) and to protease inhibitors (P = 0.011) were identified as independent factors predicting AgI(HR). Prolonged antiretroviral treatment, thus, delineates as a risk factor for systemic arterial stiffness and the associated cardiovascular mortality.

PMID: 16430198 [PubMed - indexed for MEDLINE]

Antiretroviral therapy-associated modulation of Th1 and Th2 immune responses in HIV-infected pregnant women.

[Fiore S](#), [Newell ML](#), [Trabattoni D](#), [Thorne C](#), [Gray L](#), [Savasi V](#), [Tibaldi C](#), [Ferrazzi E](#), [Clerici M](#).

Centre for Paediatric Epidemiology and Biostatistics, Institute of Child Health, University College London (UCL), London, UK. S.Fiore@ich.ucl.ac.uk

A successful pregnancy is characterised by an increase in Th2 cytokines and suppression of Th1 cytokine production. A Th1 to Th2 cytokine shift is also observed in the disease progression of HIV infection. Highly active antiretroviral therapy (HAART) suppresses HIV viremia, increases CD4+ cell counts and counteracts the Th1 to Th2 shift. We hypothesised that the increased risk of premature delivery reported in HIV-infected, HAART-treated pregnant women is mediated through changes in the cytokine environment in pregnancy. Here, we present results relating to levels of interleukin (IL)-2 (Th1) and IL-10 (Th2) in peripheral blood mononuclear cells (PBMCs) measured three times during pregnancy in 49 HIV-infected women. Slope values representing the trend of repeated cytokine (IL-2-PHA, IL-2-Env, IL-10-PHA and IL-10-Env) measurements within women during pregnancy were estimated and median values compared by prematurity and HAART use. Multiple regression adjusted for HAART and cytokine slope clarified the additional and independent effect of HAART on prematurity risk. Results showed favourable immunomodulation induced by HAART with increased IL-2 and decreased IL-10. HAART use and IL-10-Env slopes were not significantly associated with prematurity risk, but each unit increase in IL-2-PHA slope was associated with an 8% increased risk of premature delivery (AOR, 1.08; 95% CI, 1.0-1.17; p=0.005). HAART use in pregnancy provides significant benefits in delaying HIV disease progression and reducing the risk of mother-to-child-transmission, but may be counterproductive in terms of successful pregnancy outcome.

Changes in renal function associated with indinavir.

[Boubaker K](#), [Sudre P](#), [Bally F](#), [Vogel G](#), [Meuwly JY](#), [Glauser MP](#), [Telenti A](#).

Division of Infectious Diseases, Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland.

BACKGROUND: Indinavir use is associated with a spectrum of renal and urinary tract complications including nephrolithiasis, renal colic and pain without recognizable lithiasis, and a picture of crystalluria-dysuria. A frank nephropathy has not been recognized as part of the spectrum. **METHODS:** A retrospective analysis of 106 HIV-

infected individuals receiving indinavir was performed with the purpose of identifying the frequency and risk factors for indinavir-associated nephropathy and urinary complications. Individuals receiving ritonavir or nelfinavir served as controls. RESULTS: A sustained elevation of creatinine (>20%, into abnormal range) was identified in 20 (18.6%) subjects treated with indinavir but not with other protease inhibitors. Creatinine elevation was associated with treatment duration of more than 54 weeks [odds ratio (OR), 7.1; 95% confidence interval (CI), 1.8-27.7], low baseline body mass index \leq 20 kg/m² (OR, 4.0; 95% CI, 1.0-16.6), and use of trimethoprim-sulphamethoxazole (TMP-SMX; OR, 4.6; 95% CI, 1.5-13.8). Lower urinary specific gravity (P = 0.015), and leukocyturia (P<0.001) were frequently associated features of indinavir nephropathy. No patient developed severe renal impairment and abnormalities were reversible upon discontinuation of the drug. Complications (renal colic, or pain and dysuria) occurred after a mean of 36 weeks (95% CI, 23-48) of indinavir treatment in 13 subjects (12.3%), eight of whom (62%) presented elevated creatinine during follow-up. Only long-term exposure to TMP-SMX (>160 weeks) was identified as a potential risk for the occurrence of a clinical event (OR, 4.7; 95% CI, 1.2-19.2). CONCLUSIONS: A crystal nephropathy, characterized by serum creatinine elevation, loss of concentrating ability of the kidney, leukocyturia, and renal parenchymal image abnormalities, is a frequent complication of indinavir therapy. Identification of individuals at risk, particularly those with low body mass index or receiving TMP-SMX prophylaxis, may help the decision to initiate indinavir or choose an alternative protease inhibitor in order to minimize renal and urinary tract adverse events.

3'-Azido-3'-deoxythymidine (AZT) is a competitive inhibitor of thymidine phosphorylation in isolated rat heart and liver mitochondria.

[Lynx MD](#), [McKee EE](#).

Department of Biological Sciences, University of Notre Dame, Notre Dame, IN 46556, USA.

Long-term use of 3'-azido-3'-deoxythymidine (AZT) is associated with various tissue toxicities, including hepatotoxicity and cardiomyopathy, and with mitochondrial DNA depletion. AZT-5'-triphosphate (AZTTP) is a known inhibitor of the mitochondrial DNA polymerase gamma and has been targeted as the source of the mitochondrial DNA depletion. However, in previous work from this laboratory with isolated rat heart and liver mitochondria, AZT itself was shown to be a more potent inhibitor of thymidine phosphorylation (IC₅₀ of 7.0 \pm 1.0 μ M AZT in heart mitochondria and of 14.4 \pm 2.6 μ M AZT in liver mitochondria) than AZTTP is of polymerase gamma (IC₅₀ of >100 μ M AZTTP), suggesting that depletion of mitochondrial stores of TTP may limit replication and could be the cause of the mitochondrial DNA depletion observed in tissues affected by AZT toxicity. The purpose of this work is to characterize the nature of AZT inhibition of thymidine phosphorylation in isolated rat heart and rat liver mitochondria. In both of these tissues, AZT was found to be a competitive inhibitor of the phosphorylation of thymidine to TMP, catalyzed by thymidine kinase 2. The inhibition constant (K_i) for heart mitochondria is 10.6 \pm 4.5 μ M AZT, and for liver mitochondria K_i is 14.0 \pm 2.5 μ M AZT. Since AZT is functioning as a competitive inhibitor, increasing thymidine concentrations may be one mechanism to overcome the inhibition and decrease AZT-related toxicity in these tissues.

3'-Azido-3'-deoxythymidine (AZT) inhibits thymidine phosphorylation in isolated rat liver mitochondria: a possible mechanism of AZT hepatotoxicity.
[Lynx MD](#), [Bentley AT](#), [McKee EE](#).

Department of Biological Sciences, University of Notre Dame, Notre Dame, IN 46556, United States.

3'-azido-3'-deoxythymidine (AZT) is a staple of highly active antiretroviral therapy (HAART). Prior to HAART, long-term use of high-dosage AZT caused myopathy, cardiomyopathy, and hepatotoxicity, associated with mitochondrial DNA depletion. As a component of HAART, AZT causes cytopenias and lipodystrophy. AZT-5'-triphosphate (AZTTP) is a known inhibitor of the mitochondrial polymerase gamma and has been targeted as the source of the mitochondrial DNA depletion. However, in previous work from this laboratory with isolated rat heart mitochondria, AZT phosphorylation beyond AZT-5'-monophosphate (AZTMP) was not detected. Rather, AZT was shown to be a more potent inhibitor of thymidine phosphorylation (50% inhibitory concentration (IC₅₀) of 7.0±1.0 µM) than AZTTP is of polymerase gamma (IC₅₀ of >100 µM), suggesting that depletion of mitochondrial stores of TTP may limit replication. This work has investigated whether an identical mechanism might account for the hepatotoxicity seen with long-term use of AZT. Isolated rat liver mitochondria were incubated with labeled thymidine or AZT, and the rate and extent of phosphorylation were determined by HPLC analysis of acid-soluble extracts of the incubated mitochondria. The results showed that in the phosphorylation of thymidine to TMP, liver mitochondria exhibit a higher V_{max} and K_m than heart mitochondria, but otherwise heart and liver mitochondria display similar kinetics. AZT is phosphorylated to AZTMP, but no further phosphorylated forms were detected. In addition, AZT inhibited the production of TTP, with an IC₅₀ of 14.4±2.6 µM AZT. This is higher, but comparable to, the results seen in isolated rat heart mitochondria.

Concentric membranous bodies and giant mitochondria in hepatocytes from a patient with AIDS.

[Shapiro SH](#), [Klavins JV](#).

Queens Hospital Center, Department of Laboratories, Jamaica, New York 11432.

The cytoplasm of hepatocytes in a liver biopsy from a patient with acquired immunodeficiency syndrome (AIDS) treated with sulfamethazole-trimethoprim contained concentric membranous bodies (CMB) and giant mitochondria. By light microscopy the general architecture of the liver was unaltered. By electron microscopy one to three CMB were present in random distribution within several cells in equal periportal and centrilobular localization. CMB were irregularly rounded or ovoid, loosely ribosome-studded lamellar whorls. Some were agranular or in parallel arrangement. Giant mitochondria often with paracrystalline inclusions were frequently in close association with CMB. Tubuloreticular inclusions were noted in Kupffer cell cytoplasm. Since CMB have been infrequently observed in human hepatocytes, are rare in nonneoplastic human liver, and have not been previously reported in association with AIDS, their appearance may relate to regenerative changes and/or sulfamethazole-trimethoprim therapy.

Drug-induced increased mitochondrial biogenesis in a liver biopsy.

[Kamal MA](#), [French SW](#).

Department of Pathology, Long Beach VA Medical Center, Long Beach, CA 90822, USA.
mkamal@pol.net

Oncocytic changes seen in hepatocytes in patients receiving highly active antiretroviral therapy (HAART) are a result of mitochondrial damage. This is the first report that provides the electron microscopy illustration of mitochondrial proliferation as a result of the HAART drug Stavudine (Zerit) hepatotoxicity. The drug's effect on mitochondrial DNA replication leads to depleted mitochondrial-encoded proteins and configurational defects of the mitochondrial inner membrane leading to reduced and abnormal cristae, which house the electron transport chain and elementary bodies. This results in a decrease in the NAD/NADH ratio and reduces oxidative phosphorylation. The shift in the NAD/NADH ratio decreases the rate of fatty acid beta oxidation and oxidation of pyruvate by the Krebs cycle. Decreased oxidation of pyruvate drives it into an alternative pathway to form lactate leading to lactic acidosis. This mitochondrial dysfunction results in a compensatory increase in mitochondrial biogenesis, which results in oncocytic changes of the hepatocytes.

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

Brinkman K, Smeitink JA, Romijn JA, Reiss P.

Department of Internal Medicine, Onze Lieve Vrouwe Gasthuis, Amsterdam, The Netherlands.
K.Brinkman@OLVG.nl

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: N Engl J Med 1990 Apr 19;322(16):1098-105

Mitochondrial myopathy caused by long-term zidovudine therapy.

Dalakas MC, Illa I, Pezeshkpour GH, Laukaitis JP, Cohen B, Griffin JL

Division of Intramural Research, National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, MD 20892.

Both infection with the human immunodeficiency virus type 1 (HIV) and zidovudine (formerly called azidothymidine [AZT]) cause myopathy. To identify criteria for distinguishing zidovudine-induced myopathy from that caused by primary HIV infection, we reviewed the histochemical, immunocytochemical, and electron-microscopical features of muscle-biopsy specimens from 20 HIV-positive patients with myopathy (15 of whom had been treated with zidovudine) and compared the findings with the patients' clinical course and

response to various therapies. Among the zidovudine-treated patients, the myopathy responded to prednisone in four, to the discontinuation of zidovudine in eight, and to nonsteroidal anti-inflammatory drugs in two. Numerous "ragged-red" fibers, indicative of abnormal mitochondria with paracrystalline inclusions, were found in the biopsy specimens from the zidovudine-treated patients but not in those from the other patients. The number of these fibers appeared to correlate with the severity of the myopathy.

All the patients, regardless of whether they had been treated with zidovudine, had inflammatory myopathy characterized by degenerating fibers, cytoplasmic bodies, and endomysial infiltrates consisting of CD8+ cells (mean +/- SD, 60.7 +/- 6.4 percent) and macrophages (39.2 +/- 6.4 percent) associated with Class I major histocompatibility complex (MHC-I) antigens (HLA-A, -B, and -C antigens) in the muscle fibers. The numbers and percentages of CD8+ cells and macrophages were similar in both the zidovudine-treated and the untreated HIV-positive patients. Specimens obtained on repeat muscle biopsy from two patients in whom the myopathy responded to the discontinuation of zidovudine showed remarkable histologic improvement. We conclude that long-term therapy with zidovudine can cause a toxic mitochondrial myopathy, which coexists with a T-cell-mediated inflammatory myopathy that is restricted to MHC-I antigen, and is indistinguishable from the myopathy associated with primary HIV infection or polymyositis in HIV-seronegative patients.

Comment in:
N Engl J Med. 1990 Oct 4;323(14):994

1: Ital J Neurol Sci 1992 Dec;13(9):723-8

AZT-induced mitochondrial myopathy.

Tomelleri G, Tonin P, Spadaro M, Tilia G, Orrico D, Barelli A, Bonetti B, Monaco S, Salviati A, Morocutti C, et al

Istituto di Neurologia, Università di Verona.

Histochemical, electron microscopy and biochemical studies were performed on muscle biopsy specimens from 11 AIDS patients treated with zidovudine. A peculiar association of structural abnormalities and mitochondrial dysfunction was found. Focal cytochrome c oxidase (COX) deficiency was evident in muscle sections from 9 patients, 8 of whom had received long-term treatment while one had been treated for 1 month only. Electron microscopy showed changes in number, size and structure of mitochondria. Biochemical studies proved partial COX and succinate cytochrome c reductase (SCR) deficiency in 4 patients; one patient had only reduced SCR activity. Our data confirm that AZT therapy can cause toxic myopathy with mitochondrial dysfunction.

PMID: 1336487

1: Lancet 1991 Mar 2;337(8740):508-10

Depletion of muscle mitochondrial DNA in AIDS patients with zidovudine-induced myopathy.

Arnaudo E, Dalakas M, Shanske S, Moraes CT, DiMauro S, Schon EA

Department of Neurology, Columbia University College of Physicians and Surgeons, New York.

Long-term zidovudine therapy in patients with human immunodeficiency virus (HIV) infection can cause a destructive mitochondrial myopathy with histological

In

features of ragged-red fibres (RRF) and proliferation of abnormal mitochondria.

9 zidovudine-treated patients with this myopathy we found severely reduced amounts (up to 78% reduction vs normal adult controls) of mitochondrial DNA (mtDNA) in muscle biopsy specimens by means of Southern blotting. In 2 HIV-positive patients who had not received zidovudine, muscle mtDNA content did not differ from that in the 4 controls. Depletion of mtDNA seems to be reversible, since 1 patient showed a substantial reduction in RRF and a concomitant pronounced increase in muscle mtDNA content after zidovudine therapy was discontinued. Depletion of muscle mtDNA is probably due to zidovudine-induced inhibition of mtDNA replication by DNA polymerase gamma and is not a secondary effect of HIV infection.

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

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

Brinkman K, Smeitink JA, Romijn JA, Reiss P

Department of Internal Medicine, Onze Lieve Vrouwe Gasthuis, Amsterdam, The Netherlands. K.Brinkman@OLVG.nl

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: N Engl J Med 1994 Mar 17;330(11):738-43

Evaluation of the quality of life associated with zidovudine treatment in asymptomatic human immunodeficiency virus infection. The AIDS Clinical Trials Group.

Lenderking WR, Gelber RD, Cotton DJ, Cole BF, Goldhirsch A, Volberding PA, Testa MA

Statistical and Data Analysis Center, Harvard School of Public Health, Boston, MA 02115.

BACKGROUND. Zidovudine therapy is recommended for asymptomatic patients infected with the human immunodeficiency virus (HIV) who have fewer than 500 CD4+ cells per cubic millimeter. An analysis of the quality of life associated with therapy that integrated both the effects of adverse events and the benefits of delayed disease progression might influence this recommendation. **METHODS.** We applied a survival analysis adjusted for the quality of life to data from a randomized trial conducted by the AIDS Clinical Trials Group. The trial compared treatment with 500 mg of zidovudine per day, 1500 mg of zidovudine per day, and placebo (Protocol 019) in 1338 asymptomatic HIV-infected patients. **RESULTS.** The average time with neither a progression of disease nor an adverse event (symptom or laboratory finding) was 15.7, 15.6, and 14.8 months for patients receiving placebo, 500 mg of zidovudine, and 1500 mg of zidovudine, respectively. The incidence of severe symptoms was 13.8 percent in the placebo group, 15.2 percent in the 500-mg group, and 19.9 percent in the 1500-mg

group (P= 0.038). After 18 months, the 500-mg group gained an average of 0.5 months without disease progression, as compared with the placebo group, but had severe adverse events an average of 0.6 months sooner. The 500-mg group had more quality-of-life--adjusted time than the placebo group only if the time lived after the progression of disease was considered by a patient to have less value than the time after the occurrence of a severe symptom.

CONCLUSIONS. For asymptomatic patients treated with 500 mg of zidovudine, a reduction in the quality of life due to severe side effects of therapy approximately equals the increase in the quality of life associated with a delay in the progression of HIV disease.

1: Nat Med 1995 May;1(5):417-22

Mitochondrial toxicity of antiviral drugs.

Lewis W, Dalakas MC

Department of Pathology and Laboratory Medicine, University of Cincinnati College of Medicine, Ohio 45267-0529, USA.

Long-term treatment with antiviral nucleoside analogue drugs, such as AZT, can give rise to delayed and at times severe mitochondrial toxicity. Although these toxic effects are manifest in many tissues, a common disease mechanism can explain the diverse clinical events. A better understanding of these disorders will shed light on genetic mitochondrial diseases and lead to the design of safer and more effective antiviral drugs.

1: J Neurol Sci 1997 Jul;149(1):19-25

Related Articles, Books

Cellular and mitochondrial toxicity of zidovudine (AZT), didanosine (ddI) and zalcitabine (ddC) on cultured human muscle cells.

Benbrik E, Chariot P, Bonavaud S, Ammi-Said M, Frisdal E, Rey C, Gherardi R, Barlovatz-Meimon G

Groupe d'Etudes et de Recherches sur le Muscle et le Nerf (GERMEN: ER 269 et 315, Université Paris XII), Faculté de Médecine, Créteil, France.

Zidovudine (AZT), didanosine (ddI) and zalcitabine (ddC) are the reference antiretroviral therapy in patients with AIDS. A toxic mitochondrial myopathy can be observed in patients treated with AZT, but not with ddI and ddC. All 3 compounds can inhibit mitochondrial (mt)DNA polymerase and cause termination of synthesis of growing mtDNA strands and mtDNA depletion. The propensity to injure particular target tissues is unexplained. In our work, cultured muscle cells prepared from human muscle biopsies, were exposed to various concentrations of AZT (4-5000 micromol/l), ddI (5-1000 micromol/l) and ddC (1-1000 micromol/l) for 10 days. We evaluated cell proliferation and differentiation and measured lipid droplet accumulation, lactate production and respiratory chain enzyme activities. All 3 compounds induced a dose-related decrease of cell proliferation and differentiation. AZT seemed to be the most potent inhibitor of cell proliferation. AZT, ddI and ddC induced cytoplasmic lipid droplet accumulations, increased lactate production and decreased activities of COX (complex IV) and SDH (part of complex II). NADHR (complex I) and citrate synthase activities were unchanged. Zalcitabine (ddC) and, to a lesser extent, ddI, were the most potent inhibitors of mitochondrial function. In conclusion, AZT, ddI and ddC all exert cytotoxic effects on human muscle cells and induce functional alterations of mitochondria possibly due to mechanisms other than the sole mtDNA depletion. Our results provide only a partial explanation of the fact that AZT, but not ddI and ddC, can induce a myopathy in HIV-infected patients. AZT myopathy might not simply result from a direct mitochondrial toxic effect of crude AZT.

PMID: 9168161

Hepatotoxicity development during antiretroviral therapy containing protease inhibitors in patients with HIV: the role of hepatitis B and C virus infection.

Aceti A, Pasquazzi C, Zechini B, De Bac C; The LIVERHAART Group.

Department of Infectious and Tropical Diseases, II Faculty of Medicine, University of Rome La Sapienza, Rome, Italy. professoraceti@tiscalinet.it

To evaluate the occurrence of hepatotoxicity in patients during antiretroviral therapy (ART) that contains protease inhibitors and the role of hepatitis viruses in its development, we performed a retrospective study including 1325 HIV-infected patients treated with ART for at least 6 months. Presence or absence of hepatitis viruses, alanine aminotransferase (ALT), total bilirubin, CD4 cell count, and plasma HIV RNA levels were evaluated. Hepatotoxicity developed in a few study subjects without coinfection, whereas it was significantly higher in coinfecting patients. Univariate logistic regression analysis showed that viral hepatitis coinfections are independent risk factors for hepatotoxicity. After 6 months of treatment, ritonavir was associated with higher rates of severe hepatotoxicity in the coinfecting group; in fact, ritonavir seems to be the most strongly hepatotoxic agent among coinfecting patients. After 12 months of therapy, hepatotoxicity occurred more frequently in patients with hepatitis C virus who did not respond to antiretroviral therapy (ART), whereas patients who did respond to ART showed decreased ALT levels. Hepatotoxicity is not exclusively an effect of drug toxicity, and the presence of hepatitis coinfection is an independent risk factor. Moreover, chronic hepatotoxicity mainly occurs in patients who did not respond to therapy. Conversely, patients who did respond to ART seemed to show improvement of chronic liver infection.

15) Toxicities Associated with Purine Analog Therapy

Bruce D. Cheson

National Cancer Institute Bethesda, Maryland

V. Summary

The nucleoside analogs have proven to be highly effective in the therapy of lymphoid malignancies. However, they have a number of associated toxicities, some of what may be severe. Of particular concern is immunosuppression which is uniform with standard treatment programs. Each of the nucleoside analogs is associated with a profound lymphocytopenia, with a reversal of the CD4/CD8, and opportunistic infections. Whether secondary malignancies will be a long-range complication will require observation and recording of long-term follow-up results.

The frequency with which many of the nonhematologic toxicities occur is difficult to estimate. Most studies contain small numbers of patients, in whom few, if any nonhematologic toxicities are reported. Whether that reflects the actual rarity of these events or the care with which those series was evaluated is not clear. As the clinical experience with these agents become more extensive, with longer follow-up, recognized toxicities will become better characterized and new side effects may be encountered. Anecdotal reports may serve to increase the sensitivity for identification of new and unusual complications.

There are a number of unresolved issues in the use of the nucleoside analogs. The optimal schedule of administration remains unknown. A 6-month course of fludarabine has been recommended for CLL, and a similar duration of DCF for HCL. Although a single course of CDA is generally used for HCL, repeated courses have been delivered for the other lymphoid malignancies.

Nevertheless, these regimens are empiric. An accumulating body of evidence suggests that fludarabine and CdA work by a different mechanism of action, e.g., activation of apoptosis. Therefore, we may be administering more drug than is required for biological effect (199, 200). Further study of this issue is warranted to maintain efficacy while minimizing the

toxicities associated with treatment with these highly effective nucleosid analogs. As nucleosid analogs are being combined with cytotoxic and biological agents in an attempt to increase their efficacy, care must be exercised to avoid drugs with overlapping toxicities. Based on the published literature, the non-hematologic toxicities from the nucleoside analogs are relatively similar (Table 3), with the possible exception of the ocular toxicity, rash and increased severity of nausea and vomiting with DCF, and the relatively more prolonged period of immunosuppression with DCF and CdA. In general, however, they are relatively well tolerated. The decision as to which is the preferred nucleoside analog for a specific indication must be determined by their response rate, durability of responses, cost, toxicity profile and ease with wich they can be combined into effective combination regiments.

from: **Nucleoside Analogs in Cancer Therapy**
edited by Bruce D. Cheson, Michael J. Keating, William Plunkett
Marcel Dekker Inc. New York, Basel, Hong Kong 1997