Altered oxidative stress indexes related to disease progression marker in human immunodeficiency virus infected patients with antiretroviral therapy.

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Abstract

BACKGROUND: It is generally accepted that oxidative stress (OS) is implicated in immunological and metabolic abnormalities during HIV infection. The acting mechanism used by Highly Active Antiretroviral Therapy (HAART) comes to add metabolic alterations.

METHOD: This is an observational study assessing the effect of two HAART combinations on redox indicators and on progression markers of disease. A cohort of 84 healthy and 84 HIV+ subjects were followed for 6 months. Fifty-six HIV+ subjects were distributed in group I (AZT, 3TC, IND) and group II (D4T, 3TC, NEV) according to drug combination. Peroxidation potential (PP), glutathione (GSH), malondialdehyde (MDA), total hydroperoxides (HPO), superoxide dismutase (SOD), catalase (CAT), advanced oxidation protein products (AOPP), percent of DNA fragmentation (% FDNA), CD4+, CD38+, CD95+ T lymphocytes subsets, viral load and body mass index (BMI) were measured at baseline and at 6 months.

RESULTS: After HAART started, CAT values for both groups receiving treatment did not showed significant difference. For group II, all other OS indexes were significantly higher than those for group I and the HIV+ not treated group (p<0.05), except for GSH values in group II (p<0.05) which was lower than group I values. These data suggest poor prognostic for group II. Not significant differences were found between treatment groups respect CD4+, CD8+, CD38+, CD95+ T cell subset count, viral load and BMI.

CONCLUSIONS: The findings suggest that increased OS occurs additionally to persistent redox imbalance associated to HIV infection during apparently successfully HAART. This conclusion does not only underline HAART associated toxicity but it may be also methodologically important for the follow-up of further clinical studies.

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Supplemental Content
HIV-1 protease inhibitor induced oxidative stress suppresses glucose stimulated insulin release: protection with thymoquinone.

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Abstract

The highly active anti-retroviral therapy (HAART) regimen has considerably reduced the mortality rate in HIV-1 positive patients. However, long-term exposure to HAART is associated with a metabolic syndrome manifesting cardiovascular dysfunction, lipodystrophy, and insulin resistance syndrome (IRS). The inclusion of HIV-1 protease inhibitors (PIs) in HAART has been linked to the induction of IRS. Although several molecular mechanisms of PI-induced effects on insulin action have been postulated, the deleterious effects of PIs on insulin production by pancreatic beta-cells have not been fully investigated and therapeutic strategies to ameliorate insulin dysregulation at this level have not been targeted. The present study showed that exposure to several different PIs, nelfinavir (5-10 microM), saquinavir (5-10 microM) and atazanavir (8-20 microM), decreases glucose stimulated insulin secretion from rat pancreatic beta-cells (INS-1). Nelfinavir significantly increased reactive oxygen species (ROS) generation and suppressed cytosolic, but not mitochondrial superoxide dismutase (SOD) levels. Nelfinavir also decreased both glutathione and ATP and increased UCP2 levels in these cells. Simultaneous treatment with thymoquinone (TQ) (2.5 microM), an active ingredient of black seed oil, significantly inhibited the effect of nelfinavir on augmented ROS production and suppressed SOD levels. Both TQ and black seed oil exposure increased glucose stimulated insulin secretion and ameliorated the suppressive effect of nelfinavir. The present findings imply a direct role of ROS in PI induced deleterious effects on pancreatic beta-cells. Our findings also suggest that TQ may be used as a potential therapeutic agent to normalize the dysregulated insulin production observed in HAART treated patients.


Supplemental Content
Changes in antioxidant profile among HIV-infected individuals on generic highly active antiretroviral therapy in southern India.

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Abstract

OBJECTIVE: The role of oxidative stress in disease progression has been shown to be more complicated in HIV-infected individuals receiving highly active antiretroviral therapy (HAART) compared to those who remain treatment-naïve. This study examined the changes in the antioxidant profile of HIV-infected subjects who remained HAART-naïve due to a high CD4 cell count and HIV-negative controls, over a 12-month follow-up period at YRG CARE, a tertiary HIV referral centre in southern India.

METHODS: We prospectively studied 35 HIV-infected participants (18 on d4T+3TC+EFV (stavudine+lamivudine+efavirenz), eight on AZT+3TC+EFV (zidovudine+lamivudine+efavirenz), and nine who were antiretroviral therapy-naïve) and 20 HIV-negative controls. Antioxidant profile (total antioxidant status, glutathione reductase, glutathione peroxidase, uric acid, ceruloplasmin, zinc, and albumin), CD4 cell count, plasma viral load, dietary intake, and history of smoking and alcohol use were determined at baseline and at twelve months.

RESULTS: At 12 months, participants on HAART showed a significant increase in glutathione peroxidase (baseline: 1765 vs. 12 months: 2850U/l; p<0.001) and albumin (3.6 vs. 4.4g/dl; p<0.001), and a significant decrease in glutathione reductase (52.6 vs. 50.5U/l; p=0.054) and uric acid (5.4 vs. 4.8mg/dl; p=0.027) compared to baseline. Also HAART-naïve participants had a significant increase in albumin (baseline: 3.7 vs. 12 months: 4.3g/dl; p=0.023) and a significant decrease in zinc levels (baseline: 79.0 vs. 12 months: 74.5microg/dl; p=0.052) from baseline to 12 months. HIV-negative subjects had a significant increase in glutathione peroxidase at 12 months from baseline (baseline: 37 vs. 12 months: 39U/l; p=0.002). No significant difference in total antioxidant status, ceruloplasmin, and zinc levels were observed in HAART-experienced subjects and negative controls over the 12-month follow-up period.

CONCLUSION: This study documents changes in antioxidants over a period of time in HAART-experienced subjects in a southern India setting.
Oxidative stress and toxicity induced by the nucleoside reverse transcriptase inhibitor (NRTI)--2',3'-dideoxycytidine (ddC): relevance to HIV-dementia.

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Abstract

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.

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Supplemental Content

[Redox status in HIV+ patients under HAART].

[Article in French]

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Abstract

Oxidative stress decreases immune defences and is also suggested to participate in the activation of HIV virus replication. That is why we decided to explore some biomarkers of oxidative stress (reduced glutathione, lipoperoxides, true malondialdehyde and vitamin C) in 20 HIV positive patients whose HIV replication was determined by measurement of RNA viral load. Reduced glutathione is decreased in HIV positive patients, without correlation with the viral load. The patients mean content of lipoperoxides is twice that of controls but with such a large range that there is no statistical difference.


Supplemental Content


HAART drugs induce oxidative stress in human endothelial cells and increase endothelial recruitment of mononuclear cells: exacerbation by inflammatory cytokines and amelioration by antioxidants.
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**Abstract**

Highly active antiretroviral therapy (HAART) has significantly improved the prognosis of HIV-1-infected patients but is associated with significant side effects such as diabetes, atherosclerosis, and cardiovascular complications. Oxidative stress can disrupt endothelial homeostasis by dysregulating the balance between pro- and antiatherogenic factors. We hypothesized that chronic exposure to HAART results in endothelial oxidative stress and activation of mononuclear cell recruitment, an early event in atherosclerosis. We studied the effects of HAART drug combinations, consisting of zidovudine, a nucleoside reverse transcriptase inhibitor; efavirenz, a nonnucleoside reverse transcriptase inhibitor; and either of the two protease inhibitors (PIs), indinavir or nelfinavir, on human aortic endothelial cells (HAECs) by monitoring the following parameters: (1) generation of reactive oxygen species (ROS), (2) mono-nuclear cell (Jurkat or U-937) adhesion, and (3) expression of cell adhesion molecules (CAMs). HAART exposure increased ROS formation in HAECs. Exposure to PIs alone and in HAART combinations increased mononuclear cell adhesion to HAECs in a concentration-dependent manner. Mononuclear cell adhesion to HAART-exposed HAECs was significantly enhanced following acute (24-h) exposure to the inflammatory cytokines, tumor necrosis factor (TNF)-alpha or interleukin (IL)-1beta and was suppressed by the antioxidants N-acetylcysteine and glutathione. Exposure to HAART increased intercellular adhesion molecule-1 (ICAM-1) gene expression and concomitant exposure to TNF-alpha further increased ICAM-1, vascular cell adhesion molecule-1 (VCAM-1), and endothelial-leukocyte adhesion molecule cell surface protein levels. These studies indicate that chronic HAART exposure increases oxidative stress in endothelial cells and induces mononuclear cell recruitment, which may eventually precipitate the cardiovascular diseases observed in HIV-1+ individuals on antiretroviral therapy.