

Endometrial epithelial cell responses to coinfecting viral and bacterial pathogens in the genital tract can activate the HIV-1 LTR in an NF{ κ }B-and AP-1-dependent manner.

[Ferreira VH](#), [Nazli A](#), [Khan G](#), [Mian MF](#), [Ashkar AA](#), [Gray-Owen S](#), [Kaul R](#), [Kaushic C](#).

Source

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Abstract

BACKGROUND:

Sexually transmitted infections (STIs) are associated with increased human immunodeficiency virus type 1 (HIV-1) susceptibility and viral shedding in the genital tract, but the mechanisms underlying this association are poorly understood.

METHODS:

Direct activation of HIV long terminal repeats (LTRs), a proxy measure for HIV-1 replication, was measured after treatment of 1G5 T cells with Toll-like receptor (TLR) ligands, herpes simplex virus type 1 or 2 (HSV-1/2), or *Neisseria gonorrhoeae*. For indirect activation, 1G5 T cells were incubated with supernatants from female primary genital epithelial cells (GECs) previously exposed to these agents. Proinflammatory cytokines and chemokines were measured in GEC supernatants. Proinflammatory pathways were blocked to determine the mechanisms of direct and indirect HIV-LTR activation.

RESULTS:

HSV-1/2, *N. gonorrhoeae*, and TLR ligands FimH (TLR-4), flagellin (TLR-5), and Poly (I:C) (TLR-3) directly induced HIV-LTR activation in 1G5 T cells. Supernatants collected from GECs incubated with these agents indirectly induced HIV-LTR activation. Production of tumor necrosis factor α , interleukin 6, interleukin 8, and monocyte chemoattractant protein-1 was elevated in GECs exposed to copathogens. Inhibition of nuclear factor κ B and activator protein-1 (AP-1) signaling pathways in 1G5 T cells abrogated both direct and indirect HIV-LTR activation.

CONCLUSIONS:

STIs may increase HIV-1 replication in the female genital tract via proinflammatory signaling pathways directly and indirectly via their effects on GECs. This increased HIV-1 replication may enhance sexual and vertical HIV transmission.

Supplemental Content



[Lancet Infect Dis.](#) 2010 Jul;10(7):455-63.

Effect of treating co-infections on HIV-1 viral load: a systematic review.

[Modjarrad K](#), [Vermund SH](#).

Source

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Abstract

Co-infections contribute to HIV-related pathogenesis and often increase viral load in HIV-infected people. We did a systematic review to assess the effect of treating key co-infections on plasma HIV-1-RNA concentrations in low-income countries. We identified 18 eligible studies for review: two on tuberculosis, two on malaria, six on helminths, and eight on sexually transmitted infections, excluding untreatable or non-pathogenic infections. Standardised mean plasma viral load decreased after the treatment of co-infecting pathogens in all 18 studies. The standardised mean HIV viral-load difference ranged from -0.04 log(10) copies per mL (95% CI -0.24 to 0.16) after syphilis treatment to -3.47 log(10) copies per mL (95% CI -3.78 to -3.16) after tuberculosis treatment. Of 14 studies with variance data available, 12 reported significant HIV viral-load differences before and after treatment. Although many of the viral-load reductions were 1.0 log(10) copies per mL or less, even small changes in plasma HIV-RNA concentrations have been shown to slow HIV progression and could translate into population-level benefits in lowering HIV transmission risk.

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Comment in

- [An addition to the effect of treating co-infections on HIV-1 viral load.](#) [Lancet Infect Dis. 2011]

Supplemental Content

Etienne de Harven, M.D.

Measuring “Viral load” does not prove the existence of a hypothetical HIV.

http://www.ummafrapp.de/skandal/de_Harven/mvl

[J Health Popul Nutr.](#) 2011 Aug;29(4):303-9.

Prevalence of antiretroviral drug resistance mutations and HIV-I subtypes among newly-diagnosed drug-naïve persons visiting a voluntary testing and counselling centre in northeastern South Africa.

[Nwobegahay JM](#), [Bessong PO](#), [Masebe TM](#), [Mavhandu LG](#), [Iweriebor BC](#), [Selabe G](#).

Source

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Abstract

Data on antiretroviral drug resistance among drug-naïve persons are important in developing sentinel and surveillance policies. This study was conducted to determine the prevalence of antiretroviral drug resistance mutations among drug-naïve HIV-infected individuals attending a voluntary testing and counselling centre at the Mankweng Hospital in northeastern South Africa. In total, 79 drug-naïve HIV-positive individuals were sequentially recruited during February 2008-December 2008. Drug resistance mutations were determined using the calibrated population resistance tool available on the Stanford HIV drug resistance database. Viral DNA was obtained from 57 (72%) of the 79 individuals. Reliable nucleotide sequences were obtained for 54 reverse transcriptase (RT) and 54 protease (PR) gene regions from 54 individuals. Overall, five sequences (9.3%) harboured drug resistance mutations (95% confidence interval -1.53 to 16.99). Four (7.4%) of these were nucleoside RT inhibitor mutations (D67G, D67E, T69D, and T215Y), and one (1.9%) was a PR inhibitor mutation (M46I). No major non-nucleoside RT resistance mutation was detected. Several minor resistance mutations and polymorphisms common in subtype C viruses were observed in the PR and RT genes. Phylogenetic analysis of the partial pol sequences showed that 52 (96%) of

the 54 isolates were HIV-1 subtype C. One isolate (08MB08ZA) was HIV-1 subtype B while another (08MB26ZA) was related to HIV-1 subtype J. HIV-1 subtype recombination analysis with REGA assigned the pol sequence to HIV subtype J (11_cpx) with a bootstrap value of 75%. The prevalence of drug resistance mutations observed in the population studied was relatively higher than previously reported from other parts of South Africa. In addition, this is apparently the first report of an HIV-1 subtype J-like virus from northeastern South Africa.

Supplemental Content



[J Infect Dis.](#) 2009 May 1;199(9):1275-85.

Ultra-deep pyrosequencing of hepatitis B virus quasispecies from nucleoside and nucleotide reverse-transcriptase inhibitor (NRTI)-treated patients and NRTI-naïve patients.

[Margeridon-Thermet S](#), [Shulman NS](#), [Ahmed A](#), [Shahriar R](#), [Liu T](#), [Wang C](#), [Holmes SP](#), [Babrzadeh F](#), [Gharizadeh B](#), [Hanczaruk B](#), [Simen BB](#), [Egholm M](#), [Shafer RW](#).

Source

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Abstract

The dynamics of emerging nucleoside and nucleotide reverse-transcriptase inhibitor (NRTI) resistance in hepatitis B virus (HBV) are not well understood because standard dideoxynucleotide direct polymerase chain reaction (PCR) sequencing assays detect drug-resistance mutations only after they have become dominant. To obtain insight into NRTI resistance, we used a new sequencing technology to characterize the spectrum of low-prevalence NRTI-resistance mutations in HBV obtained from 20 plasma samples from 11 NRTI-treated patients and 17 plasma samples from 17 NRTI-naïve patients, by using standard direct PCR sequencing and ultra-deep pyrosequencing (UDPS). UDPS detected drug-resistance mutations that were not detected by PCR in 10 samples from 5 NRTI-treated patients, including the lamivudine-resistance mutation V173L (in 5 samples), the entecavir-resistance mutations T184S (in 2 samples) and S202G (in 1 sample), the adefovir-resistance mutation N236T (in 1 sample), and the lamivudine and adefovir-resistance mutations V173L, L180M, A181T, and M204V (in 1 sample). G-to-A hypermutation mediated by the apolipoprotein B mRNA editing enzyme, catalytic polypeptide-like family of cytidine deaminases was estimated to be present in 0.6% of reverse-transcriptase genes. Genotype A coinfection was detected by UDPS in each of 3 patients in whom genotype G virus was detected by direct PCR sequencing. UDPS detected low-prevalence HBV variants with NRTI-

resistance mutations, G-to-A hypermutation, and low-level dual genotype infection with a sensitivity not previously possible.

Comment in

- [Low-abundance drug resistance mutations: extending the HIV paradigm to hepatitis B virus.](#) [J Infect Dis. 2009]

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Supplemental Content



[J Infect Dis.](#) 2009 Dec 1;200(11):1798-9; author reply 1799-1800.

Low-abundance drug resistance mutations: extending the HIV paradigm to hepatitis B virus.

[Menzo S](#), [Vincenti D](#), [Solmone M](#), [Prosperi M](#), [Bruselles A](#), [Abbate I](#), [Rozera G](#), [Capobianchi MR](#).

Comment on

- [Ultra-deep pyrosequencing of hepatitis B virus quasispecies from nucleoside and nucleotide reverse-transcriptase inhibitor \(NRTI\)-treated patients and NRTI-naïve patients.](#) [J Infect Dis. 2009]

Supplemental Content



[J Acquir Immune Defic Syndr.](#) 2009 Oct 1;52(2):246-8.

The acute effects of HIV protease inhibitors on insulin suppression of glucose production in healthy HIV-negative men.

[Lee GA](#), [Schwarz JM](#), [Patzek S](#), [Kim S](#), [Dyachenko A](#), [Wen M](#), [Mulligan K](#), [Schambelan M](#), [Grunfeld C](#).

Source

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Abstract

BACKGROUND:

The effects of different HIV protease inhibitors (PIs) on peripheral insulin resistance have been described, but less is known about their effects on insulin suppression of endogenous glucose production (EGP).

METHODS:

We tested the acute effects of 3 PIs, indinavir, ritonavir, and amprenavir, on EGP quantified by stable isotope techniques during the hyperinsulinemic, euglycemic clamp in 3 similar placebo-controlled protocols.

RESULTS:

EGP was higher with indinavir in the hyperinsulinemic state than with placebo (4.1 ± 1.3 vs. 2.2 ± 0.8 $\mu\text{mol} \times \text{kg}^{-1} \times \text{min}^{-1}$, $P = 0.04$). A trend toward higher EGP was seen with ritonavir (3.6 ± 0.3 vs. 3.0 ± 0.5 $\mu\text{mol} \times \text{kg}^{-1} \times \text{min}^{-1}$, $P = 0.08$). There was no evidence that amprenavir blunted insulin suppression of EGP compared with placebo (2.9 ± 0.04 vs. 3.2 ± 0.7 $\mu\text{mol} \times \text{kg}^{-1} \times \text{min}^{-1}$, $P = 0.63$).

CONCLUSIONS:

Some PIs can acutely blunt the ability of insulin to suppress EGP, but, as with insulin resistance, the effects of PIs on EGP are drug-specific, not class-specific.

Supplemental Content



[J Mol Cell Cardiol](#). 2010 Nov;49(5):746-52. doi: 10.1016/j.yjmcc.2010.08.013. Epub 2010 Aug 22.

HIV protease inhibitors elicit volume-sensitive Cl⁻ current in cardiac myocytes via mitochondrial ROS.

[Deng W](#), [Baki L](#), [Yin J](#), [Zhou H](#), [Baumgarten CM](#).

Source

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Abstract

HIV protease inhibitors (HIV PI) reduce morbidity and mortality of HIV infection but cause multiple untoward effects. Because certain HIV PI evoke production of reactive oxygen species (ROS) and volume-sensitive Cl⁻ current (I_{Cl,swell}) is activated by ROS, we tested whether HIV PI stimulate I_{Cl,swell} in ventricular myocytes. Ritonavir and lopinavir elicited outwardly rectifying Cl⁻ currents under isosmotic conditions that were abolished by the selective I_{Cl,swell}-blocker DCPIB. In contrast, amprenavir, nelfinavir, and raltegravir, an integrase inhibitor, did not modulate I_{Cl,swell} acutely. Ritonavir also reduced action potential duration, but amprenavir did not. I_{Cl,swell} activation was attributed to ROS because ebselen, an H₂O₂ scavenger, suppressed ritonavir- and lopinavir-induced I_{Cl,swell}. Major ROS sources in cardiomyocytes are sarcolemmal NADPH oxidase and mitochondria. The specific NADPH oxidase inhibitor apocynin failed to block ritonavir- or lopinavir-induced currents, although it blocks I_{Cl,swell} elicited by osmotic swelling or stretch. In contrast, rotenone, a mitochondrial e⁻ transport inhibitor, suppressed both ritonavir- and lopinavir-induced I_{Cl,swell}. ROS production was measured in HL-1 cardiomyocytes with C-H₂DCFDA-AM and mitochondrial membrane potential ($\Delta\Psi(m)$) with JC-1. Flow cytometry confirmed that ritonavir and lopinavir but not amprenavir, nelfinavir, or raltegravir augmented ROS production, and HIV PI-induced ROS production was suppressed by rotenone but not NADPH oxidase blockade. Moreover, ritonavir, but not amprenavir, depolarized $\Delta\Psi(m)$. These data suggest ritonavir and lopinavir activated I_{Cl,swell} via mitochondrial ROS production that was independent of NADPH oxidase. ROS-dependent modulation of I_{Cl,swell} and other ion channels by HIV PI may contribute to some of their actions in heart and perhaps other tissues.

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Supplemental Content



[J Acquir Immune Defic Syndr](#). 2009 Jun 1;51(2):111-6. doi: 10.1097/QAI.0b013e3181a324d6.

Mitochondrial DNA haplogroups influence lipotrophy after highly active antiretroviral therapy.

[Hendrickson SL](#), [Kingsley LA](#), [Ruiz-Pesini E](#), [Poole JC](#), [Jacobson LP](#), [Palella FJ](#), [Bream JH](#), [Wallace DC](#), [O'Brien SJ](#).

Source

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Abstract

Although highly active antiretroviral therapy (HAART) has been extremely effective in lowering AIDS incidence among patients infected with HIV, certain drugs included in HAART can cause serious mitochondrial toxicities. One of the most frequent adverse events is lipoatrophy, which is the loss of subcutaneous fat in the face, arms, buttocks, and/or legs as an adverse reaction to nucleoside reverse transcriptase inhibitors. The clinical symptoms of lipoatrophy resemble those of inherited mitochondrial diseases, which suggest that host mitochondrial genotype may play a role in susceptibility. We analyzed the association between mitochondrial haplogroup and severity of lipoatrophy in HIV-infected European American patients on HAART in the Multicenter AIDS cohort Study and found that mitochondrial haplogroup H was strongly associated with increased atrophy [arms: $P = 0.007$, odds ratio (OR) = 1.77, 95% confidence interval (CI) = 1.17 to 2.69; legs: $P = 0.037$, OR = 1.54, 95% CI = 1.03 to 2.31; and buttocks: $P = 0.10$, OR = 1.41 95% CI = 0.94 to 2.12]. We also saw borderline significance for haplogroup T as protective against lipoatrophy ($P = 0.05$, OR = 0.52, 95% CI = 0.20 to 1.00). These data suggest that mitochondrial DNA haplogroup may influence the propensity for lipoatrophy in patients receiving nucleoside reverse transcriptase inhibitors.

Supplemental Content



[PLoS One](#). 2012;7(7):e41129. doi: 10.1371/journal.pone.0041129. Epub 2012 Jul 19.

HIV-1 infection and first line ART induced differential responses in mitochondria from blood lymphocytes and monocytes: the ANRS EP45 "Aging" study.

[Perrin S](#), [Cremer J](#), [Roll P](#), [Faucher O](#), [Ménard A](#), [Reynes J](#), [Dellamonica P](#), [Naqvi A](#), [Micallef J](#), [Jouve E](#), [Tamalet C](#), [Solas C](#), [Pissier C](#), [Arnoux I](#), [Nicolino-Brunet C](#), [Espinosa L](#), [Lévy N](#), [Kaspi E](#), [Robaglia-Schlupp A](#), [Poizot-Martin I](#), [Cau P](#).

Source

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Abstract

BACKGROUND:

The ANRS EP45 "Aging" study investigates the cellular mechanisms involved in the accelerated aging of HIV-1 infected and treated patients. The data reported focus on mitochondria, organelles known to be involved in cell senescence.

METHODS:

49 HIV-1 infected patients untreated with antiretroviral therapy, together with 49 seronegative age- and sex-matched control subjects and 81 HIV-1 infected and treated patients, were recruited by 3 AIDS centres (Marseille, Montpellier, Nice; France; <http://clinicaltrials.gov/NCT01038999>). In more than 88% of treated patients, the viral load was <40 copies/ml and the CD4+ cell count was >500/mm³. ROS (reactive oxygen species) production and $\Delta\Psi_m$ (inner membrane potential) were measured by flow cytometry in blood lymphocytes and monocytes (functional parameters). Three mitochondrial network quantitative morphological parameters were computed using confocal microscopy and image analysis. Three PBMC mitochondrial proteins (porin and subunits 2 and 4 of cytochrome C oxidase encoded by mtDNA or nuclear DNA, respectively) were analysed by western blotting.

RESULTS:

Quantitative changes in PBMC mitochondrial proteins were not induced by either HIV-1 infection or ART. Discriminant analysis integrating functional (ROS production and $\Delta\Psi_m$) or morphological (network volume density, fragmentation and branching) parameters revealed HIV-1 infection and ART differential effects according to cell type. First line ART tended to rescue lymphocyte mitochondrial parameters altered by viral infection, but induced slight changes in monocytes. No statistical difference was found between the effects of three ART regimens on mitochondrial parameters. Correlations between functional parameters and viral load confirmed the damaging effects of HIV-1 in lymphocyte mitochondria.

CONCLUSIONS:

In patients considered to be clinically stable, mitochondria exhibited functional and morphological modifications in PBMCs resulting from either direct or indirect effects of HIV-1 infection (lymphocytes), or from first line ART (monocytes). Together with other tissue impairments, these changes may contribute to global aging.

Supplemental Content



[Trends Pharmacol Sci](#). 2011 Dec;32(12):715-25. doi: 10.1016/j.tips.2011.07.007. Epub 2011 Sep 6.

Mitochondrial interference by anti-HIV drugs: mechanisms beyond Pol- γ inhibition.

[Apostolova N](#), [Blas-García A](#), [Esplugues JV](#).

Source

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Abstract

The combined pharmacological approach to the treatment of HIV infection, known as highly active antiretroviral therapy (HAART), has dramatically reduced AIDS-related morbidity and mortality. However, its use has been associated with serious adverse reactions, of which those resulting from mitochondrial dysfunction are particularly widespread. Nucleos(t)ide-reverse transcriptase inhibitors (NRTIs) have long been considered the main source of HAART-related mitochondrial toxicity due to their ability to inhibit Pol- γ , the DNA polymerase responsible for the synthesis of mitochondrial DNA. Nevertheless, accumulating evidence points to a more complex relationship between these organelles and NRTIs. Also, alternative pathways by which other groups of anti-HIV drugs (non-nucleoside reverse transcriptase inhibitors and protease inhibitors) interfere with mitochondria have been suggested, although their implications, both pharmacological and clinical, are open to debate. This review aims to provide a comprehensive overview of the mechanisms and factors which influence the mitochondrial involvement in the toxicity of all three major classes of anti-HIV drugs.

Supplemental Content

