Antiretroviral agents increase NO production in gp120/IFNγ-stimulated cultures of rat microglia via an arginase-dependent mechanism

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Despite the introduction of the Highly Active Antiretroviral Therapy (HAART) has significantly increased life expectancy of HIV infected patients, approximately 50% of them undergo neurological complications. This may result from a combination of factors, such as reduced effectiveness of HAART in the central nervous system (CNS), concurrent illnesses, adverse effects associated with treatments, including antiretrovirals (ARVs). With this in mind, in the present study we carried out a screening of different AVRs (Atazanavir, Darunavir, Lopinavir, Indinavir, Ritonavir, Efavirenz, Nevirapine, Abacavir and Tenofovir) for their potential pro-inflammatory effects on microglial cells. None of the ARVs screened displayed toxic effects on resting microglia neither showed pro-inflammatory actions *per se*. However, Efavirenz, Neviparine, Darunavir and Atazanavir increased nitric oxide (NO) production in microglial cells activated with $Gp120_{CN54}$ and interferon (IFN)-γ. The stimulatory effect on NO production appeared to be mediated by inhibition of arginase I (ARG) activity. Consistently, L-arginine significantly increased NO production in activated microglial cells, whereas the ARG inhibitor, $N^{(\omega)}$-hydroxy-nor-Arginine, mimicked the effects of ARVs. Take together these data suggest that ARG is an additional molecular target of different ARVs, whose inhibition can contribute to their pharmacological activity as well as explain the neurotoxic potential. Accordingly, the specific targeting of microglial activation, and particularly NO production, might be a pharmacological strategy to reduce the incidence and severity of neurological complication in HIV patients.