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HIV-1 Clade B and C Tat differentially Induces Indoleamine-2, 3-Dioxygenase (IDO) and Serotonin in Immature Dendritic Cells (IDC): Implications for Neuro-AIDS

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HIV-1 is commonly associated with immune dysfunctions and suppression of antigen presenting cells resulting in immune alterations which could lead to impaired neuronal functions, such as Neuro-AIDS. The neurotoxic factor, kynurenine and the rate limiting enzyme, Indoleamine-2, 3-Dioxygenase (IDO) and serotonin may play a role in tryptophan deficiency and behavioral disorders in Neuro-AIDS. HIV-1 transactivator regulatory protein (Tat) is known to play a major role in immune dysfunction. Previous studies suggest that HIV-1 B and C clades differentially manifest neuronal dysfunctions in infected host and the present study examine the effect of HIV-1 B and C clades derived Tat on IDO, serotonin gene expression and protein modification by dentridic cells as studied by Q-PCR and Western blot. The intracellular IDO expression, IDO enzyme activity, and the levels of kynurenine were also measured. Results indicate that HIV-1 clade B Tat upregulates IDO and down regulates serotonin gene and protein expression and simultaneously upregulated kynurenine level as compared to HIV-1 clade C Tat. These studies suggest that HIV-1 B and C Tat protein may play a differential role in the neuropathogenesis of HAD/MDC in neuroAIDS.

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Persistence of Poliovirus Type 1 Genome in Patients with the Post-Polio Syndrome

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Decades after being hit by poliovirus (PV), 40–70% of polio survivors develop the "post-polio syndrome" (PPS), a progressive condition characterized by chronic fatigue, pain, new muscular weakness, cold intolerance. The etiology and pathogenesis of PPS are undefined. Literature data suggest that PV genome fragments may persist for decades in the central nervous system of affected patients. Using molecular tests, tissue culture studies, and immunofluorescence of infected cells, low-level PV infectivity and genome fragments have been detected in 27/29 PPS patients aged 50 to 75 years (CSF and peripheral blood leukocytes). No virus was detected in negative controls (CSF from 12 adult patients with non-infectious, non-neoplastic pathology, and peripheral blood leukocytes from 18 healthy blood donors). In a few patients, PV genome fragments have also been detected in saliva and urine samples, as well as in primary cultures of skeletal muscle, peripheral nerve, and duodenal mucosa cells. PV genome fragments were present at extremely low levels, thus making whole genome sequencing impossible. Partial sequencing of the 5′UTR, VP1, and 3D (RNApol) regions indicated that amplicons from PV-positive patients were compatible with reference sequences of PV-1. Extensive mutations/deletions were detected in the 5′UTR and VP1 regions. Immunofluorescence and WB with PV-specific mAbs showed that capsid proteins were produced at low levels in primary cultures of muscle and peripheral nerve cells as well as in cell lines infected with samples of PPS patients. These data indicate that PV genome fragments can persist for several decades in polio survivors. The data do not provide a pathogenetic link between virus persistence and PPS development. However, the highly sensitive molecular tools now made available can contribute to detect and characterize PV strains in these patients, with the aim of better defining PPS pathogenesis. The financial support of Post-Polio Health International (St. Louis, MO) is gratefully acknowledged.

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Neuroprotective and Neurorestorative Effects of Fluconazole against HIV proteins and mitochondrial toxins

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Currently there is no effective neuroprotective treatment for cognitive impairment in human immunodeficiency virus (HIV)-infected patients who are on effective antiretroviral therapy. We screened nearly 2000 FDA approved and natural compounds against several screening assays and found the triazole drug, fluconazole (Diflucan®, Pfizer) to be neuroprotective. In mixed neuronal cultures, fluconazole (500 nM–1 M) protected against the mitochondrial toxin, 3-nitroproprionic acid (3NP) ($p < 0.05$) and HIV Tat protein ($p < 0.01$) as determined by an MTT-based cell survival assay. With 1M fluconazole nearly complete protection was noted against both toxins. When treated with 3NP