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The impact of HIV infection on the nervous system of children

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At the end of 2007, 33.2 million people including 2.5 million children were living with HIV; > 85% of HIV-infected children were in Africa. At the end of 2006, 115 000 children were on HAART, a global coverage rate of 15% with sub-Saharan Africa having the lowest regional coverage.

HIV affects the immature brain causing static or progressive encephalopathy (PE). PE is characterized by acquired microcephaly, failure to attain or loss of neurodevelopmental milestones, or loss of intellectual ability, and acquired symmetric motor defects. Isolated neurodevelopmental delays and peripheral nervous system disease occur as a direct consequence of HIV infection. Susceptibility to opportunistic infection (OI), due to systemic immunodeficiency, predisposes HIV-infected children to CNS infections including acute bacterial and tuberculous meningitis, CMV co-infection, EBV-associated primary lymphoma and in older children cryptococcal meningitis. HAART may induce an immune reconstitution inflammatory response to several microorganisms including *mycobacterium tuberculosis* and JC virus, causing CNS deterioration. Neurological manifestations occur in 20–80% of HIV-infected children. Complex clinical presentations may be difficult to classify with the layering effect of multiple pathologies. There are limited descriptive studies from resource-constrained countries. In one hospital-based, cross-sectional survey (n = 80, median age = 5.2 years), 60% had a variety of neurological and neurodevelopmental deficits.

The neuropathogenesis of HIV encephalopathy is incompletely understood. Several pathogenic events are involved including (1) CNS invasion following receptor/co-receptor-mediated HIV infection of monocytes/macrophages and CD4+ T-lymphocytes, (2) promotion of HIV-infected PBMC trafficking across the BBB by astrocytes and microglia (Trojan-horse effect), (3) neurotoxin elaboration induced by viral factors and inflammatory mediators, (4) CD4-independent astrocyte invasion by HIV, (4) neuronal death mediated through viral-induced chemokine receptor expression, and microglial/macrophage-dependent and microglial-independent apoptotic death, and (5) inhibition of neural stem cell proliferation by viral gp120. Both direct and indirect mechanisms are involved in neuronal injury and death.

Early initiation of HAART during infancy prevents the development of HIV encephalopathy, lowering the prevalence of progressive encephalopathy to < 2%. HAART reverses existing neurological abnormalities, although not completely, resulting in residual motor and cognitive sequelae (arrested PE) and consequent scholastic impairments. HAART also reduces the frequency of OIs and malignancy.

In conclusion, HIV-associated nervous system disease remains highly prevalent in settings where treatment is sub-optimal. Implementation of HAART during infancy and additional prophylaxis against OIs such as pneumococcal vaccination lowers the risk significantly.