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Global Perspectives

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NEURO-AIDS IN THE DEVELOPING WORLD

Despite 20 years of development, no practical vaccine for HIV is available, and HIV/AIDS remains a major health problem, with 33 million people infected and 2.6 million new infections in 2009. The infection is most prevalent in sub-Saharan Africa. Although rates of infection remain high, developments in antiretroviral regimens and changes in public health policy worldwide have significantly increased lifespans and changed the landscape of HIV complications, including the neurologic complications.

Prior to the availability of highly active antiretroviral therapy (HAART), neurologic disease was the heralding manifestation of AIDS in 7%–20% of patients and prevalence rates of neurologic infections varied from 39% to 70%. Following the introduction of HAART, neurologic disease declined significantly, particularly rates of CNS opportunistic infections (OI). Nonetheless, AIDS-related neurologic disease continues to represent a significant burden for developing countries. The spectrum of AIDS-related disease in many developing countries appears to parallel that reported in the pre-HAART era. In one study from Thailand conducted over 2 years, 2007–2008 inclusive,[1] the most common CNS disorders in order of frequency were cryptococcal meningitis (37.8%), tuberculosis (TB) (35.8%), toxoplasmosis (12.8%), progressive multifocal leukoencephalopathy (4.1%), varicella zoster meningitis (2.7%), pneumococcal meningitis (1.4%), herpes simplex meningitis, and Epstein-Barr–related primary CNS lymphoma. Similarly, in South Africa, the CNS disorders observed have mirrored those seen in the pre-ART era in developed countries; a phenomenon attributed to the relative unavailability of antiretroviral therapy.[2]

Although incompletely investigated, it is widely believed that antiretroviral therapy has reduced the prevalence of HIV-related CNS OIs in the developing world as it has in the developed world. In the pre-HAART era, toxoplasmic encephalitis (TE) and primary CNS lymphoma were commonly observed causes of mass lesion in patients with AIDS with rates of 3%–25% and 1.5%–2.5%, respectively. Following the introduction of HAART, their frequency declined substantially and it is assumed that similar findings pertain in the developing world. Some neurologic disorders that generally only occurred in the setting of profound CD4 lymphopenia (<50 cells/mL), such as cytomegalovirus encephalitis, have become vanishingly rare since the introduction of antiretroviral therapy.

In addition to lowering the prevalence of CNS OIs, antiretroviral therapy has also improved survival in those with these disorders. Substantially enhanced survival for HIV-associated TB meningitis followed the introduction of antiretroviral therapy. Survival for cryptococcal meningitis, the most common fatal, HIV-related CNS infection in the developing world, also improved with antiretroviral therapy. However, an improvement in outcome of cryptococcal meningitis with HAART has not been universally observed in developing countries due to delayed diagnosis, lack of amphotericin B, unavailability of antiretrovirals, and higher fungal burden at diagnosis.[3] Similar factors are likely responsible for a poorer than expected prognosis of other OIs in developing countries.

Some neurologic diseases whose clinical expression is affected by HIV are fairly unique to the developing world. Malaria is not an opportunistic disease for HIV-infected persons and the prevalence is the same as in the general population; however, the expression of the disease can be altered by HIV coinfection. Severe malaria is more common among HIV-infected persons and children with both malaria and HIV are approximately 4 times more likely to develop cerebral malaria than those with malaria alone. Microsporidia, an obligate, single-celled parasite, has been observed to cause CNS disease in the HIV-infected population in the setting of dissemination with associated sinusitis and keratoconjunctivitis. One very curious observation has been the lack of effect of HIV on the expression of leprosy, though

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the incidence of leprosy relapse following treatment may be higher in HIV-infected persons.[5]

As in developed countries, the immune reconstitution inflammatory syndrome (IRIS) has become a significant problem following the introduction of HAART. In one study, paradoxical neurologic worsening was observed in 28% of South African patients started on HAART.[4] IRIS has also been described with opportunistic parasitic diseases unique to the developing world, such as schistosomiasis, strongyloidiasis, and leishmaniasis.

HIV also directly affects the central and peripheral nervous systems. Prior to the introduction of HAART, moderate or severe dementia was among the most common CNS complications developing in at least 15% of patients. Following the use of HAART, the incidence of HIV dementia has declined substantially, but HIV-associated neurocognitive disorders (HAND) that impair the quality of life remain common. Peripheral neuropathies, especially HIV-associated distal sensory polyneuropathy (DSPN), are also common. Prior to HAART, up to one-third of HIV-infected patients developed a sensory neuropathy. Distinguishing HIV-related peripheral neuropathy from that occurring from neurotoxic antiretroviral therapy remains difficult. A steep decline in the 1-year incidence of DSPN has been observed when the post-HAART era is compared to the pre-HAART era; however, the prevalence of DSPN appears to be increasing with the greater longevity of HIV-infected persons. Studies from sub-Saharan Africa indicate that both HIV-related dementia and peripheral neuropathy are significant problems. For instance, in one study from Uganda in 2005, 31% of HIV-infected patients had dementia and 47% had a peripheral neuropathy.[5] Regional differences in both the prevalence and rate of progression of HIV dementia have been attributed to differences in the neuropathogenicity of different HIV subtypes.

With respect to public health measures, despite the lack of a vaccine, there has been progress on reducing HIV transmission. HAART has reduced vertical transmission of HIV from 14%–25% to less than 2% in developed countries. The rates of transmission may be higher in developing countries, but are likely the consequence of antiretroviral therapy availability rather than a lack of its efficacy. Circumcision has also lowered transmission rates in developing countries. A prospective randomized trial in South Africa showed that 0.85% of circumcised males acquired HIV over a 2-year period, while 2.1% of noncircumcised males acquired HIV. This trial may have had confounding and selection bias, since it followed men interested in a medical trial of circumcision and who received HIV counseling, but the results were unchanged when controlling for sexual behavior and condom use. Circumcision appears to confer no protection for transmission of HIV from infected males to uninfected females.

Overall, recent global developments in HIV/AIDS have been positive. With HAART, the incidence of most opportunistic infections has decreased, vertical transmission has decreased, and the incidence of HIV dementia has decreased. There are still problems with less severe forms of HAND which have either increased or been unmasked since HAART, but this has led to research into neuroprotective drugs that may have applicability beyond HIV. Still, many parts of the world, chiefly, sub-Saharan Africa, lag developed countries and have not enjoyed the same degree of improvement. Often this is due to limited availability of HAART rather than lack of efficacy. Like other infectious diseases, future challenges for HIV remain in both resource allocation as well as therapy development.

AUTHOR CONTRIBUTIONS

Dr. Dawson and Dr. Berger contributed equally to this article.

DISCLOSURE

Dr. Dawson reports no disclosures. Dr. Berger has served on a data safety monitoring board for Millennium Pharmaceuticals, Inc.; has received speaker honoraria from Bayer Schering Pharma, Teva Pharmaceutical Industries Ltd., and BiogenIdec; serves on the editorial boards of the *Journal of Neurovirology*, *ISRN Education*, *Neuroscience*, *World Journal of Rheumatology*, and *MS and Other Related Disorders*; has served as a consultant to Bayer Schering Pharma, BiogenIdec, GlaxoSmithKline, Eisai Inc., Novartis, Millennium Pharmaceuticals, Inc., and Genentech, Inc.; and receives research support from Bayer Schering Pharma, EMD Serono, Inc., BiogenIdec, and the PML Consortium.

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