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The epidemiology of human immunodeficiency virus–associated neurological disease in the era of highly active antiretroviral therapy

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Highly active antiretroviral therapy (HAART) is effective in suppressing systemic human immunodeficiency virus (HIV) viral load and has decreased mortality rates and the incidence of systemic opportunistic infections in patients with acquired immunodeficiency syndrome (AIDS). Multiple studies now suggest that the incidence rates of HIV-associated neurological disease and central nervous system (CNS) opportunistic infections also are decreasing. Since the introduction of HAART in 1996, the incidence of HIV dementia has decreased by approximately 50%. The mean CD4 cell count for new cases of HIV dementia is increasing, but it remains as a complication of moderate-advanced immunosuppression. The incidence of HIV-associated distal sensory polyneuropathy has decreased, although the incidence of antiretroviral drug–induced toxic neuropathy has increased. However, as patients with AIDS live longer as a result of HAART, the prevalence of peripheral neuropathy in HIV-seropositive patients may be increasing. The incidence rates of CNS opportunistic infections (cryptococcal meningitis, toxoplasmosis, progressive multifocal leukoencephalopathy) and primary CNS lymphoma have decreased since the introduction of HAART. As patients develop increasing resistance mutations to antiretroviral drugs and with subsequent decline in CD4 cell counts, in the near future, the incidence of HIV-associated neurological disease may begin to rise. *Journal of NeuroVirology* (2002) **8(suppl. 2),** 115–121.

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Introduction

Highly active antiretroviral therapy (HAART) is effective in suppressing systemic human immunodeficiency virus (HIV) viral load and has decreased mortality rates in patients with HIV infection (Brodt *et al*, 1997). HAART has also decreased the incidence of systemic opportunistic infections in acquired immunodeficiency syndrome (AIDS) patients (Centers for Disease Control and Prevention, 2000). However, many antiretroviral drugs do not penetrate well into the central nervous system (CNS) (Sacktor and McArthur, 1997). In addition, the vast majority of HIV-infected individuals do not have access to antiretroviral therapy and are unaffected by these recent improvements in the morbidity and mortality of HIV infection in the western world.

This review will describe the epidemiology of HIV-associated neurological disease in the initial years after the introduction of HAART. First, the global epidemiology of HIV infection will be summarized, and then, a series of case reports describing the frequency of neurological complications of HIV infection in selected countries in the developing world will be highlighted. Next, the epidemiology of HIV-associated neurological disease in the industrialized world as a result of HAART will be discussed, initially describing changes in HIV-related neurological diseases, specifically dementia and peripheral

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neuropathy, and then describing changes in CNS opportunistic infections and CNS lymphoma.

HIV/AIDS global epidemiology

According to data from the Joint United Nations Program of HIV/AIDS (UNAIDS) and the World Health Organization (WHO) (Joint United Nations Program of HIV/AIDS, 2001), as of the end of 2001, there were 40 million adults and children living with HIV infection. This total does not include the 20 million people around the world who have already died of AIDS. Of the 40 million currently alive, 37.2 million are adults, 17.6 million are women, and 2.7 million are children. In 2001, there were 5 million new cases of HIV infection in the world, and 3 million AIDS-related deaths. The vast majority, almost three quarters of HIV cases globally, are in Sub-Saharan Africa. The second major pocket of HIV infection is in South and Southeast Asia, with 6.1 million people infected. In North America, by contrast, there are 940,000 HIV-seropositive (HIV+) individuals, and in Western Europe, there are 560,000 HIV+ individuals. Areas with rapid increases in infection rates recently include Sub-Saharan Africa, China, and Eastern Europe.

In Sub-Saharan Africa, the prevalence rate among adults, aged 15 to 49, is 8.4%. In Africa where heterosexual transmission is the most common mode of transmission, 55% of HIV+ adults are women. There are now 16 Sub-Saharan African countries in which more than one-tenth of the adult population aged 15 to 49 is infected with HIV. For example, 36% of adults in Botswana are now infected with HIV. In South Africa, the percent of adults with HIV has increased from 13% in 1999 to 20% in 2001. With 4.2 million people infected, South Africa has more HIV+ cases than any country in the world. These numbers will likely have a devastating impact on the social, economic, and political development of this region.

The prevalence of neurological complications of HIV infection in developing countries is similar to that observed in industrialized countries prior to any antiretroviral therapy among patients with advanced HIV disease. For example, in a case series in Zaire (Perriens *et al*, 1992), among inpatients to an internal medicine ward, neuropsychiatric abnormalities were present in 41% of HIV+ patients, with 9% diagnosed as having possible dementia. Cryptococcal meningitis was diagnosed in 6% and tuberculosis meningitis was diagnosed in 2%. Neuroimaging was not available as part of this case series. In another case series in the Ivory Coast (Grant *et al*, 1997), meningitis (14% of all cases), due to cryptococcus, tuberculosis, and bacterial pathogens, and cerebral toxoplasmosis (7% of all cases) were the most frequent neurological infections. Similarly, in a case series in India, the most common neurological disorders presenting to a neurological institute were cryptococcal meningitis, in 46% of their cases, followed by tuberculosis meningitis in 35% (Satishchandra *et al*, 2000). Other opportunistic infections included cerebral toxoplasmosis, fulminant pyogenic meningitis, and neurosyphilis.

HIV-associated neurological disease

The epidemiology of HIV-associated neurological disease in the industrialized world has changed significantly in the era of HAART. These changes have occurred concurrently with changes in the treatment patterns for HIV infection over the past 10 years. In the Multicenter AIDS Cohort Study (MACS), a longitudinal cohort of gay/bisexual men from Baltimore, Pittsburgh, Chicago, and Los Angeles, from 1990 to 1992, monotherapy and no therapy were the predominant forms of treatment. From 1993 to 1995, multidrug therapy without protease inhibitors (i.e., dual therapy) and monotherapy were the predominant forms of treatment. From 1996 to the present, HAART has become the predominant form of treatment. Using data from the MACS (Sacktor *et al*, 2001), the past decade was subdivided into each of these three smaller time periods to compare the mean incidence of HIV dementia. Since the introduction of HAART in 1996, the incidence of HIV dementia has declined significantly by about 50% compared to the early 1990s (Figure 1**A**). We also examined the CD4 count of HIV dementia cases in these three time periods. From 1990 to 1992, the majority of HIV dementia cases occurred with advanced immunosuppression, with a CD4 count <200. In contrast, from 1996 to 1998, more cases of HIV dementia were presenting, with CD4 counts >200 (Figure 2).

These results are similar to those found by others. In a European study of homosexual men, Brodt *et al* (1997) found a decreased rate of HIV-associated CNS disease from 1992 to 1996. In the Multicenter European EuroSIDA study of 17 nations with 7300 individuals, the incidence of HIV dementia has also decreased by about 50% (Mocroft *et al*, 2000). The median CD4 count at diagnosis of HIV dementia has also increased slightly in the EuroSIDA study. In the Australian National AIDS Registry, from 1992 to 1997, Dore *et al* (1999) also reported a decreasing number of HIV dementia cases over this time period. However, HIV dementia constituted a greater proportion of AIDS-defining illnesses, relative to other conditions. They also found that the median CD4 count for HIV dementia appeared to be increasing.

Similar results are seen in a university clinic with predominantly intravenous drug users. At the Johns Hopkins HIV clinic in Baltimore, Maryland, the incidence rate for HIV dementia has significantly decreased, comparing the rates from 1994 and 1998 (Figure 3**A**) (Moore *et al*, 1999).

Risk factors for the development of HIV dementia in the pre-HAART era include a high plasma HIV

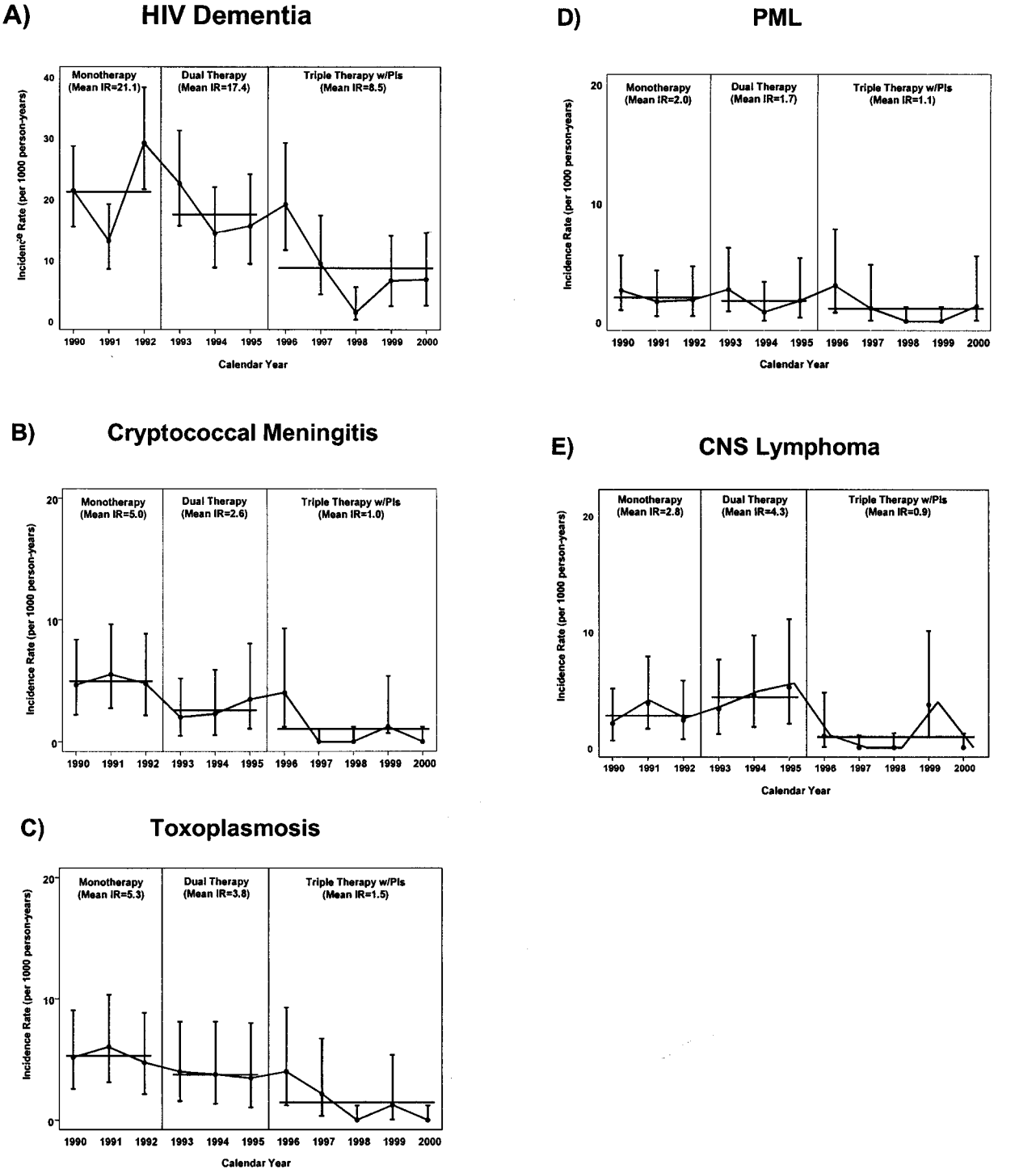

Figure 1 Incidence rates of HIV-associated neurologic diseases in the Multicenter AIDS Cohort Study: (**A**) HIV dementia; (**B**) cryptococcal meningitis; (**C**) toxoplasmosis; (**D**) progressive multifocal leukoencephalopathy (PML); (**E**) central nervous system (CNS) lymphoma. The *x*-axis corresponds to the calendar year. The *y*-axis corresponds to the incidence rate per 1000 person years. The scale of the *y*-axis for HIV dementia is different from the scale of the *y*-axis for the opportunistic infections and CNS lymphoma. The vertical bars at each calendar year correspond to the 95% CI. The horizontal bars from 1990 to 1992, 1993 to 1995, and 1996 to 2000 correspond to the mean incidence rates during those time periods.

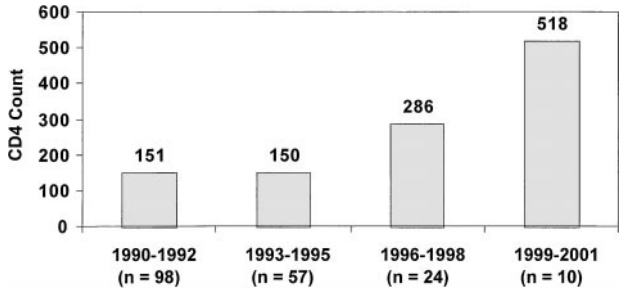

Figure 2 Mean CD4 count of newly diagnosed HIV dementia cases in the Multicenter AIDS Cohort Study.

viral load prior to the initiation of antiretroviral therapy (Childs *et al*, 1999), advanced age, low CD4 lymphocyte count, markers of systemic disease such as anemia (McArthur *et al*, 1993), and clinical features such as depression (Stern *et al*, 2001) (which can be a symptom of HIV dementia) and the presence of psychomotor slowing on neuropsychological testing (Sacktor *et al*, 1996). It remains to be determined whether these risk factors for HIV dementia persist in the era of HAART.

Data on the changes in the prevalence of HIV dementia are much less extensive. In the Johns Hopkins HIV clinic, the prevalence of HIV dementia in approximately 1300 patients has remained stable from 1994 to 2000, and may be showing a slight trend towards an increase (Figure 4**A**). In contrast, in a university clinic in Essen, Germany, evaluating 563 patients, there was a small decrease in the prevalence of HIV dementia, comparing the prevalence in 1995 and 1996, to that of 1997 and 1998 (Maschke *et al*, 2000). Further studies are needed to evaluate changes in the prevalence of HIV dementia in the era of HAART.

The epidemiology of HIV-associated sensory peripheral neuropathy has also changed. Peripheral neuropathy in advanced HIV infection is due to two predominant causes: (1) HIV-associated distal sensory polyneuropathy (DSP) and (2) toxic neuropathy due to antiretroviral drugs (ATN), specifically didanosine (ddI), zalcitabine (ddc), and stavudine (d4T). Similar to the changing incidence of HIV dementia, the incidence of HIV-associated distal sensory neuropathy has decreased by about 50% from 1994 to 2000 in the Johns Hopkins HIV clinic (see Figure 3**B**). However, the incidence of toxic (antiretroviral drug–induced) neuropathy has increased over the same time period (see Figure 3**C**). Combining the two types of neuropathy, the overall incidence of neuropathy has decreased slightly from 1994 to 2000 in this clinical cohort (see Figure 3**D**).

However, as patients with advanced HIV infection live longer as a result of HAART, the prevalence of neuropathy in HIV-seropositive patients may be increasing. In the Johns Hopkins HIV clinic, the prevalence of neuropathy has increased by almost 50% from 1994 to 2000 (see Figure 4**B**). HIV-associated neuropathy remains as the most common neurological manifestation of HIV infection in the era of HAART.

CNS opportunistic infections and primary CNS lymphoma

HAART has led to a decrease in systemic opportunistic infections in HIV infection. The incidence of CNS opportunistic infections has also decreased significantly.

The incidence of cryptococcal meningitis has decreased in the MACS since the introduction of HAART in 1996 (see Figure 1**B**) (Sacktor *et al*, 2001). Over this same time period in the MACS, there was no significant change in the use of prophylaxis medications. A similar decrease in the incidence of cryptococcal meningitis was seen in the Johns Hopkins HIV clinic between 1994 and 2000 (see Figure 3**E**).

For CNS toxoplasmosis, in the MACS, there was a trend for a decreased incidence since the introduction of HAART (see Figure 1**C**) (Sacktor *et al*, 2001). This trend could not be accounted for by changes in the use of prophylaxis medications. Similarly, at the Johns Hopkins HIV clinic, there has been a significant decrease in the incidence of toxoplasmosis since the introduction of HAART (see Figure 3**F**) (Moore and Chaisson, 1999). In the Australian National AIDS Registry, the total number of CNS AIDS-defining illnesses (defined as toxoplasmosis and cryptococcal meningitis) has decreased in the era of HAART, although the proportion of CNS toxoplasmosis and cryptococcal meningitis relative to other AIDS-defining illnesses has remained stable (Dore *et al*, 1999).

For progressive multifocal leukoencephalopathy (PML), the number of cases in both the MACS and the Johns Hopkins University Clinic was much smaller than for the other CNS opportunistic infections. There was no significant decrease in the incidence of PML, although trends for a slight decrease were noted (see Figures 1**D** and 3**G**) (Sacktor *et al*, 2001). In an Italian study examining focal brain lesions in the era of HAART, there was a slight but not significant increase in the frequency of PML from 1996 to 1998 relative to other types of focal brain lesions (Ammassari *et al*, 2000). Patient survival with PML though has improved with the initiation of HAART (Clifford *et al*, 1999).

The incidence rates for cytomegalovirus (CMV) retinitis and encephalopathy have also decreased dramatically since the introduction of HAART (Moore and Chaisson, 1999). These conditions are now seen predominantly in patients not on HAART or with poor adherence to HAART.

The incidence rate for primary CNS lymphoma, similar to the CNS opportunistic infections, has also decreased both in the MACS and the Johns Hopkins University Clinic since the introduction of HAART

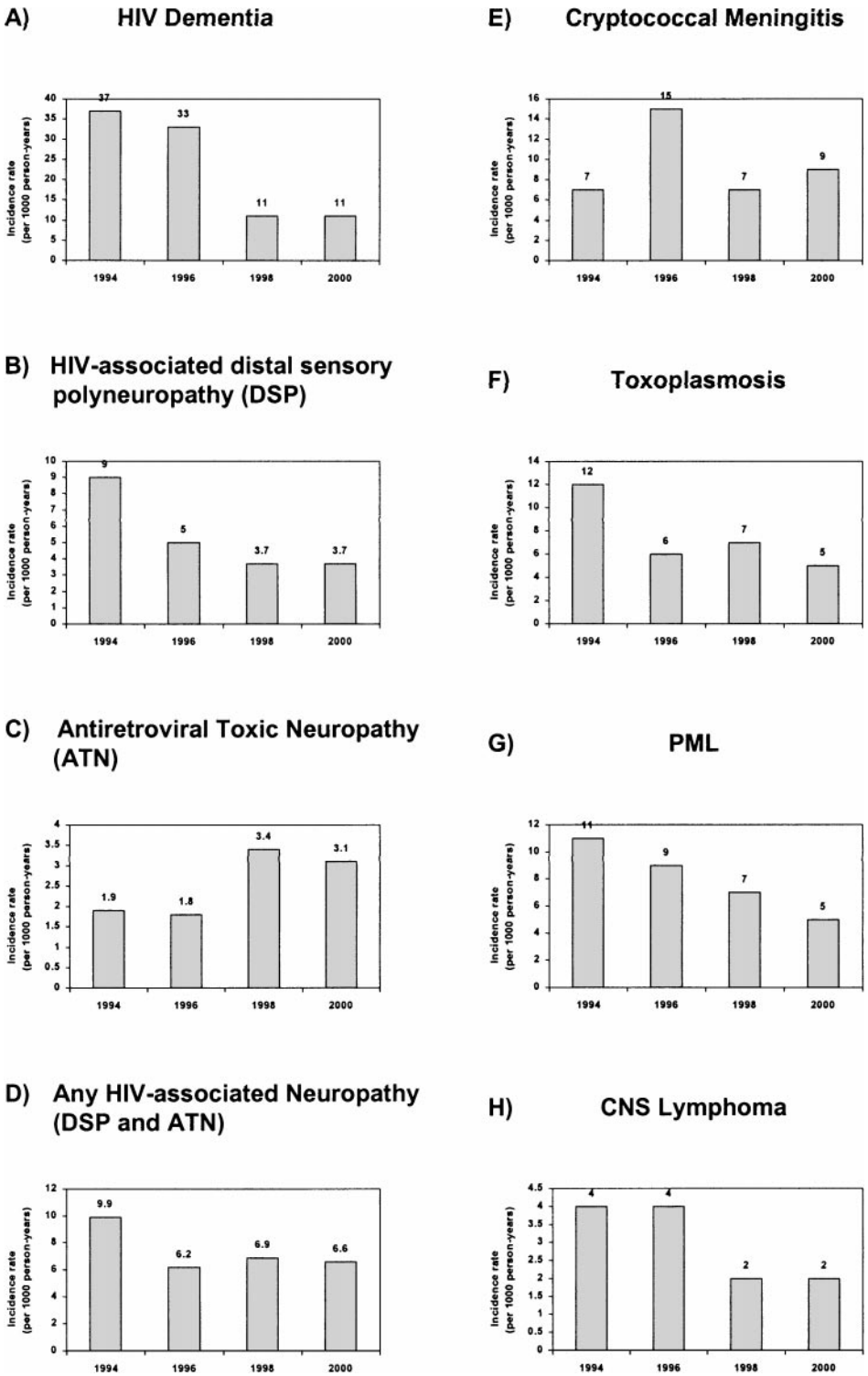

Figure 3 Incidence rates of HIV-associated neurologic diseases in the Johns Hopkins HIV clinic: (**A**) HIV dementia; (**B**) HIV-associated distal sensory polyneuropathy (DSP); (**C**) antiretroviral toxic neuropathy (ATN); (**D**) any HIV-associated neuropathy (DSP and ATN); (**E**) Cryptococcal meningitis; (**F**) toxoplasmosis; (**G**) progressive multifocal leukoencephalopathy (PML); (**H**) central nervous system (CNS) lymphoma. The *x*-axis corresponds to the calendar year. The *y*-axis corresponds to the incidence rate per 1000 person years. The scales of the *y*-axis for HIV dementia and each neuropathy type are different from the scales of the *y*-axis for the opportunistic infections and CNS lymphoma.

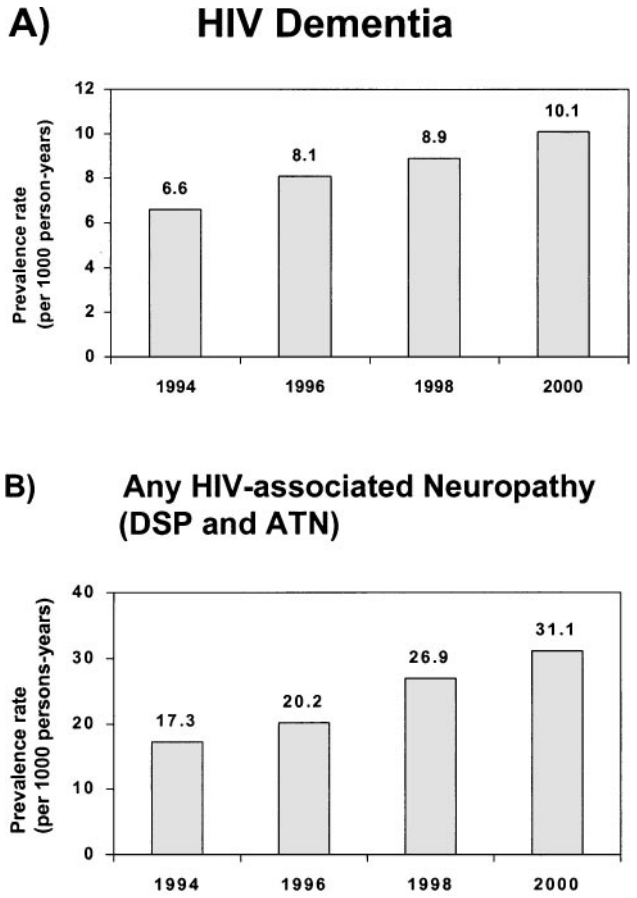

Figure 4 Prevalence rates for (**A**) HIV dementia and (**B**) any HIV-associated neuropathy (distal sensory neuropathy (DSP) and antiretroviral toxic neuropathy (ATN) in the Johns Hopkins HIV clinic. The *x*-axis corresponds to the calendar year. The *y*-axis corresponds to the prevalence rate per 1000 person years. The scale of the *y*-axis for HIV dementia is different from the scale of the *y*-axis for any HIV-associated neuropathy.

(see Figures 1**E** and 3**H**) (Sacktor *et al*, 2001). Similar results were obtained in the Italian study of focal brain lesions in the era of HAART where a significant decrease in the proportion of primary CNS lymphoma diagnoses was noted from 1996 to 1998 (Ammassari *et al*, 2000).

Future prospects

In summary, the incidence rates of HIV-associated neurological disease and CNS opportunistic processes have decreased significantly in the industrialized world since the introduction of HAART. The incidence of toxic neuropathy, in contrast, has increased.

HIV-associated dementia and sensory neuropathy, however, continue to be major public health problems, particularly in the developing world where access to antiretroviral medications is poor. As a result, HIV is now becoming one of the leading causes of dementia worldwide along with Alzheimer's disease and vascular dementia. HIV is also now becoming one of the leading causes of neuropathy worldwide, along with diabetes and leprosy. In developing countries, the infrastructure for health care delivery systems and research need to be established with support from local governments. Access to antiretroviral drugs at low cost needs to be provided. Studies to evaluate the prevalence, natural history, and response to therapy for HIV-associated neurological complications globally need to be performed.

In the industrialized world, as patients develop increasing resistance mutations to antiretroviral drugs and with subsequent decline in CD4 counts, in the near future, the incidence of HIV-associated neurological disease may begin to rise. New treatments such as fusion inhibitors or immunomodulatory therapies may temporarily decrease the incidence of HIV-associated neurological disease, but resistance may develop to each of these new types of therapies as well. Continued vigilance to evaluate these epidemiological changes are necessary, and further developments in unraveling the pathogenesis and improving treatment for these conditions are essential.

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