

# HIV-associated neurologic disease incidence changes: Multicenter AIDS Cohort Study, 1990–1998

**Article abstract**—This study examined the temporal trends in the incidence rates of HIV dementia, cryptococcal meningitis, toxoplasmosis, progressive multifocal leukoencephalopathy, and CNS lymphoma from January 1990 to December 1998 in the Multicenter AIDS Cohort Study. The incidence rates for HIV dementia, cryptococcal meningitis, and lymphoma decreased following the introduction of highly active antiretroviral therapy (HAART). The proportion of new cases of HIV dementia with a CD4 count in a higher range (i.e., 201 to 350) since 1996 may be increasing.

NEUROLOGY 2001;56:257–260

N. Sacktor, MD; R.H. Lyles, PhD; R. Skolasky, MA; C. Kleeberger, MAS; O.A. Selnes, PhD; E.N. Miller, PhD; J.T. Becker, PhD; B. Cohen, MD; J.C. McArthur, MBBS, MPH; and the Multicenter AIDS Cohort Study\*

Highly active antiretroviral therapy (HAART) is effective in suppressing plasma HIV viral load,<sup>1</sup> but its effect on the incidence rates of HIV-1-associated neurologic disease is largely unknown. Prior to the use of HAART, from 1985 to 1992, the incidence rates of cryptococcal meningitis, toxoplasmosis, progressive multifocal leukoencephalopathy (PML), and primary CNS lymphoma were all increasing, whereas the incidence rate of HIV dementia remained stable.<sup>2</sup> This study examines the temporal trends in the incidence rates of these conditions in the Multicenter AIDS Cohort Study (MACS) during the time HAART was introduced.

**Methods.** The MACS is a prospective study of the natural history of HIV infection among homosexual men in Baltimore, Pittsburgh, Chicago, and Los Angeles.<sup>3</sup> Participants undergo an interview, clinical assessment, neurologic screening tests, and laboratory measurements every six months. Questionnaires on medical conditions, antiretroviral drug therapy, and opportunistic infection prophylaxes are also included. Medical records are obtained for all participants with HIV who report the development of AIDS-defining conditions and neurologic disorders. The research diagnostic criteria for HIV dementia, cryptococcal meningitis, toxoplasmosis, PML, and CNS lymphoma have been described previously.<sup>2,4</sup> Antiretroviral therapy regimens of MACS participants were classified as monotherapy, combination therapy without protease inhibitors

(dual therapy), and HAART,<sup>1</sup> which was defined according to 1997 US NIH guidelines.<sup>5</sup>

The study included all 2734 MACS men with HIV during the study period. Participants were recruited from 1984 to 1985 (88%), and 1987 to 1991 (12%). The follow-up rate was 90%. Overall, 79.1% were Caucasian. Fifty percent had at least a college degree, and the median (SD) age at study entry was 37.4 (7.3) years.

The outcomes of interest were the incidence rates of five HIV-1-associated neurologic conditions. The incidence rate was defined as the ratio between the number of cases of that specific condition and the number of person-years at risk for that condition during that period.

The study period for this analysis was from January 1990 to December 1998. This nine year study period was divided into three smaller periods. Monotherapy was the predominant form of treatment from January 1990 to December 1992, dual therapy and monotherapy were predominant from January 1993 to December 1995, and HAART was predominant from January 1996 to December 1998. Similar time period borders were used in previous analyses within the MACS<sup>1</sup> to serve as proxies for the different regimens. Incidence rates during each of these three time periods were then compared using Poisson regression analysis.

**Results.** Table 1 and figure 1 show the incidence rates during each of the three time periods from 1990 to 1998. With the introduction of HAART from 1996 to 1998, there was a decreased incidence rate compared with both the incidence rate of HIV dementia from 1990 to 1992 (pairwise comparison,  $p = 0.0005$ ) and the incidence rate from 1993 to 1995 (pairwise comparison,  $p = 0.02$ ). Of the 20 new cases of HIV dementia from 1996 to 1998, 40% were on HAART, 20% were on dual therapy, 5% were on monotherapy, and 35% were on no therapy.

From 1990 to 1992, the majority (70%) of HIV dementia cases occurred with advanced immunosuppression (CD4 count <200) (table 2). In contrast, from 1996 to 1998, cases of HIV dementia were more equally distributed among the three CD4 count ranges. The incidence rates for those with CD4 <200 show a marked tendency toward a decrease by calendar period ( $p < 0.004$  for 1996 to 1998 compared with 1990 to 1992;  $p = 0.001$  for 1993 to 1995 compared with 1990 to 1992).

For cryptococcal meningitis and toxoplasmosis, the use of prophylaxis medications for each calendar year was

\*See the Appendix on page 260 for a list of members of the Multicenter AIDS Cohort Study (MACS).

From the Department of Neurology (Drs. Sacktor, Selnes, and McArthur), Johns Hopkins University School of Medicine, and the Department of Epidemiology (Dr. Lyles, R. Skolasky, and C. Kleeberger), Johns Hopkins School of Hygiene and Public Health, Baltimore, MD; Neuropsychiatric Institute (Dr. Miller), University of California, Los Angeles; Neuropsychology Research Program (Dr. Becker), University of Pittsburgh Medical Center, PA; and the Department of Neurology (Dr. Cohen), Northwestern University Medical School, Chicago, IL.

Dr. Lyles is now at the Department of Biostatistics, Rollins School of Public Health of Emory University, Atlanta, GA.

Supported by NIH grants AI35039, AI35040, AI35041, AI35042, AI35043, RR00722, and NS26643.

Received May 3, 2000. Accepted in final form September 22, 2000.

Address correspondence and reprint requests to Dr. Ned Sacktor, Johns Hopkins Bayview Medical Center, Department of Neurology, 4940 Eastern Avenue, B-Building, Rm 122, Baltimore, MD 21224; e-mail: sacktor@jhmi.edu

**Table 1** Mean incidence rate of HIV-1-associated neurologic diseases during three time periods in the Multicenter AIDS Cohort Study: 1990–1992, 1993–1995, 1996–1998

Disease	1990–1992, predominantly monotherapy	1993–1995, predominantly dual therapy*	1996–1998, predominantly HAART	Overall <i>p</i> value
HIV dementia	21.1	17.8	10.5	0.002†
Cryptococcal meningitis	5.0	2.5	1.5	0.02†
Toxoplasmosis	5.4	3.8	2.2	0.08
PML	2.0	1.8	1.5	0.84
CNS lymphoma	2.8	4.3	0.4	0.003†

Incidence rates are no./1000 person-years.

\* Combination therapy without protease inhibitors.

†  $p < 0.05$  By Poisson regression analysis.

HAART = highly active antiretroviral therapy; PML = progressive multifocal leukoencephalopathy.

without meaningful change from 1992 to 1998. Using the incidence rates from 1990 to 1992 as the reference, there was a decreased incidence rate from 1996 to 1998 (pairwise comparison,  $p = 0.008$ ) for cryptococcal meningitis, and a trend for a decreased incidence rate for toxoplasmosis which was not significant after adjustment for multiple comparisons (see table 1 and figure 1). There was no difference in the incidence rate for PML across these three periods. There was a decreased incidence rate for CNS lymphoma from 1996 to 1998 compared with the incidence rate from 1990 to 1992 (pairwise comparison,  $p = 0.008$ ) and the incidence rate from 1993 to 1995 (pairwise comparison,  $p = 0.0005$ ). All cases of cryptococcal meningitis, toxoplasmosis, PML, and CNS lymphoma from 1990 to 1998 occurred in patients with a CD4 count  $<200$ .

**Discussion.** Although new cases of HIV dementia, cryptococcal meningitis, and CNS lymphoma are still developing in patients with HIV, the incidence rates for these conditions have decreased dramatically since the introduction of HAART in 1996, compared to the incidence rates from 1990 to 1992. In addition, the proportion of new cases of HIV dementia with a CD4 count in a higher range (i.e., 201 to 350) since the beginning of 1996 may be increasing compared to the early 1990s, as shown in table 2. In patients on HAART, screening for HIV dementia may need to begin in patients with a CD4  $<350$ .

Our data are consistent with another cohort of homosexual men, where there was a decreased incidence rate from 1992 to 1996 for toxoplasmosis, and a combined group of HIV dementia and PML cases.<sup>6</sup>

In an urban clinical practice with predominantly IV drug users, a decreased incidence for HIV dementia and toxoplasmosis was also suggested during the period of 1996 to 1997, compared to the period of 1993 to 1995.<sup>7</sup> In contrast, HIV dementia constituted a greater proportion of AIDS-defining illnesses in Australia<sup>8</sup> in the period of 1996 to 1997, compared to 1992 to 1995. However, that study did not evaluate incidence changes for HIV dementia; rather, it was a comparison of HIV dementia relative to other AIDS-defining illnesses.

There are a variety of mechanisms proposed by which HAART may cause such decreased incidence rates. By decreasing systemic HIV viral load, HAART may decrease the risk of seeding of HIV into the CNS. However, the CNS may serve as a sanctuary site for the virus, and neurologic dysfunction such as HIV dementia may result when the CNS serves as a reservoir for virological escape. In contrast, the development of opportunistic infections and lymphoma within the CNS require advanced immunosuppression.

There are several limitations to the current study. HIV-1-associated neurologic diseases within the MACS are detected by medical records, active surveillance, and neuropsychological screening tests,<sup>9</sup> and there may be some individuals who developed dementia or a CNS condition that were never identified. Our study was performed in a cohort of homosexual men with a relatively high education level and excellent medication adherence. It is unknown

**Table 2** Number of observed cases (*N*) and incidence rate (*IR*) per 1000 person-years of HIV dementia stratified by CD4 cell count

CD4 count	1990–1992, N (IR)*	1993–1995, N (IR)*	1996–1998, N (IR)*	Overall <i>p</i> value
≤200	70 (80.7)	31 (41.3)	9 (26.9)	0.001
201–350	10 (14.0)	3 (4.9)	6 (13.6)	0.18
>350	18 (8.7)	8 (6.4)	7 (6.6)	0.70

\* Incidence rate per 1000 person-years given in parentheses.

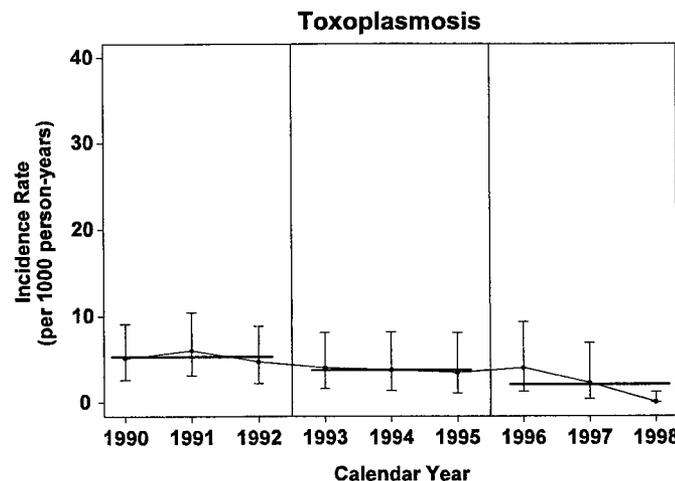
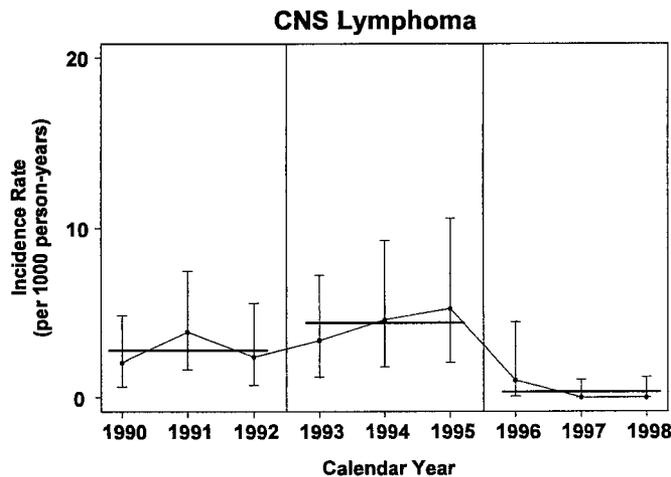
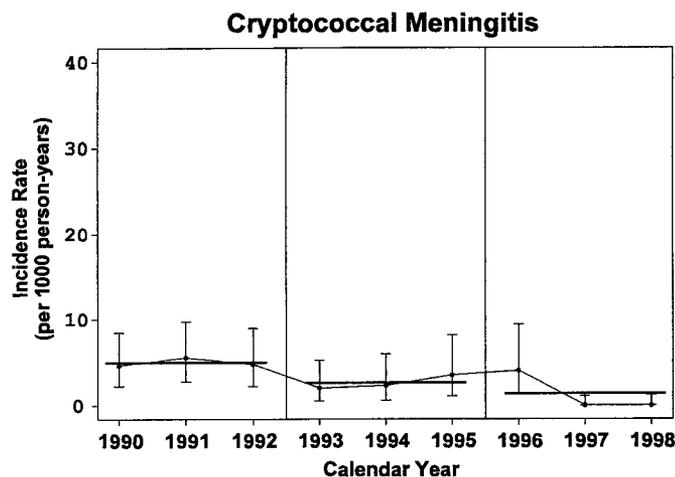
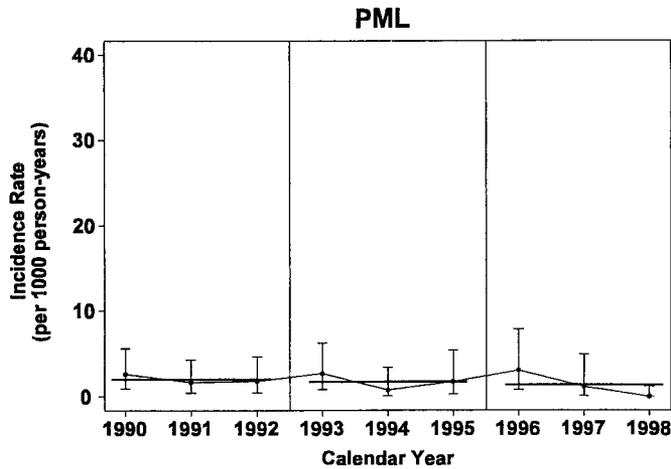
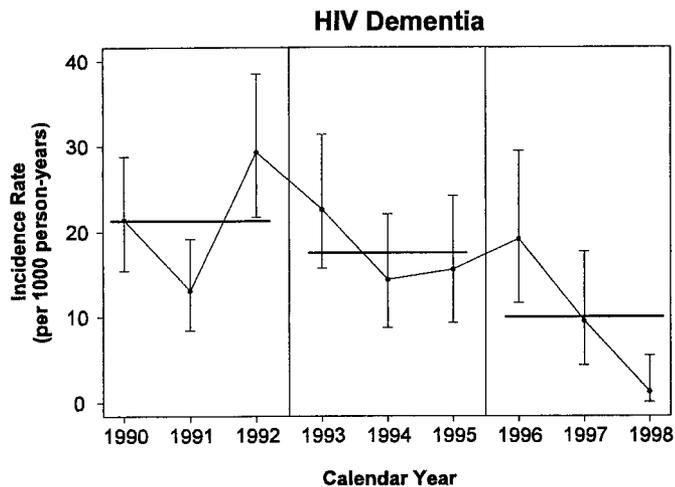


Figure. Incidence rates of HIV-associated neurologic diseases. The x-axis corresponds to the calendar year. The y-axis corresponds to the incidence rate per 1000 person years. The scale of the y-axis for CNS lymphoma is different from the scale of the y-axis for HIV dementia and the opportunistic infections. 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 1998 correspond to the mean incidence rates during those time periods.

whether similar results would be obtained in other groups of patients such as IV drug users, patients with less education, or patients with poor adherence.

As patients develop increasing resistance to HAART regimens, and with the failure of HAART to suppress HIV viral replication in some cases,<sup>10</sup> it is possible that the incidence and prevalence rates of HIV-1-associated neurologic diseases could increase. As the balance between new and more potent anti-

retroviral therapies and viral resistance shifts within the AIDS epidemic, it will be important to document and react to these possible changes in the incidence rates for HIV-1-associated neurologic diseases.

#### Acknowledgment

The authors appreciate the assistance of Glen McFarlane in the data analysis.

## Appendix

We appreciate the participation of all the volunteers in the Multicenter AIDS Cohort Study (MACS) and all the support staff who have contributed to the many aspects of collecting and analyzing these data. Drs. Frank Polk and Alfred Saah provided support and encouragement in the performance of this study. In addition to the listed authors, the MACS includes the following: The Johns Hopkins University School of Hygiene and Public Health, Baltimore, MD—Joseph Margolick (Principal Investigator), Hartoutone Armenian, Homayoon Farzadegan, Ellen Taylor; Howard Brown Health Center, Northwestern University Medical School, Chicago, IL—John P. Phair (Principal Investigator), Joan S. Chmiel, Daina Variakojis, Steven M. Wolinsky; University of California, UCLA Schools of Public Health and Medicine, Los Angeles, CA—Roger Detels (Principal Investigator), Barbara R. Visscher, John L. Fahey, Janis V. Giorgi, Oto Martinez-Maza, Hal Morganstern, Parunagi Nishanian, John Oishi, Jeremy Taylor, Harry Vinters; University of Pittsburgh Graduate School of Public Health and School of Medicine, Pittsburgh, PA—Charles A. Rinaldo, Jr. (Principal Investigator), Lawrence Kingsley, Phalguni Gupta, John Mellors, Sharon Riddler, Anthony Silvestri; Data Coordinating Center, The Johns Hopkins University School of Hygiene and Public Health, Baltimore, MD—Alvaro Munoz (Principal Investigator), Cheryl Enger, Stephen Gange, Lisa P. Jacobson, Cindy Kleeberger, Steven Piantadosi, Sol Su; NIH—National Institute of Allergy and Infectious Diseases, Bethesda, MD—Lewis Schragger; and National Cancer Institute—Sandra Melrick.

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## CME Dopa-responsive dystonia simulating spastic paraplegia due to tyrosine hydroxylase (TH) gene mutations

**Article abstract**—Spastic paraplegia is not widely recognized to occur in dopa-responsive dystonia (DRD). The authors found a compound heterozygote for novel mutations of the human tyrosine hydroxylase (TH) gene (*TH*). The patient was initially diagnosed as having spastic paraplegia, but responded completely to levodopa therapy. Exercise-induced stiffness in the patient's father, who had a *TH* deletion, also responded to levodopa. The data expand the clinical spectrum of TH deficiency and suggest that *TH* mutations may account for some patients with DRD simulating spastic paraplegia.

NEUROLOGY 2001;56:260–263

Y. Furukawa, MD; W.D. Graf, MD; H. Wong, MSc; M. Shimadzu, PhD; and S.J. Kish, PhD

Dopa-responsive dystonia (DRD) is a syndrome characterized by childhood-onset dystonia and a dramatic and sustained response to levodopa.<sup>1,2</sup> There are two

known causative genes for DRD: 1) the gene (*GCH1*) coding for GTP cyclohydrolase I (GTPCH), the enzyme in the biosynthetic pathway of tetrahydrobiopterin, the cofactor for tyrosine hydroxylase (TH); and 2) the human TH gene (*TH*).<sup>1</sup> Many DRD families have *GCH1* mutations.<sup>1</sup> In contrast, only one pedigree with typical DRD was reported to have a *TH* mutation.<sup>3</sup> In six other genetically confirmed families with TH deficiency, all patients developed severe motor retardation, truncal hypotonia, and hypokinesia rather than dystonia.<sup>1,4</sup>

Approximately 20% of DRD patients present with severe dystonia of the lower extremities simulating spastic paraplegia.<sup>2</sup> Thus, the differential diagnosis of spastic paraplegia should include DRD. This, how-

From the Movement Disorders Research Laboratory (Dr. Furukawa and H. Wong) and Human Neurochemical Pathology Laboratory (Dr. Kish), Centre for Addiction and Mental Health, Toronto, Ontario, Canada; Departments of Pediatrics and Neurology (Dr. Graf), University of Washington School of Medicine, Seattle; and Department of Genetics (Dr. Shimadzu), Mitsubishi Kagaku Bio-Clinical Laboratories, Inc., Tokyo, Japan.

Supported in part by the Centre for Addiction and Mental Health Foundation.

Received August 21, 2000. Accepted in final form September 22, 2000.

Address correspondence and reprint requests to Dr. Yoshiaki Furukawa, Movement Disorders Research Laboratory (R 211), Centre for Addiction and Mental Health-Clarke Division, 250 College Street, Toronto, Ontario, Canada M5T 1R8; e-mail: Yoshiaki\_Furukawa@camh.net

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N. Sacktor, R.H. Lyles, R. Skolasky, et al.  
*Neurology* 2001;56;257-260  
DOI 10.1212/WNL.56.2.257

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