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Trends in encephalitis-associated deaths in the United States

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SUMMARY

The United States national mortality statistics and HIV/AIDS surveillance data were analysed to determine trends in encephalitis-associated deaths and to assess the impact of HIV infection on those deaths during 1979–1998, a period when ICD-9 codes were used for coding deaths in the United States. A total of 25 125 encephalitis deaths were reported; 4779 of them (19%) had concurrent HIV infection. Overall encephalitis death rates remained stable, but they increased for groups where HIV infection was common and declined or remained unchanged for others. For persons without HIV infection, the rates declined in all demographic groups. Encephalitis deaths in HIV-infected persons followed general trends for HIV deaths in the United States. The rates in the HIV-infected population were several hundred- to thousand-fold higher than in the HIV-uninfected population. HIV infection was largely responsible for the lack of overall decline in the considerable mortality associated with encephalitis in the United States during 1979–1998.

INTRODUCTION

Encephalitis is a serious, potentially fatal condition that can result from a variety of viral, bacterial, parasitic, and other infectious organisms as well as from toxins and autoimmune reactions to vaccines [1, 2]. The cause of encephalitis is often difficult to diagnose, and remains unknown in a large proportion of cases [3–6]. In the United States, encephalitis has been associated with an estimated 19 000 hospitalizations, 230 000 hospital days, and $650 million in hospitalization costs annually [6]. These estimates are based on the analysis of the National Hospital Discharge Survey (NHDS) data, which also suggested a substantial impact of human immunodeficiency virus (HIV) epidemic on encephalitis epidemiology [6]. In that study, HIV-infected persons accounted for 15% of all encephalitis-associated admissions during 1988–1997 and hospitalized encephalitis patients with HIV infection appeared to have higher mortality than those without HIV infection [6]. HIV infection has been recognized as a major cause of an increase in mortality due to infectious diseases in the United States since the early 1980s [7]. However, until now, nationwide estimates of encephalitis-associated mortality in general or in relation to HIV infection have

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not been available. In this study, we describe trends in encephalitis-associated deaths in the United States during 1979–1998 and correlate them with the trends in HIV epidemic during the respective period.

METHODS

Multiple cause-of-death mortality data for the United States were obtained from the National Center for Health Statistics, Centers for Disease Control and Prevention (CDC) [8]. To ensure comparability of the results over time, we restricted the study to the 20-year period from 1979 to 1998, when the 9th revision of the International Classification of Diseases (ICD-9) [9] was used to code causes of death in the United States.

An encephalitis-associated death was defined as one for which any of the ICD-9 codes consistent with encephalitis (Table 1) were listed anywhere on the death record [9]. Encephalitis deaths with none of the cause-specific codes listed were classified as those due to encephalitis of unknown cause. An encephalitis-associated death in an HIV-infected person was defined as the one for which a code consistent with HIV infection was also listed (Table 1). HIV encephalitis/encephalopathy was defined by the presence of the code for HIV infection causing specified diseases of the central nervous system (043.1) in addition to any encephalitis code. As a surrogate for toxoplasmic encephalitis, we used the code for toxoplasmosis in general (130) in combination with encephalitis codes. Because the use of the code 130 does not necessarily imply that encephalitis was caused by *T. gondii*, these deaths were included in the group with unknown cause.

To estimate the risk of encephalitis-associated death in the general population, the age-adjusted and age-specific death rates were calculated using national census data for the United States resident population [10]. The age-adjusted annual death rates for the United States were calculated by the direct method, using the 1990 US census population as the standard. Rates were calculated for individual years for the entire group and by HIV status of the deceased. The rates were also calculated for the periods of 1979–1988 and 1989–1998 for the entire group and for the group without known HIV infection. All rates were expressed per 1 000 000 persons. Age-specific rate ratios (RRs) and age-adjusted RRs with 95% confidence intervals (CIs) were calculated using Poisson regression analysis [11].

To compare the rate of encephalitis-associated death in HIV-infected and uninfected populations, annual crude rates of encephalitis-associated death for the respective populations were calculated using the CDC surveillance data for AIDS and HIV infection. The rates for populations with AIDS were calculated for the entire nation on the basis of the CDC annual estimates of numbers of people living with AIDS. The years before 1984 were excluded from this analysis because the population with AIDS was too small to calculate reliable rates. The rates for the HIV-infected populations, including those with or without AIDS, were calculated on the basis of the CDC estimates of people living with HIV infection. This analysis was restricted to the 25 states† that conducted confidential name-based surveillance for non-AIDS HIV infection, as well as AIDS, during 1994–1998. The latter data were not available for the years before 1994.

RESULTS

General trends

Of the 25 125 encephalitis-associated deaths in the United States reported during the 20-year study period, 12 128 occurred during 1979–1988 and 12 997 occurred during 1989–1998, with average annual age-adjusted rates of 5·3 and 5·1/1 000 000 respectively. For the entire study period, the rates were consistently higher for males than for females and higher for blacks than for whites and other races (Table 2, Fig. 1*b*, *c*). The age-specific rates were highest for the very young (aged <1 year) or the elderly (aged ⩾65 years) (Table 2, Fig. 1*d*).

Although the rates of deaths associated with all causes of encephalitis remained stable over the 20-year study period (Table 2, Fig, 1*a*), further analysis revealed differences in category-specific trends between the two 10-year periods (1979–1988 and 1989–1998). There was a significant increase among blacks and young adults aged 20–44 years. The rate among males remained stable, and there was a significant decline for females, whites, and other races, as well as all age groups except the 20–44 years group (Fig. 1*b–d*, Table 2).

† Alabama, Arizona, Arkansas, Colorado, Idaho, Indiana, Louisiana, Michigan, Minnesota, Mississippi, Missouri, Nevada, New Jersey, North Carolina, North Dakota, Ohio, Oklahoma, South Carolina, South Dakota, Tennessee, Utah, Virginia, West Virginia, Wisconsin, Wyoming.

Table 1. *Encephalitis-associated deaths by category and study period, United States, 1979–1998*

Category	ICD-9 codes	Records listing the given category, No. (%)*	
		1979–1988	1989–1998
Meningococcal encephalitis	036.1	20 (0·2)	22 (0·2)
HIV encephalitis/encephalopathy	043.1†	39 (0·3)‡	240 (1·8)
Acute bulbar poliomyelitis	045.0	0	1 (<0·1)
Other non-arthropod-borne viral encephalitis	049.8	85 (0·7)	72 (0·6)
Herpesvirus encephalitis	054.3	1955 (16·1)	1368 (10·5)
Post-measles encephalitis	055.0	34 (0·3)	7 (0·1)
Mosquito-borne viral encephalitis	062.0–8	37 (0·3)	60 (0·5)
Tick-borne viral encephalitis	063.0–8	0	1 (<0·1)
Viral encephalitis transmitted by other and unspecified arthropods	064	2 (<0·1)	3 (<0·1)
Rabies	071	11 (0·1)	21 (0·2)
Mumps encephalitis	072.2	9 (0·1)	0
Meningoencephalitis due to *Naegleria*	136.2	12 (0·1)	13 (0·1)
Arthropod-borne viral encephalitis	323.3	0	0
Other encephalitis due to infection	323.4	0	0
Post-immunization encephalitis	323.5	34 (0·3)	4 (<0·1)
Post-infectious encephalitis	323.6	0	0
Toxic encephalitis	323.7	0	0
Other encephalitis	323.8	83 (0·7)	55 (0·4)
Encephalitis due to unknown cause§	049.9, 062.9, 063.9, 323.9, excluding 043.1	9883 (81·5)	11 200 (86·2)
All encephalitis	Any of the above-mentioned codes	12 128 (100·0)	12 997 (100·0)
HIV infection¶ in a person with encephalitis	Any of the following codes: 136.3, 279.1, 279.3, 279.9, 795.8, 042–044, plus any of the encephalitis codes	1110 (9·2)	3669 (28·2)

* Per cent of all encephalitis-associated deaths during given study period. More than one cause of death consistent with encephalitis was listed in 0·6% of the records for 1979–1988 and 0·5% of the records for 1989–1998. Consequently, the sum of deaths in each category exceeds the total, and the sum of percentages exceeds 100%.

† Introduced in 1987.

‡ This per cent includes the period before the introduction of the code 043.1. During 1987–1988, the only 2 years during this study period for which 043.1 was available, HIV encephalitis/encephalitis accounted for 1·5% of 2601 encephalitis deaths.

§ 'Encephalitis due to unknown cause' includes deaths coded as 'unspecified encephalitis' (323.9), 'unspecified viral encephalitis' (049.9), 'encephalitis due to unspecified mosquito-borne virus' (062.9), and 'encephalitis due to unspecified tick-borne virus' (063.9), with the exception of deaths also coded with 043.1.

¶ The codes 136.3, 279.1, 279.3, 279.9, which represent pneumocystosis and immunodeficiencies, are not specific for HIV infection but were used as a surrogate for it, and were included for 1979–1986 only. HIV-specific codes (042–044 and 795.8) were introduced in 1987.

The increase in encephalitis-associated death rates among blacks started in the mid-1980s and occurred among males only (increase from 9·1 during 1979–1988 to 12·0/1 000 000 during 1989–1998; RR 1·37, 95% CI 1·27–1·49). The large increase in rates over time in the 20–44 years age group also started in mid-1980s and was also restricted to males (increase from 4·1 during 1979–1988 to 6·6/1 000 000 during 1989–97; RR 1·63, 95% CI 1·54–1·73). When analysed by race and age group, the significant increase in rates was restricted to 20- to 44-year-old whites (from 2·7 during 1979–1988 to 3·5 during 1989–1998; RR 1·31, 95% CI 1·24–1·38), and to 20- to 44-year-old blacks (from 5·8 to 10·5; RR 1·81, 95% CI 1·65–1·99) and 45- to 64-year-old blacks (from 10·6 to 12·2; RR, 1·15, 95% CI 1·02–1·30).

Encephalitis-associated deaths by HIV infection status

Since the above described category-specific increases were observed in the groups most affected by HIV/AIDS in the United States (males, blacks and young

Table 2. *Rates (per 1 000 000 persons) and numbers of encephalitis-associated deaths and proportion of HIV-infected among the deceased by study period, sex, race, and age group in the general population of the United States, 1979–1998*

Category	1979–1988			1989–1998			1989–1998 *vs.* 1979–1988
	Rate	No. (%)	% HIV(+)	Rate	No. (%)	% HIV(+)	RR (95% CI)
All deaths	5·3	12 128 (100)	9·2	5·1	12 997 (100)	28·2	1·02 (0·99–1·05)
Sex							
Male	6·4	6557 (54·1)	15·5	6·5	7843 (60·3)	40·0	1·01 (0·99–1·03)
Female	4·4	5571 (45·9)	1·7	3·6	5154 (39·7)	10·4	0·81 (0·78–0·84)
Male *vs.* female, RR (95% CI)	1·42 (1·37–1·47)			1·82 (1·76–1·89)			
Race							
White	5·1	10 122 (83·4)	8·6	4·6	10 062 (77·4)	24·2	0·90 (0·85–0·91)
Black	7·6	1803 (14·9)	12·9	9·4	2677 (20·6)	44·4	1·24 (1·15–1·29)
Other	3·7	203 (1·7)	2·5	2·9	258 (2·0)	15·9	0·78 (0·62–0·90)
Black *vs.* white, RR (95% CI)	1·53 (1·45–1·61)			2·16 (2·07–2·26)			
White *vs.* other, RR (95% CI)	1·30 (1·12–1·49)			1·55 (1·37–1·75)			
Age group (yr)							
<1	14·9	550 (4·5)	0·7	9·3	370 (2·8)	0·8	0·62 (0·54–0·71)
1–4	3·1	425 (3·5)	1·9	1·6	245 (1·9)	2·9	0·52 (0·45–0·61)
5–19	1·4	750 (6·2)	0·5	0·9	506 (3·9)	4·2	0·64 (0·58–0·73)
20–44	3·0	2775 (22·9)	29·4	4·4	4392 (33·8)	62·6	1·47 (1·37–1·50)
45–64	6·8	3034 (25·0)	8·1	5·5	2790 (21·5)	30·1	0·81 (0·77–0·85)
⩾65	16·6	4593 (37·9)	0·7	14·3	4694 (36·1)	1·0	0·86 (0·83–0·90)

RR, Rate ratio; CI, confidence interval.
Rates are rounded to one decimal point. Rates by sex and race are age-adjusted.

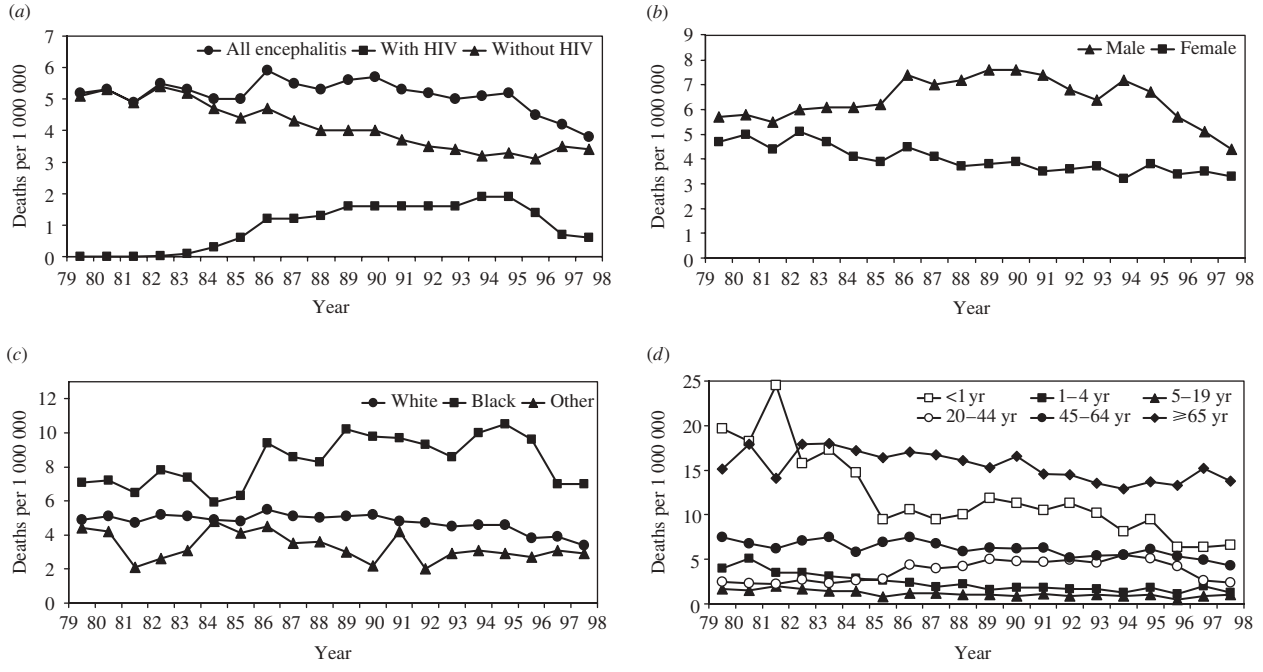

Fig. 1. Encephalitis-associated death rates in the general population of the United States by year, 1979–1998. (*a*) Overall rates and rates of encephalitis deaths with and without concurrent HIV infection; (*b*), rates by sex; (*c*), rates by race; (*d*), rates by age group. All rates except those by age group are age-adjusted.

Table 3. *Rates (per 1 000 000 persons) and numbers of encephalitis-associated deaths without concurrent HIV infection by study period, sex, race, and age group, 1979–1998*

Category	1979–1988		1989–1998		1989–1998 *vs.* 1979–1988
	Rate	No. (%)	Rate	No. (%)	RR (95% CI)
All deaths	4·7	11 018 (100)	3·6	9328 (100)	0·73 (0·71–0·75)
Sex					
Male	5·4	5543 (50·3)	4·0	4709 (50·5)	0·67 (0·65–0·70)
Female	4·4	5475 (49·7)	3·2	4619 (49·5)	0·73 (0·70–0·76)
Male *vs.* female, RR (95% CI)	1·24 (1·19–1·29)		1·29 (1·23–1·34)		
Race					
White	4·6	9250 (84·0)	3·3	7623 (81·7)	0·69 (0·67–0·72)
Black	6·6	1570 (14·3)	5·4	1488 (16·0)	0·75 (0·70–0·80)
Other	3·6	198 (1·7)	2·6	217 (2·3)	0·63 (0·52–0·76)
Black *vs.* white, RR (95% CI)	1·47 (1·39–1·56)		1·68 (1·59–1·78)		
White *vs.* other, RR (95% CI)	1·17 (1·02–1·35)		1·25 (1·09–1·43)		
Age group (yr)					
<1	14·9	546 (5·0)	9·2	367 (3·9)	0·66 (0·49–0·64)
1–4	3·1	417 (3·8)	1·6	238 (2·6)	0·47 (0·40–0·54)
5–19	1·4	746 (6·8)	0·9	485 (5·2)	0·63 (0·56–0·71)
20–44	2·1	1958 (17·8)	1·6	1643 (17·6)	0·63 (0·59–0·67)
45–64	6·2	2788 (25·3)	3·9	1949 (20·9)	0·59 (0·56–0·63)
⩾65	16·5	4562 (41·3)	14·2	4646 (49·8)	0·85 (0·82–0·89)

RR, rate ratio; CI, confidence interval.
Rates are rounded to one decimal point. Rates by sex and race are age-adjusted. Age was missing for one person during 1979–1988.

adults), we analysed encephalitis-associated deaths by HIV status of the deceased. Encephalitis in persons without known HIV infection accounted for 20 346 deaths in the United States during 1979–1998. The age-adjusted rate of encephalitis-associated death in persons without HIV infection declined significantly (27% overall) in all demographic groups (Table 3, Fig. 1*a*); the rates were significantly higher for males than for females and for blacks than for whites and other races, while the age-specific rates were highest among those aged ⩾65 years, followed by children aged <1 year (Table 3).

The trends for the decedents with HIV-infection were very different from those of the decedents without HIV infection (Fig. 1*a*). During 1979–1980, the ICD-9 codes for certain immune deficiency disorders used for coding HIV infection before the introduction of HIV-specific codes, were identified on <1% of death certificates of persons who died of encephalitis. By 1983, these codes became more common among persons dying with encephalitis (2%; rate 0·1/1 000 000) and increased sharply to 20·0% in 1986 (rate 1·2/1 000 000). In 1987, when azidothymidine, the first reverse transcriptase (RT) inhibitor was approved by the FDA, HIV-infected persons accounted for 22·2% (rate 1·2/1 000 000) of all encephalitis-associated deaths. During the period when RT inhibitors were the only approved group of anti-HIV drugs, encephalitis deaths with concurrent HIV continued to increase, albeit at a slower pace, reaching the peak rate of 1·9/1 000 000 in 1995 and accounting for 36·6% of all encephalitis-associated deaths that year. After the introduction of the highly active anti-retroviral therapy (HAART) in 1995, the rates began to decline rapidly and reached 0·6/1 000 000 in 1998 (14·2% of all encephalitis-associated deaths for the year). Overall, throughout the entire 20-year period, a total of 4779 (19·0%) encephalitis-associated deaths had ICD-9 codes indicative of HIV infection, most of which occurred after the mid-1980s. The proportional distribution of HIV-infected individuals by demographic group reflects a predominance of males, blacks, and persons aged 20–44 years (Table 2).

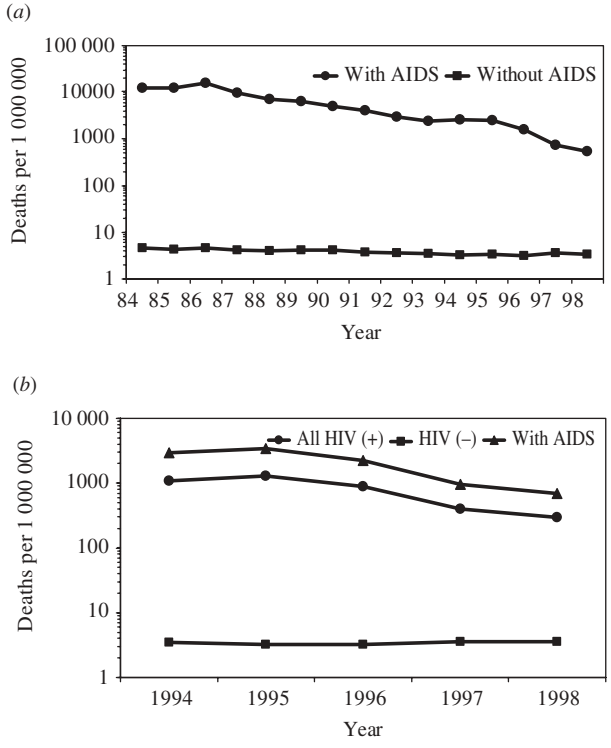

Fig. 2. Encephalitis-associated death rates in the HIV-infected and uninfected populations. (*a*) In populations with and without AIDS, United States, 1984–1998; (*b*), among total HIV-infected, AIDS, and HIV-uninfected populations in the 25 states conducting confidential name-based HIV/AIDS surveillance, 1994–1998.

The rates of encephalitis-associated death within the HIV-infected population were several hundred- to several-thousand fold higher than those in the HIV-uninfected population (Fig. 2). The rates in the population with AIDS declined considerably during the study period from the high of 15 900 in 1986 to 540 in 1998 (Fig. 2*a*). The rates in the entire HIV-infected population in the 25 states reporting both AIDS and non-AIDS HIV infections to CDC during 1994–1998 were ~2·5-fold lower than the rates among those with AIDS, but still several hundred-fold higher than the rates for the population without HIV (Fig. 2*b*).

Encephalitis-associated deaths by aetiology

Most encephalitis-associated deaths were attributed to an unknown cause (Table 1). The proportion of deaths with unknown cause among all encephalitis deaths increased from 81·5% during 1979–1988 to 86·2% during 1989–1998; this proportion was even higher (89·0% for both decades) among the deceased with concurrent HIV infection. Herpesvirus was the most common known cause of encephalitis-associated death (Table 1) and accounted for 16·1% of all encephalitis deaths during 1979–1988 and 10·5% of all encephalitis deaths during 1989–1998. Throughout the study period, the rates of death due to herpesvirus encephalitis declined from 0·9 during 1979–1988 to 0·5/1 000 000 during 1989–1998 (RR 0·77, 95% CI 0·75–0·79). HIV encephalitis/encephalopathy was noted for 279 deaths during 1987–1998 (1·8% of all encephalitis-associated deaths and 6·5% of all encephalitis-associated deaths with HIV infection). Toxoplasmosis was reported for 387 or 1·5% of all encephalitis-associated deaths beginning in 1983, with 379 (97%) reports since 1985. Other specified aetiologies accounted for a small proportion of encephalitis deaths each (Table 1). Mortality due to encephalitis associated with vaccine-preventable causes and post-immunization encephalitis remained low during the study period. No encephalitis deaths associated with mumps virus were reported after 1986, and five (71%) of seven post-measles encephalitis deaths occurred during 1990–1992, at the time of a resurgence of measles in the United States [12]. There were no considerable changes over the study period in the numbers of deaths due to other specific causes, such as arboviruses, rabies, meningococcal infection and *Naegleria* (Table 1). Because of the small numbers in each category, the rates for the individual causes other than herpesvirus were not calculated.

No clinical data to verify diagnosis or evaluate the relative importance of the listed multiple causes of death are available from the national mortality dataset. However, the analysis of the underlying causes of death showed that encephalitis (all codes) was the most common underlying cause, listed for 10 697 or 42·6% of all encephalitis-associated deaths. Most records, however, had conditions other than encephalitis listed as the underlying cause of death. HIV infection in general was the second major category among underlying causes accounting for 3886 deaths (15·4% of all encephalitis-associated deaths and 80·9% of those with concurrent HIV infection). Of these, 253 deaths (1·0%) had HIV encephalitis/encephalopathy listed as the underlying cause of death (90·7% of those with HIV encephalitis/encephalopathy), while 3615 (14·4%) had encephalitis associated with causes other than HIV infection *per se*. Other major diagnostic groups listed among underlying causes were diseases of circulatory system (ICD-9 codes 390–429) (2383 or 9·5% of all encephalitis deaths), neoplasms (ICD-9 codes 140–239)

(2183 or 8·7%), other infections (ICD-9 codes 1–139, except the HIV codes and encephalitis causes listed in Table 1), some of which could be causally related to encephalitis (1275 or 5·1%), and diseases of respiratory system (ICD-9 codes 460–519) (1168 or 4·6%). The above diagnostic groups combined accounted for underlying causes of 85·9% of all encephalitis deaths, while all others accounted for the remaining 14·1%.

DISCUSSION

This study found considerable mortality associated with encephalitis and revealed a substantial impact of HIV on its epidemiology in the United States during 1979–1998. HIV infection, both as an underlying condition or a direct cause of encephalitis, was largely responsible for the lack of an overall decline and for the remarkable changes in the demographics of encephalitis-associated deaths in the United States during the study period. The increased morbidity and mortality due to infections in immunocompromised persons, including those with HIV, is a well-known fact. Our study confirmed the increased risk of death from encephalitis of any cause among HIV-infected individuals suggested by the earlier study of encephalitis-associated hospitalizations [6] and allowed us to obtain previously unavailable population-based estimates.

Throughout the study period, encephalitis mortality rates in the United States increased only in the groups most heavily affected by HIV infection and declined in the groups, in which HIV infection was less common [13, 14]. HIV-infected persons accounted for one in every five encephalitis-associated deaths, and the risk of encephalitis-associated death was much higher in the HIV-infected population, than in the HIV-uninfected population. In addition, HIV encephalitis/encephalopathy was the underlying cause of death for nearly all deceased with this condition, and HIV infection in general was the second most common underlying cause of death after encephalitis itself, accounting for ~15% of all encephalitis-associated deaths. However, even these enormous rates observed among the HIV-infected population may still be underestimated. As shown in a recent study, death certificates of about 20% of deaths attributed to underlying HIV infection (which probably include some encephalitis-associated deaths) do not mention causes of death other than HIV/AIDS [15].

In the general population, trends in the rate of death with concurrent encephalitis and HIV infection, and the demographic groups with the highest rates followed those for mortality due to HIV infection in the United States [16]. Similar to the trends for HIV/AIDS in general, the improved diagnostics and increasing availability of antiretroviral treatment had a considerable impact on encephalitis-associated deaths among HIV-infected persons. The increase in encephalitis-associated death rates with concurrent HIV infection slowed down after the introduction of RT, and reversed after the introduction of the HAART [14, 17, 18]. The dramatic, almost 30-fold decline in encephalitis-associated death rates in HIV-infected population between 1986 and 1998 indicated a substantial reduction of the risk of dying of encephalitis for an HIV-infected person, also coinciding with the introduction of antiretrovirals [17].

In the HIV-uninfected population, a continuous downward trend across all demographic groups was noted. This decline was largely attributable to general improvement in patient care and advances in treatment of some encephalitis causes, first of all, herpesviruses [19, 20], throughout the study period.

Over the past decades, the aetiological profile of encephalitis has undergone considerable changes associated with the advances in therapeutic and prevention options, the decline in vaccine-preventable causes, and emergence of new pathogens [19–24]. Our study confirmed these observations. Most notably, mortality associated with herpesvirus encephalitis declined significantly, probably due to the introduction and increasing use of acyclovir and related compounds during the study period [20]. HIV infection *per se* was the second most common specified cause of encephalitis-associated death after herpes simplex virus. Toxoplasmic and herpesvirus encephalitides were the most common known categories of encephalitis-associated hospitalizations in the 1990s, each of them accounting for 11·5% of all hospital admissions due to encephalitis [6]. However, toxoplasmic encephalitis appeared to be a less important contributor to encephalitis-associated mortality than it was to hospitalizations. The availability of effective treatment and potential repeated hospitalizations probably contributed to this difference. Vaccine-preventable diseases and immunizations with certain vaccines were once among major causes of encephalitis. Widespread childhood immunization and the discontinuation of the use of the vaccines commonly associated with neurological complications (e.g.

smallpox vaccine, older rabies vaccines) [25, 26], led to their dramatic reduction in the years prior to the study period. Further expansion of infant immunization, especially throughout the 1990s [27], reduced the contribution of vaccine-preventable causes to encephalitis mortality to the minimum levels observed in our study.

The proportion of encephalitis deaths due to unknown cause in our study was very high, especially among HIV-infected persons. These proportions are substantially higher than the 60% observed during the 1990s in the National Hospital Discharge Survey-based hospitalization study [6]. This difference may have resulted in part from differences in encephalitis codes between the ICD-9 and its clinical modification (ICD-9-CM) used for morbidity data, since the codes for certain encephalitides, such as toxoplasmic, rubella, varicella-zoster-associated, are only included in ICD-9-CM [28]. However, these causes are not expected to contribute a large enough portion of encephalitis deaths to fully account for this difference. Less common or unusual pathogens could also cause encephalitis and lead to death, especially in HIV-infected individuals, but they might remain undiagnosed, or even if identified, they often cannot be recorded as encephalitis causes because the corresponding ICD-9 codes do not exist. This again underscores the limitations of vital statistics data which are suitable for evaluating general trends in encephalitis, but far less helpful for detailed analysis of individual aetiologies.

Beginning in 1999, the United States adopted the 10th revision of the International Classification of Diseases (ICD-10) for coding deaths [29]. In the analysis of the impact of this transition on different conditions using a limited dataset [30], the impact on encephalitis could not be reliably quantified because of the small numbers. Therefore, the deaths from 1999 onwards were not included in the study. However, once the ICD-10-based mortality data become available for a reasonably long period of time, they could offer additional opportunities for evaluating further trends and estimating the impact of certain encephalitides that have agent-specific codes introduced for the first time. Of importance, these conditions include toxplasmic encephalitis, encephalitis due to varicella-zoster virus, enteroviruses, adenoviruses, and several other causes, as well as infection with West Nile virus, an important cause of encephalitis recently introduced into the Western hemisphere [21].

In conclusion, encephalitis mortality in the United States is substantial, especially in HIV-infected persons. The rates of encephalitis deaths among non-HIV infected persons declined significantly over the study period, presumably because of better treatment options and expanded use of vaccines. Improvements in treatment of HIV infection appear to have decreased the risk of encephalitis-associated death for HIV-infected persons. However, further reductions are likely to be difficult to achieve without a better understanding of encephalitis causes and without improved aetiological diagnosis of encephalitis. Concerted efforts to optimize strategies for encephalitis prevention and treatment, interventions aimed at reducing the burden of HIV infection, and continued research to better define the causes of encephalitis should promote the trend towards a reduction in the encephalitis-associated mortality seen in HIV-uninfected persons during the study period.

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