Cryptococcosis: Population-Based Multistate Active Surveillance and Risk Factors in Human Immunodeficiency Virus–Infected Persons

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To determine the incidence of cryptococcosis and its risk factors among human immunodeficiency virus (HIV)–infected persons, population-based active surveillance was conducted in four US areas (population, 12.5 million) during 1992–1994, and a case-control study was done. Of 1083 cases, 931 (86%) occurred in HIV-infected persons. The annual incidence of cryptococcosis per 1000 among persons living with AIDS ranged from 17 (San Francisco, 1994) to 66 (Atlanta, 1992) and decreased significantly in these cities during 1992–1994. Among non–HIV-infected persons, the annual incidence of cryptococcosis ranged from 0.2 to 0.9/100,000. Multivariate analysis of the case-control study (158 cases and 423 controls) revealed smoking and outdoor occupations to be significantly associated with an increased risk of cryptococcosis; receiving fluconazole within 3 months before enrollment was associated with a decreased risk for cryptococcosis. Further studies are needed to better describe persons with AIDS currently developing cryptococcosis in the era of highly active antiretroviral therapy.

An uncommon disease before the human immunodeficiency virus (HIV) epidemic, cryptococcosis, a systemic infection caused by the yeast *Cryptococcus neoformans,* has emerged as an important cause of illness and death in persons infected with HIV in the United States [1]. Precise estimates of the incidence of cryptococcosis have not been available because surveillance was lacking. The association of cryptococcosis with exposure to pigeon droppings, the best known of the putative exposure risk factors for this disease, comes almost exclusively from information about the isolation of *C. neoformans* from the environment [2] and a few anecdotal reports [3–5]. Outbreak investigations, which often clarify the epidemiology of infectious diseases, have not been described for cryptococcosis. Moreover, the pathogenesis of cryptococcosis is not well understood. For example, it is not clear whether cryptococcosis in HIV-infected persons is caused by acute infection, reactivation, or both, which has important implications for prevention of disease in HIV-infected persons. Although the occurrence of cryptococcosis is suspected to vary substantially throughout the United States, as does endemic distribution of coccidioidomycosis and histoplasmosis, variations in geographic distribution have not been established for cryptococcosis.

To estimate the incidence of cryptococcosis, describe demographic features of persons with cryptococcosis, and identify risk factors for disease, we conducted active, population-based surveillance for cryptococcosis in four areas of the United States and a case-control study of risk factors for this disease in HIV-infected persons. Here we report the results of these studies.

Methods

Population-based surveillance. Surveillance for cryptococcosis was conducted as part of an active, laboratory-based surveillance project for invasive bacterial and mycotic diseases, using previously described methods [6]. Cryptococcosis surveillance was established in four areas of the United States with an aggregate population of 12,454,732: metropolitan Atlanta (8 counties; 2,468,387 population), Houston (1 county; 2,971,775 population), Alabama (statewide; 4,137,512 population), and the San Francisco Bay Area (3 counties; 2,877,078 population). The surveillance population was ~71% white, 22% African American, and 7% other races or ethnicities. Of all persons in the surveillance population, 42% were 20–44 years old and 29% were ≥45 years old. Surveillance was done prospectively for 30 months (from 1 January 1992 to 30 June 1994) in Atlanta and San Francisco and for 18 months (from 1 January 1993 to 30 June 1994) in Alabama and Houston.

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Each eligible case-patient was contacted through his or her physician for permission to participate in the case-control study. This study was approved by institutional review boards at the Centers for Disease Control and Prevention and all participating institutions at both sites.

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For surveillance purposes, an incident case of cryptococcosis in a resident of a surveillance area was defined as a positive culture for *C. neoformans* from any body site; detection of cryptococcal antigen in blood, cerebrospinal fluid, or urine; or histopathologic findings consistent with cryptococcosis. For incidence calculations, we included cases first diagnosed during the surveillance period, counting each case only once, even if subsequent cultures or cryptococcal antigen tests were positive. Personnel working in the surveillance areas identified cases of cryptococcosis through regular contact with laboratories in each acute-care hospital and reference laboratories in these areas. Laboratory audits were done every 6–12 months during the study period to evaluate completeness of reporting and to identify cases that had not been reported. For each case identified, medical records were reviewed for demographic data and the presence of underlying medical conditions, as reported by physicians. Outcome of all incident cases was assessed at the end of hospitalization. All available isolates of *C. neoformans* were sent to the Centers for Disease Control and Prevention for confirmation [7].

Incidences were calculated by use of the US Census Bureau population estimates for 1992. To calculate the incidence of cryptococcosis in persons living with AIDS, the denominator was the number of all persons with AIDS at each site during each of 1992, 1993, and 1 January through 30 June 1994 and was defined as the total number of persons reported with AIDS by the end of each surveillance period minus the number of persons with AIDS who had died by the midpoint of the same surveillance period for each site (Georgia Department of Health, Alabama Department of Public Health, California Department of Health Services, and Houston Department of Health). Because surveillance in 1994 was conducted for the first 6 months only, incidences for this year were annualized. Cryptococcosis cases in which the HIV infection status was unknown ($n = 17$) were excluded from analyses in which cases were stratified by HIV infection status.

To evaluate the occurrence of cryptococcosis among persons with diabetes mellitus, we used data about the prevalence of diabetes mellitus in persons ⩾18 years old in 1992. These data were provided by the Centers for Disease Control and Prevention's Division of Diabetes Translation for each state, based on averages of 1991–1993 data of prevalence estimates of self-reported diabetes from the Behavioral Risk Factor Surveillance System. The denominator was the estimated number of diabetics in each surveillance area, based on the proportion of each state's population included in our surveillance.

Statistical analysis was done with SAS for Windows (version 6.12; SAS Institute, Cary, NC) and Epi Info (version 6.02) software. The χ^2 test was used to compare proportions of categorical variables among patients with cases of cryptococcosis. To compare rates of disease by sex, age, and race, we analyzed only the data from 1993, which included 1 full year of data from all four sites.

Case-control study in persons with AIDS. Two surveillance sites participated in the case-control study: metropolitan Atlanta and the San Francisco Bay Area. For the case-control study, a case was defined as isolation of *C. neoformans* from a normally sterile site in an HIV-infected resident of the surveillance area. Controls were systematically selected from a list of patients admitted to the same hospital as the case-patient within 3 months of the case's reference date; matching was accomplished by finding controls with the most recent CD4 cell count in the same category. Three HIV-infected controls matched for CD4 cell count category were enrolled for each case. For the purpose of matching, CD4 cell counts were divided into three categories: <100, 100–200, and >200/mm^3. For cases, the reference date was defined as the date of diagnosis of cryptococcosis and for controls, the date of hospitalization.

Standardized data collection forms were used to interview cases and controls and abstract information from their medical records. Information was collected about demographic characteristics; occupational history; food, alcohol, and smoking histories; clinical history of current and past illnesses; outpatient medications; and various exposures. The latter included direct exposures to various animals, particularly various birds (handling pigeons, parakeets, canaries, or other birds and cleaning bird cages), and being in places likely to harbor birds (e.g., barns, farms, warehouses, and public parks) during the month preceding the reference date. Owning pet birds and seeing pigeons in outdoor and indoor settings were investigated for the year prior to the reference date. Information was obtained by interview of cases and controls. Surrogates were interviewed when cases or controls were unable to respond to the questionnaire because of impaired mental status or death. Laboratory data were obtained through medical record review.

We performed matched univariate and multiple conditional logistic regression analyses using the SAS for Windows procedure PHREG (SAS version 6.12; SAS Institute) to estimate the risk for cryptococcosis associated with characteristics of subjects and exposures. We used stepwise backward selection, incorporating variables that were significant ($P < .05$) in the univariate analysis and other potential confounding variables, to identify a final model for the multivariate analysis. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated.

Results

Population-Based Surveillance

Incidence. A total of 1083 incident cases of cryptococcosis were identified in the surveillance. Most cases (88%) occurred in men 20–44 years old (table 1). From 1 January 1992 through 30 June 1994 (a period of 30 months), 296 cases were identified in metropolitan Atlanta and 475 in the San Francisco Bay Area. From 1 January 1993 through 30 June 1994 (18 months), 193 cases were identified in metropolitan Houston and 119 in Alabama. The annual incidence of cryptococcosis ranged from 1.8/100,000 in Alabama in 1994 to 6.7/100,000 in San Francisco in 1993 (figure 1). No seasonal variation in rates of cryptococcosis was detected.

Underlying conditions and outcome. Of the 1083 crypto-

Table 1. Demographic characteristics of patients with cryptococcosis, by HIV infection status.

Characteristic	HIV-uninfected ($n = 135$)	HIV-infected ($n = 931$)	Total ($n = 1083$)
Male sex	76 (56)	866 (93)	953 (88)
Age 20–44 years	37 (27)	742 (80)	788 (73)
African American race	41 (30)	379 (41)	427 (39)

NOTE. Data are no. (%).

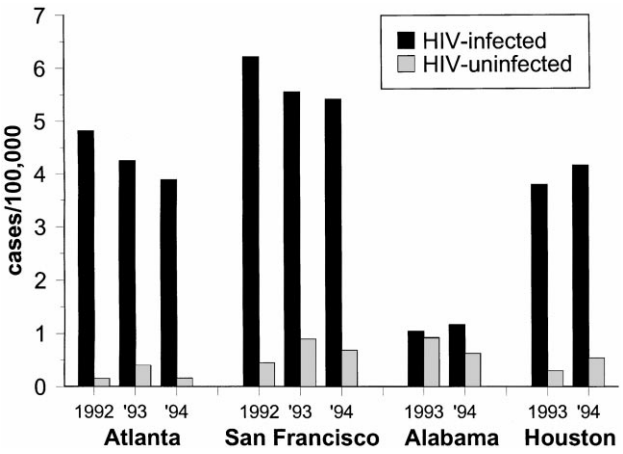

Figure 1. Incidence of cryptococcosis, by site, year, and HIV infection status, 1992–1994.

coccosis cases, 931 (86%) occurred in persons known to be HIV-infected, 135 in persons with negative HIV antibody test results, and 17 in persons whose HIV infection status was unknown because they had not been tested. The overall case-fatality rate was 12% (12% for HIV-infected patients, 17% for HIV-uninfected patients). The proportion of cryptococcosis cases in conjunction with HIV infection varied by site: 92% of all cases in Atlanta, 91% in Houston, 88% in San Francisco, and 56% in Alabama (figure 1). Of the 135 patients with cryptococcosis who were HIV-uninfected, 94 (70%) had at least one underlying medical condition reported (table 2). Cancer was the most commonly reported condition, followed by diabetes mellitus. Other immunocompromising conditions included receiving steroid therapy (during the month prior to diagnosis) in 25 (18%) and a rheumatologic or immunologic disorder in 17 (13%), of whom 5 (4%) had sarcoidosis.

Diagnostic and clinical characteristics. Of the 931 cryptococcosis cases in HIV-infected persons, 557 (60%) were diagnosed by isolation of *C. neoformans* in culture (310 [56%] from cerebrospinal fluid, 208 [37%] from blood, and 26 [5%] from a pulmonary source), 352 (38%) were diagnosed on the basis of a latex agglutination test alone, and 22 (2%) were diagnosed on the basis of histopathologic findings alone. Most HIV-infected patients with cryptococcosis (89%) presented with meningitis or fungemia; pulmonary cryptococcosis was the presenting syndrome in 54 patients (6%).

Of the 135 HIV-uninfected persons with cryptococcosis, 106 (78%) had the disease diagnosed by isolation of *C. neoformans* in culture (40 [34%] from cerebrospinal fluid, 39 [34%] from respiratory sources [23 bronchoalveolar lavage samples, 9 lung biopsy samples, and 7 sputum specimens], and 14 [12%] from blood), 23 (17%) had the disease diagnosed on the basis of a latex agglutination test alone, and 6 (4%) had a diagnosis based on histopathologic findings alone. Forty-four (29%) had pulmonary cryptococcosis alone, a much larger proportion than the 6% observed among HIV-infected persons. In 12 patients with pulmonary cryptococcosis, *C. neoformans* was isolated from a lung biopsy, but the majority of persons with pulmonary cryptococcosis were diagnosed by isolation of *C. neoformans* from sputum (7 cases) or bronchial washing (22 cases).

Geographic distribution. We compared the incidences of cryptococcosis among the four surveillance sites during 1993, when we had a full year of data for each site. The overall incidence of cryptococcosis was highest in San Francisco (7/100,000 population); in contrast, the incidence of cryptococcosis in persons with AIDS was significantly lower in San Francisco than in the three other sites ($P < .005$). The highest incidence of cryptococcosis in persons with AIDS in 1993 occurred in Atlanta (40/1000). In HIV-uninfected persons, the incidence of cryptococcosis was the same in Alabama and San Francisco (0.9/100,000), more than double the incidence of cryptococcosis in Atlanta (0.4/100,000) and Houston (0.3/100,000).

Cryptococcosis in Persons with AIDS

Among persons with AIDS, the annual incidence of cryptococcosis ranged from 66/1000 in Atlanta in 1992 to 17/1000 in San Francisco in 1994 (figure 2). In Atlanta and San Francisco (where data were collected for >2 years), the incidence of cryptococcosis decreased significantly during 1992–1994 (χ^2 for trend: $P < .001$ in Atlanta and <.05 in San Francisco) (figure 2). The demographic characteristics of all HIV-infected persons with cryptococcosis are summarized in table 1. The incidence of cryptococcosis in 1993 was significantly higher among African Americans (31/1000) than among whites (23/1000; relative risk [RR] = 1.3, 95% CI, 1.1–1.6). There was no significant difference in the rates of cryptococcosis between men and women with AIDS.

Cryptococcosis in HIV-Uninfected Persons

Among persons without HIV infection, the annual incidence of cryptococcosis ranged from 0.16/100,000 in Atlanta in 1994

Table 2. Reported underlying conditions in HIV-uninfected persons with cryptococcosis (n = 135).

Illness[a]	No. (%)	Comments
None reported	41 (30)	
Cancer	31 (23)	
Diabetes mellitus	30 (22)	14 had no other disease
Steroid therapy	25 (18)	
Rheumatologic or immunologic disease	17 (13)	5 with sarcoidosis
Lung disease	16 (12)	
Organ transplant	6 (4)	
Renal failure/dialysis	5 (4)	
Chronic liver disease	5 (4)	
Other[b]	8 (6)	

[a] Patients may have had >1 underlying illness or condition.
[b] Pregnancy (2), ectopic pregnancy, alcohol abuse, seizure disorder, necrotizing pancreatitis, chronic osteomyelitis, and hypothyroidism (1 each).

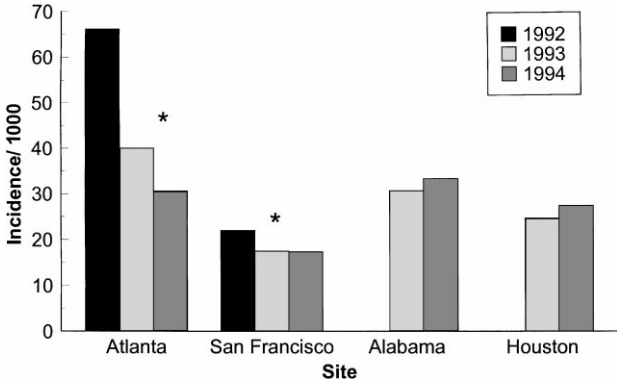

Figure 2. Incidence of cryptococcosis in persons with AIDS, by site, 1992–1994. * In Atlanta and San Francisco, disease significantly declined each subsequent year (χ^2 for trend: $P < .001$ in Atlanta and <.05 in San Francisco).

to 0.93/100,000 in Alabama in 1993 (figure 1). Annual incidence in persons without HIV infection did not decrease significantly over time in San Francisco or Atlanta.

The median age of persons with cases of cryptococcosis was 55 years (range, 3–89); 93 (69%) were ⩾45 years old. Rates of cryptococcosis in 1993 were slightly higher for African Americans and males, but these differences were not statistically significant. The rate of cryptococcosis was three times as high for persons ⩾45 years old (0.9/100,000) as for persons <45 years old (0.3/100,000; RR = 3.1, 95% CI, 1.8–5.2).

Cancer, a well-established risk factor for cryptococcosis, was the most common underlying illness reported, followed by diabetes mellitus. Persons with diabetes were nearly four times more likely than the general population to develop cryptococcosis (RR = 3.8, 95% CI, 2.2–6.8). However, most persons with diabetes also had one or more immunocompromising conditions. Analysis of data for persons with diabetes as the only underlying illness indicated that they were still at increased risk for cryptococcosis, but the association was not statistically significant (RR = 1.4, 95% CI, 0.6–3.4).

Pediatric Cryptococcosis

Very few cases of cryptococcosis were reported in children. Only 4 persons <18 years old were reported with cryptococcosis; 3 were female. Two were HIV-infected (ages 13 and 15), and 2 had no underlying medical condition reported (ages 3 and 6).

Case-Control Study

A total of 158 cases (84 from Atlanta and 74 from San Francisco) and 423 matched controls (252 from Atlanta and 171 from San Francisco) were enrolled in the case-control study. Cases and controls did not differ significantly by sex, age, race, and level of CD4 lymphocytes (table 3).

In the univariate analysis, cryptococcosis was significantly associated with various demographic and behavioral factors (African American race, smoking, and alcohol and intravenous drug use) and occupational or environmental exposures (working with soil and having been a landscaper or builder) (table 4). Several medications were found to be associated with decreased risk for cryptococcosis, including fluconazole, acyclovir, dapsone, and zidovudine.

We evaluated the differences between cases and controls in exposures to birds, particularly pigeons, during the month preceding the reference date. No bird exposures, alone or in combination, were found to be significantly associated with cryptococcosis (table 4).

In the multivariate analysis, administration of fluconazole in the 3 months preceding diagnosis was significantly associated with a decreased risk of cryptococcosis (OR = 0.3, 95% CI, 0.2–0.7), reducing the risk by 70%. When other factors were controlled for, cryptococcosis patients were significantly more likely to be current smokers (OR = 1.9, 95% CI, 1.1–3.3) or to have a history of outdoor occupations (e.g., landscaping or building) (OR = 1.8, 95% CI, 1.03–3.2) (table 4).

Discussion

This study has estimated the incidence of cryptococcosis in the four surveillance sites to be 1.8–6.7 cases per 100,000 population and up to 0.9 cases per 100,000 in the HIV-uninfected population. Of all cases, 86% occurred in persons with AIDS, a proportion that varied among the surveillance areas depending on the prevalence of AIDS. During the surveillance period of 1992–1994, we found that 2%–5% of persons with AIDS in the surveillance areas developed cryptococcosis per year.

In Atlanta and San Francisco, the incidence of cryptococcosis among persons with AIDS decreased during 1992–1994. This decline may be associated with the increasing use of azoles in HIV-infected persons, as well as other advances in health care for HIV-infected persons. Data from the case-control study suggest that fluconazole was commonly used (24% of all persons enrolled in the study had used fluconazole during the 3 months preceding the study) and that fluconazole, even when used occasionally, was associated with a decreased risk of cryptococcosis. These data corroborate the results of previous stud-

Table 3. Characteristics of case-patients and controls, cryptococcosis risk factor study, Atlanta and San Francisco, 1992–1994.

Characteristic	Case-patients (n = 158)	Controls (n = 423)
Male sex	146 (93)	385 (92)
Age 20–44 years	137 (87)	358 (84)
Race		
White	73 (46)	221 (52)
African American	83 (52)	197 (47)
CD4 cell count <100/mm^3	141 (89)	380 (90)
Death	18 (13)	19 (5)

NOTE. Data are no. (%).

Table 4. Risk factors for cryptococcosis in HIV-infected persons, Atlanta and San Francisco, 1992–1994, univariate and multivariate analysis.

Characteristic	Cases	Controls	Matched odds ratio (95% confidence interval)	*P*
Univariate analysis				
African American race	83 (52)	197 (47)	1.9 (1.2–3.0)	.01
Intravenous drug user	55 (37)	115 (28)	1.7 (1.1–2.6)	.01
Sex with intravenous drug user	51 (42)	96 (29)	2.1 (1.3–3.4)	.003
Current smoker	64 (42)	96 (29)	1.8 (1.1–2.8)	.01
Alcohol use	115 (74)	251 (60)	2.0 (1.3–3.0)	.001
Working with soil	31 (20)	51 (12)	1.9 (1.1–3.2)	.02
Outdoor building or landscaping	43 (27)	84 (20)	1.89 (1.2–2.8)	.002
Fluconazole in last 3 months	19 (14)	122 (32)	0.3 (0.2–0.6)	.0001
Zidovudine in last year	73 (51)	249 (61)	0.7 (0.4–1.0)	.05
Acyclovir in last 3 months	28 (20)	118 (30)	0.5 (0.3–0.8)	.007
Dapsone in last 3 months	16 (12)	102 (26)	0.4 (0.2–0.7)	.0009
Handling birds in past month	9 (5.7)	20 (4.7)	1.2 (0.5–2.7)	.7
Being in places likely to harbor pigeons in past month[a]	120 (76)	292 (69)	1.4 (0.9–2.2)	.1
Multivariate analysis				
Fluconazole in last 3 months			0.3 (0.1–0.6)	
Current smoker			2.0 (1.1–3.4)	
Outdoor building or landscaping			1.8 (1.0–3.2)	

NOTE. Case and control data are no. (%).
[a] Includes warehouses, barns, farms, train stations, and parks.

ies, including a randomized clinical trial [8] and an observational study [9]. The observation that the incidence of cryptococcosis among HIV-uninfected persons did not decline over time suggests that changes in environmental exposures to the organism were not responsible for the decline in the incidence of cryptococcosis in HIV-infected persons.

The incidence of cryptococcosis varied among these four surveillance sites, principally because of differences in the incidence of AIDS among the sites. However, differences in the incidence of cryptococcosis in persons with AIDS also contributed. Differential rates of fluconazole use in the different sites could have contributed to differences in cryptococcosis incidence in persons with AIDS, which is supported by data from the case-control study: 33% of all persons enrolled in San Francisco had received fluconazole during the 3 months preceding the interview, compared with only 23% of those enrolled in Atlanta. The incidence of cryptococcosis also varied among HIV-uninfected persons. Although it is possible that these differences reflect differences in endemicity of *C. neoformans,* this study was unable to define clear geographic variations in the endemic occurrence of cryptococcosis. Although known geographic differences exist in the distributions of the two varieties of *C. neoformans, gattii* and *neoformans* [10], almost all (99%) of our surveillance isolates were *C. neoformans* var. *neoformans* [7].

The finding that the race-specific incidence of cryptococcosis was higher in African Americans than in whites is similar to previous studies [11, 12]. However, the case-control study did not find an association between cryptococcosis and race, suggesting that race may be a surrogate for the presence of other conditions or exposures.

HIV-infected persons who were current smokers were at increased risk for cryptococcosis. Smoking adversely affects the respiratory system by inhibiting mucociliary clearance and disrupting the respiratory epithelium and has been associated with other pathogens acquired through the respiratory route (e.g., *Neisseria meningitidis* [13]).

The case-control study failed to identify a variety of exposures to be risk factors for cryptococcosis in HIV-infected persons, including various exposures to pigeons, other birds, or bird droppings. Apart from a conclusion that these exposures are not risk factors for cryptococcosis, several other factors could explain these findings. First, the exposures in question are quite common, perhaps requiring a larger study to detect differences in these exposures between cases and controls. Second, we focused on exposures that occurred in the month preceding onset of disease. If the usual incubation period of cryptococcosis in HIV-infected persons were longer than that, we might not have targeted the right time period for questioning. Third, it is possible that some cryptococcosis cases in HIV-infected persons are due to reactivation of a latent infection rather than to acute infection and thus that relevant exposures occurred long ago. Reactivation was suggested as a possible mechanism for development of cryptococcosis [14] and for development of disseminated histoplasmosis in HIV-infected persons [15]. Exploring a possible role for reactivation in cases of cryptococcosis would be a challenge for study design and would probably require better skin and serologic tests for cryptococcosis. Acute cryptococcosis in HIV-infected persons has been reported following intense exposure to pigeon droppings [16], which led to recommendations to avoid massive exposures to pigeon droppings [17]; the findings in the case-control study do not provide evidence that would contradict these recommendations.

Among HIV-uninfected persons, about two-thirds of patients with cryptococcosis also had at least one underlying immunocompromising condition. Cancer, treatment with cortico-

steroids, rheumatologic conditions, organ transplantation, and sarcoidosis, all conditions associated with decreased cell-mediated immunity, were the most common underlying conditions. Persons with diabetes mellitus appeared to be at increased risk for cryptococcosis, but many of them also had other conditions. Because of the small numbers and lack of information on severity of diabetes in these patients, our study may not have been able to assess the full role of diabetes mellitus, which adversely affects T lymphocyte function [18].

To follow up trends of cryptococcosis in the United States, especially since the introduction of highly active antiretroviral therapy (HAART), active population-based surveillance was reinitiated in two surveillance sites (Atlanta and Houston) in July 1996. Over the last 2 years, the effect of HAART on decreasing the incidence of various opportunistic infections has become more obvious [19]. Ongoing surveillance will be helpful to determine the current burden of cryptococcosis and to better describe persons with AIDS who are still developing this opportunistic infection.

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Study Group Members

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