

HIV/AIDS MAJOR ARTICLE

Aspergillosis among People Infected with Human Immunodeficiency Virus: Incidence and Survival

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Aspergillosis is a life-threatening fungal infection in immunocompromised people, including people infected with human immunodeficiency virus (HIV). We determined the incidence of aspergillosis among HIV-infected people and survival after aspergillosis diagnosis by use of a national HIV surveillance database. Among 35,252 HIV-infected patients, the incidence of aspergillosis was 3.5 cases per 1000 person-years (p-y; 95% confidence interval [CI], 3.0–4.0 per 1000 p-y). Incidence was higher among people aged ≥ 35 years (4.1 per 1000 p-y, 95% CI, 3.5–4.8), among people with CD4 counts of 50–99 cells/mm³ (5.1 per 1000 p-y, 95% CI, 2.8–7.3), or CD4 counts of < 50 cells/mm³ (10.2 per 1000 p-y, 95% CI, 8.0–12.2), versus people with CD4 counts of > 200 cells/mm³, people with ≥ 1 acquired immune deficiency syndrome–defining opportunistic illness (8.6 per 1000 p-y, 95% CI, 7.4–9.9), and people who were prescribed at least one medication associated with neutropenia (27.7 per 1000 p-y, 95% CI, 21.0–34.3). Median survival time after diagnosis of aspergillosis was 3 months, and 26% survived for ≥ 1 year. These findings suggest that aspergillosis is uncommon, occurs especially among severely immunosuppressed or leukopenic HIV-infected people, and is associated with poor survival.

Aspergillosis, a fungal infection, is life-threatening in immunocompromised hosts. Risk factors for aspergillosis include neutropenia, corticosteroid use, hematologic neoplasms, diabetes mellitus, underlying lung disease, and AIDS [1–4]. The most commonly implicated factors for invasive disease are neutropenia and long-term corticosteroid use [1, 5]. Aspergillosis may be especially important for people infected with HIV because, compared with patients with hematological malignancies and aspergillosis, those with HIV infection have a lower median survival [6].

Aspergillosis was included in the 1982 Centers for Disease Control surveillance case definition for AIDS [7] but was removed from the list of AIDS-defining conditions in 1984, because at that time, information suggested that aspergillosis was not associated with cellular immune deficiency [8–10]. None-

theless, aspergillosis occurs in HIV-infected people, and > 75 cases have been reported in the scientific literature since 1984 [3, 4, 11, 12]. Most of the studies in the medical literature are descriptive reports of clinical outcomes and treatment of aspergillosis, and few epidemiologic studies have been published.

To better understand the occurrence of aspergillosis in HIV-infected people, we reviewed the cases of aspergillosis reported in a national surveillance project. We describe here the incidence of aspergillosis and survival time among HIV-infected patients with aspergillosis.

Methods

We analyzed data collected from medical records of HIV-infected people observed in the Adult and Adolescent Spectrum of HIV Disease project (ASD) from January 1990 through January 1998. The methods used in ASD have been described [13]. For ~ 100 medical inpatient and outpatient facilities in 10 US cities, HIV-infected people ≥ 13 years of age were selected at their first health care visit after the project was initiated. Data abstractors reviewed all available medical records for demographic characteristics, mode of HIV exposure, and occurrences of AIDS-defining opportunistic illnesses (AIDS-OIs) [14]. Initial enrollment included information from the preceding 12 months (baseline period) on infectious (such

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as AIDS-OIs and other culture-confirmed bacterial and fungal infections) and noninfectious (such as cancer) conditions, medications prescribed, and laboratory values, with review of medical records every 6 months thereafter until death or loss to follow-up.

For patients with *Aspergillus* infections, an additional standardized supplemental abstraction form was completed. This form collected information on *Aspergillus* species, body site where *Aspergillus* was cultured, presence of invasive disease, and WBC count closest to the date of aspergillosis diagnosis. Aspergillosis was defined as detection of *Aspergillus* species in tissue or on a mucous surface, and invasive aspergillosis was defined as *Aspergillus* species detected in a sterile tissue specimen confirmed by either a pathology report demonstrating invasion of tissue or the finding of *Aspergillus* in blood cultures.

For incidence calculations, we analyzed data from all people without a history of aspergillosis at the time of enrollment for whom prospective follow-up information was available. Aspergillosis incidence per 1000 person-years of observation was computed for strata of sex, race, HIV exposure, WBC count, CD4⁺ T lymphocyte count, prior AIDS-OI diagnosis, facility of care (public vs. private), prescription of antiretroviral therapies, and prescription of drugs that can cause (ganciclovir, doxorubicin, bleomycin, and vinblastine) or be markers for (filgrastim and granulocyte-macrophage colony-stimulating factor) neutropenia. We assumed a Poisson distribution and constructed 95% CIs.

For patients with a diagnosis of aspergillosis, we analyzed data for the diagnosis of other selected opportunistic illnesses (cytomegalovirus disease, *Pneumocystis carinii* pneumonia, pulmonary tuberculosis, and other pneumonias) in the 6-month interval before the interval of aspergillosis diagnosis. The results are presented as a proportion of the people diagnosed with aspergillosis who had the prior illness. For patients missing information about WBC count and missing the date of diagnosis from the supplemental form, the most recent WBC count within 6 months of observation was used, and the diagnosis date was assumed to be the midpoint of the follow-up interval. The distribution of WBC counts among aspergillosis patients with a count on the supplemental form was compared with that of aspergillosis patients without supplemental data by the Wilcoxon rank sum test [15]. Because the distributions of WBC counts were not statistically different, we used all available WBC counts for determining WBC strata.

Survival time after diagnosis of aspergillosis was estimated by the Kaplan-Meier method [16]. Median and 1-year survival times with 95% CIs are given.

Results

There were 228 cases of aspergillosis among 35,252 people observed in ASD. The overall incidence of aspergillosis was 3.5 cases per 1000 person-years. The incidence of aspergillosis was significantly higher among people ≥ 35 years of age, people whose probable mode of HIV infection was engaging in male-male sex, people with a WBC count $< 2500 \text{ mm}^3$, those with CD4⁺ T lymphocyte counts $< 100 \text{ cells}/\mu\text{L}$, people with history of an AIDS-OI before the interval of observation, and people who were prescribed medications associated with neutropenia during the interval preceding observation (table 1).

Of the 228 cases of aspergillosis, 40 (18%) were diagnosed with *P. carinii* pneumonia, 36 (16%) were diagnosed with other pneumonias, 17 (7%) were diagnosed with pulmonary tuberculosis, and 11 (5%) were diagnosed with cytomegalovirus disease in the 6-month interval before the interval of aspergillosis diagnosis.

Of the 228 cases of aspergillosis, 144 (63%) patients with aspergillosis had a completed supplemental questionnaire. Of those patients, the most common body sites for *Aspergillus* isolation were lung ($n = 114$), blood ($n = 8$), and sinuses ($n = 7$) (table 2). The most common species isolated from all body sites was *A. fumigatus* (40%). However, a large proportion of isolates was not speciated (34%). Invasive aspergillosis was documented for 26 (18%) of 144 patients with aspergillosis. Among these 26, the anatomic sites of invasion were lung ($n = 11$), sinuses ($n = 3$), bone ($n = 2$), and skin and eye ($n = 1$ each), and 8 had disseminated invasion.

Among the 228 people with aspergillosis, the median survival was 3 months after diagnosis of aspergillosis. The percentage of patients alive 1 year after diagnosis of aspergillosis was 26% (95% CI, 20–32).

Discussion

Aspergillosis occurs uncommonly among people with HIV infection, but it is an important infection in that it is associated with short survival after diagnosis. The surveillance data collected through the ASD Project allowed calculation of incidence rates for aspergillosis, which have not been reported previously. Incidence of aspergillosis was higher among people with severe immunosuppression and an advanced stage of HIV disease, among older people, and among people with leukopenia and prescription markers of neutropenia.

Neutropenia [5, 17, 18], CD4 lymphocytopenia [4], and AIDS-OI diagnosis [4, 10, 11, 17] have been previously reported to be associated with aspergillosis among people with HIV infection, and these were also associated with higher rates of aspergillosis in our analysis. Although decreased incidence of many AIDS-OIs has been described among HIV-infected people receiving effective combination antiretroviral therapies [19], the incidence of aspergillosis did not vary by prescription of antiretroviral therapy for people in our analysis.

The median survival of our study patients was similar to survival times of HIV-infected people with aspergillosis reported elsewhere [11, 20, 21], comparable to survival following diagnosis of progressive multifocal leukoencephalopathy [22], and shorter than survival after diagnosis of *Mycobacterium avium* complex [23]. Furthermore, a large proportion of cases of aspergillosis are diagnosed postmortem [21], suggesting that underdiagnosis of infections antemortem may contribute to poor survival. HIV-infected people with aspergillosis, AIDS, and a CD4⁺ T lymphocyte count $\leq 50 \text{ cells}/\mu\text{L}$ have been reported to have poor clinical outcomes despite treatment, and among patients with aspergillosis, those with immunosuppression related to HIV in-

Table 1. Incidence of aspergillosis per 1000 person-years by a variety of criteria in patients who were part of the Adult/Adolescent Spectrum of HIV Disease Project, 1990–1998.

Variable	Aspergillosis cases, n (%)	No aspergillosis, n (%)	Person-years	Incidence (95% CI)
Age, y				
<35	77 (34)	18,121 (47)	29,463	2.6 (2.0–3.2)
≥35	151 (66)	20,381 (53)	36,670	4.1 (3.5–4.8)
Sex				
Male	198 (87)	28,619 (82)	53,842	3.7 (3.2–4.2)
Female	30 (13)	6405 (18)	12,292	2.4 (1.6–3.3)
Race				
White	122 (54)	14,764 (42)	29,834	4.1 (3.4–4.8)
Black	72 (31)	14,879 (42)	26,458	2.7 (2.9–3.5)
Hispanic	33 (14)	4887 (14)	8907	3.7 (2.4–5.0)
Other ^a	1 (<1)	494 (1)	934	1.1 (0.0–3.2)
HIV exposure mode				
Male-male sex	143 (63)	17,737 (50)	34,942	4.1 (3.4–4.8)
Injecting drug use	32 (14)	5943 (17)	10,697	3.0 (2.0–4.0)
Male-male sex and injecting drug use	23 (10)	3705 (11)	7196	3.2 (1.9–4.0)
Heterosexual sex	14 (6)	3101 (9)	6006	2.3 (1.1–3.6)
Receipt of blood products	4 (2)	662 (2)	1220	3.3 (0.1–6.5)
No identified risk	12 (5)	3980 (11)	6073	2.0 (0.9–3.1)
WBC count, ^b cells/mm ³				
5000	44 (19)	21,252 (27)	19,460	2.3 (1.6–2.9)
2500–4999	98 (43)	24,843 (31)	25,507	3.8 (3.1–4.6)
1000–2499	59 (26)	8389 (11)	4949	12.0 (8.9–15.0)
0–999	4 (2)	652 (<1)	169	24.0 (0.5–47.0)
CD4 T lymphocyte count, cells/mm ³				
≥200	24 (10)	18,689 (25)	24,622	1.0 (0.6–1.4)
100–199	6 (3)	9620 (13)	6326	1.0 (0.2–1.7)
50–99	19 (8)	7175 (9)	3746	5.1 (2.8–7.3)
0–49	88 (38)	12,369 (16)	8659	10.2 (8.0–12.2)
AIDS-defining opportunistic illness				
Absent	35 (15)	26,190 (60)	43,798	3.5 (2.7–4.3)
Present	193 (85)	17,281 (40)	22,336	8.6 (7.4–9.9)
Care facility				
Public	153 (67)	24,629 (70)	21,480	3.5 (2.7–4.3)
Private	75 (33)	10,395 (30)	44,653	3.4 (2.9–4.0)
Antiretroviral therapy				
Monotherapy	98 (43)	21,709 (36)	27,199	3.6 (2.9–4.3)
Dual therapy	34 (15)	9842 (16)	8894	3.8 (2.5–5.1)
Triple therapy	4 (2)	1877 (3)	1452	2.8 (0.1–5.5)
None	88 (38)	24,806 (41)	27,631	3.2 (2.5–3.8)
Medications associated with neutropenia ^c				
Present	67 (29)	3422 (10)	2421	27.7 (21.0–34.3)
Absent	161 (71)	34,449 (98)	63,713	2.5 (2.1–2.9)
Total	228 (100)	35,024 (100)	66,134	3.5 (3.0–4.0)

NOTE. Totals for some variables do not add up to 100% because of missing values, and totals for some variables may be >100% because people may have contributed to >1 category.

^a Includes Asian/Pacific Islander, American Indian, and Alaska Native.

^b Total WBC count in the 6-month interval before the interval of aspergillosis diagnosis.

^c Drugs that can cause neutropenia (ganciclovir, doxorubicin, bleomycin, and vinblastine) or that can be markers for neutropenia (filgrastim, granulocyte-macrophage colony-stimulating factor).

fection had a lower median survival in comparison with those with hematological malignancy-associated immunosuppression [6].

Our study has several limitations. Although ASD is a very large observational study and includes a diverse patient population, patients observed in ASD do not represent all people with HIV infection in the United States. Also, we did not have complete information on several factors frequently associated with aspergillosis, including neutropenia, prescription of immunosuppressive drugs such as corticosteroids, hematological

malignancies, underlying lung disease, and diabetes mellitus. Because we were lacking these critical data, we did not conduct regression analysis to determine risk factors for aspergillosis. Supplemental questionnaires were not completed for all identified cases of aspergillosis, and we were not able to assess the representativeness of the patients with supplemental abstractions. For those patients without supplemental data collection, we were not able to determine which patients harbored colonies of *Aspergillus* or were infected with aspergillosis.

Although aspergillosis occurs uncommonly among people

Table 2. Species of *Aspergillus* isolated and anatomic site for aspergillosis for patients in the Adult/Adolescent Spectrum of HIV Disease Project, 1990–1998.

Site	Species						Total
	<i>A. fumigatus</i>	<i>A. niger</i>	<i>A. flavus</i>	Other	Unspecified	>1 species	
Lung ^a	50 (44)	11 (10)	10 (9)	5 (4)	36 (31)	2 (2)	114 (100)
Blood	1 (13)	2 (25)	0 (0)	2 (25)	3 (37)	0 (0)	8 (100)
Sinus	3 (43)	0 (0)	0 (0)	0 (0)	4 (57)	0 (0)	7 (100)
Skin	3 (60)	0 (0)	0 (0)	0 (0)	2 (40)	0 (0)	5 (100)
Ear	1 (20)	3 (60)	0 (0)	0 (0)	1 (20)	0 (0)	5 (100)
Bone	0 (0)	0 (0)	0 (0)	0 (0)	1 (100)	0 (0)	1 (100)
Other ^b	0 (0)	0 (0)	1 (33)	0 (0)	2 (67)	0 (0)	3 (100)
>1 site	0 (0)	0 (0)	0 (0)	0 (0)	1 (100)	0 (0)	1 (100)

NOTE. Data are no. (%).

^a Includes sputum and biopsy samples.^b Includes feces, vagina, and eye.

with HIV infection, the short survival associated with aspergillosis underscores the importance of prompt recognition of this condition and appropriate treatment. Physicians should be aware that aspergillosis occurs with higher incidence among patients with more advanced HIV disease, patients with leukopenia, and people aged ≥ 35 years.

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