# Trends in the Postmortem Diagnosis of Opportunistic Invasive Fungal Infections in Patients With AIDS

## A Retrospective Study of 1,630 Autopsies Performed Between 1984 and 2002

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## Abstract

*We retrospectively evaluated autopsy-proven invasive fungal infections (IFIs) in patients with AIDS who died between 1984 and 2002. IFIs were identified in 297 (18.2%) of 1,630 autopsies. Their prevalence significantly decreased over time (from 25.0% in 1984-1988 to 15% in 1998-2002;* P = *.004), mainly owing to a significant decrease in pneumocystosis (*P = *.017) and cryptococcosis (*P = *.003), whereas the prevalence of aspergillosis and histoplasmosis remained relatively stable and of candidiasis and zygomycosis tended to increase in the last years (*P = *.028 and* P = *.042, respectively). IFIs were suspected or confirmed during life in only 46.8% of the cases; this proportion did not vary significantly over time (*P = *.320). The infections contributed to the deaths of 103 patients (34.7%), and their global impact on mortality was 6.3%. Of fatal cases, 38 (36.9%) were characterized by missed antemortem diagnoses, 17 (45%) of which met Goldman criteria for class I errors.*

*The epidemiology of IFIs in patients with AIDS is evolving and not completely mirrored by clinical diagnoses or current diagnostic methods. Our results confirm the valuable role of autopsy data, even with highly effective therapies and advanced technologies.*

Invasive fungal infections (IFIs) are major causes of morbidity and mortality in immunocompromised patients.[1] Pneumocystosis, cryptococcosis, and histoplasmosis are typically associated with AIDS,[2-4] but other fungi (particularly, *Candida albicans* and *Aspergillus* spp) may also cause overwhelming diseases during the course of HIV infection.[5,6]

During the last 10 years, the incidence of major AIDS-related IFIs has progressively declined as a result of the widespread use of anti–*Pneumocystis* pneumonia (PCP) prophylaxis and the availability of highly active antiretroviral therapy (HAART),[7] but little is known about the epidemiologic trends of other IFIs in the HIV population. The frequency and outcome of most IFIs are difficult to assess on the basis of clinical data alone because, with the possible exception of PCP and cryptococcal meningitis, they are still difficult to diagnose, particularly at an early stage, and many of them remain undetected during life.[8] However, although autopsy data have proved to be extremely useful in providing information about the epidemiology of IFIs and their contribution to death in patients with hematologic cancer and transplant recipients,[8,9] it seems that they have not yet been used in relation to patients with AIDS.

The aim of this study was to determine time trends in the frequency of occurrence, disease patterns, and concordance between antemortem and postmortem diagnoses of IFIs in a large series of autopsied patients with AIDS who died during an 18-year period at a large university hospital in Italy.

## Materials and Methods

We retrospectively reviewed the pathologic records of all patients with AIDS who underwent autopsy at L. Sacco

Hospital, Milan, Italy, between 1984 and 2002. L. Sacco Hospital is a university teaching hospital whose 500 beds include 76 in the Department of Infectious Diseases, thus making it the largest care provider for HIV+ subjects in the city of Milan. The diagnosis of HIV infection had been confirmed during life by means of enzyme-linked immunosorbent assay and Western blotting or, in the years in which HIV serology was not available, was based on the US Centers for Disease Control and Prevention standard criteria for a diagnosis of AIDS.[10]

All of the autopsies were performed in accordance with the standard Rokitansky technique, which involves the removal and examination of all visceral organs and the central nervous system (CNS). In addition to examining gross lesions, all organs were systematically sampled. The autopsy reports were reviewed for the presence of IFIs and the extent of the organ involvement and their contribution to the patient's death.

IFIs were defined as the presence of fungal elements in tissues (other than mucosal surfaces) with necrosis and etiologically classified on the basis of morphologic criteria supported by stains with Grocott methenamine silver, period acid–Schiff for fungi, and immunohistochemical reactions (WF-AF-1, DAKO, Carpinteria, CA) for *Aspergillus* species. Fungal infections localized to the mucosal surfaces of the upper gastrointestinal and upper respiratory tracts to the tracheal bifurcation were not considered. Disseminated disease was defined as the involvement of 2 or more noncontiguous visceral organs.

The morphologic features used to recognize tissue-located fungi were as follows: *Aspergillus* spp, small (3-6 μm wide) and uniform, dichotomously branching hyphae, "septated" at regular intervals; *Candida* spp, oval budding yeast cells with a diameter of 3 to 6 μm, pseudohyphae, and occasional true hyphae; *Cryptococcus* spp, 2- to 20-μm pleomorphic budding yeast cells without hyphae and with mucicarmine-positive capsules; *Histoplasma* spp, intracellular oval yeast cells with a diameter of 2 to 4 μm and variable narrow neck budding; *Pneumocystis jirovecii*, typical cup-shaped cysts (about 5 μm in diameter) with intracystic bodies or free trophozoites; and Zygomycetes spp, broad (6-25 μm wide), thin-walled, aseptate, or sparsely septate hyphae with haphazard branching.

The IFIs were considered the primary cause of death when they were the predominant pathologic process as indicated by the extent and pattern of vital organ involvement or a contributory cause when they were not primarily responsible for the death itself. The clinical charts relating to the last hospitalization of each patient with an IFI were reviewed to verify the concordance between the antemortem diagnosis and autopsy findings. Any discrepancies were categorized as major or minor on the basis of the theoretical impact of the missed or incorrect clinical diagnosis on the patient's management and survival according to the Goldman criteria.[11]

### Statistical Analysis

To analyze time trends of IFIs in relation to changes in the availability of antiretroviral therapies, the study period (1984-2002) was divided into 4 therapy-based intervals: 1984-1988, no therapy and initial monotherapy (zidovudine); 1989-1993, consolidated monotherapy (zidovudine, didanosine); 1994-1997 (dual combination therapy and initial triple combination therapy or HAART); and 1998-2002 (consolidated HAART).

The $\chi^2$ for trend was used to compare proportions in the ordered time intervals of the study. All analyses were made using the SPSS 14 software package for Windows (SPSS, Chicago, IL). A *P* value of less than .05 was considered statistically significant.

## Results

During the study period, 2,101 patients died of AIDS in our hospital, and 1,630 (77.6%) underwent autopsy; the autopsy rate decreased from 87.8% in 1984-1988 and 88.1% in 1989-1993 to 77.5% in 1994-1997 and 33.4% in 1998-2002 ($P < .001$). IFIs were found in 297 (18.2%) of the autopsied patients, 255 men (85.9%) and 42 women (14.1%) with a median age of 34 years (range, 21-75 years); all but 11 (3.7%) of the patients were of Caucasian origin. The risk factors for HIV infection included active or past intravenous drug use (238 patients [80.1%]), homosexuality (37 patients [12.5%]), heterosexual contacts (20 patients [6.7%]), and blood transfusion (2 patients [0.7%]). Most of the patients had advanced HIV infection with a median CD4 cell count at the time of death of 30/μL (range, 0-469/μL).

Pneumocystosis was the most frequent IFI (131 cases [44.1%]), followed by aspergillosis (83 [27.9%]), cryptococcosis (62 [20.9%]), candidiasis (15 [5.1%]), histoplasmosis (4 [1.3%]), and zygomycosis (2 [0.7%]). The overall prevalence of IFIs at autopsy decreased significantly over time, from 25.0% in 1984-1988 to 19.3% in 1989-1993, 14.2% in 1994-1997, and 15.1% in 1998-2002 ($P = .004$), although there were differences in the trends of the individual IFIs **Table 1**. The prevalence of pneumocystosis and cryptococcosis decreased from 11.6% to 3.2% ($P = .017$) and from 7.4% to 0% ($P = .003$), respectively, during the study period, whereas that of invasive candidiasis and zygomycosis significantly increased from 1.4% to 3.2% ($P = .03$), and from 0% to 1%, respectively ($P = .04$); the frequency of aspergillosis and histoplasmosis also increased (from 4.6% to 6.4% and from 0% to 1%, respectively), but the differences were not statistically significant.

The most frequently affected organ was the lung (83.5% of cases), which was followed by the CNS (22.6%) and




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**Table 1**
**Prevalence of IFIs at Autopsy***

| IFI | 1984-1988 (n = 216) | 1989-1993 (n = 820) | 1994-1997 (n = 501) | 1998-2002 (n = 93) | *P* |
|---|---|---|---|---|---|
| Aspergillosis | 10 (4.6) | 43 (5.2) | 24 (4.8) | 6 (6.5) | .888 |
| Candidiasis | 3 (1.4) | 6 (0.7) | 3 (0.6) | 3 (3.2) | .028 |
| Cryptococcosis | 16 (7.4) | 34 (4.1) | 12 (2.4) | 0 (0) | .003 |
| Histoplasmosis | 0 (0) | 2 (0.2) | 1 (0.2) | 1 (1.1) | .248 |
| Pneumocystosis | 25 (11.6) | 73 (8.9) | 30 (6.0) | 3 (3.2) | .017 |
| Zygomycosis | 0 (0) | 0 (0) | 1 (0.2) | 1 (1.1) | .042 |
| Total | 54 (25.0) | 158 (19.3) | 71 (14.2) | 14 (15.1) | .001 |

IFIs, invasive fungal infections.
* Data are given as number (percentage).

kidneys (13.1%); disseminated disease was observed in 83 cases (27.9%). There were differences in the pattern of organ involvement **Table 2**. Pneumocystosis was limited to the lungs in 88.5% of the cases and disseminated in 11.5%. Aspergillosis was confined to the lung in 73% (61/83) and disseminated in 23% (19/83), with the lung, CNS, kidney, and heart the most frequently affected sites. *Cryptococcus neoformans* infections were confined exclusively to the CNS in 34% of the cases (21/62) and disseminated in 39 cases (63%), with the CNS, lungs, lymph nodes, kidney, liver, and spleen the most frequently affected sites. Histoplasmosis was disseminated in all 4 cases, and *Candida* infection was limited to the lungs in 6 (40%) of 15 cases and disseminated in 6 (40%).

IFIs were the only opportunistic diseases revealed by autopsy in 58 cases (19.5%), whereas 239 cases had 1 or more other concomitant opportunistic diseases. It is interesting to note that cytomegalovirus infection was the most frequent concomitant disease (98 cases [41.0%]), followed by HIV encephalopathy and non-Hodgkin lymphoma **Table 3**. Mixed IFIs were identified in 9 patients: cerebral or disseminated cryptococcosis with pulmonary pneumocystosis, 6; disseminated histoplasmosis with pulmonary pneumocystosis, 1; pulmonary pneumocystosis with disseminated aspergillosis, 1; and pulmonary pneumocystosis with renal aspergillosis, 1.

IFIs had been suspected or confirmed antemortem in 46.1% of all of the cases, but there were fungus-related differences in the discrepancy rate **Figure 1**. Cryptococcosis was diagnosed during life in nearly all cases (59/62 [95%]) and pneumocystosis in 50.4%; the lowest rates of diagnosis during life related to histoplasmosis (1/4 [25%]), aspergillosis (10/83 [12%]), and candidiasis (3/15 [20%]). The overall discrepancy rate between the clinical and postmortem diagnoses did not significantly change over time **Table 4**.

In 103 cases (34.7%), IFIs were judged to be the primary (58 cases) or a contributory cause of death (45 cases); the global impact of IFIs on mortality was 6.3%. Of the fatal cases, 38 (36.9%) were characterized by missed antemortem diagnoses, 17 (45%) of which met the Goldman criteria for class I errors **Table 5**.

## Discussion

To our knowledge, this is the largest single-institution study of autopsy-proven IFIs in patients with AIDS during a period covering the years preceding and following the widespread use of PCP prophylaxis and HAART. The overall prevalence of IFIs at autopsy was 18.2%, with PCP, aspergillosis, and cryptococcosis the most frequent.

The most compelling finding of our study is that the postmortem prevalence of IFIs decreased from 25.0% in 1984-1988 to 15% in 1998-2002, in parallel with the evolution of antiretroviral therapies. This differs from the observations of Masliah et al,[12] of the University of California, who found a steady decline in the autopsy frequency of systemic opportunistic infections during a 15-year period (1982-1998) but no change in the frequency of fungal infections. However, our observation period was longer (and, therefore, reflects the greater impact of more potent antiretroviral therapies), and the number of autopsies was higher.

Furthermore, we were able to define the specific time trends of individual mycoses. Like other studies,[12-14] we found a significant decrease in the postmortem prevalence of PCP, which is consistent with the significant reduction in the incidence and mortality of this infection since the introduction of PCP prophylaxis and antiretroviral therapy.[7] However, PCP continues to be one of the most frequent opportunistic infections in patients with HIV infection, particularly patients who are unaware of their serostatus,[15] and a low index of suspicion and delayed diagnosis in patients with occult HIV infection may account for the considerable discrepancy between the clinical and postmortem findings of PCP in the last years of our study. *P jirovecii* involved the lung in nearly all cases, but 11.5% of patients had disseminated disease, and the spleen was the most frequently involved organ after the lung. This rate of disseminated PCP is in line with the 10% reported by Afessa et al[14] in the United States and the 13% reported by Cury et al[16] in Brazil.

Intriguingly, autopsy-diagnosed cryptococcosis had completely disappeared by the last period of our study, a finding




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**Table 2**
**Distribution of Organs Affected by AIDS-Related Invasive Fungal Infections***

| Microorganism | Lungs | CNS | Kidneys | Lymph Nodes | Liver | Spleen | Heart | Adrenal Glands |
|---|---|---|---|---|---|---|---|---|
| *Pneumocystis jirovecii* (n = 131) | | | | | | | | |
| Total | 130 (99.2) | 0 (0) | 3 (2.3) | 3 (2.3) | 3 (2.3) | 9 (6.9) | 2 (1.5) | 2 (1.5) |
| Exclusive | 116 (88.5) | — | — | — | — | — | — | — |
| *Cryptococcus neoformans* (n = 62) | | | | | | | | |
| Total | 25 (40) | 52 (84) | 19 (31) | 21 (34) | 18 (29) | 18 (29) | 8 (13) | 8 (13) |
| Exclusive | — | 21 (34) | — | — | — | 1 (1.6) | — | — |
| *Aspergillus* spp (n = 83) | | | | | | | | |
| Total | 81 (98) | 12 (14) | 12 (14) | 1 (1) | 2 (2) | 3 (4) | 10 (12) | 2 (2) |
| Exclusive | 61 (73) | 2 (2) | 1 (1) | — | — | — | — | — |
| *Candida* spp (n = 15) | | | | | | | | |
| Total | 11 (73) | 1 (7) | 4 (27) | 0 (0) | 3 (20) | 1 (7) | 3 (20) | 1 (7) |
| Exclusive | 6 (40) | — | — | — | — | — | — | — |
| *Histoplasma capsulatum* (n = 4) | | | | | | | | |
| Total | 4 (100) | 1 (25) | 1 (25) | 3 (75) | 3 (75) | 3 (75) | 1 (25) | 1 (25) |
| Exclusive | — | — | — | — | — | — | — | — |
| Zygomycetes (n = 2) | | | | | | | | |
| Total | 1 (50) | 1 (50) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| Exclusive | — | — | — | — | — | — | — | — |
| Total (n = 297) | 252 (84.8) | 67 (22.6) | 39 (13.1) | 28 (9.4) | 29 (9.8) | 34 (11.4) | 24 (8.1) | 14 (4.7) |

CNS, central nervous system.
* Data are given as number (percentage).

**Table 3**
**Concomitant Opportunistic Infections or Neoplasms Observed at Autopsy in Patients With Invasive Fungal Infections***

| | CMV | HIV Encephalopathy | Non-Hodgkin Lymphoma | Toxoplasmosis | *Mycobacterium avium* Complex | Kaposi Sarcoma |
|---|---|---|---|---|---|---|
| *Pneumocystis jirovecii* (n = 106) | 44 (41.5) | 39 (36.8) | 7 (6.6) | 13 (12.3) | 15 (14.2) | 7 (6.6) |
| *Cryptococcus neoformans* (n = 40) | 14 (35) | 7 (18) | 7 (18) | 5 (13) | 3 (8) | 5 (13) |
| *Aspergillus* spp (n = 73) | 34 (47) | 20 (27) | 12 (16) | 9 (12) | 7 (10) | 6 (8) |
| *Candida* spp (n = 15) | 6 (40) | 0 (0) | 5 (33) | 3 (20) | 0 (0) | 1 (7) |
| *Histoplasma capsulatum* (n = 3) | 0 (0) | 1 (33) | 0 (0) | 1 (33) | 0 (0) | 0 (0) |
| Zygomycetes (n = 2) | 0 (0) | 0 (0) | 2 (100) | 0 (0) | 0 (0) | 0 (0) |
| Total (n = 239) | 98 (41.0) | 67 (28.0) | 33 (13.8) | 31 (13.0) | 25 (10.5) | 19 (7.9) |

CMV, cytomegalovirus; PML, progressive multifocal leukoencephalopathy.
* Data are given as number (percentage).

that is consistent with the reported decreasing incidence of cryptococcosis since the introduction of HAART[17] and the marked and steady decline in mortality due to this infection between 1980 and 1997 in the United States.[1] The clinical presentation of cryptococcosis in patients with AIDS is identified by the presence of meningoencephalitis in more than 90% of cases but, in line with previous studies,[18,19] we found disseminated disease in nearly 65% of our cases. The rate of discrepancies between the antemortem and postmortem diagnoses of cryptococcosis was one of the lowest (<5%), largely because it can be microbiologically diagnosed by means of a rapid and highly sensitive antigen assay.[20]

It is interesting to note that invasive aspergillosis was the second most frequently identified mycosis and that its prevalence did not significantly change over time. Although *Aspergillus* hyphae cannot be morphologically distinguished from those of other pathogenic molds (eg, *Fusarium* spp, *Penicillium* spp, and *Pseudallescheria boydii*), given the rarity of these other fungi in the setting of AIDS and the availability of a specific monoclonal antibody against *Aspergillus*, we believe that the overwhelming majority of these cases represent true *Aspergillus* disease. Pulmonary disease was found in nearly all cases of invasive aspergillosis and dissemination in 23%; the brain and kidney were the most frequently involved organs after the lung. The rate of discordance between the antemortem and postmortem diagnoses of aspergillosis was the highest and may be explained by the fact that it is generally considered a rare opportunistic infection in patients with AIDS[21] and may, therefore, not be considered in the differential diagnosis of pulmonary diseases. Furthermore, the well-known diagnostic challenge of aspergillosis in other settings (eg, hematologic malignancies and bone marrow transplantation) has not been improved in HIV-infected patients by the techniques now routinely used




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| Thyroid | Skin | Pancreas | Other Organs | Disseminated |
|---|---|---|---|---|
| | | | | 15 (11.5) |
| 1 (0.8) | 0 (0) | 0 (0) | 3 (2.3) | |
| — | — | — | — | |
| | | | | 39 (63) |
| 2 (3) | 3 (5) | 2 (3) | 4 (6) | |
| — | — | — | — | |
| | | | | 19 (22.9) |
| 3 (4) | 0 (0) | 0 (0) | 3 (4) | |
| — | — | — | — | |
| | | | | 6 (40) |
| 0 (0) | 0 (0) | 0 (0) | 3 (20) | |
| — | — | — | 3 (20) | |
| | | | | 4 (100) |
| 1 (25) | 2 (50) | 0 (0) | 4 (100) | |
| — | — | — | — | |
| | | | | 0 (0) |
| 0 (0) | 0 (0) | 0 (0) | 0 (0) | |
| — | — | — | — | |
| 7 (2.4) | 5 (1.7) | 2 (0.7) | 17 (5.7) | 83 (27.9) |

| *Pneumocystis jirovecii* | PML | *Mycobacterium tuberculosis* | Bacterial Sepsis |
|---|---|---|---|
| 0 (0) | 1 (0.9) | 3 (2.8) | 3 (2.8) |
| 6 (15) | 2 (5) | 2 (5) | 1 (3) |
| 2 (3) | 5 (7) | 3 (4) | 1 (1) |
| 0 (0) | 1 (7) | 0 (0) | 1 (7) |
| 1 (33) | 0 (0) | 0 (0) | 0 (0) |
| 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| 9 (3.8) | 9 (3.8) | 8 (3.3) | 6 (2.5) |

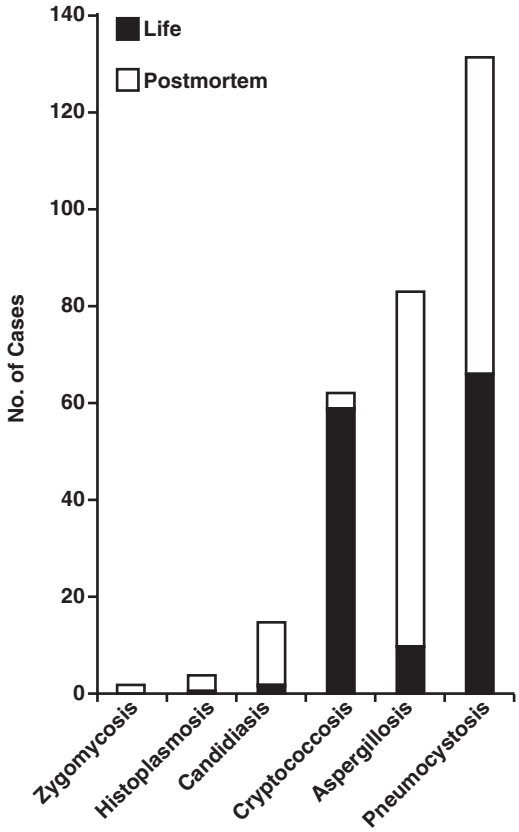


**Figure 1** Frequency of diagnosis of invasive fungal infections during life and at postmortem examination.

for patients with hematologic diseases (*Aspergillus* galactomannan and computed tomography scan).[22,23]

The frequency of invasive candidiasis increased during the study period. Some earlier studies reported that disseminated candidiasis was common and significant in HIV+ patients,[24-26] but others found no cases or only superficial infections in the tracheal or gastric mucosa.[27] It has been said that candidemia is a rare complication of AIDS, typically associated with advanced HIV infection and the use of indwelling venous catheters.[28] We found a prevalence of 5.1% of invasive candidiasis, similar to that observed between 1983 and 1996 in a French study.[29] It can be hypothesized that cases of invasive aspergillosis and candidemia in the last periods of our study were due to the

**Table 4**
**Invasive Fungal Infections Diagnosed During Life in the Different Study Periods***

| | 1984-1988 | 1989-1993 | 1994-1997 | 1998-2002 | *P* |
|---|---|---|---|---|---|
| *Pneumocystis jirovecii* | 11/25 (44) | 37/72 (51) | 17/30 (57) | 1/4 (25) | .812 |
| *Cryptococcus neoformans* | 16/16 (100) | 33/34 (97) | 10/12 (83) | 0/0 (0) | .080 |
| *Aspergillus* spp | 1/10 (10) | 5/44 (11) | 3/23 (13) | 1/6 (17) | .999 |
| *Candida* spp | 0/3 (0) | 2/6 (33) | 0/3 (0) | 1/3 (33) | .763 |
| *Histoplasma capsulatum* | 0/0 (0) | 0/2 (0) | 1/1 (100) | 0/1 (0) | ND |
| Zygomycetes | 0/0 (0) | 0/0 (0) | 0/1 (0) | 0/1 (0) | ND |
| Total | 28/54 (52) | 77/158 (48.7) | 31/70 (44) | 3/15 (20) | .320 |

ND, not done.
* Data are given as number/total (percentage).




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**Table 5**
**Invasive Fungal Infections as a Major Cause of Death and the Goldman Criteria***

| | Primary Cause of Death | Contributory Cause of Death | Missed Diagnosis During Life | Discrepancy Class | | | | Class I Discrepancy (%) |
|---|---|---|---|---|---|---|---|---|
| | | | | I | II | III | IV | |
| *Pneumocystis jirovecii* | 29 | 12 | 14 (34) | 9 | 5 | 0 | 0 | 64 |
| *Cryptococcus neoformans* | 17 | 19 | 3 (8) | 3 | 0 | 0 | 0 | 100 |
| *Aspergillus* spp | 9 | 9 | 16 (89) | 1 | 7 | 8 | 0 | 6 |
| *Candida* spp | 2 | 1 | 1 (33) | 1 | 0 | 0 | 0 | |
| *Histoplasma capsulatum* | 1 | 3 | 3 (75) | 3 | 0 | 0 | 0 | 100 |
| Zygomycetes | 0 | 1 | 1 (100) | 0 | 1 | 0 | 0 | 0 |
| Total | 58/297 (19.5) | 45/297 (15.2) | 38/103 (36.9) | 17 | 13 | 8 | 0 | 45 |

* Data are given as number, number (percentage), or number/total (percentage) of cases unless otherwise indicated. The Goldman criteria are as follows: I, major missed diagnosis that would have led to a change in management with possible increased survival or cure; II, major missed diagnosis that would not have impacted survival because no treatment was available, treatment was given even though the diagnosis was unknown, or the patient refused further treatment; III, missed minor diagnosis related to the terminal disease process but not directly related to the cause of death; IV, missed minor diagnosis that did not contribute to the cause of death but ultimately may have been significant had the patient survived the major illness.

increasing number of lymphoproliferative diseases observed among patients with AIDS.

AIDS-associated histoplasmosis is rarely observed in Europe. Most of the reported cases are due to imported disease, but nearly 10% have been autochthonous, and most of these have occurred in Italy.[30] The main cause of the high rate of discordance between clinical and autopsy diagnoses of histoplasmosis, as well as the 75% rate of Goldman class I errors, was probably the low index of suspicion in a country outside endemic areas.

It is interesting to note that the last 2 periods of the study saw the emergence of zygomycosis, a rare infection in previous years. Zygomycosis has rarely been reported among HIV-infected patients, and most of the patients had other predisposing conditions such as diabetes or malignancies.[31] As the use of the latest antiretroviral regimens may predispose patients with HIV infection to diabetes[32] and an increasing incidence of malignancies is being reported,[33] zygomycosis may become more common in the future.

The majority of the patients with postmortem diagnoses of IFIs showed profound CD4 cell depletion, and 80.5% had other opportunistic diseases, the most frequent of which was CMV infection. There is evidence that CMV may adversely affect innate and adaptive immune responses[34] and accelerate the progression of HIV infection.[35] Moreover, it has been observed that prolonged ganciclovir therapy is significantly associated with a greater risk of invasive fungal infection in bone marrow transplant recipients.[36] It is therefore likely that combined CMV- and ganciclovir-mediated immunosuppression and myelosuppression may account for the frequent association between CMV and IFIs in our cases.

One third of the IFIs in our study were significantly related to the patients' deaths, and fewer than half were diagnosed during life. The highest discrepancies between premortem and postmortem diagnoses concerned aspergillosis, histoplasmosis, and pneumocystosis, and the fact these rates did not change significantly over time highlights the continuing difficulties in clinically diagnosing some IFIs despite the use of advanced diagnostic technologies.[37]

One possible limitation of our study is the significant reduction in autopsy rates toward the end of the observation period, an alarming trend that has also been reported in other studies[38]: the autopsy rate among patients with AIDS in the United States decreased from 57% in 1983 to 10% in 1991.[39] We cannot exclude the possibility that these lower autopsy rates may have affected our findings, although the 33% autopsy rate in the last period of our study is still above the 30% minimum recommended for statistical analyses.[40]

Our findings show that the epidemiology of IFIs in patients with AIDS is evolving and is not completely mirrored by clinical diagnoses. This study confirms the valuable role of autopsies of patients with AIDS, even in the era of highly effective therapies and advanced technologies.

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