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Postmortem findings and opportunistic infections in HIV-positive patients from a public hospital in Peru

Dominique Eza[a,b,*], **Gustavo Cerrillo**[a], **David A.J. Moore**[b,c], **Cecilia Castro**[a], **Eduardo Ticona**[d], **Domingo Morales**[a], **Jose Cabanillas**[a], **Fernando Barrantes**[a], **Alejandro Alfaro**[a], **Alejandro Benavides**[a], **Arturo Rafael**[a], **Gilberto Valladares**[a], **Fernando Arevalo**[a], **Carlton A. Evans**[b,c], and **Robert H. Gilman**[b]

[a]Departamento de Laboratorio y Anatomía Patológica, Hospital Nacional Dos de Mayo, Parque Historia de la Medicina Peruana s/n, Altura de Cuadra 13 Avenida Grau, Lima 1, Perú

[b]Department of Biomedical Research, Asociación Benéfica Proyectos de Informática, Salud, Medicina y Agricultura (PRISMA), Calle Carlos Gonzales 251, Urbanización Maranga, San Miguel, Lima 32, Perú

[c]Wellcome Trust Centre for Clinical Tropical Medicine, Imperial College London (Hammersmith Campus), Du Cane Road, London W12 0NN, UK

[d]Departamento de Enfermedades Infecciosas, Hospital Nacional Dos de Mayo, Parque Historia de la Medicina Peruana s/n, Altura de Cuadra 13 Avenida Grau, Lima 1, Perú

Abstract

There is a paucity of HIV autopsy data from South America and none that document the postmortem findings in patients with HIV/AIDS in Peru. The purpose of this autopsy study was to determine the spectrum of opportunistic infections and the causes of mortality in HIV-positive patients at a public hospital in Lima. Clinico-epidemiological information regarding HIV infection in Peru is also reviewed. Sixteen HIV-related hospital postmortems, performed between 1999 and 2004, were included in this retrospective analysis. The primary cause of death was established in 12 patients: one died of neoplasia and 11 of infectious diseases, including 3 from pulmonary infection, 7 from disseminated infection, and 2 from central nervous system infection (one case had dual pathology). Opportunistic infections were identified in 14 cases, comprising cytomegalovirus, histoplasmosis, cryptococcosis, toxoplasmosis, *Pneumocystis* pneumonia, aspergillosis, tuberculosis, varicella zoster virus, and cryptosporidiosis. Fourteen patients had at least one AIDS-related disease that had been neither clinically suspected nor diagnosed premortem. Moreover, 82% of the diagnoses considered to be of important clinical significance had not been suspected antemortem. The spectrum and frequency of certain opportunistic infections differed from other South American autopsy studies, highlighting the importance of performing HIV/AIDS postmortems in resource-limited countries where locally specific disease patterns may be observed.

*Corresponding author. Department of Biomedical Research, Asociación Benéfica Proyectos de Informática, Salud, Medicina y Agricultura (PRISMA), Calle Carlos Gonzales 251, Urbanización Maranga, San Miguel, Lima 32, Perú. Tel.: +51 1 464 0221; fax: +51 1 464 0781. dominiqueeeza@yahoo.co.uk (D. Eza)..

Conflicts of interest statement

The authors have no conflicts of interest concerning the work reported in this paper.

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Keywords

Autopsy; Opportunistic infection; HIV; Pathology; Peru

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Introduction

The incidence of HIV infection is increasing globally, and almost three million people died of AIDS worldwide in 2003 [40]. UNAIDS and WHO estimated that 82,000 adults and children were living with HIV/AIDS in Peru by the end of 2003 [41]. Moreover, in 2003, WHO estimated that 9,700 adults in Peru were in need of antiretroviral therapy (ART), but as of June 2004, only 1,900 adults with advanced HIV infection were receiving such treatment [41].

The adult HIV prevalence in Peru (population c.28 million) is 0.5% overall [41], and the HIV epidemic is concentrated in specific sectors of society. The prevalence of infection is 11–18% among men who have sex with men [2,37] and 2% in female sex workers [41], although this figure rises to 10% in unlicensed female sex workers [24]. The principal mode of HIV transmission in Peru is among men who have sex with men and heterosexuals [25], accounting for 42% and 40%, respectively [41], whereas only 1% of AIDS cases between 1983 and 2005 were attributed to intravenous drug use (IVDU) [31].

Fifty percent of Peruvians live in poverty, and 20% in extreme poverty [23]. However, the general population does not have free access to medication and is expected to pay for the majority, if not all, of the costs incurred throughout their stay in public hospitals, including those for diagnostic tests that are consequently inaccessible to many [8,46]. The people most affected by HIV/AIDS in Peru are from the poorest strata in society [36], where there is little community awareness of HIV [11] and limited access to ART [3,36]. HIV-positive patients from such communities often present to hospital with advanced disease associated with a high mortality [11]. It is hoped that the 2-year program established in December 2003 by the Global Fund in collaboration with the Peruvian Government, which aims to increase free access to ART (hitherto unavailable in the public healthcare sector), will help to ameliorate this situation [11].

The causes of morbidity and mortality in HIV-infected patients vary according to geographical location [12,21,29,34], patient risk factors for HIV infection[10,18], and the socioeconomic circumstances of the country in question [12,34]. Cross-sectional insights into the regional prevalence and spectrum of opportunistic infections in HIV-positive patients are essential for informing patient management strategies [21] and for determining appropriate preventative measures in resource-poor countries [15,19]. Autopsy studies have an important role to play in this process, as it is widely recognized that discrepancies between antemortem and postmortem diagnoses in HIV/AIDS patients are frequent [1,4,5]. Several large HIV autopsy studies have been carried out in many parts of the world [7,13,20,21,33], but there remains a paucity of data from South America. Moreover, the majority of the South American studies reported have been carried out in Brazil, and many of the studies in the literature either focus on specific sub-groups, such as patients with HIV and tuberculosis co-infection [16], or specific-organ pathology, e.g. adrenals [34], lungs [32]. To our knowledge, there are no publications that define the pathology and postmortem findings in the HIV/AIDS patient population in Peru, and neither is it possible to glean relevant data from reports published from other sources. For example, the widespread availability of highly active antiretroviral therapy (HAART) in Brazil (free access to HAART was introduced in 1996) has altered the relative frequency of AIDS-related diseases [29], with consequent changes in the cause of death, as has been reported elsewhere

[28,35,39]. Trends in the mode of HIV-transmission in Brazil have varied considerably over the years, with an increase in heterosexual transmission and a relative decline in the proportion of cases due to IVDU since the early 1990s. In 2002, the approximate ratio of incidence rates for AIDS cases, in people over the age of 13, was 1:2:3:10, respectively, for each of the following categories: transfusion/hemophiliacs; IVDU; homosexuals/bisexuals; heterosexuals [17].

The main purpose of this postmortem study was to determine the spectrum of opportunistic infections and the causes of mortality in HIV-positive patients in one of the main inner city, public hospitals in Lima, Peru. A secondary objective was to determine what proportion of the postmortem diagnoses had been clinically suspected or diagnosed antemortem.

Materials and methods

This retrospective study was conducted at Hospital Nacional Dos de Mayo in Lima.

Study site

Lima is the capital city of Peru, and Callao is the adjacent main port; together they have a population of just over 8 million [7], and currently account for approximately 75% of all Peruvian HIV/AIDS cases [27]. The public health sector in Peru is responsible for providing healthcare to more than 70% of the population, who have no access to healthcare from the social security system (EsSalud), nor the resources for private healthcare [11].

Hospital Nacional Dos de Mayo is a large university teaching hospital that serves the general population of lower socioeconomic status who live in nearby districts and in the Lima metropolitan area. It is a national referral center for HIV-positive patients and is one of 10 public hospitals that provide care for most HIV-infected individuals living in Lima and Callao, although it specifically provides care to the largest number of these patients [7]. AIDS is the most frequent, clinically determined, primary cause of death in Hospital Nacional Dos de Mayo [26,38]. Historically, some of the city's hospitals served either men or women; hence, the patient population at the hospital remains gender-biased, serving predominantly male patients [38,46].

Study population and design

Departmental records of all the hospital autopsies carried out between June 1999 and July 2004 were reviewed ($n = 281$). It was not possible to include autopsies performed prior to June 1999, because archived histological slides relating to these necropsies were no longer available. All patients with a prior clinical diagnosis of HIV infection (positive enzyme-linked immunosorbent assay, with confirmation by Western blot assay), in addition to those who were clinically suspected of being HIV-positive and who fulfilled the Centers for Disease Control and Prevention (CDC) surveillance criteria for the case definition for AIDS [9,30], were included ($n = 15$ and 1, respectively). Two patients who were clinically suspected of being HIV-positive, but who did not fulfill the previously mentioned CDC criteria, were excluded from the study. Prior informed consent for a full postmortem examination had been obtained from an immediate member of the deceased's family, as is legally required in Peru, following the protocol in place in the hospital.

Each case was reviewed in its entirety. Data on age, gender, duration of hospitalization, and the estimated time of HIV diagnosis, as well as on clinical manifestations and laboratory tests, were extracted from the autopsy reports which included a clinical summary. Very few families have the means to pay for certain diagnostic tests; hence, we did not have access to more complete patient information such as CD4/CD8 counts or a quantification of viral load. The macroscopical description of the body and organs at autopsy was reviewed, along

with re-examination of all the slides and tissue blocks available. When tissue sampling for histological examination was found to be incomplete, additional residual archived tissue was processed, cut, and stained. Histopathological examination of organs and tissues included staining with routine hematoxylin and eosin, with the use of “special stains” whenever a lesion was seen, comprising Ziehl–Neelsen (for the identification of Mycobacteria, Cryptosporidium, Isospora), periodic acid-Schiff and Grocott silver stain (for the identification of fungi, *Pneumocystis jiroveci* [previous nomenclature: *Pneumocystis carinii*] and Nocardia). In this geographical setting, the presence of acid fast bacilli on a Ziehl–Neelsen stain in the right histological background is most likely to represent *Mycobacterium tuberculosis*. Immunohistochemistry with antibodies for CD20 (B-cell marker), CD45Ro (marker for T-cell subsets) and CD45 (leukocyte common antigen) was also performed where indicated.

A full postmortem examination had been carried out in the majority of cases ($n = 12$); however, the central nervous system (CNS) was not examined in four cases.

Results

The available data shows that 18% (112/624) of deaths and 25% (140/562) of deaths occurring in Hospital Nacional Dos de Mayo, in 1999 and 2000, respectively, were clinically believed to be due to AIDS [38]. However, only 1.4% (2) of AIDS-related deaths in 2000 resulted in an autopsy, compared to 9% (51) of hospital deaths in general.

Between June 1999 and July 2004, a total of 281 hospital postmortems were performed, 16 of which (5.7%) were conducted on HIV-infected patients, all of whom satisfied the CDC surveillance criteria for the definition of AIDS [9,30]. Ten patients (62.5%) were men with a median age of 33.5 years, whereas female patients had a median age of 31.5 years (overall age range 19–62 years).

The duration of hospitalization prior to death ranged from 1 to 81 days (median 18 days). Three patients were newly diagnosed as HIV-positive while hospitalized immediately prior to death; the date of the HIV diagnosis in three patients was not documented, and that for the 10 remaining patients ranged from 5 months to 8 years prior to their final admission to hospital. Thus, at least seven (44%) of the cases had been diagnosed as HIV-positive within 1 year of dying from AIDS.

It was possible to establish the primary cause of death in 12 of the 16 cases (see Table 1). One patient died of non-Hodgkin’s lymphoma, and 11 patients died from opportunistic infections. Of those 11, 3 died from pulmonary infection, 7 from disseminated infectious diseases, and 2 from infection of the CNS. One of the latter patients had dual pathology contributing to death (disseminated and CNS infection). The immediate cause of death in the remaining four patients could not be determined definitively due to incomplete patient data and limited clinical and pathological resources. However, they still satisfied the CDC criteria for the definition of AIDS due to the premortem diagnoses of a Category C condition. It is noteworthy that three of these patients had both a recent history of tuberculosis and histological features suggestive of an on-going or recurrent infection. It is possible, therefore, that the cause of death in these patients was tuberculosis.

Of the 16 autopsies performed, one patient showed no evidence of either an infectious or a neoplastic disease. The cause of death in this individual was uncertain (although the clinical history and postmortem findings were suggestive of HIV wasting syndrome), and death occurred within 48 h of admission to hospital. Two cases revealed evidence of neoplasia: one had disseminated non-Hodgkin’s lymphoma with no evidence of co-infection, while the

second revealed pulmonary Kaposi's sarcoma with coexisting opportunistic infection (pulmonary cryptococcoma).

Opportunistic infections were identified in 14 cases (Table 2), and two or more coexisting infections were observed in 7 of these patients. Cytomegalovirus (CMV) was the most common opportunistic agent diagnosed on autopsy and was identified in seven patients, although none had been clinically suspected antemortem. Organs in which multiple co-pathologies were noted included the lungs (4 cases) and the CNS (1 case).

The etiology of the CNS infections included toxoplasmosis (2), disseminated cryptococcosis (1), and disseminated histoplasmosis (1). An additional case showed necrotizing encephalitis of unknown etiology, which could represent partially treated tuberculous meningoencephalitis and cerebral toxoplasmosis [5] in view of the patient's recent hospital admission and diagnosis of these two conditions.

Amongst the 16 patients, 88% (14) had at least one AIDS-related disease that had not been clinically suspected premortem. Only 5 (20%) of the 25 AIDS-related diagnoses that were made at postmortem examination were suspected clinically (see Table 3). Furthermore, 68% (17/25) of the conditions diagnosed at postmortem were deemed of important clinical significance by constituting either the primary or the contributory cause of death in 13 individuals, and 82% of these clinically important diagnoses had not been suspected antemortem. The exact etiological cause of death was correctly suspected by the clinicians in only 3 of the 12 cases (25%), where a primary cause could be accurately determined.

Discussion

The key findings were that the range and frequency of infectious diseases encountered at postmortem differed from studies performed elsewhere in South America (principally Brazil), and that the majority of the AIDS-related diseases diagnosed on autopsy had not been clinically diagnosed or suspected antemortem. These observations highlight the importance of performing postmortems on people dying with HIV in resource-limited countries where locally specific disease patterns may be observed.

Brazilian postmortem studies [12,32] reported incidences of *Pneumocystis* pneumonia (PCP) that were similar to that seen in our study (15.2% and 19.1% versus 12.5%, respectively), but they appeared to report a somewhat lower incidence of histoplasmosis (5.4% and 4.8% versus 19%, respectively) and cryptococcosis (4.3% and 9.5% versus 19%, respectively). Aspergillosis was not identified in several Brazilian necropsy studies [5,12,29,32] in contrast to our study, where invasive pulmonary aspergillosis was identified in 2/16 cases (12.5%). This apparent rarity of aspergillosis among HIV patients in Brazil may be the result of a generally recognized decline in frequency following the introduction of HAART [35].

Cytomegalovirus (CMV) was identified in seven (44%) individuals included in our study, although CMV had not been suspected clinically. This is probably due to the lack of specific symptoms and the fact that diagnosis depends predominantly on histopathological examination [5] or tests that are unavailable in most resource-poor settings. Our findings are consistent with other autopsy studies [5,13].

There was a relatively low rate of tuberculosis in our postmortem review, although hospital statistics revealed that 40% of patients admitted with known HIV infection to Hospital Nacional Dos de Mayo were suffering from tuberculosis [11], and 43% of these co-infected patients are estimated to have multi-drug resistant tuberculosis [7]. The reasons for this are likely to be multi-factorial; one probable factor is that, due to the lack of resources for

confirmatory microbiological culture, the postmortem diagnosis of tuberculosis was established on histology alone. Three of the four cases, in whom the primary cause of death was uncertain, had a recent history of tuberculosis and histological features, suggesting on-going or recurrent infection. Anti-tuberculous treatment at the time of death may explain the absence of acid-fast bacilli on microscopy and, hence, the lack of an unequivocal diagnosis of mycobacteriosis; it may, therefore, be possible to attribute the death of these three patients to *Mycobacterium tuberculosis*.

An additional factor contributing to the low diagnostic rate of tuberculosis may be selection bias. Despite the relatively high HIV-related mortality rate at Hospital Nacional Dos de Mayo (an average of 15 deaths per month in 2004 [26]), autopsies on HIV-infected patients are requested only in a small minority of cases, and usually when clinicians are uncertain of the cause of death. Consequently, for HIV-positive patients strongly suspected of having coexisting tuberculosis, clinicians are likely to consider the cause of mortality obvious and are less inclined to request permission to perform a postmortem examination from the deceased patient's relatives. The low autopsy rate [46] in the hospital (9% of all hospital deaths versus 1.4% of AIDS-related deaths in 2000) is consistent with the well-recognized global decline in autopsy rates for both HIV-infected and uninfected subjects [22,44], the reasons for which are complex [4,43-45].

Our study showed that the majority of the HIV-infected patients (14 cases, 87.5%) had at least one AIDS-related disease that had not been clinically suspected or diagnosed antemortem. Sixty-eight percent of these postmortem diagnoses were deemed of important clinical significance, and 82% of these clinically important diagnoses had not been suspected premortem. Furthermore, the immediate cause of death was correctly suspected by clinicians in only 3 of the 12 patients, where the primary cause of mortality could be ascertained on postmortem (comprising PCP; miliary tuberculosis; non-Hodgkin's lymphoma). These results are comparable with other studies in both HIV-negative [6,14] and HIV-positive populations [1,4,5,29,42], where a considerable discrepancy exists between clinical and postmortem diagnoses.

We believe that the data collated here provides unique information on the causes of morbidity and mortality due to HIV in Peru, and illustrates the importance of the postmortem process in supporting clinical management and diagnosis. Currently, the prohibitive cost of certain diagnostic tests in Peru [46], the absence of characteristic clinical signs or symptoms, and the short duration of hospitalization prior to death are resulting in the failure to diagnose a significant proportion of AIDS-related diseases antemortem. The range of disease and infection that is reported is biased to reflect those easily and accurately diagnosed by physical examination or by inexpensive laboratory techniques (e.g., sputum microscopy). Infections that require relatively expensive diagnostic methods (e.g., PCP and CMV disease) are, comparatively, commonly under-reported [19].

Our study was necessarily limited. The lack of supplementary immunohistochemical stains may have resulted in some opportunistic infections (e.g., CMV or toxoplasmosis) being under-estimated. Neither is autopsy sensitive for the diagnosis of cryptosporidia or microsporidia [21,33] due to postmortem autolysis of the gastrointestinal tract. However, despite the small number of patients included in our analysis, we believe the data collated here provide some important background information that can form the basis of future, more comprehensive, systematic studies. Furthermore, we have shown that autopsies can be a valuable means of determining the range and relative frequency of infectious diseases [21], and that this can potentially have an immediate impact on patient care by suggesting appropriate interventions based on the results [15,19,21].

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Table 1

Demographic details, time of HIV diagnosis, length of hospitalization, and primary or contributory cause of death

Age and gender	Time of HIV diagnosis relative to hospital admission	Length of hospital stay (days)	Primary (Ia, b, c) and contributory (II) causes of death
26 Male	5 months (CD4: 350 at 3 months)	20	Ia. Disseminated histoplasmosis Ib. HIV/AIDS
44 Male	During admission to hospital	34	Ia. Disseminated histoplasmosis Ib. HIV/AIDS
24 Male	21 months	2	Ia. Uncertain (possible HIV wasting syndrome) Ib. HIV/AIDS
30 Female	Prior diagnosis, uncertain when	1	Ia. PCP Ib. HIV/AIDS
30 Male	3 years previously	27	Ia. Disseminated cryptococcosis and cerebral toxoplasmosis Ib. HIV/AIDS II. PCP
19 Female	Within 1 year	3	Ia. Miliary tuberculosis Ib. HIV/AIDS
62 Male	During admission to hospital	48	Ia. Disseminated histoplasmosis Ib. HIV/AIDS
33 Male	6 months (CD4<30 at time of HIV diagnosis)	81	Ia. Uncertain (possible tuberculosis) Ib. HIV/AIDS II (contributory cause at least). Pulmonary Kaposi's sarcoma
39 Male	Prior diagnosis, uncertain when	2	Ia. Multi-organ failure Ib. Miliary tuberculosis and cardiac pathology (of uncertain etiology) Ic. HIV/AIDS
33 Male	Prior diagnosis, uncertain when	7	Ia. Cerebral toxoplasmosis Ib. HIV/AIDS
58 Male	5 years previously	2	Ia. Disseminated cryptococcosis Ib. HIV/AIDS II. Cryptosporidiosis causing malnutrition
33 Female	8 years previously	8	Ia. Invasive pulmonary aspergillosis Ib. HIV/AIDS II. CMV pneumonitis
35 Male	Diagnosed on admission	31	Ia. Disseminated non-Hodgkin's lymphoma Ib. HIV/AIDS
43 Female	7 months previously	16	I. Uncertain (possible tuberculosis) Ib. HIV/AIDS II (contributory cause at least)

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Age and gender	Time of HIV diagnosis relative to hospital admission	Length of hospital stay (days)	Primary (Ia, b, c) and contributory (II) causes of death
			Necrotizing meningo-encephalitis of uncertain etiology
27 Female	8 years previously	80 approx.	Ia. Invasive pulmonary aspergillosis Ib. HIV/AIDS
49 Female	2.5 years previously	21	I. Uncertain (possible tuberculosis) Ib. HIV/AIDS

Ia = primary/immediate cause of death due to (as a consequence of) the disease or condition written in Ib, which, in turn, is due to the disease written in Ic; II = another significant condition contributing to death.

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Table 2

Details of AIDS-related diseases, number of cases involved, and the contribution of each disease to cause of death

Disease	Involved organs (number of cases)	*N* (%) of cases involved	*N* where either (I) primary or (II) contributory cause of death
Cytomegalovirus	Isolated organs 3: intestinal 1; lung 1; adrenal 1; disseminated 4 (adrenal 3, pancreas 1, lungs 2, liver 1, spleen 1, large bowel 1, oesophagus 1)	7 (44)	(I) 0 (II) 1
Histoplasmosis	Disseminated (liver 2, lungs 3, small intestine, large intestines 1, lymph nodes 2, spleen 2, larynx 1, trachea 1, brain 2).	3 (19)	(I) 3 (II) 0
Cryptococcosis	Pulmonary cryptococcoma 1; disseminated 2 (liver 2, spleen 2, kidney 1, lungs 1, meninges 1, lung 1, lymph nodes 1).	3 (19)	(I) 2[a] (II) 0
Pneumocystis (PCP)	Pulmonary 2	2 (12.5)	(I) 1 (II) 1
Aspergillosis	Invasive pulmonary 2	2 (12.5)	(I) 2 (II) 0
Tuberculosis	Disseminated 2 (liver 2, oesophagus 2, lymph nodes 2, lungs 2, cervix 1, ovaries 1, uterus 1, kidney 1, thyroid 1, spleen 1, kidney 1, adrenal 1). Possibly three additional cases[b]	2 (12.5) [or 5[b] (31)]	(I) 2(or 5[b]) (II) 0
Toxoplasmosis	Cerebral 1; disseminated 1 (cerebrum; bladder)	2 (12.5)	(I) 2[a] (II) 0
Varicella zoster virus (shingles)	Skin 1	1 (6)	(I) 0 (II) 0
Cryptosporidiosis	Intestinal 1	1 (6)	(I) 0 (II) 1
Non-Hodgkin's lymphoma	Disseminated 1	1 (6)	(I) 1 (II) 0
Kaposi's sarcoma	Pulmonary 1	1 (6)	(I) 0 (II) 1
Unknown agent		4 (25)	(I) 0 (II) 0

Key: N = number of cases. I = primary cause of death. II = another significant condition contributing to death.

[a]Dual pathology in one patient, i.e. toxoplasmosis and disseminated cryptococcosis.

[b]Three patients had a recent history of tuberculosis for which they were still undergoing treatment at the time of death (see text).

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Table 3

Agreement between antemortem and postmortem diagnoses

Disease	Clinical diagnosis	Postmortem diagnosis			
	Suspected	Confirmed	Previously suspected	Previously unsuspected	Total
Cytomegalovirus	1	0	0	7	7
Toxoplasmosis	2[a]	0	0	2	2
Tuberculosis	10	4[a,b]	1 (or 4[b])	1	2 (or 5[b])
Histoplasmosis	0	0	0	3	3
Cryptococcosis	3	0	1	2	3
Pneumocystis (PCP)	2	0	1	1	2
Aspergillosis	0	0	0	2	2
Varicella zoster virus (shingles)	2	0	1	0	1
Candidiasis	2	2	0	0	0
Cryptosporidiosis	1	2	0	1	1
Isosporiasis/microsporidiosis	1	0	0	0	0
Non-Hodgkin's lymphoma	2	0	1	0	1
Kaposi's sarcoma	0	0	0	1	1
Non-HIV related conditions:					
Cysticercosis/malaria	2	0	0	0	0
Total	28	8	5	20	25

[a]One patient with a recent history of tuberculous meningoencephalitis and cerebral toxoplasmosis, who showed evidence of necrotizing encephalitis histologically, but with no evidence of acid-fast bacilli, *Toxoplasma gondii*, or any other organisms on microscopy. The primary cause of death could not be ascertained in this patient, although the possibility of residual, partially treated infection could not be excluded.

[b]Three patients (including the patient mentioned in the footnote above[a]) had a recent history of tuberculosis for which they were still undergoing treatment at the time of death. These cases showed features on histopathological examination that were suspicious of ongoing tuberculosis; however, no acid-fast bacilli were identified on microscopy to confirm the diagnosis.