# The mortality and pathology of HIV infection in a West African city

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**Background:** HIV disease is epidemic in Africa, but associated mortality, underlying pathology and CD4+ T-lymphocyte counts have not previously been evaluated in a representative study. Such data help to determine the management of HIV-positive people. Both HIV-1 and HIV-2 infections are prevalent in Côte d'Ivoire, and the pathology of HIV-2 infection in Africa is unclear.

**Methods:** Consecutive adult medical admissions to a large city hospital in Côte d'Ivoire were studied in 1991, and a sample of HIV-positive deaths autopsied.

**Results:** Of 5401 patients evaluated, 50% were HIV-positive; 38% of these died, with a median survival of 1 week. At autopsy (n = 294, including 24% of HIV-positive deaths in hospital), tuberculosis (TB), bacteraemia (predominantly Gram-negative rods) and cerebral toxoplasmosis caused 53% of deaths. TB was seen in 54% of cadavers with AIDS-defining pathology and *Pneumocystis* pneumonia in 4%. The median CD4+ T-lymphocyte counts in those who died was $<90 \times 10^6$/l. Compared with HIV-1-positives, patients with HIV-2-positivity had a greater frequency of severe cytomegalovirus infection, HIV encephalitis and cholangitis.

**Conclusions:** In this population, HIV-positive adults present to hospital with advanced disease associated with high mortality. The three major underlying pathologies (TB, toxoplasmosis and bacteraemia) are either preventable or treatable. TB is an underestimated cause of the 'slim' syndrome in Africa. The patterns of pathology in HIV-2-positive patients suggest a more prolonged terminal course compared with HIV-1. There is an urgent need for attention towards the issues of therapy and care for HIV disease in developing countries.

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**[For editorial comment, see pp 1675–1676]**

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## Introduction

AIDS is now the documented leading cause of death among adults in two African cities — Abidjan, Côte d'Ivoire and Kinshasa, Zaïre [1,2]. Ninety per cent of deaths among child-bearing women in Kigali, Rwanda, are attributable to HIV disease [3] and AIDS is the most common cause of in-hospital mortality in Uganda [4]. However, few data are available on the survival and causes of death among hospitalized HIV-positive patients in Africa [5–8].

Clinical studies on selected groups of HIV-positive adult patients in Africa have shown that tuberculosis (TB) and bacteraemia are major opportunistic infections [9–11], that coccidian parasites are frequently associated with diarrhoea and the wasting 'slim' syndrome [4,12–14], and that *Pneumocystis* pneumonia is an uncommon cause of pulmonary symptoms [15–18]. There has been no pathological evaluation of a representative sample of HIV-positive patients in Africa to describe the relative prevalences of opportunistic infections, tumours and other HIV-associated pathologies. Neurologically, whilst cryptococcal meningitis is prevalent among HIV-positive patients in Africa [19–22], the only pathological data on intracranial lesions such as toxoplasmosis and lymphoma are anecdotal [16,23].

Autopsy surveys can provide disease prevalence data. The previous autopsy series of HIV disease in Africa, in Côte d'Ivoire [24], Uganda [16] and Zaïre [25], studied selected patients and, except in Uganda, without removing the brains. Both HIV-1 and HIV-2 infections are prevalent in Côte d'Ivoire [26] and autopsies can readily be performed. The objectives of this study were: (1) to document the outcome of admission of hospitalized HIV-positive adults; (2) to describe the visceral and cerebral pathology in HIV-positive adults who died in hospital or before admission, and to compare this with the pathology of HIV-negative adults; (3) to evaluate the pathology of HIV-2 infection; (4) to correlate CD4+ T-lymphocyte counts with outcome and pathology in a hospitalized HIV-positive African population; and (5) to suggest appropriate interventions based on these results.

## Methods

### Patient population and methods

The study population was adults (aged >14 years) seen at Abidjan's two largest hospitals: A and B (the same hospitals referred to in previous work [1,27]). Three patient groups were studied: (1) those admitted to the medical wards of hospital A (a 1000-bed hospital); this group represents the general medical hospitalized population; (2) those brought in dead to the mortuary of hospital A; (3) those admitted to the neurology ward of hospital B (like A, a referral hospital for the indigent of the city).

The total study duration was 11 months in 1991. For the first 10 months, consecutive adult admissions to all the medical wards of hospital A (infectious diseases, pulmonary medicine, emergency medicine, internal medicine, and dermatology) were questioned and examined for symptoms and signs of HIV infection [28], and had blood taken for HIV-1 and HIV-2-antibody testing. Admissions to the hospital B neurology ward were similarly studied. Blood was also taken for CD4+ T-lymphocyte counts from consecutive HIV-positive patients on the infectious diseases ward of hospital A. Patients were managed in the routine fashion of the hospitals. Outcome — death or discharge — was determined for each patient, with follow-up continuing for 1 month for patients still hospitalized at the end of the screening period.

The autopsy component had three phases. For 4 months, a sample of known HIV-positive and HIV-negative patients dying on hospital A infectious diseases ward was autopsied. Cadavers were selected without reference to pre-mortem diagnosis or appearance; the most recent deaths were preferred in order to minimize autolysis. For 2 months, a sample of deaths on the other medical wards of hospital A was similarly studied (a shorter period since twice as many deaths occurred on infectious disease wards). Finally, a sample of brought-in-dead cadavers was autopsied after immediate on-site HIV testing. Patients who had died on the neurology ward at hospital B with clinically defined central nervous system lesions were selected by the clinicians for autopsy. The only systematic bias in selection was to obtain a high autopsy rate of known HIV-2-positive cadavers. Since consent to autopsy is not required in Abidjan's teaching hospitals, no bias ensued from this factor.

### Serology and CD4+ T-lymphocyte methodology

In admitted patients, antibodies to HIV-1 and HIV-2 were detected by whole virus enzyme-linked immunosorbent assay (ELISA; Genetic Systems, Seattle, Washington, USA); repeatedly reactive specimens were supplementally tested using synthetic peptide based tests ('Pepti-LAV 1-2', Diagnostics Pasteur, Paris, France) as described previously [29]. Serology results were available the same day as blood-taking. For brought-in-dead cadavers, the HIV rapid-tests ('TestPack', Abbott Laboratories, Frankfurt, Germany; or 'Genie-1/2', Genetic Systems) were confirmed as described above [29]. Blood CD4+ T lymphocytes were determined by flow cytometry as described elsewhere [30].

### Pathology

Complete autopsies were performed, including removal of brain (but not spinal cord or eyes) on all cases except four brought-in-dead cadavers in which

the brain was not studied. Cadavers in which subjectively scored for wasting on a three-point scale of none, moderate, and skeletal wasting. All organs were sampled for histopathology, which included haematoxylin & eosin (H&E) stains, Ziehl–Neelsen for mycobacteria, Grocott silver stain for fungi, *Pneumocystis carinii* and *Nocardia*, Wade–Fite for *Nocardia*, and Gram stains for bacteria. In certain cases, immunocytochemistry was used to confirm cytomegalovirus (CMV), *Toxoplasma* and *Nocardia asteroides* infections, and to evaluate the lymphomas.

TB was diagnosed on histopathological appearance: the spectrum includes paucibacillary, giant cell, caseating granulomas and the multibacillary non-reactive pattern [31,32]. Atypical mycobacteriosis consistent with *Mycobacterium avium intracellulare* (MAI) infection was identified by its distinctive histology of clusters or sheets of non-necrotic macrophages filled with bacilli [33]. Autopsy tissue from certain cases was transported in cetylpyridium chloride solution to the Centers for Disease Control and Prevention (CDC), Atlanta, Georgia, for mycobacterial culture and confirmation by high-performance liquid chromatography [34,35]. Post-mortem blood and tissue cultures for pyogenic bacteria were not performed. Bacteraemia was diagnosed pathologically by the presence of two or more foci of pyogenic inflammation in non-contiguous organs with similar bacteria seen on Gram stains.

The severity of the various pathological processes was rated semi-quantitatively according to the amount and severity of disease present. A pathological prime cause of death was established, and other lesions were totalled to provide overall specific pathology prevalences. Due to lack of investigative facilities, pre-mortem clinical diagnoses did not contribute significantly to establishing causes of death, except in those with diabetes, tetanus or cholera where the pathology was uninformative.

The pathologies in HIV-positive cadavers were considered to be HIV-related if: (1) a CDC AIDS-defining pathology was present [36,37]; or (2) the patients had fulfilled the criteria for the HIV wasting syndrome [28] during admission and had not died of a condition generally considered unrelated to HIV infection (for example, trauma, cholera, tetanus, amoebiasis, carcinoma); or (3) the cause of death was bacterial infection; or (4) the cadavers were skeletally wasted and had no excluding non-HIV-related pathology.

Statistical analyses was performed using Epi Info, version 5.01 [38]. Odds ratios (OR) and their 95% confidence intervals (CI) were calculated as summary measures of association. When numbers were small, Fisher's exact test was used. Differences in mean values for continuous variables were assessed using Student's t-test. For the non-Gaussian distributed CD4+ T-lymphocyte counts, the Mann–Whitney U test was used. The alpha level was set at 0.05, and all tests were performed using a two-sided alternative hypothesis.

The study was approved by the Ethics and Research Sub-Committee of the National AIDS Committee of Côte d'Ivoire.

## Results

### Study population

During the first 10 months of the study, 6340 adult patients (aged >14 years) were admitted to the medical wards of hospital A (group I). Of these, 65% were men (median age, 36 years), and 34% were women (median age, 29 years); for 1% the sex was not recorded. All subjects were black Africans. Of all admitted patients, 5401 (85%) were examined and HIV-serotested (Fig. 1). The prevalence of HIV-1 infection was 37%, HIV-2 infection 4%, and dual reactivity 9%. The overall HIV seroprevalence was higher in men (56%) than in women (40%; OR, 1.9; 95% CI, 1.7–2.1). Of the evaluable HIV-positive patients, 12% (299 out of 2544) had been admitted to hospital A within the previous 2 years.

Of the 6340 patients admitted, 2215 (35%) died. The overall prevalence of HIV infection in patients who died was 66%. Patients with HIV infection had a mortality rate of 38% (1020 out of 2714) compared with 19% (518 out of 2687) for HIV-negative patients (OR, 2.5; 95% CI, 2.2–2.9). HIV-2-positive patients were more likely to die than HIV-1-positive patients (44%, 90 out of 205 versus 35%, 706 out of 2021; OR 1.5; 95% CI, 1.1–2). HIV-positive men had a higher mortality rate (41%, 791 out of 1925) than women (29%, 227 out of 786; OR, 1.7; 95% CI, 1.4–2.1), which pertained for all HIV types. Among the 939 patients who were not serotested on admission the mortality rate was 72%, mainly because they were admitted and died overnight.

### CD4+ T-lymphocyte counts

CD4+ T-lymphocyte counts were performed on 623 out of 5401 (12%) patients who had been HIV-serotested. Table 1 compares mean and median values in patients according to serostatus and outcome. In all seropositive groups, the median values were significantly lower in patients who died ($\leq 88 \times 10^6$/l) than in those who survived ($\geq 175 \times 10^6$/l). HIV-positive patients with CD4+ T-lymphocyte counts $< 200 \times 10^6$/l had a significantly higher mortality rate (50%, 164 out of 331) than those who did not (23%, 43 out of 191; OR, 3.4; 95% CI, 2.2–5.2). For HIV-positive patients with CD4+ T-lymphocyte counts $\geq 200 \times 10^6$/l, the mortality rate (23%, 43 out of 191) was the same as that in HIV-negative patients with known CD4+ T-lymphocyte counts (23%, 22 out of 96).

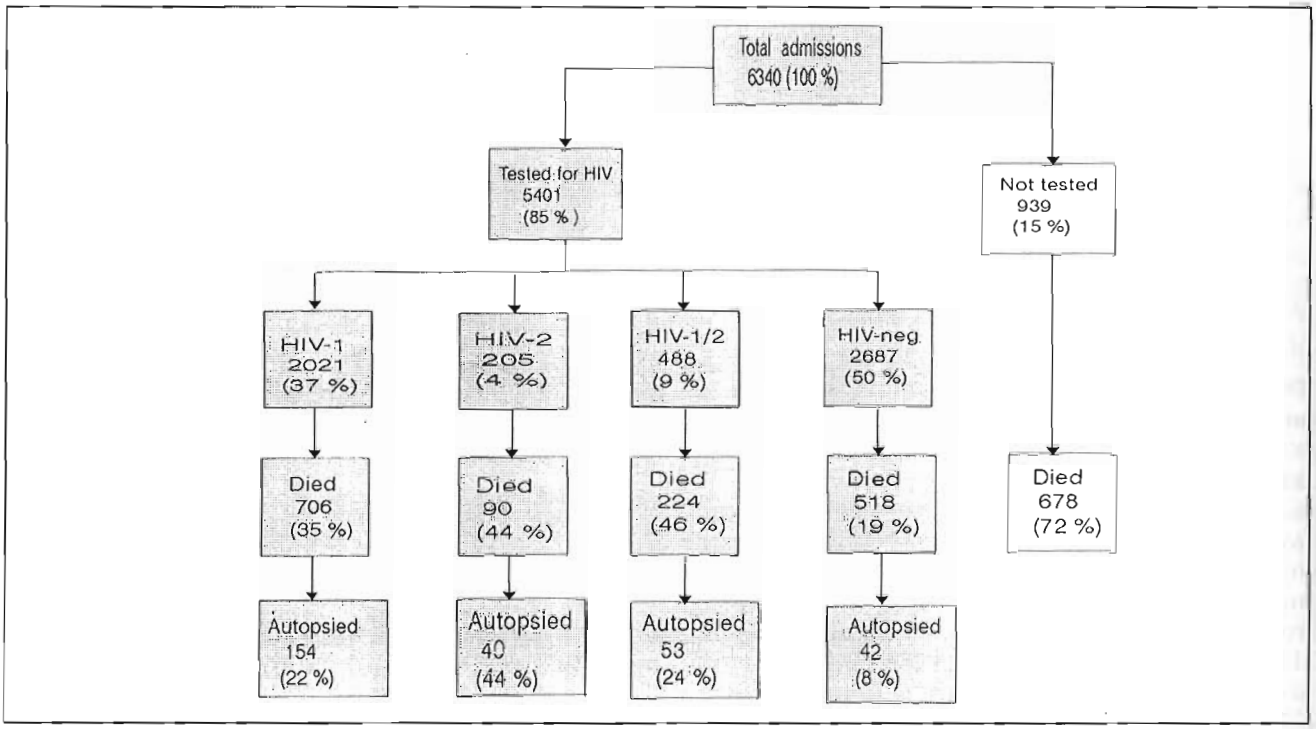


**Fig. 1.** Adult medical admissions to hospital A (patient group I): HIV status, deaths and autopsies on 6340 consecutive admissions in 1991. (For two patients who were rapid-tested as HIV-1-positive, supplemental testing was not performed). Percentages refer to the population from which the sample was drawn.

**Table 1.** CD4+ T-lymphocyte counts ($\times 10^6$/l) in hospitalized patients by HIV status and outcome.

| | | HIV serostatus | | | |
|---|---|---|---|---|---|
| | CD4+ count | HIV-1 | HIV-2 | HIV-1/2 | HIV-neg. |
| Died | Median | 88 | 61 | 42 | 692 |
| | Mean | 141 | 238 | 114 | 707 |
| | (s.d.) | (161) | (547) | (192) | (364) |
| | No. | 133 | 19 | 57 | 23 |
| Survived | Median | 177 | 358 | 175 | 765 |
| | Mean | 273 | 383 | 216 | 859 |
| | (s.d.) | (311) | (299) | (183) | (698) |
| | No. | 233 | 22 | 60 | 78 |

neg., negative.

## Survival

For all HIV-positive patients who died, the median survival was 6.5 days (HIV-1 = 7 days, HIV-2 = 5 days, dually reactive = 6 days); their modal survival was 1 day (14% of deaths). HIV-negative patients who died had a median survival of 4 days; their modal survival was 2 days (17% of deaths).

## Hospital B, neurology ward

Of 375 group III patients, 365 (97%) were serotested. Ninety (25%) were HIV-positive: 19% HIV-1, 2% HIV-2, 4% dually reactive (67 men, 23 women). Twenty-seven (30%) HIV-positive patients died.

## Autopsy sample

The autopsy sample of group I patients was 247 (154 HIV-1, 40 HIV-2, 53 dually reactive), or 24% of all deaths (Fig. 1). The sample included 45% of all HIV-positive deaths on the infectious disease ward and 63% of all HIV-positive deaths on the other medical wards during the respective sampling periods. There were 187 men and 60 women. The autopsied sample was comparable for sex ratio, age, and duration of survival with the non-autopsied HIV-positive patients. The median CD4+ T-lymphocyte counts of autopsied versus non-autopsied patients who died were 101 and 87 (HIV-1), 50 and 196 (HIV-2), and 54 and $19 \times 10^6$/l (dually reactive), respectively; within HIV types these differences were not significant. Forty-two HIV-negative group I adults were autopsied: 29 men, (median age, 43 years) and 13 women (median age, 22 years).

Thirty-seven brought-in-dead cadavers (group II) were autopsied (24 HIV-1, one HIV-2, eight dually reactive and four HIV-negative): of the HIV-seropositive cadavers there were 26 men (median age, 40 years), and seven women (median age, 27 years). Of the HIV-positive group III deaths, 14 out of 27 (52%) were autopsied: 11 HIV-1, two HIV-2, one dually reactive; 10 men (median age, 36 years), four women (median age, 38 years).

## Autopsy pathology

*Group I, hospital A*

Of the 247 HIV-positive patients autopsied, 230 (93%) died of HIV-related disease. AIDS-defining pathologies were found in 175 out of 230 (76%): 101 out of 175 (58%) had one, 57 (33%) had two, 15 (9%) had three, one had four and one had five such pathologies. The prime causes of death and specific pathology prevalences in the HIV-positive cadavers are shown in Table 2.

**Table 2.** The prime causes of death and pathology prevalences in autopsy sample of group I patients; denominators are the total group (n = 247), and those having one or more Centers for Disease Control and Prevention (CDC)-listed AIDS-defining pathologies (AIDS-path; n = 175).

| | Prime cause of death (n = 247) | Pathology prevalence (all patients) (n = 247) | Pathology prevalence (AIDS-path) (n = 175) |
|---|---|---|---|
| | n (%) | n (%) | n (%) |
| Tuberculosis | 80 (32) | 94 (38) | 94 (54) |
| Atypical mycobacteriosis | 0 | 7 (3) | 7 (4) |
| Bacteraemia | 26 (11) | 40 (16) | 12 (7) |
| Nocardiosis | 5 (2) | 10 (4) | 8 (5) |
| Cytomegalovirus | 5 (2) | 45 (18) | 45 (26) |
| Herpes simplex | 0 | 5 (2) | 5 (3) |
| Zoster dermatitis* | 0 | 10 (4) | 5 (3) |
| PML | 1 (0.5) | 3 (1) | 3 (2) |
| HIV encephalitis | 0 | 8 (3) | 6 (3) |
| Cryptococcosis | 5 (2) | 8 (3) | 8 (5) |
| Histoplasmosis | 1 (0.5) | 5 (2) | 5 (3) |
| Aspergillosis | 0 | 5 (2) | 5 (3) |
| *Pneumocystis* pneumonia | 6 (2) | 7 (3) | 7 (4) |
| Cerebral toxoplasmosis | 24 (10) | 37 (15) | 37 (21) |
| Cryptosporidiosis | 3 (1) | 7 (3) | 7 (4) |
| Strongyloidiasis | 1 (0.5) | 8 (3) | 2 (1) |
| Kaposi's sarcoma | 4 (2) | 22 (9) | 22 (13) |
| Non-Hodgkin lymphoma | 5 (2) | 7 (3) | 7 (4) |
| Pyogenic pneumonia | 19 (8) | 74 (30) | 36 (21) |
| Purulent meningitis | 12 (5) | 12 (5) | 2 (1) |
| Pyonephritis | 1 (0.5) | 25 (10) | 8 (5) |
| Non-specific enteritis | 8 (3) | 24 (10) | 21 (12) |
| Glomerulonephritis | 4 (2) | 7 (3) | 4 (2) |
| Carcinoma/leukaemia† | 6 (2) | 6 (2) | 2 (1) |
| Undetermined | 10 (4) | | |

The remaining pathologies as prime causes of death and overall prevalence, respectively, (n/n) were: cerebral malaria (1/1), amoebiasis (2/3), human African trypanosomiasis (1/1), cirrhosis (1/5), fulminant hepatitis (1/1), non-specific shock (9/31), pyogenic peritonitis (1/1), amyloidosis secondary to tuberculosis (1/1), tetanus (4/4). *Nine out of ten were old scarred lesions. †These malignancies were one case each of hepatocarcinoma, cholangiocarcinoma, bronchial carcinoma, prostatic carcinoma, and two cases of myeloid leukaemia. PML, progressive multifocal giant-cell encephalitis. HIV encephalitis, multinucleate giant-cell encephalitis.

### Tuberculosis

Tuberculosis was the prime cause of death in 80 (32%) HIV-positive cadavers. The overall prevalence of TB was 38% (94 out of 247). Of the evaluable TB patients, 48% (39 out of 82) had chronic diarrhoea on admission. TB was disseminated widely except in 10 patients; in four patients, disease was limited to the lungs, and in six to the lymph nodes only. Nineteen (20%) had TB meningitis and 19 had foci of tuberculous enteritis. Of the 175 cadavers with AIDS-defining pathology, 54% had TB.

In 92 out of 94 cases, acid-fast bacilli were visible histologically. In 16 cases sampled, tissue cultures grew *M. tuberculosis*, with no atypical mycobacteria isolated. The predominant histological pattern of HIV-associated TB at autopsy was non-reactive and multibacillary: abundant granular necrosis, ill-formed or absent granulomas, scanty or no giant cells, scanty or no epithelioid cells, and high densities of acid-fast bacilli [32].

Histology indicative of atypical mycobacteriosis was seen in seven (3%) cadavers. The lesions were small, involving lung (four patients), visceral lymph nodes (seven), small intestine (one), liver (four), spleen (three), kidney (one) and bone marrow (two). In no patient was atypical mycobacteriosis the prime cause of death.

### Bacteraemia

Bacteraemia as defined pathologically was the second most common cause of death (11%), and was present in 40 (16%) cadavers. In 22 out of 40 (55%), there was bilateral pyonephritis (and patients were not catheterized). Other pathological associations included pyogenic pneumonia (17, 43%), enteritis (10, 25%), hepato-biliary disease (seven, 18%), and gynaecological sepsis (five, 13%). In 31 out of 40 (78%) cases the organisms identified histologically were Gram-negative rods, and in nine out of 40 (23%), Gram-positive cocci.

### Toxoplasmosis

The third most common cause of death was cerebral toxoplasmosis at 10%; including minor lesions, a total of 37 out of 247 brains (15%) had toxoplasmosis. Of those with AIDS-defining pathology, 21% had cerebral toxoplasmosis. Infection was disseminated viscerally in six patients.

### Pyogenic pneumonia

Pyogenic pneumonia was judged the prime cause of death in 8% but was present in 74 out of 247 (30%) of patients. Gram stains showed Gram-negative rods in 20 and Gram-positive cocci in 22 cases.

### Lymphoma

Seven cases of lymphoma were found (3%), or 4% of the cadavers with AIDS-defining pathology. All were in men and were high-grade B-cell, non-Hodgkin lymphomas. Three were primary cerebral lymphoma and four extracerebral.

### *Pneumocystis carinii* pneumonia

Seven (3%) cadavers had *P. carinii* pneumonia (PCP; 4% of those with AIDS-defining pathology), which was the cause of death in six (2%). Associated pulmonary pathologies included pyogenic pneumonia, nocardiosis and cryptococcosis. No extrapulmonary pneumocystosis was present in any cadaver.

### Kaposi's sarcoma

Twenty-two (9%) of the HIV-seropositive cadavers had Kaposi's sarcoma (KS), but the lesions were judged severe and disseminated sufficient to be the cause of death in only four (2%).

### Cytomegalovirus infection

Severe disseminated CMV infection was the cause of death in five (2%) patients. Including minor lesions, 45 out of 247 (18%) cadavers had evidence of infection.

### Cryptococcosis

Cryptococcosis was found in eight cadavers (3%) and was the cause of death in five (2%). In six, there was a meningo-encephalitis associated with visceral spread and in two, visceral involvement only.

### Nocardiosis

Nocardiosis was the cause of death in five patients (4%) and present in a further five. There was necrotizing pneumonia in all 10; in six there was systemic spread, three patients having cerebral lesions. No patient had co-existing TB.

### Cryptosporidiosis

Cryptosporidial enteritis was the prime cause of death in three patients (1%), but was also present in a further four (total prevalence 3%). In three, there was hepato-biliary cryptosporidiosis.

### Enteritis and glomerulonephritis

Enteritis (small or large bowel inflammation and ulceration) that was not associated with CMV, *Cryptosporidium*, strongyloidiasis or typhoid was the prime cause of death in eight patients (3%) and present in a total of 24 (10%). Seven of the 247 (3%) HIV-positive patients had glomerulonephritis, focal or diffuse, with glomerulosclerosis in four.

### Wasting

Sixty-one out of 247 (25%) cadavers had moderate wasting and 112 (45%) were skeletally wasted. In 10 out of 247 cadavers (4%), there was skeletal wasting but no significant pathology to account for death. A pre-mortem diagnosis of diarrhoea was not more frequent in those with skeletal wasting compared with those without wasting. However, 44% (54 out of 123) of skeletally wasted cadavers had TB compared with 39% (30 out of 76) of moderately wasted and 23% (21 out of 91) of non-wasted cadavers ($\chi^2$ for linear trend = 9.4; $P = 0.002$).

### Brought-in-dead cadavers (group II)

Among the HIV-positive cadavers autopsied who had died outside hospital, 27 out of 33 (82%) had one or more AIDS-defining pathology: the others died of trauma (n = 4), abortion (one) or of no obvious cause (one). The patterns and frequencies of pathology resembled those of admitted (group I) patients. Disseminated multibacillary TB was found in 11 (33%). Bacteraemia was found in six (18%), and cerebral toxoplasmosis in three (9%) of cadavers overall. Other specific pathologies included pyogenic pneumonia (eight, 24%), pyonephritis (seven, 21%), PCP and strongyloides (two cases each, 9%), and KS (three, 9%). CMV infection, purulent meningitis and histoplasmosis were also found 3% (once each).

### Cerebral pathology, and group III patients

In the group I HIV-positive sample, 59 out of 247 (24%) died primarily of intracerebral disease, toxoplasmosis being the dominant lesion (Table 2). Tuberculous meningitis was present in 19 out of 175 (11%) of patients with an AIDS-defining pathology, but only two tuberculomas were seen, both < 5 mm in diameter. Although eight out of 247 patients had cryptococcosis, only six had meningo-encephalic involvement. Three patients (1%) had mild CMV encephalitis. Of the 12 (5%) patients with purulent meningitis, Gram stains showed Gram-positive cocci in six, Gram-negative cocci in one, gram-negative rods in three, and no organisms identical in two. There were 3 patients (1%) with primary cerebral lymphoma. Excluding vascular lesions such as infarcts, 115 out of 247 (47%) HIV-positive cadavers had cerebral lesions.

Among the 27 brought-in-dead cadavers with HIV-related disease (group II), three had toxoplasmosis (11%) and one had Gram-positive coccal meningitis (4%).

All 14 autopsied deaths on the neurology ward of hospital B (group III) had AIDS-defining pathologies: 12 (86%) cerebral toxoplasmosis, one progressive multifocal leukoencephalopathy and one disseminated TB with probable spinal cord compression. Multinucleate giant-cell encephalitis was seen in two patients (14%). None had cerebral lymphoma.

### HIV-negative deaths

The major pathologies in 46 HIV-negative autopsies (groups I and III) were bacterial pneumonia (22%), cancer (13%), hypertension (13%) and purulent meningitis (9%). The cancers were carcinomas or leukaemias, with no cases of lymphoma or KS. Comparison with HIV-positive deaths revealed no significant association between HIV infection and the following diseases: amoebiasis, malaria, purulent meningitis, schistosomiasis, tetanus, cholera, non-KS/non-lymphoma malignancies, and strongyloidiasis (although the three patients with disseminated infection were HIV-positive). TB was found in three

HIV-negative cadavers, but was the cause of death in only one. Two patients (4%) had evidence of bacteraemia; none had toxoplasmosis. Apart from the three TB cases and one of herpetic oesophagitis associated with myeloid leukaemia, no potentially AIDS-defining pathologies were seen in HIV-negative cadavers. Including all autopsy sample groups, TB was present in 36% (107 out of 294) HIV-positive and 7% (three out of 46) HIV-negative cadavers (OR, 8.2; 95% CI, 2.4-34).

### HIV-2-seropositive deaths

Among all 294 HIV-positive cadavers examined, 43 (15%) were HIV-2-positive; 40 out of 43 (93%) had died of HIV-related disease. The HIV-2-positive cadavers studied in hospital A represented 44% of all HIV-2-positive deaths over the study period (Fig. 1). The pathologies in HIV-2-positive cadavers were similar to those in 174 HIV-1-positive cadavers, except for three conditions, all significantly more frequent in HIV-2 cadavers: (1) severe multiorgan CMV infection; (2) multinucleate giant cell encephalitis; and (3) intra- or extra-hepatic cholangitis (Table 3).

**Table 3.** HIV-2 versus HIV-1 pathology. Data on the three pathologies with significantly different prevalences in combined group I–III patients with HIV-related causes of death.

| | HIV-1 (n=174*) | HIV-2 (n=40) | OR |
|---|---|---|---|
| | n (%) | n (%) | (95% CI) |
| Severe CMV infection | 4 (2) | 5 (18) | 6 (1.3–29) |
| HIV encephalitis | 1* (1) | 7 (18) | 36 (4–800) |
| Cholangitis | 0 | 7† (18) | ($P<0.001$) |

*170 brains examined from 174 HIV-1-positive cadavers. †Associated with cytomegalovirus (CMV) 1, cryptosporidiosis 2, both CMV and cryptosporidiosis with sclerosing cholangitis 2, Gram-negative rods with acute cholangitis 2, and sclerosing cholangitis without pathogens 1. OR, odds ratio; CI, confidence interval.

### Sex ratio and disease

Combining the three autopsy samples, of the 270 cadavers who had HIV-related disease, 66 (24%) were women and 204 (76%) men. The prevalences of specific diseases by sex (excluding gynaecological sepsis) were not significantly different, except for lymphoma and nocardiosis — all seven and 10 patients, respectively, were men. No HIV-positive or HIV-negative female cadavers had carcinoma of the cervix.

### CD4+ T-lymphocyte counts

The CD4+ T-lymphocyte counts of 96 HIV-positive autopsied patients, classified by specific disease, are given in Table 4. The median CD4+ T-lymphocyte values for patients who had disseminated TB with tuberculous meningitis were significantly higher ($137\times10^6$/l) than tuberculous patients without meningitis ($40\times10^6$/l). The prevalences of specific pathologies in the 40 autopsied patients with CD4+ T-lymphocyte counts $\leq50\times10^6$/l compared with the 56 patients with CD4+ T-lymphocyte counts $>50\times10^6$/l showed no significant differences for TB (17 out of 40 versus 18 out of 56) or toxoplasmosis (nine out of 40 versus 10 out of 56, respectively). However, the prevalances of CMV infection in those with counts $\leq50\times10^6$/l and $>50\times10^6$/l were 30% (12 out of 40) and 7%, respectively (four out of 56; OR, 5.6; 95% CI, 1.5–23); for bacteraemia the prevalences were 3% (one out of 40) and 23% (13 out of 56; OR, 0.08; 95% CI, 0–0.7) in patients with counts $\leq50\times10^6$/l and $>50\times10^6$/l, respectively.

**Table 4.** CD4+ T-lymphocyte counts ($\times10^6$/l) correlated to specific pathologies in HIV-positive deaths, with three or more observations per diagnosis (patient groups I and III).

| Pathology | No. | Median | Range |
|---|---|---|---|
| Purulent meningitis | 4 | 166 | 73–700 |
| Bacteraemia | 14 | 135 | 2–715 |
| Strongyloides | 5 | 113 | 56–230 |
| Non-Hodgkin's lymphoma | 4 | 100 | 34–175 |
| Cryptococcosis | 6 | 99 | 8–197 |
| Kaposi's sarcoma | 7 | 76 | 6–341 |
| Cerebral toxoplasmosis | 20 | 50 | 1–1013 |
| Cytomegalovirus infection | 16 | 40 | 1–341 |
| Cryptosporidiosis | 4 | 32 | 15–61 |
| HIV encephalitis | 3 | 15 | 1–61 |
| *Pneumocystis* pneumonia | 3 | 14 | 8–80 |
| Oesophageal candida | 6 | 12 | 2–295 |
| Herpes simplex | 3 | 8 | 1–18 |
| Atypical mycobacteriosis | 3 | 1 | 1–40 |
| Disseminated TB without TB meningitis | 22 | 40* | 4–221 |
| TB meningitis | 13 | 137* | 26–537 |

*Mann–Whitney U test: $P=0.034$. TB, tuberculosis.

## Discussion

### Mortality

In sub-Saharan African countries where the adult HIV seroprevalence is >5%, HIV-related disease is the most common cause of death [1,39]. With 5401 patients evaluated, the present study is the largest to follow-up hospitalization related to HIV infection in Africa. From the main study population (medical admissions to hospital A) the demographic data emphasize that in this now typical African population where half of medical hospitalizations are HIV-positive, (1) patients are being seen for the first time, (2) they present with advanced disease, and (3) their mortality is high and rapid [5]. With the HIV seroprevalence rising in many African countries and the facilities for health care being progressively compromised by falling socioeconomic conditions [40,41], one may question the function of large acute hospitals. Increasing numbers of late-presenting HIV-

infected patients will be arriving at such hospitals expecting care. Without either the facilities for the rapid diagnosis and therapy of HIV-related diseases [4,42], or the institutional structures to provide appropriate prophylaxis against HIV-related conditions, these hospitals may be doing little beyond providing terminal care — an inappropriate role for large hospitals in developing countries [42–44].

### Pathology — tuberculosis

Previous, selective, studies provided a partial view of the HIV disease spectrum in Africa [4,5]. The prevalence of TB among HIV-positive patients in Africa presenting to medical services is uncertain; rates of 11–40% have been reported [5,45]. Autopsies on selected patients dying of AIDS in Zaïre found 41% with TB [25], and a previous study of HIV-positive deaths on the pulmonary wards of hospital A in Abidjan found 43% to have TB [24].

The present data underline the overwhelming significance of TB in all aspects of HIV disease in Africa [46]. As the most common cause of death, it was present in 38% of all cadavers and in 54% of those dying with AIDS-defining pathology. An unexpected 20% of all TB patients had tuberculous meningitis, or 11% of all cadavers with AIDS-defining pathology. A high proportion (10%) of TB meningitis among TB patients has been reported from Spain [47], but nowhere else.

The dominant form of TB in the Abidjan patients was disseminated and multibacillary, mostly undiagnosed before death, and associated with chronic diarrhoea and severe wasting. The HIV wasting ('slim') syndrome is regarded as an enteropathy caused by parasitic infections (particularly cryptosporidiosis) and/or HIV itself [12–14,48,49]. This study has shown a strong correlation between wasting and TB. The 3% prevalence of cryptosporidiosis in the main autopsy sample is probably an underestimate (due to autolysis). However, it is likely that systemic TB contributes to the 'slim' syndrome in Africa to a greater degree than thought previously.

The median CD4+ T-lymphocyte count of patients dying of TB was $40 \times 10^6$/l in those without, and $137 \times 10^6$/l in those with, tuberculous meningitis. This indicates an earlier presentation during HIV disease by those with tuberculous meningitis [46]. They might be saved with rapid diagnosis and treatment; whilst those with non-meningitic, disseminated disease are more likely to have end-stage immunodeficiency.

The ratio of 87 patients with pulmonary TB to 10 with pulmonary nocardiosis — which mimicks TB clinically and radiologically [50,51] — suggests that a proportion of clinically diagnosed, smear-negative 'tuberculosis' may be nocardiosis.

### Bacteraemia

Bacteraemia in HIV-positive patients in Africa is predominantly a pneumococcaemia in those with pulmonary disease or a non-typhoid salmonellosis in those with an acute enteric fever-like illness [11,52,53]. In the present study, morphologically defined bacteraemia was present in 16% of HIV-positive deaths, but in only 7% of those with an AIDS-defining pathology. Infection with Gram-negative rods predominated. The CD4+ T-lymphocyte counts available (median = $135 \times 10^6$/l) suggest that bacteraemia can present before the terminal phase of HIV disease, as only 7% (one out of 14) of patients had a CD4+ T-lymphocyte count $<50 \times 10^6$/l. The definition for bacteraemia used here must have a lower sensitivity compared with haemoculture, and these prevalences are therefore minimum estimates. It is possible that some of those admitted patients who died before serotesting (Fig. 1) had rapidly fatal Gram-negative bacteraemia. Nonetheless, 18% of brought-in-dead cadavers had bacteraemia by morphological criteria, not significantly different from group I patients.

### Central nervous system lesions

Of those in the main patient sample (I) who had died of HIV-related disease, 59 out of 230 (26%) died primarily of intracerebral disease, and 99 (43%) had normal brains. In Africa, focal neurological signs have been reported in 9–11% of HIV-positive adult admissions and the AIDS dementia complex in 9–54% [19,23]. In group I patients, cerebral toxoplasmosis was the predominant intracerebral lesion (15%), 12 times more frequent than primary cerebral lymphoma. Twelve of the 13 patients from the neurology ward with a defined cerebral lesion had toxoplasmosis, underlining the importance of this reactivated infection [54]. In Abidjan, 69% of pregnant women have antibodies to *Toxoplasma* (Projet RETRO-CI, unpublished data). The widely differing adult seroprevalences of *Toxoplasma* infection reported in Africa (11–78% [55,56]) suggest that the prevalence of cerebral toxoplasmosis in HIV-positive people may also vary within Africa. Previous clinical series in Africa with pathology reported 3–13% prevalences of cryptococcal meningitis in AIDS patients [20,57], likewise suggesting a geographical variation. The prevalence in this series (3% in those with AIDS-defining pathology) is at the lower end of the scale.

### HIV-2 infection

Three pathological differences emerged between HIV-1 and HIV-2-positive patients. All the cholangitis lesions were in HIV-2-positive cadavers (HIV-2-associated cholangitis has been reported previously [58]). Severe CMV infection and multinucleate giant cell encephalitis (HIV encephalitis [59]) were almost restricted to HIV-2-positive patients: neither lesion has previously been reported in HIV-

2-seropositive Africans. All three lesions are associated with extreme immunosuppression and with prolonged survival with HIV infection [60,61]. Since the sampling for autopsy was qualitatively no different for each HIV type, this and the lower median CD4+ T-lymphocyte counts in autopsied patients with HIV-2 compared with HIV-1 positivity (50 versus $101 \times 10^6$/l) suggest a modified natural history for HIV-2: such patients may survive longer in the terminal stage of HIV infection. Natural history cohort studies of the two infections could clarify this phenomenon.

### The value of autopsies

Autopsy studies were fundamental in the early description of AIDS in industrialized countries [62–64]. This is the first study in Africa to analyse the pathology of representative samples of HIV-infected patients, mostly undiagnosed. In circumstances where systematic clinical investigation is not possible and where survival in hospital is brief, autopsies are the means of determining the range and prevalences of specific diseases. They can have immediate impact on patient care, by highlighting, for example, the frequency of tuberculous meningitis. The pattern of pathology in the brought-in-dead cadavers was similar to that in patients dying in the general medical hospital. This indicates that further HIV autopsy studies could be performed in Africa and elsewhere, by examining such cadavers when permission for autopsy is difficult to obtain.

### Possible interventions for HIV-positive people in Africa

The data presented here reinforce the need to address TB [44]. In HIV-positive people it is considered to be a reactivation of latent infection in most cases [10,65], and systematic prophylaxis could reduce its frequency [66,67]. Bacteraemia presents relatively early on in HIV disease in this population, so rapid diagnosis and treatment might enable more patients to survive [11]. Cerebral toxoplasmosis is treatable and potentially preventable [54,68], and for empirical therapy may be assumed to be the aetiology underlying focal cerebral lesions.

### Intercontinental comparisons

Comparison of the major pathologies in AIDS patients between the present autopsy series and those in industrialized countries reveals striking differences. The following four diseases were relatively uncommon in Abidjan: *Pneumocystis* pneumonia (4 versus 38–56% [69,70]), atypical mycobacteriosis (4 versus 17–50% [70,71]), lymphoma (4 versus 9–13% [70,72]), and CMV infection (26 versus 50–81% [70,72]). However, *Pneumocystis* and MAI are prevalent in the African environment [73,74], and 77% of pregnant women in Abidjan have antibodies to CMV (Projet RETRO-CI, unpublished data). The low CD4+ T-lymphocyte counts associated with pneumocystosis, CMV infection and atypical mycobacteriosis suggest that few patients in Africa survive long enough to develop these low-virulence infections, and a similar argument may apply to lymphoma [75]. Conversely, TB (54% prevalence in Abidjan) is more common than in industrialized countries (0–10% [70,72]) reflecting the higher latent infection rate in Africa [46] and its greater virulence. The latent infection rates of *Toxoplasma* vary widely internationally, and the 21% prevalence of cerebral toxoplasmosis in Abidjan is intermediate between those of Texas, USA (4% [76]) and France (51% [77]). Comparable data for bacteraemia are not available.

In summary, analysis of 5401 hospitalized adults in Abidjan found an HIV prevalence rate of 50% and late presentation of disease. The mortality among seropositives was 38%, half the patients dying within 1 week. Autopsies showed that three infections —TB, bacteraemia and cerebral toxoplasmosis — together accounted for >50% of deaths. The conditions that dominate the management of AIDS in industrialized countries — *Pneumocystis* pneumonia, CMV infection, lymphoma, and atypical mycobacteriosis — were all uncommon. The patterns of pathology and CD4+ T-lymphocyte counts indicate short survival at very low counts in this population, and suggest a more prolonged terminal course for patients with HIV-2 infection. The logistics of caring for the increasing number of HIV-infected patients who will present ill and dying to resource-poor hospitals in Africa need urgent attention.

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