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Autopsy Causes of Death in HIV-Positive Individuals in Sub-Saharan Africa and Correlation with Clinical Diagnoses

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Abstract

Despite the persistently high HIV-related mortality in sub-Saharan Africa, limited information on the causes of death is available. Pathological autopsies are the gold standard to establish causes of death. In this review we describe the autopsy series performed among HIV-infected individuals in sub-Saharan Africa over the last two decades. We identified nine complete and 11 partial or minimally invasive autopsy series. Complete autopsies were performed in 593 HIV-positive adults and 177 HIV-positive children. Postmortem diagnoses were mainly infectious diseases. Tuberculosis was the most frequent, present in 21-54% of HIV-positive adults and was considered the cause of death in 32-45%. Overall, pulmonary infections accounted for approximately 66% of pathology and central nervous system infections for approximately 20%. A high discordance between clinical and postmortem diagnoses was observed. This review emphasizes the need for reliable information on causes of death in order to improve HIV patient care, guide further research, and inform health policy. **(AIDS Rev. 2010;12:183-94)**

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Key words

HIV. Sub-Saharan Africa. Autopsy. Postmortem diagnosis.

Introduction

Since the worldwide rollout of antiretroviral treatment (ART), mortality due to HIV has dramatically decreased[1,2]. However, substantial AIDS mortality persists; in 2008, the number of deaths due to AIDS in sub-Saharan Africa was estimated to be 1.4 million[3]. A large proportion of these are children and adults in sub-Saharan Africa who still lack access to HIV treatment[3]. But also among those on ART, mortality remains high despite good immunologic and virologic responses[4]. In this group, most deaths occur in the first months after the start of ART[5,6]. This early mortality seems to be caused mainly by HIV-related opportunistic infections and malignancies. The immune reconstitution inflammatory syndrome (IRIS) and ART toxicity seem to be less important causes of early death, but how much these conditions contribute to mortality remains to be determined[4,6,7].

Most information on the causes of HIV-related death in Africa comes from clinical studies and studies using verbal autopsies[4,8,9]. However, pathological autopsy, a macro- and microscopic postmortem examination of the body, is the gold standard to determine causes of death. Despite improved diagnostic facilities, there is a high discrepancy between clinical and postmortem diagnoses. A study reviewing autopsies done in HIV-positive individuals who died in the United Kingdom showed that in 70% of autopsies, the cause of death

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was different from the clinical diagnosis and that 36% of the opportunistic infections were clinically missed[10]. In resource-limited settings, this discrepancy is expected to be even higher because of the limited access to pre-mortem examinations.

A better knowledge of the causes of death is essential to improve clinical practice, to guide further research, and to inform policy makers. In this paper we review the results of autopsy studies done in sub-Saharan Africa in HIV-positive individuals and the correlation between autopsy and clinical diagnoses.

Search method

See box 1.

Box 1. Search strategy and definitions

The Medline electronic database was searched via PubMed without language or time limitations. The following Medical Subject Headings (MESH) were used: "Africa South of the Sahara", "HIV", "Acquired Immunodeficiency Syndrome", and "Autopsy". This returned 264 articles. Original studies describing complete autopsies, partial autopsies and minimally invasive autopsies in at least eight HIV-positive individuals in sub-Saharan Africa were considered. Sub-studies of larger postmortem series and studies describing verbal autopsy results or clinical causes of death were not considered for review. Reference lists of relevant papers were used to identify additional publications. The abstracts (2001-2010) of the CROI and of the International AIDS Society conferences were searched. Experts in the field were contacted to suggest any additional studies.

A complete autopsy was defined as a macro- and microscopic examination of all thoracic and abdominal organs and the brain. A partial autopsy was defined as a macro- and microscopic examination of a number of organs or a particular organ. Minimally invasive autopsies included blind or targeted percutaneous needle biopsies and examinations using endoscopic or laparoscopic techniques.

Literature overview

Description of the studies

We identified 19 reports and one abstract from 10 different African countries, describing nine complete and 11 partial or minimally invasive autopsy series. Table 1 summarizes the study and patient characteristics[11-31]. Ten of these autopsy series also included HIV-negative individuals (Table 1)[12-15,17,19,20,22,23,26]. Seven of these studies compared autopsy findings to clinical diagnosis (Table 2)[11,14,21,23-26].

Complete autopsies were performed in 593 HIV-positive adults and 177 HIV-positive children. Partial autopsies varied from sampling of lung tissue only to sampling all organs except for the brain. Partial autopsies were chosen for various reasons. In the Democratic Republic of Congo, they were done because of poor acceptance of complete autopsies[24]. Among South African miners, they were done to evaluate lung pathology for compensation purposes[23]. Studies using minimally invasive autopsies were only conducted in children and designed to answer organ- or disease-specific research questions[15,17,27,28,30].

Nearly all studies were performed in major tertiary level health institutions and among hospitalized patients. Some studies also included a limited number of dead persons brought to the hospital from outside[16,19,20]. Kibayashi, et al. selected HIV suspects from a large sample of forensic autopsies[18]. Chakraborty, et al. included non-hospitalized orphans[29]. The focus of the studies varied widely, including patients from very different hospital wards[12,13,19,22,31]. Two studies specifically stated they prioritized patients with an unknown cause of death[13,24].

In four studies, no informed consent was required for the autopsy. In these studies, autopsy rates of 24-100% were reported[12,19,20,29]. Why these four studies did not have autopsy rates of 100% was mainly because of capacity restraints, but a positive outcome is that the cases examined could be more representative, i.e. unselected. Menedez, et al. consecutively included all maternal death that occurred in the hospital, resulting in 78% coverage[22]. For the other studies, the precise mode for inclusion was not stated. The three studies from the Ivory Coast were the only ones that included HIV serotype 2-infected patients; 113 adults (45 HIV-2 and 68 dually reactive) and two children (both HIV-2 infected)[12,19,20].

Inclusion periods mostly did not exceed two years and the number of autopsies varied between 10 and 247. The median CD4 count in adults varied between 48-101 cells/µl[19,21,26]. For children, a mean CD4 percentage of 14.8% was reported[28]. The median number of hospitalization days before death was 4-6 days[13,14,19,21] with one study reporting a modal survival of one day (14% of deaths)[18]. None of the studies reported that patients received ART. Only Chakraborty, et al. mentioned that all children included in their postmortem study had been on prophylactic co-trimoxazole[29].

All studies used hematoxylin and eosin (H&E) stains on all tissues and added Ziehl Neelsen (ZN), Gram, Periodic acid Schiff, and Grocott silver staining as

Table 1. Study and patient characteristics and main autopsy findings in HIV positive and HIV-negative* individuals

First author, country, publication year	Type of study Setting Population Specification autopsy*	Number of autopsies/ number of deaths	Median age (years)	Sex: % ♂	Main causes of death	Main pathology findings
Complete autopsies adults						
Lucas, et al.[19] Ivory Coast, 1993	Prospective 2 large urban hospitals, different medical wards plus community deaths Age > 14 years, known serostatus, preference HIV-2	247/1020 (24%)	36	65	Tuberculosis 32% Bacteremia 11% Cerebral toxoplasmosis 10% Bacterial pneumonia 8% Bacterial meningitis 5%	Tuberculosis 38% Bacterial pneumonia 30% Cytomegalovirus 18% Bacteremia 16% Cerebral toxoplasmosis 15% Non-Hodgkin's lymphoma 3%
Lucas, et al.[19] Ivory Coast, 1993	HIV-negative individuals	42/518 (8%)	♂ 43 ♀ 22	69		Bacterial pneumonia 22% Cancer 13% Hypertension 13% Bacterial meningitis 9% Tuberculosis 7%
Rana, et al.[26] Kenya, 1999	Prospective 2 acute medical wards of a tertiary hospital Adults, known serostatus	75/155 (48%)	33	47	Tuberculosis 45% Bacterial pneumonia 27% Interstitial pneumonia 15% Cryptococcal disease 4% Cytomegalovirus pneumonitis 4%	Tuberculosis 50% Bacterial pneumonia 30% Interstitial pneumonia 17% Lymphocytic meningitis 11% Focal/multifocal bacterial sepsis 11% Non-Hodgkin's lymphoma 1%
Rana, et al.[26] Kenya, 1999	HIV-negative individuals	47/141 (16%)	35	57	Bacterial pneumonia 38% Tuberculosis 13% Interstitial pneumonia 9% Malignancy 9% Malaria 6%	Bacterial pneumonia 40% Malignancy 26% Tuberculosis 15% Interstitial pneumonia 11% Sepsis 9%
Ansari, et al.[13] Botswana, 2002	Prospective, All medical wards of a referral hospital Age > 13 years, mainly with pulmonary symptoms	104/565 (18%)	35	54	Tuberculosis 37% Pneumonia 14% *Pneumocystis jiroveci* pneumonia 11% Kaposi's sarcoma 7% Cryptococcosis 6%	Tuberculosis 40% Pneumonia 23% Cytomegalovirus 15% *Pneumocystis jiroveci* pneumonia 11% Kaposi's sarcoma 11% Non-Hodgkin's lymphoma 3%
Ansari, et al.[13] Botswana, 2002	HIV-negative individuals	24/380 (6%)	53	54	Pneumonia 21% Cardiac disease 21% Non-Hodgkin's lymphoma 13% Cerebral hemorrhage 5% Intestinal infarction 5% Other malignancies 5%	Pneumonia 29% Cardiac disease 17% Non-Hodgkin's lymphoma 13% Cerebral hemorrhage 5% Intestinal infarction 5% Other malignancies 5%
Partial autopsies adults						
Abouya, et al.[12] Ivory Coast, 1992	Prospective Pulmonary ward of university hospital Age > 14 years, known serostatus Lungs only	53/71 (75%)	–	–	Pulmonary tuberculosis 40% Non-specific pneumonia 34% *Pneumocystis jiroveci* pneumonia 8% Kaposi's sarcoma 6% Other cancers 4%	Pulmonary tuberculosis 43% Non-specific pneumonia 34% *Pneumocystis jiroveci* pneumonia 9% Kaposi's sarcoma 8% Other cancers 4%
Abouya,et al.[12] Ivory Coast, 1992	HIV-negative individuals	25/29 (86%)	–	–	Cancer, primary or secondary 64% Non-specific pneumonia 28% Pulmonary tuberculosis 4%	Cancer, primary or secondary 64% Non-specific pneumonia 28% Tuberculosis 12%
Nelson, et al.[24] Zaire, 1993	Prospective 3 hospitals: urban general, urban referral, rural Adults, AIDS on chart or death certificate, death shortly after admission of unknown cause Complete, except brain	63/–	36	44	–	Extrapulmonary tuberculosis 41% Bacterial pneumonia 34% Candidiasis 31% Extrapulmonary cryptococcosis 19% Kaposi's sarcoma 16% Cytomegalovirus 13%

Continue

Table 1. Study and patient characteristics and main autopsy findings in HIV positive and HIV-negative* individuals *(continued)*

First author, country, publication year	Type of study Setting Population Specification autopsy*	Number of autopsies/ number of deaths	Median age (years)	Sex: % ♂	Main causes of death	Main pathology findings
Kibayashi, et al.[18] Tanzania, 1999	Prospective, 1,615 forensic autopsies, 30 HIV+ suspects selected, 10 confirmed HIV+ University hospital Focus on neuropathology Sampling of brain, heart, lungs, liver and kidneys	10/–	29	100	–	Neuropathology findings Lymphocytic meningitis 50% Tuberculous meningitis + abscess 10% Bacterial meningitis 10% Cryptococcal meningitis 10% Intracerebral hemorrhage 10% No abnormalities 20%
Agyei, et al.[11] Ghana, 2004	Prospective HIV unit in major teaching hospital Adults, HIV+ Autopsy procedure not specified	134/224 (60%)	–	–	–	Tuberculosis 54% Bacterial pneumonia 28% Cerebral toxoplasmosis 16% Bacterial meningitis 6% Malignancies 6%
Murray, et al.[23] South Africa, 2007	Prospective cohort of miners† Cardio-respiratory organs	66/242 (27%)	–	100	–	Any respiratory infection 83% Pulmonary tuberculosis 21% Cryptococcal pneumonia 17% *Pneumocystis jiroveci* pneumonia 14%
Murray,et al.[23] South Africa, 2007	HIV-negative individuals	38/115 (33%)	–	100	–	Any respiratory infection 37% Pulmonary tuberculosis 16%
Tuberculosis studies complete autopsy						
Martinson, et al.[21] South Africa, 2007	Prospective 2 sites: large tertiary hospital and inpatient tuberculosis facility Tuberculosis suspects, > 18 years	50/1000 (5%)‡ (47 HIV+)	35	45	Tuberculosis 49% Bacterial pneumonia 11% Interstitial pulmonary disease 5% Cytomegalovirus pneumonitis 4% *Pneumocystis jiroveci* pneumonia 4%	Tuberculosis 79% Bacterial pneumonia 17% Cytomegalovirus pneumonitis 11% *Pneumocystis jiroveci* pneumonia 6% Non-Hodgkin's lymphoma 2%
Maternal mortality complete autopsies						
Menendez, et al.[22] Mozambique, 2008	Prospective Tertiary hospital Women who died during pregnancy or within 42 days after delivery	139/179 (78%)‡ (65 HIV+)	–	–	Non-obstetric conditions 71% HIV-related conditions in 28%: Tuberculosis 15% *Pneumocystis jiroveci* pneumonia 8% Kaposi's sarcoma 3% Malignant lymphoma 2%	–
Menendez, et al.[22] Mozambique, 2008	HIV-negative individuals	58/–		0	Non-obstetric conditions 55%: Bacterial pneumonia 16% Severe malaria 14% Bacterial meningitis 5% Neoplasm 5% Other and unknown 10%	–
Children complete autopsy						
Lucas, et al.[20] Ivory Coast, 1996	Prospective Mortuary based, largest hospital of Abidjan plus community deaths Age 1 month to 12 years	78/80 (98%)	18 months	50	Pneumonia 41% Measles 17% Meningitis 15% *Pneumocystis jiroveci* pneumonia 11% Enteritis 8%	Severe malnutrition 55% Bacterial pneumonia 42% Cytomegalovirus infection 32% Enteritis 30% Interstitial pneumonitis/bronchiolitis 18%

Continue

Table 1. Study and patient characteristics and main autopsy findings in HIV positive and HIV-negative* individuals *(continued)*

First author, country, publication year	Type of study Setting Population Specification autopsy*	Number of autopsies/ number of deaths	Median age (years)	Sex: % ♂	Main causes of death	Main pathology findings
Lucas, et al.[20] Ivory Coast, 1996	HIV-negative individuals	77/328 (23%)	21 months	–	Malaria 23% Pneumonia *(Pneumocystis jiroveci* pneumonia excluded) 22% Meningitis 12% Measles 12% Other 31%	Bacterial pneumonia 31% Malaria 30% Severe malnutrition 26% Enteritis 18% Interstitial pneumonitis/bronchiolitis 18%
Chakraborty, et al.[29] Kenya, 2002	Retrospective Urban orphanage Age 1 month to 18 years	33/33 (100%)	71 months	39	Bacterial bronchopneumonia 58% Bacterial meningitis 18% Interstitial pneumonia 6% Herpes encephalitis 6% Disseminated tuberculosis 3%	Bacterial meningitis 58% Dilated cardiomyopathy 21% Bacterial meningitis 18% Myocarditis 12% Nephritis 12%
Ansari, et al.[14] Botswana, 2003	Prospective Referral hospital Age 1 month to 13 years	35/126 (28%)	7 months	45	Interstitial pneumonitis/ bronchiolitis 34% *Pneumocystis jiroveci* pneumonia 29% Pneumonia 11% Tuberculosis 11% Disseminated cytomegalovirus 11%	Interstitial pneumonitis/bronchiolitis 60% Disseminated cytomegalovirus 43% Enterocolitis 31% *Pneumocystis jiroveci* pneumonia 29% HIV encephalitis 14%
Ansari,et al.[14] Botswana, 2003	HIV-negative individuals	12/124 (10%)	16 months	–	Pneumonia 42% Interstitial pneumonitis/ bronchiolitis 17% Cardiomyopathy/myo-or pericarditis 17% Tuberculosis 8%	Enterocolitis 50% Pneumonia 42% Cardiomyopathy/myo-or pericarditis 25% Interstitial pneumonitis/bronchiolitis 17% Tuberculosis 8%
Children partial/minimal invasive autopsies						
Ikeogu, et al.[16] Zimbabwe, 1997	Prospective Referral and teaching hospital Age < 5 years, < 3 hours dead on arrival or dead shortly after arrival Lung sampling	122/334 (37%)	10 months	51	–	*Pneumocystis jiroveci* pneumonia 16% Lymphoid interstitial pneumonia 9% Cytomegalovirus 7% Tuberculosis 5%
Jeena, et al.[17] South Africa, 1996	Prospective ICU unit of large hospital Percutaneous biopsies of lung and liver	31/43 lung (72%) 34/43 liver (79%)	4.3 months	45	–	Lung biopsies: *Pneumocystis jiroveci* pneumonia 52% Cytomegalovirus 52% Bacterial pneumonia 26% Liver biopsies: Steatosis 65% Cytomegalovirus 15%
Jeena, et al.[17] South Africa, 1996	HIV-negative individuals	34/§	4 months	45	–	Lung biopsies: Bacterial pneumonia 32% Unspecified pneumonia 18% Adenovirus 15% Liver biopsies: Steatosis 59% Cytomegalovirus 6%
Nathoo, et al.[30] Zimbabwe, 2001	Prospective University hospital Children who died of pneumonia 4 percutaneous biopsies of lung	21/618 (3%)	3 months	46		*Pneumocystis jiroveci* pneumonia 29% Interstitial pneumonia 19% Cytomegalovirus 10% Bacterial pneumonia 5%

Continue

Table 1. Study and patient characteristics and main autopsy findings in HIV positive and HIV-negative* individuals *(continued)*

First author, country, publication year	Type of study Setting Population Specification autopsy*	Number of autopsies/ number of deaths	Median age (years)	Sex: % ♂	Main causes of death	Main pathology findings
Chintu, et al.[15] Zambia, 2002	Prospective Referral and teaching hospital Age 1 month to 16 years admitted with respiratory illness Chest only	264/1,603 (18%)† 180 HIV+	8 months	52	–	Bacterial pneumonia 41% *Pneumocystis jiroveci* pneumonia 29% Cytomegalovirus 22% Tuberculosis 18% Shock lung 13%
Chintu, et al.[15] Zambia, 2002	HIV-negative individuals	84/–	11.5 months	52	–	Bacterial pneumonia 50% Tuberculosis 26% Interstitial pneumonitis 18% Pulmonary edema 11% Pneumocystis jiroveci pneumonia 7%
Rennert, et al.[27] South Africa, 2002	Prospective Large teaching hospital, pre-mortem diagnosis of lung disease Percutaneous biopsies of lung and liver	93/–	10.5 months	53		Cytomegalovirus 31% *Pneumocystis jiroveci* pneumonia 20% Viral infection other than cytomegalovirus 14% Non-specific pneumonitis 12% Bacterial pneumonia 8%
Ruffini, et al.[28] South Africa, 2002	Prospective Secondary and tertiary level hospital Age < 2 years HIV+ or clinically suspected HIV+ Admitted with severe pneumonia Percutaneous lung biopsies	18/29 (62%)	3.5 months	–		*Pneumocystis jiroveci* pneumonia 44% Cytomegalovirus pneumonia 44% Non-specific interstitial pneumonitis 28%
Complete autopsies combined adults, maternal mortality and children						
Garcia-Jardon, et al.[31] South Africa, 2010	Retrospective 2000-2005 Prospective 2006-2008 Tertiary level hospital All HIV+ deaths	86/–	58% 18-55 years 36% < 18 years	35		Disseminated tuberculosis 19% Pulmonary tuberculosis 13% Pneumonia 22% Bacterial meningitis 10% Liver failure 10% Heart conditions 10%

*When applicable; †we report only on those that died of a natural cause.
‡Autopsies HIV+ and HIV–/total number of deaths.
§Age, sex and race matched controls out of 123 autopsies in HIV– children.

appropriate. Most studies also had immunohistochemical analysis at their disposal, with antibody testing against cytomegalovirus (CMV), *Toxoplasma gondii*, Epstein-Barr virus (EBV), respiratory syncytial virus, and adenovirus[12-15,19-22,26,28,29]. One study used immunohistochemistry for lymphoma diagnostics[19]. For suspected tuberculosis (TB) diagnostics, some studies used besides ZN staining, cultures[19,21,27], or polymerase chain reaction[21].

Pathology findings

Adults

Infectious diseases

The overall majority of postmortem diagnoses were infectious diseases (Table 1). Tuberculosis was the most frequent diagnosis, observed in 21-54% of

Table 2. Comparison of clinical versus autopsy diagnosis

First author	Clinical case definition	Source of clinical diagnosis	Diagnosis	Comparison clinical/autopsy diagnosis
Adults				
Agyei, et al.[11]	Not defined	Not defined	Tuberculosis	Sens 59%
Murray, et al.[23]	Not defined	Mine personnel records, assurance records, hospital records, Employment Bureau records, national death register, autopsy database at National Institute of Occupational Health	Pulmonary tuberculosis Respiratory infection	Sens 43% Spec 67% Sens 51% Spec 55%
Nelson, et al.[24]	Not defined	Chart review	Tuberculosis Overall diagnosis	PPV 56% Sens 27%
Rana, et al.[26]	Not defined	Recorded at death by study team	Tuberculosis	Sens 54% Spec 74%
Tuberculosis suspects				
Martinson, et al.[21]	Not defined	Pre-mortem diagnosis by attending doctor	Tuberculosis	PPV 79-80% NPV 28%
Maternal mortality				
Ordi, et al.[25]	Not defined	Listing by the clinician	HIV-related conditions	Sens 33% Spec 97% PPV 67% NPV 90%
Children				
Ansari, et al.[14]	Using several case definitions	Medical records	*Pneumocystis jiroveci* pneumonia	Sens 40-100% Spec 48-91% PPV 36-71%

Sens: sensitivity; Spec: specificity; PPV: positive predictive value; NPV: negative predictive value.

HIV-positive adults and considered as the cause of death in 32-45%[11,13,19,23,24,26]. Tuberculosis was as common in patients selected from pulmonology wards as in unselected hospitalized patients and was disseminated in at least 80% of cases[12,13,19,26]. Martinson, et al. autopsied 47 HIV-positive patients suspected of TB during hospitalization. Tuberculosis was confirmed in 79% of these. Of these, 92% had disseminated TB. The remaining 21% had bronchopneumonia (60%), CMV pneumonitis (50%) and Kaposi's sarcoma (KS) (20%)[21].

Other important pulmonary infections were bacterial pneumonia (present in 23-34%), interstitial pneumonia (present in 17%) and *Pneumocystis jiroveci* pneumonia (PJP, present in 9-14%)[11-13,19,23,24,26]. Only one study reported nocardiosis in 4% of cases[19,32]. Overall, pulmonary infections were present in at least two out of three patients and were the cause of death in nearly half of the patients.

The central nervous system (CNS) was the second most affected organ-system by infections. Bacterial meningitis, tuberculous meningitis, lymphocytic meningitis, cryptococcal meningitis, and cerebral toxoplasmosis were the main diagnoses, together accounting for approximately 20% of the pathology[13,19,26]. Later re-examination of some cases from the Ivory Coast adult series[17] with immunohistochemistry demonstrated both pneumococcal and meningococcal meningitis infections (Lucas S, personal communication).

Noninfectious diseases

Malignancies caused 11-16% of pathology. This consisted mainly of Kaposi's sarcoma (KS). Non-Hodgkin's lymphoma (NHL) appeared rarely if at all in the studies[13,24]. A sub-study from Ivory Coast showed a prevalence of 2.8% NHL in adults, consisting of 1.6% visceral NHL and 1.2% cerebral NHL[33]. Cerebral

lymphoma was reported in only 1% of cases[19,26,33]. Only one recent study from South Africa reported heart conditions, including dilated cardiomyopathy and myocarditis, in 10% of autopsies[31]. None of the studies diagnosed HIV-associated multicentric Castleman's disease, which is increasingly recognized in rich countries as an important cause of multiorgan failure and death in HIV disease[34].

HIV-2 infection

Postmortem findings in HIV-2-infected and dual-HIV-reactive patients were similar to HIV-1-infected patients; only severe multiorgan CMV infection, multinucleate giant cell encephalitis and cholangitis (secondary to CMV and/or cryptosporidium infection) were significantly more frequent in HIV-2-infected patients, occurring in 18% of HIV-2 cases[12,19].

HIV-negative adults

Three complete autopsy series and two partial autopsy series reported on autopsy findings in HIV-negative adults (Table 1). The two main pathology findings were pneumonia (22-40%) and malignancies (13-64%). Tuberculosis was found in 4-16% and caused death in 4-13%. Cardiovascular diseases were described in 13-27% of cases[12,19,23,26]. Abouya, et al. reported a remarkably high prevalence of lung malignancies (64%): 36% primary lung carcinoma, 24% metastatic lung cancer, and 4% NHL.

Maternal death

The prevalence of HIV among 123 women in Mozambique who died during or shortly after pregnancy in the capital referral hospital was 53%[22]. In 65 HIV-positive women, an autopsy was performed. Seventy-one percent of them died of non-obstetric conditions, including HIV/AIDS-related conditions (28%) (15% TB, 8% PJP, 3% KS, 2% malignant lymphoma), bacterial pneumonia (12%), severe malaria (9%), and bacterial meningitis (9%). The main obstetric causes of death were puerperal septicemia (13%) and eclampsia (13%)[22].

Fifty-five percent of the 58 HIV-negative women died of non-obstetric conditions, mainly infections: bacterial pneumonia (16%), severe malaria (14%), and bacterial meningitis (5%). There were no significant differences in obstetric and non-obstetric causes of death (HIV-related conditions excluded) when comparing HIV-positive to HIV-negative women[22].

Children

In the three complete autopsy series, respiratory tract infections, including TB and PJP, were the main diagnoses (89-94%) and the main cause of death (64-79%)[14,20,29]. Bacterial pneumonia was found in 11-58% of children and TB in 1-11%. Interstitial pneumonitis/bronchiolitis ascertained 6-60% of the pulmonary infections and was caused by viral infections (CMV, respiratory syncytial virus, and adenovirus infections), HIV-related lymphoid interstitial pneumonia, or by an unspecified organism. Two of the three complete autopsy series found PJP to be the main opportunistic infection in children, with prevalences of 14-28%[14,20]. *Pneumocystis jiroveci* pneumonia was only found in children under the age of one year. The third study did not find any PJP in the 33 children examined, but included only children on co-trimoxazole prophylaxis[29]. Disseminated CMV infection was reported in 3-43% of children[14,20,29]. Enteritis/enterocolitis was reported in approximately 30% of children and caused death in 0-15%[14,20].

Partial and minimally invasive autopsy series documented PJP in 16% of unselected HIV-positive children and in 20-44% of HIV-positive children with pulmonary complaints[15-17,27,28,30]. *Pneumocystis jiroveci* pneumonia was significantly more prevalent in children under one year old and within this group it was more prevalent in the youngest children[15,16,27]. Other common pulmonary pathogens were CMV (present in 7-44%) and bacteria (present in 5-41%). Tuberculosis was found in 5-18% of the specimens obtained by partial autopsies and in 0-4% of the specimens obtained by percutaneous biopsies[15-17,27,30].

HIV-negative children

Two complete autopsy series and two partial autopsy series reported on HIV-negative children (Table 1)[14,15,17,20]. Respiratory tract diseases were the dominant causes of death in all children, but were more often seen in HIV-infected children (OR: 5.0; 95% CI: 2.4-10.5)[20]. Severe malnutrition was found significantly more often in HIV-positive children and malaria was significantly more often the cause of death in HIV-negative children[20]. Tuberculosis was found in 3-8% of the HIV-negative children[14,20]. *Pneumocystis jiroveci* pneumonia was found significantly more often in HIV-positive children, but was also found in the lung tissue of 7% of the 84 HIV-negative children[15].

Correlation of clinical and pathology findings

Seven studies compared autopsy and clinical diagnoses (Table 2)[11,14,21,23-26]. The clinical diagnosis of TB in adults had a sensitivity of 43-80%, a specificity of 67-76%, a positive predictive value of 56-80% and a negative predictive value of 28%[11,21,23,24,26]. Ordi, et al. reported on the clinicopathologic discrepancies in diagnosis of maternal death for the HIV-positive and HIV-negative autopsy cases together. Diagnostic errors involving cause of death were detected in 40% of maternal deaths. The clinical diagnosis of HIV-related conditions showed a sensitivity of 33% and a positive predictive value of 60%[25]. A clinical diagnosis of PJP in children reached a sensitivity of 50%, a specificity of 91%, and a positive predictive value of 71% if a combination of clinical criteria was being used. Adding chest x-ray results did not improve the accuracy of the clinical diagnosis[14].

Discussion

Major autopsy findings in sub-Saharan Africa

Autopsy studies show that infectious diseases are almost exclusively responsible for the pathology in HIV-positive individuals in sub-Saharan Africa. Tuberculosis is the main cause of death, responsible for almost half of all mortality. *Pneumocystis jiroveci* pneumonia is uncommon in adults, but frequent in children. Cytomegalovirus infection is more common in children. Apart from Kaposi's sarcoma, malignancies are uncommonly reported.

None of the studies mentioned that patients had been on ART. With the ongoing rollout of ART, and with the prolonged use of ART, pathology will probably change[19]. Postmortem studies from developed countries in patients on ART and co-trimoxazole prophylaxis report a decrease in prevalence of opportunistic infections, a decrease in Kaposi's sarcoma, an increase of bacterial infections, and a variable effect on lymphoma[35-37].

In sub-Saharan Africa, so far, the only information on causes of death of patients on ART is based on clinical information from observational cohort studies. These studies mainly describe mortality within the first 12 months after the start of ART[4,6,38]. Leading causes appear to be TB and cryptococcal meningitis, both accounting for approximately 16% of the early mortality after starting ART[4,6,38,39]. The impact of IRIS on mortality seems limited, but may be more important when related to CNS infections[6,7,38,40,41]. Many patients in sub-Saharan Africa still lack timely access to ART and will therefore present to healthcare facilities with advanced HIV disease. The data from the reviewed studies, despite being old, is therefore still valuable since, sadly enough for many patients, circumstances have not yet changed.

Quality of reviewed studies

The quality of the reviewed studies varied widely. Most studies did not describe in detail their inclusion and selection procedure. Many studies included less than 50% of the potential autopsy cases or did not report the number of deaths they did not include. Information of the cases that were not included regarding, for example, demographics or clinical diagnosis is often missing. Some studies mention limited resources compelling them to select only a limited number of patients. Moreover, many studies did not have microbiology or immunohistochemistry at their disposal. This might have led to over- or underreporting of some diseases, e.g. atypical mycobacterial disease, multicentric Castleman's disease and lymphoma. Almost no studies described the definitions used to establish clinical or pathological diagnoses. Many studies did not have access to clinical information to complete the pathology findings to establish a final diagnosis.

Different studies had different objectives and included different populations, making it difficult to compare results. Nevertheless, the reviewed studies invariably show the importance of infectious diseases in all study groups. The comparison of autopsy findings in HIV-positive and HIV-negative individuals is difficult since all studies included HIV-negative individuals from wards where the HIV prevalence was high and therefore they are not representative of all HIV-negative deaths.

Correlation of clinical and pathology findings

The described autopsy series show a weak correlation between clinical diagnosis and pathology findings. Possible reasons may be a low level of suspicion by clinicians, atypical disease presentation, a lack of resources to perform investigations, poor yield of diagnostics, and/or a selection bias in the reviewed studies with over-representation of patients with an unknown clinical cause of death. Another problem is the high proportion of patients admitted to the hospital with first

time HIV diagnosis and advanced clinical disease. These patients are often either too sick to perform diagnostic tests and/or die before any diagnostic tests can be performed. Finally, many studies were done 10-20 years ago when the clinical learning curve of HIV-related clinical pathology was still upward.

Value of autopsy

Autopsy is an important tool. For the bereaved relatives it can answer questions regarding the death of a beloved one and reveal conditions that might have consequences for family members in the longer term. On an institutional level, autopsies can be used for teaching purposes and quality control of the clinical care. Two examples of how pathology findings can influence clinical practice come from the Ivory Coast autopsy cohort[19,32,33]. This study showed the ratio of CNS toxoplasmosis to lymphoma was so high that empirical toxoplasmosis treatment for focal CNS lesions was the rational approach[12]. Also, the 4% prevalence of nocardiosis, an imitator of TB both clinically and radiologically, indicated – yet again – that the diagnosis and management of (smear-negative) TB is not always straightforward (Lucas S, personal communication).

For governments, widespread autopsy practices are the ultimate tool to provide epidemiological data on changing and emerging disease patterns, particularly relating to infectious diseases. Reliable information should guide resource allocation. The pathophysiology of relatively new phenomena, like IRIS, can be studied. Clinically unsuspected conditions including drug toxicities can be revealed and studied at a cellular level. And it is likely that unanticipated new syndromes will emerge among long-term ART-treated patients, which may be drug-related or novel HIV-immune-related; autopsies should identify these.

Challenges to perform autopsies

As the reviewed studies show, autopsies can be done in sub-Saharan Africa. However, a number of obstacles impede their widespread use. To perform autopsies you need a well-equipped mortuary and histopathology department with trained staff able to perform autopsies in a safe manner. Also, ready access to microbiology diagnostics should be available. These requirements are costly and within sub-Saharan Africa often only met in a very limited number of large tertiary teaching facilities or large international study settings. So, the feasibility of autopsy as a common practice intervention is limited and autopsy study results are often only applicable for patients hospitalized in large tertiary teaching facilities. Moreover, standard guidelines for performing autopsies and evaluating the histological findings are lacking.

Another difficulty that arises at a population level is the poor cultural and social acceptance of autopsy practices. This negatively influences both request and acceptance rates. There are at least four autopsy scenarios: consent given by relatives; medico-legal instruction for autopsy without consent (i.e. forensic cases); autopsy by default with opt-outs by relatives (none in this study set); and no consent required at all and no opt-outs (as pertained in four studies[12,19,20,29]). Only the last scenario can provide an epidemiologically representative sampling of cases. However, it is questionable how ethical this scenario is since it disregards the opinions and emotions of relatives and patients.

As shown by Menendez, et al., autopsy rates of 78% can be reached, with consent from family members and without incentive. This is in contrast to the belief that within African society, autopsies are unacceptable because of cultural or religious reasons. Two studies from sub-Saharan Africa report on factors interfering with the acceptance of autopsies by relatives. They found that the uselessness of the results for the relatives, fear of mutilation, concern about delaying the funeral or prior transport arrangements made, traditional beliefs and objection by the deceased prior to death negatively influenced the acceptance of autopsy by the relatives[42,43].

Alternative methods

An option to solve some of the feasibility and acceptance issues is to perform partial or minimally invasive autopsies. In the studies we reviewed, those that performed partial and minimally invasive autopsies included 25-65% of the deaths, compared to 5-78% in those that performed complete autopsies. Because partial and minimally invasive autopsies can focus on an organ of particular interest, they take less time, are less costly, and less mutilating. The tradeoff is incomplete information due to sampling error and the loss of visual judgment of all organs by the pathologist. A study comparing results of needle autopsies with conventional autopsies in adults found a concordance in the cause of death of 67%. In the same study, however, conventional autopsies found an additional major diagnosis in 87% of cases[44]. In neonates, full concordance in cause of death between conventional

autopsy and needle autopsy results was found in 56% of cases and partial concordance in another 12%[45].

Noninvasive autopsy practices, using magnetic resonance imaging and/or multislice computer tomography, can be of additional value if combined with minimally invasive autopsy, but are not yet well enough validated to be used as a replacement for the conventional autopsy[46,47]. Considering the high costs of these techniques and their low availability, they are however not considered a suitable alternative for sub-Saharan Africa in the near future.

Verbal autopsy procedures are an indirect, retrospective method to identify the probable cause of death by questioning the relatives or other associates of the deceased. Afterwards, a doctor reviews the answers and establishes a cause of death. This relatively cheap method is used mainly in resource-limited settings to acquire knowledge on causes of mortality[48]. The information gathered relies on clinical record keeping and the (long-term) memory of relatives or other associates of the deceased. So far, verbal autopsies have only been validated with clinical diagnoses as gold standard[49,50]. Given the earlier discussed high discordance between clinical and postmortem diagnoses, the accuracy and therefore the value of verbal autopsies for HIV-infected persons is very questionable.

Conclusion

Autopsy is an important tool to develop more evidenced-based diagnostic and treatment guidelines, to detect and document adverse events of new treatments, to improve our understanding of the pathophysiology of HIV infection, to discover future research areas, to provide epidemiologic data on disease patterns, and to detect medical errors and weaknesses in healthcare delivery.

Autopsy studies are possible in Africa, yet hurdles need to be overcome to allow a more widespread practice. So far, nearly all autopsy studies in sub-Saharan Africa were performed before the introduction of ART and none of them included patients on ART. In view of the persistently high mortality rates in sub-Saharan Africa and the large-scale use of new treatment regimens, it remains important to determine causes of death, identify emerging syndromes, and describe drug-induced pathology. Partial autopsies can adequately address certain clinical and research questions, but complete autopsies should remain the gold standard in individual patient care. Verbal autopsies, although a feasible alternative, still need adequate validation before solid conclusions can be drawn from their results.

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