Pattern of Diseases in Human Immunodeficiency Virus/AIDS Patients in Lagos University Teaching Hospital: A 1-Year Prospective Autopsy Study

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Abstract

Background and Objective: Nigeria has the second largest number of individuals living with human immunodeficiency virus/AIDS (HIV/ AIDS) in the world after South Africa and contributes about 9% of the global HIV burden. It has also been estimated that there are 336,379 annual new HIV infections and about 192,000 of these individuals die of HIV/AIDS annually in Nigeria. Yet, there is a paucity of autopsy data among HIV/AIDS deaths in Nigeria. The objective of this study was to describe autopsy findings in HIV/AIDS cases in Lagos University Teaching Hospital (LUTH), a tertiary health center in Southwest Nigeria, which has one of the highest autopsy rates in the country. Materials and Methods: This 1-year prospective descriptive study included all HIV-1- and HIV-2-positive cases referred for autopsy examination at the Anatomic and Molecular Pathology Department of LUTH, Lagos, Nigeria. The study population included HIV-positive cases of all ages and sex. Results: Seven hundred and fifty-four autopsies were performed over the study period giving an autopsy rate of 33.1%. Forty-four patients (21 males and 23 females) were found to be HIV positive representing a prevalence of 5.8%. Of these, 23 (53.3%) cases were diagnosed antemortem, while 21 (47.7%) were diagnosed in the autopsy room. The patients' age ranged from 6 h to 69 years with a median age of 34 years. Infections were seen in 27 (61.4%) cases, out of which 13 (48.1%) were AIDS defining infections: 8 (18.2%) of them had tuberculosis, 2 (4.5%) cases of nontuberculous bacterial pneumonia, 1 (2.3%) case each of cryptococcosis, *Pneumocystis jiroveci* pneumonia, and progressive multifocal leukoencephalopathy (2.3%). Two (4.5%) patients had neoplasms (one case each of non-Hodgkin lymphoma and pleomorphic sarcoma). Miscellaneous causes of death included hypertensive heart disease, perforated strangulated right inguinal hernia, perforated ileoileal intussusceptions, and penetrating perineal injury. Conclusion: This study showed a demographic pattern of HIV infection comparable with previous national surveillance data, but a higher HIV seroprevalence than the most recent national surveillance data. Opportunistic infections were the most common cause of mortality in HIV infection and about half of HIV infected persons presented to the autopsy room undiagnosed.

Keywords: Autopsy, human immunodeficiency virus/AIDS, infections

INTRODUCTION

The human immunodeficiency virus (HIV) was discovered in America in 1981 and since then millions of individuals worldwide have been affected by the disease. An estimated 33.4 million individuals are living with HIV worldwide, 2.7 million individuals were newly infected in 2008 and 2 million individuals died of AIDS-related illness in 2008.^[1] In Nigeria, the Federal Ministry of Health indicated that 2.98 million individuals were living with HIV/AIDs in Nigeria in 2009, giving an estimated prevalence of 3.6% in

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a population-based survey.^[2] Nigeria has the second largest number of individuals living with HIV/AIDS in the world after South Africa and contributes about 9% of the global HIV burden.^[2]

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It has also been estimated that there are 336,379 annual new HIV infections and about 192,000 individuals die of AIDS annually in Nigeria.^[2] Scientifically, the study of HIV and AIDS over the past 25 years has been fascinating but it has not led to a cure for the infection, and we do not yet have any really promising leads for microbicides or for vaccines,^[3] and as such, individuals infected with HIV/AIDS have continued to die in significant numbers.

Opportunistic infections causing death in AIDS patients are often times not diagnosed before death.^[4] Autopsy may identify diseases that were not clinically suspected or diagnosed and permit additional assessment of the effectiveness of treatment modalities and diagnostic tests.^[4,5] For this reason, the performance of autopsy on patients who have died of HIV/AIDS can be of great value to physicians caring for these patients.^[4-6] In the early days of the HIV/AIDS pandemic, autopsy played a major role in establishing AIDS-defining diseases and described organ changes in HIV/AIDS. The contributions of autopsy in HIV include clinicopathological follow-up, descriptive clinical pathology, epidemiology of HIV disease, endpoints in clinical trials, drug efficacy and toxicity, specific organ banks, and education.^[4,5]

The use of highly active antiretroviral therapy (HAART) has increased the survival rate of HIV infected patients giving room for profound organ changes in these patients. Although effective prevention and treatment has helped to ameliorate the development of certain AIDS-related conditions, it has also allowed other illnesses to quickly become the cause of death.^[6] While some HIV-positive Nigerians have access to HAART, a large number of individuals living with HIV/AIDS do not have access to treatment either because of distance from health centers, ignorance of HAART centers, lack of awareness, fear of stigmatization or denial of their HIV status, or beliefs in some sort of religious or traditional cure for the disease. Thus, the number of people dying from the disease may actually be more than is estimated.

Yet, there is a paucity of autopsy data among HIV/AIDS deaths in Nigeria, dearth of information about the number of HIV-positive patients submitted for autopsy and the autopsy pathology in HIV/AIDS disease in the country. The objective of this study is to describe the autopsy findings in HIV/AIDS cases in Lagos University Teaching Hospital (LUTH), a tertiary health center in Southwest Nigeria, which has one of the highest autopsy rates in the country.

MATERIALS AND METHODS

This 1-year prospective descriptive study consisted of all HIV-1- and HIV-2-positive cases referred for autopsy examination at the Anatomic and Molecular Pathology Department of LUTH, Lagos, Nigeria. Cases with previously known HIV-positive status, as well as cases initially detected just before postmortem examination were included in the study. Patients whose HIV-positive status was confirmed antemortem by Western blot or PCR were not screened. The study population included HIV-positive cases of all ages and gender. Ethical approval for the study was obtained from the Ethics Committee of LUTH, while informed consent for autopsy was obtained from family members of the deceased.

At autopsy, 2 mls of blood was collected from the heart or jugular veins of patients of unknown HIV status referred for autopsy using 2 mls syringes. Blood samples collected were tested within minutes of blood collection using ELISA-based techniques: Determine^R HIV-1/2, an *in vitro* visually read, qualitative immunoassay for the detection of antibodies to HIV-1 and HIV-2 in human serum, plasma, or whole blood (Inverness Medical Japan Co., Ltd., Chiba, Japan). All the whole blood or sera that reacted to this test kit were further tested using another ELISA-based test kit Uni-GoldTM HIV^R (Trinity Biotech Plc., Bray, Ireland). The whole blood or serum that reacted to both test systems was considered HIV positive. The two test kits used were sensitive to both HIV-1 and HIV-2 but could not distinguish between the two.

The results of these tests were handled with utmost confidentiality and were strictly used for research purposes and not for the relatives of the deceased. All clinical data and results of investigations were retrieved from the patients' files and these were correlated with the autopsy findings.

Complete autopsy was performed including removal of brain (but not spinal cord or eyes) on all cases. The macroscopic morphological changes in the organ systems as seen at autopsy were documented. Representative 2–3 tissue sections each were taken from the brain, lungs, liver, and kidneys. The tissue sections were fixed immediately in 10% formalin for a minimum of 72 h. Histological slides were prepared from the tissue sections and examined microscopically. All sections were stained with hematoxylin and eosin (H and E). In addition, special stains were applied as required to confirm diagnosis that was suggested by H and E: Ziehl–Neelsen stain to demonstrate mycobacteria, Grocott's methenamine silver stain, and periodic acid Schiff (PAS) stain to detect fungal organisms. The histological diagnosis of neoplasms was based on the standard diagnostic criteria for the respective tumors.

The cause of death was based on autopsy and histopathological findings. Cause of death was categorized as primary or secondary cause. The primary cause of death was the disease that resulted in death without which the death would not have occurred at that time. The secondary cause of death was any coexisting disease that was involved in causing death but was not the immediate disease that led to death. The data obtained were subjected to descriptive analysis and results displayed as charts and tables.

RESULTS

There were 2278 deaths in LUTH, Lagos and 754 autopsies were performed between January 1, and December 31, 2011. The autopsy rate during the study year was 33.1%. Forty-four

of the 754 cases were found to be HIV-1 and HIV-2 positive. Hence, the seroprevalence of HIV among autopsies done at LUTH within the study period was 5.8%. The ages of these patients ranged between 6 h and 69 years [Figure 1]. The median age was 34 years. There were 21 males and 23 females with a male-to-female ratio of 0.9:1. The peak age of occurrence was found in the 30–39 years age group. Of the 44 HIV-positive patients, 23 (53.3%) were diagnosed antemortem, while 21 (47.7%) were diagnosed in the autopsy room.

None of the patients had the possible route of infection documented. Six (13.6%) of the 44 patients were aged <1 year at the time of demise - 6 h, 7 days, 3 weeks, 3 months, 7 months, and 8 months old, respectively. Five of these six patients were diagnosed antemortem while one was diagnosed postmortem. All these patients were born to retroviral disease positive mothers with a possible route of infection being vertical transmission following perinatal exposure. Four were delivered by spontaneous vertex delivery while two were delivered by emergency cesarean section at term. Prevention of mother-to-child transmission (PMTCT) was practiced in only two of these six cases.

Eleven (47.8%) of the 23 cases diagnosed with HIV antemortem had the date of diagnosis and the duration of illness documented. Of these 11 patients, 6 of them were diagnosed <1 year before their demise, one was diagnosed a year before demise, two of them two years before demise and two were diagnosed 4 years before demise.

Of the 23 cases diagnosed antemortem, 9 (39.1%) had records about the use of HAART. Eight of these had been on HAART while one patient who had been diagnosed <1 year before demise had not been placed on HAART. The reason for not commencing HAART in this patient was not stated in the clinical records. One of the patients on HAART was diagnosed 4 years before demise and had been on HAART on and off in the entire period. The reason for this could not be ascertained from the records.

Most of the patients presented to the hospital late in their illnesses and died shortly after presentation. Twelve (27%) of the 44 patients were brought in dead and little or no clinical history was provided. 20 (45%) patients died within 24 h of presentation and another 12 (27%) died after 24 h of presentation.

Table 1 summarizes the primary causes of death seen in HIV/AIDS patients at autopsy. The most common findings were infective cases which were seen in 27 (61.4%) patients. There were 8 (18.2%) cases of tuberculosis confirmed by Ziehl–Neelsen stain [Figures 1-3]. All eight cases had pulmonary involvement, 7 had hepatic involvement, 3 had splenic involvement, 2 had intestinal involvement, and 1 had renal involvement. One of the 8 patients, a 47-year-old male had a left occipital tuberculoma. There were also three cases of nontuberculous pneumonia. Of the 4 patients with septicemia, one each had fecal peritonitis and puerperal

Table 1: C	auses of	death	in	human	immunodeficiency
virus/AIDS	patients	s seen	at	autopsy	1

Cause of death	Male	Female	Total (%)
Infections			
Tuberculosis	4	4	8 (18.2)
Meningitis/encephalitis	0	5	5 (11.4)
Septicemia	3	1	4 (9.1)
Pneumonia	0	3	3 (6.8)
Gastroenteritis	2	1	3 (6.8)
Progressive multifocal leukoencephalopathy	1	0	1 (2.3)
Disseminated cryptococcosis	1	0	1 (2.3)
Puerperal sepsis	0	1	1 (2.3)
Septic abortion	0	1	1 (2.3)
Neoplasms			
Non-Hodgkin lymphoma	1	0	1 (2.3)
Pleomorphic sarcoma	0	1	1 (2.3)
Hematological diseases			
Sickle cell anemia	0	1	1 (2.3)
Disseminated intravascular coagulopathy	0	1	1 (2.3)
Severe anemia	0	1	1 (2.3)
Perinatal disorders			
Prematurity	1	1	2 (4.5)
Meconium aspiration	1	0	1 (2.3)
Miscellaneous disorders			
Hypertensive heart disease	4	0	4 (9.1)
Intraventricular hemorrhage	0	1	1 (2.3)
Intussusception	0	1	1 (2.3)
Strangulated inguinal hernia	1	0	1 (2.3)
Subtotal lung collapse	1	0	1 (2.3)
Traumatic rectal perforation	1	0	1 (2.3)
Total	21	23	44 (100)

sepsis and the cause is unknown in two cases. Three patients had nontuberculous pneumonia. One case each had lobar pneumonia, *Pneumocystis jiroveci* pneumonia, and disseminated *Cryptococcus neoformans* infection with bronchopneumonia and meningitis, the organisms were demonstrated by PAS and Gomori methanamine silver stains [Figures 4 and 5]. There was one case of progressive multifocal leukoencephalopathy (PML) [Figure 6].

AIDS-defining opportunistic infections were found in 13 (29.5%) of the 44 patients seen in this study. Eight (18.2%) of them had tuberculosis, two (4.5%) cases of nontuberculous bacterial pneumonia, and one (2.3%) case each of cryptococcosis, *P. jiroveci* pneumonia, and progressive multifocal leukoencephalopathy. There were two cases of oral candidiasis which did not involve the esophagus.

Hypertensive heart disease was the primary cause of death in four cases (9.1%). Two of these cases had congestive cardiac failure and one patient had uremic pericarditis.

Two (4.5%) patients had malignant neoplasms: one had non-Hodgkin lymphoma (NHL), [Figure 7] while the other had retroperitoneal pleomorphic sarcoma [Figure 8]. Both

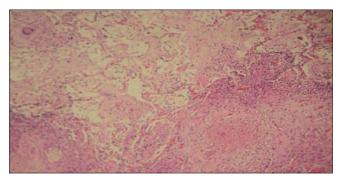


Figure 1: Pulmonary tuberculosis in a 48 year old man showing caseating granulomas with a Langhans type giant cell seen in the top left corner (H and E, $\times 100)$

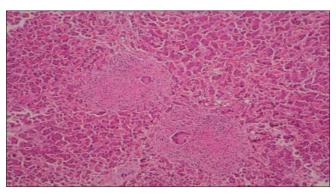


Figure 2: Granulomatous hepatitis in a 26-year-old woman showing caseating granulomas with central necrosis, epithelioid cells, and giant cells (H and E, \times 100)

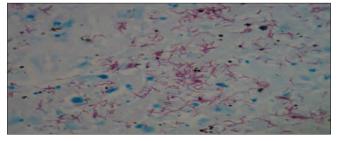


Figure 3: Photomicrograph showing pink staining acid–fast bacilli on a blue background (Ziehl–Neelsen stain, $\times 1000$)

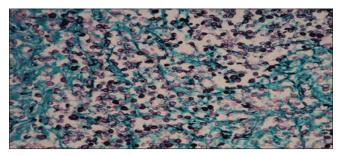


Figure 5: Pulmonary cryptococcosis in a 42-year-old male shows budding cells of *Cryptococcus neoformans* (Gomori methanamine silver stain, \times 400)

malignancies had spread to the lungs and the liver at the time of the autopsy.

Miscellaneous causes of death included perforated strangulated right inguinal hernia, perforated ileoileal intussusception, and a case of penetrating perineal injury in an architect who fell astride a sharp object at a building site.

Significant wasting was seen in 10 patients. Four of these patients had pulmonary and/or disseminated tuberculosis, two each had severe anemia and malignant neoplasms, while one had septicemia and another patient had bilateral nontuberculous bronchopneumonia.

The spectrum of liver pathology seen in this study was variable. Steatosis was the most common finding, occurring in 20 (45.5%) cases. Other findings were 7 (15.9%) cases of granulomatous hepatitis, 5 (11.4%) cases of chronic

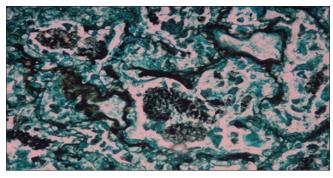


Figure 4: *Pneumocystis jiroveci* pneumonia in a 32-year-old pregnant woman showing pulmonary intraalveolar exudates that contain cysts of *Pneumocystis jiroveci* (Gomori silver methanamine stain, ×400)

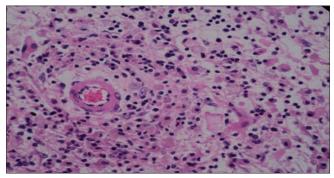


Figure 6: Progressive multifocal leukoencephalopathy in a 53-year-old male shows bizarre astrocytes, foamy macrophages, and large oligodendrocytes with intranuclear inclusions (H and E, \times 400)

nonspecific hepatitis, and 1 (2.3%) case each of metastatic NHL and pleomorphic sarcoma. Five (11.4%) cases showed necrosis while the remaining five (11.4%) cases showed normal histology.

The most common renal finding in this study was acute tubular necrosis seen in 17 (38.6%) cases. There were individual cases of end-stage renal disease and HIV-associated nephropathy. Features of renal tuberculosis were seen in one patient and a cholesterol granuloma in a patient with hypertensive heart disease and congestive cardiac failure. Renal infarcts were seen in a patient with disseminated intravascular coagulation.

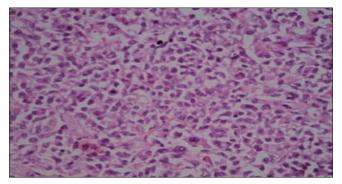


Figure 7: Non-Hodgkin lymphoma in a 42-year-old male showing a section of a lymph node with large pleomorphic lymphocytes that contain nuclei with open chromatin. There are abnormal mitotic figures (H and E, $\times 100$)

DISCUSSION

The autopsy rate during this study period was 33.1%. Autopsy rates in LUTH have been relatively high and with the introduction of the Coroner's law by Lagos State Government in 2008, the rate has further increased and appears to have steadied between 30% and 40%. Pediatric autopsy rate of 25.3% was previously reported in this center by Abdulkareem *et al.*^[7] Our autopsy rate was high compared with autopsy rates of 3.6%–19.9% in Ibadan^[8] and in northern Nigeria where Rafindadi^[9] recorded 140 autopsy cases in 2 years. Religious and cultural practices are known to exert a strong influence in the decision of the relatives of the deceased to accede to a request for postmortem.^[10-12]

Our 5.8% HIV seroprevalence rate concurs with the 5.4% and 5.7% obtained in the unlinked anonymous sentinel surveillance system and among emergency room patients in LUTH, respectively.^[13,14] The unlinked anonymous sentinel surveillance system is the mainstay of HIV surveillance system in Nigeria. The 2010 sentinel survey^[15] puts the national prevalence at 4.1% which is lower than that found in this study. The fact that about half of our cases were diagnosed postmortem supports the claim that HIV prevalence in the country is under-reported. The peak age of occurrence of HIV in this study falls within the 30–39-year age group. This corroborates the findings from other local^[16] and international studies^[17] which show the highest prevalence in the sexually active age group.

Six (13.6%) of the HIV-positive cases seen in this study were found in infants <1 year. Only two of these patients were born to a mother who had PMTCT. Mother-to-child transmission of HIV occurs when an HIV-infected woman passes the virus to her baby during pregnancy, labor, and delivery or breastfeeding. PMTCT is done by effective voluntary testing and counseling, access to antiretroviral therapy, safe delivery practices, and the widespread availability of breast-milk substitutes.^[18]

Twelve (27%) cases seen in this study were brought in dead and 20 (45%) others died within 24 h of presentation. Lucas

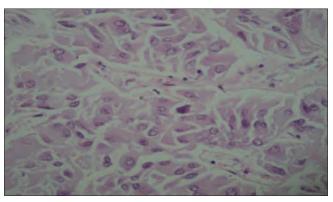


Figure 8: Pleomorphic sarcoma in a 30-year old woman showing numerous large bizarre mesenchymal cells with abundant eosinophilic cytoplasm (H and E x 400)

et al.^[19] working in Abidjan's two largest hospitals showed that HIV-positive patients presented to the hospital with advanced disease and high mortality in the first 24 h of presentation. The reasons for late presentation and high mortality may be due to inadequate health awareness, lack of accessible treatment centers, remaining in denial of the retroviral status even after being diagnosed, religious beliefs or belief in the use of alternative medicine. Thus, there is a need for greater awareness on the benefits of early diagnosis of HIV and commencement of antiretroviral therapy to ensure longer survival time.

Opportunistic infections remain the major cause of death in most AIDS patients in most parts of the world^[6] and accounts for most common postmortem findings in HIV/AIDS.^[20] This is not surprising since HIV targets CD4 + T-cells which play a central role in both cellular and humoral immunity. Opportunistic infections were found in 13 (29.5%) of patients seen in this study. The 18.1% prevalence of tuberculosis is in keeping with European studies which recorded tuberculosis infection rates of 11%-40% among HIV patients.^[21,22] Tuberculosis is known to be a common immediate and contributory cause of death in HIV-positive patients.^[23-25] The introduction of HAART has significantly reduced the incidence of opportunistic infections.^[26] One of our patients who died of disseminated tuberculosis stopped taking her antiretroviral drugs 4 months before she presented with the illness. The reason for discontinuing her HAART drugs could not be ascertained from the clinical records. Most often, opportunistic infections are not diagnosed antemortem.^[27] Thus, a high index of suspicion of all possible infections is required from physicians for diagnosis and adequate management of these patients. In this study, the prevalence of P. jiroveci pneumonia was 2.3% which is similar to reports from Abidjan^[19] and Mumbai^[28] but at variance with Western studies^[6] where higher prevalence was reported.

Two (4.5%) of the cases had malignant neoplasms; one had NHL and another retroperitoneal pleomorphic sarcoma. The incidence of NHL after HIV seroconversion rises exponentially with increasing duration of HIV infection and there is a 12-fold relative increase in older patients.^[29] By controlling HIV

replication with combination therapies, HAART improves immune function and its use is associated with reduce incidence of Kaposi sarcoma and NHL, the two most common AIDS-associated cancers.^[30,31] The only case of NHL found in this study was in a 42-year-old male and was found at autopsy to have spread to the liver and the spleen. A Mexican study^[32] recorded NHL prevalence of 9.0%.

Pulmonary lesions are the most common causes of morbidity and mortality in HIV infection.^[19,33] Pulmonary pathology was seen in 15 (38.1%) of our cases. This study found that tuberculosis (18.1%) was the most common pulmonary infection followed by bacterial pneumonia (4.5%) and then 2.3% each of cryptococcal and *P. jiroveci* pneumonia infections. Lucas^[5] reported similar findings of 38% tuberculosis and 3% each of cryptococcosis and *P. jiroveci* pneumonia.

Central nervous system lesions were found in 11 (25%) patients, a finding consistent with a study in USA,^[34] in which 32% of their patients had CNS affectation, but at variance with other studies in India^[35] where they found CNS diseases in 79% of cases. This variation may be due to small sample size in this study. PML is a fatal progressive demyelinating brain disease due to infection by the polyomavirus JC. The only case found in this study was in 53-years old known HIV-positive male who was being managed for an organic brain disorder in a neuropsychiatric center. He later developed tonic–clonic seizures and inability to move the left side of his body. Autopsy revealed multiple areas of softening of the right hemispheric white matter. Histology showed foamy macrophages, bizarre astrocytes, and large oligodendrocytes with intranuclear inclusion body.

Steatosis was the most common hepatic pathology seen in this study. Steatosis is a common histopathological finding in the liver in AIDS and it may be a rare complication of antiretroviral therapy.^[36] Liver biopsy in adult AIDS patients will often show granulomas, and most of these are due to mycobacterial infection.^[36] In this study, all granulomatous hepatic lesions seen were due to mycobacterial infection. The two malignancies seen in this study both involved the liver. Our one (2.3%) case of NHL with metastasis to the liver is in keeping with the findings of Echejoh et al. who reported 3% of secondary lymphoma in HIV/AIDS patients in Jos.[37] NHL may appear in liver in association with widespread dissemination and only rarely as a primary tumor.^[36] No case of liver cirrhosis was found. If chronic liver disease is present, it is probably part of a process that preceded HIV infection, but the clinical course may be more aggressive than in the non-HIV infected patient.[36,38]

The most common renal lesion found in this study was acute kidney injury in 38.6% of cases. Tubulointerstitial injury which includes acute tubular necrosis, interstitial nephritis, diffuse infiltrative lymphocytosis syndrome, renal infection, and neoplasms predominates in most autopsy-based studies, whereas glomerular disease is most frequently identified in biopsy-based studies.^[39] Sepsis, vomiting, diarrhea, and a

number of pharmacological agents used to treat opportunistic infections seen in AIDS are all possible causes of acute tubular necrosis.^[40] The antiretroviral agents cidofovir and ritonavir can also produce ATN.^[40] This study found HIV-associated nephropathy (HIVAN) in one (2.3%) patient. The most common histological finding in HIVAN is collapsing focal segmental glomerulosclerosis.[40-42] Other findings in HIVAN include epithelial cell hypertrophy and proliferation, microcystic dilatation of the tubules, and interstitial infiltration with inflammatory cells and cast (debris) in the tubular lumen.^[40] The only case with HIVAN in this study had collapsed glomeruli, acute kidney injury, subintimal hyalinosis of the arterioles, and interstitial fibrosis. HIVAN occurs almost exclusively in patients of African descent^[40,43] and patients with end-stage renal disease (ESRD) secondary to HIVAN are more likely to have a family history of ESRD.^[40,43]

CONCLUSION

This study showed a demographic pattern of HIV infection comparable with previous national surveillance data but a higher HIV seroprevalence than the most recent national surveillance data. Opportunistic infections were the most common cause of mortality in HIV infection and about half of the HIV-infected persons presented to the autopsy room undiagnosed.

Recommendation

The use of HAART has drastically reduced the prevalence of AIDS defining illnesses but requires access and compliance to the use of the drugs on the side of the patient. Thus, sustained awareness campaign is required to sensitize the public on the need to encourage HIV-positive patients to access and use these drugs. There is also a need for care providers to have a high index of suspicion of all types of opportunistic infection in HIV patients. Early identification and treatment of these infections will optimally benefit the patients. Strict adherence to universal safety precautions in handling every autopsy case is advised.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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