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CLINICAL AND LABORATORY CHARACTERISTICS OF HOSPITALISED PATIENTS WITH NEUROLOGICAL MANIFESTATIONS OF HIV/AIDS AT THE NAIROBI HOSPITAL

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ABSTRACT

Objective: To determine the profile of clinical and laboratory characteristics of hospitalised HIV positive patients with neurological complications at a private hospital in Nairobi, Kenya from January 2000 to June 2005.

Design: Retrospective observational study.

Setting: The Nairobi Hospital, Nairobi, Kenya.

Subjects: One hundred and fifty hospitalised patients.

Results: Records of 708 HIV positive hospitalised patients were reviewed, 150 patients had neurological complications; giving a six-year point prevalence of 21.2%. Males were 86 (57.3%) and females 64 (42.7%) M: F ratio = 1.3:1. Mean age was 38.84 years. The five commonest neurological complications were; cryptococcal meningitis 33 (22%), encephalitis 28 (18.7%), cerebral toxoplasmosis 19 (12.7%), stroke 19 (12.7%) and tuberculous meningitis 16 (10.7%). Overall, 72 patients (63%) had CD4+ counts done. Cryptococcal meningitis patients' CD4+ count, (mean 60, median 17, range 1-273/cmm). Encephalitis patients' CD4+count, (mean 82, median 54, range 3-495/cmm). Cerebral toxoplasmosis patients' CD4+count, (mean 59, median 58, range 11-120 /cmm). Stroke patients' CD4+ count, (mean 120, median 30, range 15-394/cmm) and Tuberculous meningitis patients' CD4+ count, (mean 67, median 62 and range 12-1 54/cmm). The other rare neurological manifestations included peripheral neuropathy, HIV associated dementia (HAD), myelopathy and myopathy amongst others. One hundred and eight (72%) patients were on anti-retroviral therapy. The commonest drugs used in various regimen combinations included efavirenz and combivir. Fourteen (9.3%) patients died while in hospital; eight of them were among those with the top five neurological complications.

Conclusion: The findings show that patients come to hospital when severely immune compromised and hence have overwhelming opportunistic infections. The profile of opportunistic infection is comparable to that observed in studies elsewhere. Some of the facts observed here may not reflect the situation in public health institutions where resources are scarce.

Recommendation: To do a multi-centre prospective study of neurological manifestations of HIV/AIDS.

INTRODUCTION

Human Immune-deficiency virus causes multi-system infections; therefore Acquired Immune Deficiency Syndrome is a multi-system disease.

Many organ-systems including the lungs, reticulo-endothelial system, gastro-intestinal system, cardiovascular system and the nervous system amongst others are involved. Involvement of the nervous system is fraught with significant morbidity and hence adverse economic consequences. Diagnosis of neurological manifestations is often delayed because often time's clinical presentation is mundane and subtle in the early stages of disease.

Human immune-deficiency virus infects glial cells and astrocytes but not the neurons. It has been documented that central nervous system infection occurs very early possibly as early as the first week of acquiring HIV infection. The virus is neurotropic; it enters microglial cells via surface receptors and co-receptors. The primary receptor is the CD4+ molecule and co-receptors are CCR5 and CxCR4; CxCR4 seems to be common in blacks and is probably more pathogenic than CCR5 (1-5).

Viral tropism may influence HIV-related pathogenesis. This may explain their increased pathogenicity (2,6).

The Blood Brain Baffler (BBB) plays a significant role in HIV infection and presumably; efficacy of anti-retroviral therapy. The central nervous system has been documented as one of the sanctuary sites for HIV infection (7-9).

Some anti-retroviral drugs cross the BBB in significant virological efficacious concentrations; these include zidovudine (has the highest CSF penetration), followed by abacavir and nevirapine; the others are lamivudine, stavudine, efavirenz and lopinavir/ritonavir (Kaletra). Indinavir is the only PI that is least protein bound and hence crosses the BBB in significant concentrations. Some suggestions have been made for neuro-HAART regimen consisting of at least three of these drugs; be used in patients with neurological complications of HIV/AIDS. Controversy exists as regards this suggestion; studies are on-going (10-14).

Some antiretroviral drugs have been associated with mitochondrial toxicity manifesting as peripheral neuropathy and myopathy, these particularly include the 'D' drugs: ddl, d4T and ddC (15-17).

Adjuvant therapy has been advocated; they are thought to protect the CNS against neurotoxicity of HIV infection. These drugs include pentoxyphylline, nimodipine, and selegline. They may be tried but no express recommendations are yet available from evidence based studies (18).

There are some factors that increase the incidence of opportunistic infections in HIV/AIDS patients. These include HIV related immune dysfunction, CD4+ cell depletion, chronic hyper immune activation and neuronal damage brought about by proliferation of cytokines such as tumour necrosis factor (TNF-α) and Alfa μ-RNA; neurotoxic viral components such as gpl2o, gp 160, Tat, Nef and Vpr. (19-23).

Neurological manifestations in HIV/AIDS are basically of two categories. There are those manifestations thought to be related to the primary HIV infection such as aseptic meningitis, minor cognitive motor disorders, HIV-Associated Dementia (HAD), vacuolar myelopathy, peripheral neuropathy and myopathy. The other category comprises opportunistic infections; these include cryptococcal meningitis, cerebral toxoplasmosis, encephalitis, tuberculous meningitis, tuberculoma, encephalitis, herpes zoster infection, progressive multifocal leuco-encephalopathy (PML), primary CNS lymphoma (PCNSL) amongst others (9).

There are a group of manifestations such as ischaemic stroke, intra-cerebral haemorrhage, cerebral venous sinus thrombosis (CVST) sub-dural haematoma and deep venous thrombosis which are related to the phenomenon of vasculitis and deficiency of factors like Anti-thrombin 111, Proteins and Protein-C (24-27). Various neurological manifestations in HIV/AIDS have been shown to occur at various CD4+ cell counts levels (28).

Complications such as Guillaine Barre like syndrome, myopathy, aseptic meningitis, Bell's palsy, herpes zoster dermatosis occurs very early in disease at CD4+ cell counts above 500 c/ml.

Mono-neuritis multiplex is seen at CD4+ cell counts between 200 and 500 c/ml. A majority of severe complications such as PML, HIV associated dementia complex, vacuolar myelopathy, progressive radiculopathy and tuberculous meningitis tend to occur when CD4+ cell counts fall below 200c/ml.

In severe immune compromised state; with CD4+ cell counts below 100c/ml complications

such as herpes simplex encephalitis, disseminated CMV infection, cerebral toxoplasmosis, cryptococcal meningitis and PCNSL are seen.

Patients seen in developing countries with resource poor health facilities tend to develop the latter complications. Approximately 15% of patients with one related CNS opportunistic infection have a second CNS opportunistic infection present. Clinicians must not lose touch of this (29- 33). The advent of HAART has tremendously changed the epidemiology neuro-AIDS (34,35).

The study was conducted to evaluate clinical and laboratory profile of patients with neurological manifestations of HIV/AIDS in a leading private hospital in Nairobi, Kenya.

MATERIALS AND METHODS

This was a retrospective descriptive study. The study period was January 2000 to June 2005. All consecutive file records of patients admitted to the hospital under the Division of Medicine with HIV infection were isolated from the records department of The Nairobi Hospital.

The files were scrutinised and those patients who had neurological manifestations were further isolated. These later files were perused in detail and the following data extracted; age, gender, the presenting clinical symptoms and signs, CD4+ cell counts and HIV viral load at admission. The final diagnosis/es of neurological manifestation/s were recorded.

Case Definition

Cryptococcal meningitis: CSF positive for Indian ink stain and/or positive for CRAG

Encephalitis: The diagnosis of encephalitis was clinical. Aetiology of encephalitis was presumed viral if CSF studies were negative for bacterial, fungal and or syphilis infections as on record.

The patients were subsequently put on acyclovir or cymervene therapy with observable recorded responses.

Cerebral toxoplasmosis: The diagnosis of cerebral toxoplasmosis was presumptive; based on clinical presentation, neuro-imaging study results and response to appropriate therapy as on record.

Stroke: (Ischaemic and haemorrhagic) Diagnosed by exclusion: Patients with neurological deficits due to lesions such as cerebral toxoplasmosis, cryptococcoma, Acute Disseminated Encephalomyelitis (ADEM), cerebral abscess, tuberculoma, Primary CNS Lymphoma (PCNSL), encephalitis etc were excluded having perused records of neuro-imaging on file.

Tuberculous meningitis: Diagnosis of tuberculous meningitis was based on clinical picture, raised CSF protein, neuro-imaging features of basal meningeal enhancement or negative bacterial antigen assay for bacterial meningitis and response to anti-tuberculosis therapy as on record.

The use of anti-retroviral therapy and their various combinations was recorded. The final outcome at the end of hospital stay was recorded. The various neuro-imaging methods performed were recorded but is not the subject of this write-up.

If patients were re-admitted with the same neurological manifestations as that of the previous admission/s, no repeat record was made, however, if patients were re-admitted with different neurological manifestations from that of previous admission; these were recorded as separate entities and the CD4+ cell count and viral load count were recorded as well.

Data was computerised using SPSS 10.0 software. Data cleaning and verification before analysis was done using SPSS 10.0 and Epi.1 Info. 2002 software. Data analysis was basically frequency analysis giving rise to mean, mode, median and descriptive proportions.

RESULTS

A total of 708 HIV positive patients were admitted to the hospital under the Division of Medicine during the study period of January 2000 and June 2005.One hundred and fifty of these patients had neurological manifestations; giving a six-year point prevalence for neuro-AIDS of 21.2% amongst hospitalised patients in the Division of Medicine.

The 150 patients who had neurological manifestations were analysed in detail. Males comprised 86 (57.3%) and females 64 (42.7%) (M:F ratio = 1.3:1). Figure 1 shows the age group distribution of these patients.

The five most frequent neurological manifestations are shown in Table 1. The miscellaneous diagnostic category in Table 1 includes peripheral neuropathy,
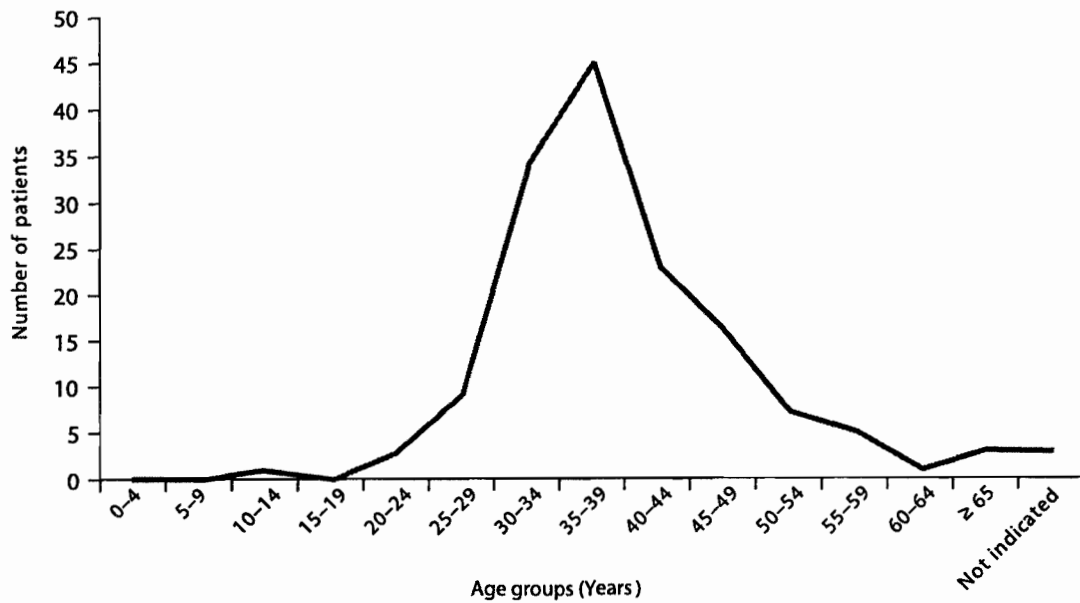
Table 1

The various neurological manifestations observed

Neurological manifestation	Frequency	(%)
Cryptococcal meningitis	33	22.0
Encephalitis	28	18.7
Cerebral toxoplasmosis	19	12.7
Stroke syndrome	19	12.7
Tuberculous meningitis	16	10.7
HAD.PN/Myelopathy/Myopathy	21	14.0
Miscellaneous	14	9.3
Total	150	100.1

HAD = HIV Associated Dementia

PN = Peripheral Neuropathy

HIV associated dementia, myelopathy and myopathy amongst others. These are neurological manifestations thought to be primarily related to HIV infection, the prevalence of which has dropped significantly in the HAART era.

Patients with the five most frequent neurological complications were analysed in more detail. Their age, gender distribution, clinical presentation, CD4+ cell count, viral load count and outcome at end of hospital stay were noted. Each of the complications i.e. cryptococcal meningitis, encephalitis, cerebral toxoplasmosis, stroke and tuberculous meningitis is detailed.

In the review of treatment sheets, one observes 'blanket therapy' in patients with tuberculous meningitis including broad spectrum antibiotic therapy and anti-tuberculosis therapy.

Cryptococcal meningitis (33 patients): Males were 21 (63.6%); females were 12 (36.4%) (M:F ratio= 1.8:1). Mean age was 38.4 years. Clinical presentation; symptoms were multiple, 31 (93.5%) patients had headache, 15 (45.5%) had confusion, eight (24.2%) had projectile vomiting, eight (24.2%) had fever, eight (24.2%) had cranial nerve palsies, four (12.1%) had visual obscurations. Other rare clinical presentations included seizures, impaired hearing

and limb weakness. CD4+ count, (mean 60, median 17 and range 1-273/cmm). One patient died, 29 were discharged home and three were transferred to other hospitals.

Encephalitis (28 patients): Males were 17 (60.7%), females 11 (39.3%) (M:F ratio = 1.5:1). Mean age was 40.8 years. Clinical presentation; 22 (78.6%) had confusion, 17 (60.7%) had various focal motor neurological deficits, 10 (35.7%) had headaches, nine (32.1%) had seizures, nine (32.1%) had fever, six (31.4%) presented in coma. Other rare clinical presentations included bladder sphincter dysfunction, speech disorders, gait ataxia, and cranial nerve palsies. CD4+ count, (mean 82, median 54, range 3-495/cmm). Five (17.9%) patients died, 18(64%) were discharged home and five (17.9%) were transferred to other hospitals.

Cerebral toxoplasmosis (19 patients): Males were eight (42.1%), females 11 (57.9%) (M:F ratio = 0.7:1). Mean age was 36.7 years. Clinical presentation; 19 (100%) patients had various forms of focal motor neurological deficits, 12 (63.2%) had headaches, eight (42.1%) had confusion, five (26.3%) had seizures and four (21.1%) had fever. Rare clinical presentation included speech disorders, vomiting and visual obscurations. CD4+ count, (mean 59,

median 58 and range 11-120/cmm). One patient died, 17 (89.5%) were discharged home and one was transferred to another hospital.

Stroke (19 patients): Males were 11 (57.9%) and females eight (42.1%) (M:F ratio = 1.4:1). Mean age was 39 years.

Clinical presentation: Nineteen (100%) patients had motor deficits in various limbs, 14 (73.7%) had headaches, 11(57.9%) had speech disorders, nine (47.4%) had seizures and four (21.1%) had fever. CD4+ count, (mean 120, median 30 and range 15-394/cmm). One patient died, 18 were discharged home.

Tuberculous meningitis (16 patients): Males were 11(68.8%) and females were five (31.3%) (M:F ratio = 2.2:1). Mean age was 32.9 years.

Clinical presentation: Eleven (68.8%) patients had headaches, eight (50%) had focal motor deficits, eight (50%) had confusion, five (31.3%) had fever, and five (31.3%) had projectile vomiting. Rare clinical manifestations included bladder sphincter disturbance, visual obscurations and speech disorders. CD4+ count, (mean 67, median 62 and range 12-154/cmm). All the patients were discharged home.

Table 2

The different ARTs combinations used in the study patients

Anti-retroviral drug combinations	Frequency	(%)
Combivir+ Efavirenz	46	30.7
Didanosine+Stavudine+Efavirenz	17	11.3
Combivir+Nevirapine	9	6.0
Combivir +Indinavir	9	6.0
Stavudine+Efavirenz+Lamivudine	7	4.7
Didanosine+Stavudine+Nevirapine	5	3.3
Lopinavir+Trizivir	3	2.0
Nelfinavir+ Ritonavir+ Saguingvir	1	0.7
Combvir+Efavirenz+Retrovir	1	0.7
Combivir+Nelfinavir	1	0.7
Stavudine+Indinavir+Lamivudine	1	0.7
Stavudine+Combivir+Efavirenz	1	0.7
Didanisine+Stavudine+Zidovudine	1	0.7
Didanosine+Efavirenz+Nevirapine	1	0.7
Abacavir+Combivir+Ritonavir+Saguinavir+Efavirenz	1	0.7
Not given	42	28.0
Total	150	100

E A S T A F R I C A N M E D I C A L J O U R N A L

One hundred and eight (72.0%) patients were on anti retroviral therapy. Table 2 shows the various anti-retroviral drug combination therapies used.

Outcome: Overall; fourteen (9.3%) patients died, eight from the top five neurological manifestations and the rest from all other miscellaneous neurological manifestations. The patients who were discharged had various morbidities including hemi-plegia, cognitive impairment, painful peripheral neuropathy, blindness, persistent headaches, myalgia and general weakness. Sixty eight (45.3%) of the patients were reviewed by a neurologist.

DISCUSSION

Acquired immunodeficiency syndrome has been a growing pandemic since the first case was diagnosed in 1982 in San Francisco (28,36) and in 1984 in Kenya (37). It is a multi-system disease and transverses internal medicine from dermatology, gastroenterology and endocrinology, psychiatry to the cardiovascular and nervous systems. Diagnoses of some of these systemic manifestations are relatively straightforward and hence appropriate management effected timely where resources are available and affordable.

The purpose of this study was to highlight the characteristics of neurological manifestations of HIV/AIDS in a hospital in Kenya. Such studies have been done elsewhere mainly in the industrialised countries; findings here will be compared and contrasted. The hospital chosen for the study is a leading private one in Nairobi, Kenya. It was chosen because it has world-class diagnostic and therapeutic facilities. The patients are drawn mainly from the local populace but also from across the borders. Overall, 708 patients amongst those admitted to the hospital in the study period were HIV positive. There were 404(57.1%) males and 304(42.9%) females; (M: F ratio =1.3:1), 150 of these patients had neurological manifestations; males comprising 86(57.3%) and females 64(42.7%).

The six-year point prevalence of neurological manifestations amongst hospitalised HIV-infected patients in the Division of Medicine is 21.2%.

Acquired immune-deficiency syndrome is an expensive disease. There is often prolonged hospital stay; particularly during management of opportunistic infections. This impact negatively on the already burdened health care system in resource poor countries. Complications such as HIV-Associated Dementia, peripheral neuropathy, vacuolar myelopathy and myopathy; thought to be directly related to HIV infection; accounted for only 9.3% of HIV-1 infected patients with neurological manifestations in this study. Other studies show similar trends. This is particularly so in the post HAART era (38,39).

Opportunistic infections are, however, common as a majority of our patients present with very low CD4+ cell counts. Over half (51.3%) of the patients with neurological manifestations presented with CD4+ cell counts below 200 cc mm and hence were severely immune-compromised.

The top five neurological manifestations i.e. cryptococcal meningitis (22%), encephalitis (18.7%), cerebral toxoplasmosis (12.7%), stroke (12.7%) and tuberculous meningitis (10.6%) were analysed in detail. These complications accounted for 75.8% of all neurological manifestations observed. The data closely mirrors the author's personal experience in managing HIV infected patients with neurological manifestations (40).

Cryptococcal meningitis was the commonest neurological complication in hospitalised HIV infected patients with neurological manifestations. Prevalence studies in Africa indicate 21% in Zimbabwe; 13% in South Africa, 19% in Rwanda and 16.6% in India (41,42). A hospital based study showed that cryptococcal neoformans was the commonest cause of meningitis in HIV-1 infected patients (43). The clinical profile for cryptococcal meningitis is the same as in other studies (44-47). Appropriate management of cryptococcal meningitis was possible at the private hospital due to availability of resources. Amphotericine-B therapy is the gold standard and was used. However, 5-Flucytosine is not available locally and is therefore not used (48). Immediate outcome of cryptococcal meningitis was favourable; only one patient out of 33 died. This is compared to 17.9% of patients with encephalitis who died. Encephalitis had the highest case specific mortality rate in the group of patients with neurological manifestations. It is, however, important to do prospective studies to follow up patients with cryptococcal meningitis to evaluate the relapse rate considering the fact that we do not use 5-Flucytosine/Amphotericine-B combination therapy as advocated in several studies (48,49).

Encephalitis comprised 18.6% of the cases. The diagnosis of encephalitis was clinical (50). This being a retrospective study, it was not possible to have specific aetiological agent certification of encephalitis in all cases, however, herpes simplex and cytomegalovirus infection was isolated in sporadic cases. Aetiology of encephalitis was presumed viral as CSF studies were negative for bacterial, fungal and syphilis infections. The patients were subsequently put on acyclovir or cymervene therapy with favourable responses. It is, however, imperative that prospective studies be done to attempt to isolate specific viral pathogens. This would require doing various viral antigen/antibody and PCR testing.

Cerebral toxoplasmosis comprised 12.7% of neurological manifestations in HIV-1 infected patients. The diagnosis of cerebral toxoplasmosis was presumptive; based on clinical presentation, neuro-imaging studies and response to appropriate therapy. Definite diagnosis of cerebral toxoplasmosis requires direct demonstration of tachyzoite form of T. gondii in brain, CSF or blood; this, however, is not mandatory in HIV/AIDS patients (50). Looking at the records, induction therapy comprised mainly intravenous clindamycin 600 mg four times a day and pyrimethamine 50 mg or 75 mg once a day per oral without loading with 200 mg as recommended in most western literature studies (51- 53). Radiological clearance of the ring enhancing lesions was confirmed by repeat neuro-imaging. Maintenance therapy comprised pyrimethamine 50 mg taken once a day or sulphadiazine. Use of clarithromycin and dapsone in management of patients with cerebral toxoplasmosis was not observed.

Stroke syndromes, mainly ischaemic strokes, were seen in 12.7% of patients. The patients had no other major risk factors for strokes. Suggestion of vasculitic pathophysiology is very plausible. Issues in management of these patients include the role of anti-inflammatory; anti-platelet and anti-thrombosis agents. Whether the cerebral ischaemia should be considered a primary event related to HIV infection or not is debatable.

Diagnosis of tuberculous meningitis was based on clinical picture, raised CSF protein, neuro-imaging features of basal enhancement, negative bacterial antigen assay for bacterial meningitis and response to anti-tuberculosis therapy. Yield of AAFB in CSF is very low (50,54-56).

One observes 'blanket therapy' in HIV/AIDS patients; including antibiotic therapy, anti-tuberculosis therapy and therapy for cryptococcal meningitis in resource poor set up due to lack of investigative facilities. This practice is a more expensive process and attempts must be made to make available basic laboratory essentials for appropriate diagnosis. Overall the clinical presentation of the common opportunistic infections is similar in pattern to that observed in other studies (44,50,54).

Our, patients, however, presented with very low CD4+ cell counts; a fact observed even in this high profile private hospital where cost is often not an issue. About 50% of the patients with neurological manifestations presented with CD4+ cell count <200 cc mm. It is not clear why this is so. Rare complications such as cerebral venous sinus thrombosis were encountered (24).

About 72% of these patients were on anti-retroviral therapy. Anecdotally, this does not reflect the national state of affairs as regards anti-retroviral therapy. It is a private institution. Public health institutions all over the country are currently aggressively setting up HIV/AIDS comprehensive care centers and therefore it is hoped that availability of anti-retroviral drugs will improve.

The most common anti-retroviral drugs used are efavirenz and combivir in various combinations (Table 2). Protease inhibitors are comparatively more expensive and therefore are not widely used.

The outcome of patient care in this institution was impressive with a mortality rate of 9.3%. The mortality rate here, however, may not reflect the state in public health institutions where drugs for opportunistic infections and anti-retroviral therapy are still not readily available.

CONCLUSION

Human immunodeficiency virus infection and AIDS is a pandemic. Sub-Saharan Africa is home to 62% (26 million) of the 42 million believed to be living with the virus worldwide (57). This puts unbearable pressure on provision of health services in sub-Saharan Africa.

The pattern of neurological manifestations is comparable to that seen elsewhere (58). The six-year point prevalence of neurological manifestations noted here is 21.2% and is comparable to 7-20% reported elsewhere (58).

Patients presented with very low CD4+ cell counts, hence had fulminate opportunistic infections. Poly-pharmacy was noted to be practiced; this should be discouraged and attempts to make specific diagnoses encouraged.

We recommend to do a multi-centre prospective study of neurological manifestations of HIV/AIDS.

ACKNOWLEDGEMENTS

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