Spectrum and prognostic significance of opportunistic diseases in HIV/AIDS patients in Ilorin, Nigeria.

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Summary

Background: **Opportunistic diseases (ODs) of varying types and severities have been reported amongst HIV infected patients around the world, this made us to define the incidence, spectrum and effects of ODs on HIV infected Nigerians' CD4⁺ cells count and survival rate.**

Design: **Retrospective analyses of HIV register from February 2002 to July 2004.**

Results: **ODs developed in 201 (68.6%) patients, 107 (53.2%) were AIDS-defining viz; TB, HIV-encephalopathy, scopulariopsis meningitis, cutaneous kaposis sarcoma and pulmonary candidiasis. Mean CD4⁺ count was lower with ODs compared to the controls, 138/ul vs 211/ul, p<-0.0006. It was low with non-AIDS-defining infection, 221.6/ul, lower with non-infectious AIDS-defining diseases, 192.4/ul and lowest with AIDS-defining infections, 117.7/ul. Mortality rate was 29.4%; 51 infectious and 8 non-infectious ODs against 19 (18.4%) from the controls. Risk of death was four folds higher with ODs over the controls, 59 vs 19, OR=3.98, 95%CI= 2.20- 7.27, X=24.2, p-<0.0001. This risk was also higher with infectious AIDS-defining illnesses compared to non-infectious ones, 48 vs 8, RR=4.83, 95%CI=2.80- 8.34, X= 51.7, p-<0.0001. Death from TB was over 2½ times higher than deaths from other AIDS-defining diseases, 45 vs 14, RR=2.7,95%CI=2.01-3.73,x=37.3, p-<0.0001. Average survival was shorter with ODs; 12.3weeks compared to controls, 37.8weeks, p-<-0.039. Mean survival was longest with EPTB, 29.8weeks and shortest with fungal meningitis, 1.9weeks.**

Conclusion: **incidence of ODs was high, 68.6%; it was associated with lower CD4⁺ count and shorter patient's survival especially when it was infectious and AIDS defining.**

Key-words: ***HIV, Opportunistic diseases, Prognosis, CD4⁺ cells and mortality.***

Résumé

Introduction: Des malades opportunistes (MOs) des types et gravités diverses ont été rapportées parmi des patients invectés par le VIH autour du monde; ainsi nous allons déterminer l'incidence et effets de MOs sur les Nigérians infectés par le VIH comptes des cellules CD4 et des survivants.

Plan: Une analyse rétrospective des inscriptions de VIH du février 2002 au juillet 2004.

Résultats: MOs atteints chez 201 soit 68,6% des patients, 107 soit 53,2% étaient SIDA déterminé par: VIH – encéphalopathie, méningite scopulariopse, sarcome de Kaposi cutané et candidose pulmonaire, compte de CD4+ moyen était inférieur avec MOs par rapport au groupe de témoin, 138/ul vs 211/ul, P<-0.0006. Il était inférieur avec aucune infection de SIDA déterminée. 221,6/ul, inférieur avec aucune infection de malaide de SIDA déterminée, 192,4/ul et le plus bas avec des infections de SIDA déterminées, 117,7/ul. Taux de mortalité était 29,4%, 51 cas des infections et 8 cas des MOs non infectueuse contre 19 soit 18,4% de groupe de témoin. Risque de mortalité était quatre fois plus élevé avec MOs sur les témoins, 59 vs 19, OR = 3,98, 95% cl = 2,20 –7,27, X = 24,2. P – <0.0001. Ce risque était également élevé avec des maladies infectueuses de SIDA déterminées par rapport aux maladies non infectueuses, 48 vs 8, RR = 4,83, 95% cl = 2,80–8,34, X = 51,7, P – <0,0001. Mortalité à travers TB était plus de 2 et demi fois plus élevé que des mortalité à travers des autres maladies de SIDA déterminées, 45 vs 14, RR = 2,7, 95%cl = 2,01 – 3,73, X = 37,3, P–<0,0001. Moyen de survie était plus inférieur avec MOs, 12,3 semaines par rapport aux groupes de témoin, 37,8 semaines, P– <-0,039. Moyen de survie était plus élevé avec EPTB, 29,8 semaines et inférieur avec méningite mycose, 1,9 semaines.

Conclusion: Incidence de MOs était élevée, 68,6%, elle était liée au compte CD4+ inférieur avec peu de survie des patients surtout quand elle est infectueuse et SIDA déterminée.

Introduction

HIV infection is a global problem, but of varying prevalence from one region of the world to the other. It is a major public health problem in most developing countries especially those in the sub Sahara Africa. Prevalence of the disease is quite high in this region[1], so is the prevalence of other infectious diseases like tuberculosis (TB), *salmonellosis* and *toxoplasmosis*[2]. This makes infectious disease a common feature of HIV infection in this part of the world, often as its complication. However, the type of infection in a given HIV infected patient is dependent on the patient's immune

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status and the relative frequency of endemic infections in a particular geographical area[3]. TB is one of the most common infectious ODs in HIV infected patients in Africa[4]. It occurs in close to one third of the patients at presentation[5]. Other common infections among African AIDS patients include oesophageal candidiasis, cryptosporidiosis and cryptococcosis[6]. Oropharyngeal candidiasis and multidermatomal herpes zoster are some of the mucocutaneous features of HIV infection that are more common in Africa than in the West[3]. In fact, multidermatomal herpes zoster has been found to have a positive predictive value of over 90% for HIV disease[7]. Non-infectious ODs are not uncommon, but the prevalence of infectious diseases is more common in the third world setting like Nigeria. Incidences of most of these ODs have significantly reduced in the developed countries with the introduction of combination of ARV compared to the pre HAART era[8] and the spectrum of AIDS- defining diseases is changing from infectious processes to non-infectious conditions like AIDS-dementia complex, non-Hodgkin's and central nervous system lymphomas as well as progressive multifocal leukoencephalopathy and other rare syndromes[9-11]. Anecdotal report has indicated a fall in the incidence of TB in HIV infected patients in Kenya following the introduction and effective utilization of ARV drugs[12]. In the same vein, with the introduction of combination ARV therapy in Nigeria, incidence of most of the ODs are expected to decline, albeit gradually along with the associated morbidity and mortality as it is being now experienced in the advanced world. This paper therefore, aims to define the incidence and spectrum of ODs amongst HIV infected Nigerians and to evaluate the prognostic significance of each of these ODs.

Materials and methods

HIV/AIDS patients are routinely evaluated and have baseline CD4+ count at diagnosis, then reviewed monthly in the follow up clinic for maintenance care and replenishing of ARV drugs or whenever there is complaint. We analyzed the charts of patients on the HAART pilot programme for record of ODs from February 1st 2002 to July 31st 2004. At the end of two and a half years of observation patients were divided into 2 groups; those with ODs (AIDS-defining and non-AIDS-defining: infectious, non-infectious) and those without. Their age, sex and baseline CD4+ cells count were recorded. To compare for differences, controls were selected from those without ODs to match the cases in age (within ±5 years), sex and time of commencement of ARV therapy (within 4 weeks) in a ratio of 2 cases to 1 control. The end point was the length of survival from the time of diagnosis till the time of death or duration of ARV therapy from the time of diagnosis till time of this report.

NB: PTB was diagnosed by 2 positive sputum smears for acid and alcohol fast bacilli (AAFB) or a positive smear for AAFB and suggestive x-ray features of active PTB[13]. EPTB was diagnosed by clinical (meningeal and skeletal), aspiration cytology, tissue histology and autopsy[14]. Mycotic infection was by repeated growth of only yeast-like organism from sputum from lung abscess and cerebrospinal fluid inoculated in saboraud's dextrose agar[15]. KS was by histology and HIV-encephalopathy was by mini-mental assessment and elevated CSF protein and pleocytosis. HIV infection was diagnosed by two enzyme linked immuno-sobent assays (ELIZA) using the wellcozyme HIV recombinant EIA (Enzyme Immuno-assay) and Murex HIV 1 & 2 kit (Murex Diagnostics, Dartford, UK). Patients that had paired positive tests had their CD4+ cells estimated by Dynal T_4 Quant method (Dynal Biotec ASA, Oslo, Norway).

Statistics

The frequencies of ODs and the means of all the variables (age, CD4+ cell, and period of survival) were determined for both the cases and the controls. Differences between the means were assessed by Student's t-test and chi-square technique was used to determine differences between proportions of variables. Odds ratio (OR) was used for risk of death between cases and control while relative risk (RR) was used for risk of death between variables. P-value less than 0.05 was upheld as statistically significant.

Results

ODs developed in 201 (68.6%) of the total 293 patients seen, comprising 88 males (43.8%) and 113 females (56.2%), aged 19-60 years, mean of 33.9 years. Infectious cases occurred over 14 times more than the non–infectious cases; 188 (93.5%) vs 13 (6.5%). Table 1. Ninety-four (46.8%) of these were AIDS-defining and comprise; PTB, 64 (36.3%), EPTB, 27 (13.4%), pulmonary candidiasis, 2 (1%), and a case (0.5%) of filamentous fungal meningitis. Thirteen other non-infectious AIDS-

Table 1 Frequency of opportunistic diseases in HIV infected patients

Disease	Frequency (%)
Number on HAART	293
Number with ODs	201 (68.6)
Infectious cases.	**188 (93.5)**
Oropharyngeal candidiasis	73 (36.3)
*PTB	64 (31.8)
*EPTB	27 (13.4)
Gram negative bacterial pneumonia	9 (4.5)
Herpes zoster	9 (4.5)
*Pulmonary candidiasis	2 (1.0)
Intestinal amoebiasis	2 (1.0)
*Scopulariopsis meningitis	1 (0.5)
Strongyloidiasis	1 (0.5)
Non-infectious cases	**13 (6.5)**
*HIV-encephalopathy	11 (5.5)
*Kaposis sarsoma	2 (1.0)

**AIDS-defining ODs*

Table 2 Average CD4⁺ cells of patients with and without opportunistic diseases

Opportunistic diseases	HIV/AIDS patients Cases (mean)	Controls (mean)	Difference in means	P value
Pneumonia	215	244	29	NS
Kaposis sarcoma	236	269	33	NS
HIV-encephalopathy	148.8	281	132.2	0.001
PTB	176.3	205.2	28.9	NS
EPTB	107.2	182.5	75.3	0.026
Oropharyngeal candidiasis	273.8	296.9	23.1	NS
Herpes zoster	176.5	183.6	12.1	NS
Pulmonary candidiasis	103.2	198.6	95.4	0.0018
Scopulariopsis meningitis	84	170	90	0.0021

defining diseases were; HIV-encephalopathy, 11(5.5%) and cutaneous KS, 2(1%). Pre-enrolment CD4⁺ count for patients with ODs ranged from 40/ul-310/ul, mean of 138.2/ul while that of the controls was 70-370/ul, mean of 211.6/ul, p-value= 0.00068. Mean CD4⁺ counts for AIDS-defining infections was 117/ul while that of the non-AIDS-defining ones was 221.6/ul. Oropharyngeal candidiasis had the highest average count, 273.8/ul while fungal meningitis had the lowest, 84/ul. PTB also had significantly higher CD4⁺ count than EPTB (176.3cells/ul against 107.4cells/ul, p- value 0.0036), table 2. Mean CD4⁺ count for non-infectious diseases was 192.4/ul; however, KS had a higher CD4⁺ count than HIV-encephalopathy 236cells/ul vs 148.8cells/ul p- < 0.0021

In the final outcome one hundred and thirty-three patients (66%) remained alive and on maintenance care, table 3. Forty-two (31.2%) of them had AIDS-defining illnesses as against 91 (68.8%) that had non-AIDS-defining conditions, RR=0.33, 95%CI, 0.26-0.43, X2=63.1, p-< -0001. There were 59 deaths (29.4%); 51 infectious and 8 non-infectious as against 19 (18.4%) from the controls. TB was the most common cause of death accounting for 76.3% of the cases, table 3. The risk of death was about four folds higher in patients with ODs over the controls, 59 vs 19, OR=3.98, 95%CI= 2.20- 7.27, X=24.2, p-<0.0001. The risk of death was also higher with infectious AIDS-defining diseases compared to non-infectious ones, 48 vs 8, RR=4.83, 95%CI=2.80- 8.34, X= 51.7, p-<0.0001. Death from TB was over 2 ½ times higher than death from other AIDS-defining diseases, 45 vs 14, RR=2.7,95%CI=2.01-3.73,x=37.3, p-<0.0001. Pulmonary form had about three times the risk of dying compared to the extra pulmonary cases; RR= 2.77, 95%CI 1.78-4.32, X2=22.9, p-value < 0.0001. Average length of survival of the patients with AIDS-defining ODs from the time of diagnosis till death was significantly shorter than that of controls, 12.3 weeks versus 37.8 weeks, p value= -0.039, table 4. Survival was longest with EPTB; mean 29.8 weeks and shortest with fungal meningitis, 1.9 weeks. The average survival for HIV-encephalopathy (non-infectious) was 9.3 weeks, range 2.3-17.2weeks.

Discussion

Incidence of ODs in HIV infected patients was 68.6% and a larger percentage were infectious in nature (93.5%). TB was the most common (45.2%), presenting

Table 3 Outcome of opportunistic diseases in HIV infected patients.

Opportunistic diseases	Patients outcome Alive (%)	Died (%)	Unknown (%)
Oropharyngeal candidiasis n=73	70 (52.6)	3 (5.1)	-
PTB n=64	22 (16.5)	35 (59.3)	7 (77.8)
EPTB n=27	15 (11.5)	10 (17.0)	2 (22.2)
HIV-encephalopathy n=11	3 (2.3)	8 (13.5)	-
Bacterial pneumonia n=9	9 (6.8)	- -	- -
Herpes zoster n=9	9 (6.8)	- -	- -
Pulmonary candidiasis n=2	- -	2 (3.4)	- -
Kaposis sarcoma n=2	2 (1.5)	- -	- -
Scopulariopsis meningitis n=1	- -	1 (1.7)	- -
Amoebiasis n=2	2 (1.5)	- -	- -
Strongyloidiasis n=1	1 (0.7)	- -	- -
Total 179	**133**	**59**	**9**

Table 4 Average survival of patients with and without opportunistic diseases

Opportunistic diseases	HIV/AIDS patients			
	Cases (mean in weeks)	Controls (mean in weeks)	Difference in means	P value
PTB	13.3	39.6	26.3	0.024
EPTB	29.8	37.2	7.4	NS
Pulmonary candidiasis	5.3	36.6	31.3	0.013
Scopulariopsis meningitis	1.9	38.3	36.4	0.001
HIV-encephalopathy	9.3	42.1	32.8	0.001

as PTB and EPTB; followed by oropharyngeal candidiasis (36.3%); HIV-encephalopathy, a non-infectious disease, was the third most common ODs (5.5%). AIDS-defining protozoa like *toxoplasmosis, cryptococcosis* and *cryptosporidiosis* that are frequently found in HIV infected patients in developing countries[16] were not reported in this study principally because they are not easily diagnosed in our setting. $CD4^+$ cell count used to determine the immune status of the patients was significantly lower in those with ODs 138.2 cells/ul compared to the controls, 211.6cells/ul. Patients with non-AIDS-defining oropharyngeal candidiasis had the highest mean count of 273.8/ul, it was the earliest feature of a low $CD4^+$ count, thus a good monitoring index of disease progression. The fungus has been recognized contrary to our own experience as the most common infectious OD in HIV infected patients[17]. It has also been described as a harmless microbe that helps to keep bacteria levels in check in both HIV negative and positive patients[18]. Two patients, however, developed pulmonary candidiasis, another had scopulariopsis meningitis. These visceral fungal infections reflected the extent of damage to these patients' immune status by HIV. The trio had the lowest range of $CD4^+$ count, 84cells/ul-103cells/ul. HIV is known to promote the fungus adhesiveness to tissue surfaces[19] by inducing it to express more fibronectin, this together with the inhibitory effect of the virus on phagocytes, allow overgrowth of the fungus. In agreement with our earlier report[14], $CD4^+$ cells count was significantly higher in PTB than EPTB cases (176.3cells/ul against 107.4cells/ul, p- <0.0036). This fact was corroborated by similar work from Burundi[20]. HIV-encephalopathy and cutaneous KS were the two non-infectious AIDS-defining ODs seen, the former occurred in very low $CD4^+$ count, mean 148.8/ul while the latter occurred at varying level of $CD4^+$ count, 125/ul and 350/ul, mean 237.5/ul. This variable presentation of KS confirms its unpredictable nature and its ability to manifest at any stage of the HIV infection, sometimes, in patients with normal $CD4^+$ count[21]. The spectrum of $CD4^+$ cell count in this report showed lower count in patients with ODs; mean 138.2/ul, compared to the controls; mean 211/ul. And amongst patients that had ODs, AIDS-defining infections had the lowest mean count, 117.7/ul followed by non-infectious AIDS-defining diseases, 192/ul and then non-AIDS-defining infections, 221.6/ul. The infectious and non-infectious AIDS- defining diseases in this report satisfy the local laboratory AIDS definition suggested by Njoku *et al*[22].

Management outcome of these patients showed that 133 of them (66.2%) remained alive while 59 (29.4%) died, the remaining 9 (5%) were lost to follow-up. The average survival of patients with ODs was quite shorter, 12.3 weeks compared to 37.8 weeks for the controls. Patients with EPTB had the longest period of survival averaging about 29.8 weeks and the shortest period of 1.9 weeks was recorded in the case of fungal meningitis. The chance of surviving with non-AIDS–defining infections like oropharyngeal candidiasis or herpes zoster was more than 4 times higher than with AIDS-defining ones like TB or visceral cadidiasis, indicating that survival with an AIDS-defining infection was often less favourable. This fact is reflected in the mortality ratio that was three times higher with infectious AIDS-defining ODs compared to non-infectious ones.

Survival with AIDS- defining diseases amongst Africans has been found to be shorter than what is obtained in the developed world[23], where survival with AIDS- defining conditions is in excess of 120 weeks[24]. This may among other things be due to late hospital presentation by majority of our patients till the later stage of their illnesses when their immunity would have been severely destroyed as reflected by the uniformly low $CD4^+$ count in this report; the often-present wasting that is multifactorial in our patients and the lack of routine prophylaxis against most of the infectious ODs are some of the other factors responsible for early death in our patients. Advanced HIV disease is associated with low $CD4^+$ count, however, combination ARV therapy impacts positively on the count when therapy is initiated early. Increase in the level of $CD4^+$ count would translate to a decrease in the risk of ODs in most patient[25]. This is what makes $CD4^+$ count a strong predictor of survival or death in HIV infected patients[10,26]. Of the total deaths recorded, TB accounted for over two thirds; PTB, 65% and EPTB, 19.6%. The risk of death from PTB was over 2½ times higher than death from other AIDS-defining diseases combined. Perhaps because of the high prevalence of TB in Nigeria[13,14], and

the fact that anti-TB treatment is rarely initiated early in the course of TB infection due largely to late presentation[24].

In conclusion; ODs are common in HIV infected patients; the infectious AIDS-defining cases were associated with very low $CD4^+$ cells count and shorter patients' survival.

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