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Prevalence and Risk Factors for Opportunistic Infections in HIV Patients Receiving Antiretroviral Therapy in a Resource-Limited Setting in Nigeria

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Abstract

Background: The introduction of Highly Active Antiretroviral Therapy (HAART) has led to decline in HIV-related opportunistic infections in high-income settings. We determined the prevalence and risk factors for opportunistic infections among patients receiving HAART in a resource-limited setting in Nigeria.

Methodology: A descriptive and analytical cross-sectional study among adult HIV-infected patients receiving HAART for a median duration of 3 years at the Federal Medical Centre, Owerri, Nigeria was conducted. Data on pre-HAART socio-demographic, clinical and laboratory characteristics were obtained. Post-HAART data were collected through history, physical examination and laboratory investigations.

Result: The mean age of the participants was 41.1 ± 10.0 years; and females were in the majority (65.8%). Half (50.4%) belonged to the lower socio-economic class. At baseline (pre-HAART), 72.3% of the participants belonged to World Health Organization (WHO) clinical stage 1 or 2. The median pre-HAART CD4 cell count of the patients was 200 (110-263) cells/µl while the median post-HAART CD4 cell count was 357 (211-496) cells/µl. The majority (77.6%) were adherent on HAART. Out of 339 patients, 76 (22.4%) had opportunistic infections. The leading conditions were candidiasis (8.6%), tuberculosis (7.7%), dermatitis (5.6%), chronic diarrhea (1.5%) and sepsis (1.5%). The independent risk factors for opportunistic infections were household income ₦ 20,000 (Adjusted odds ratio [AOR] = 2.70, 95% CI 1.18-6.18), advanced baseline WHO clinical stage (AOR=9.49, 95% CI 4.20-21.42), baseline hemoglobin <10 g/dl (AOR= 3.50, 95% CI 1.47-8.36), post-HAART CD4 cell count <200 cells/µl (AOR= 3.43, 95% CI 1.49-7.92), and HAART non-adherence (AOR= 5.28, 95% CI 2.52-11.08).

Conclusion: Opportunistic infections remain a challenge in patients receiving HAART in resource-limited settings. There is need to intensify the management of opportunistic infections despite HAART use.

Keywords: Candidiasis; Highly active antiretroviral therapy; Human immunodeficiency virus; Opportunistic infections; Resource-limited setting; Tuberculosis

Background

With the history of HIV/AIDS in Nigeria spanning well over two decades, it is not surprising that the number of people living with HIV (PLHIV) has substantially increased over these years. Nigeria currently has one of the highest HIV burden worldwide, with 3.1 million PLHIV and about 215, 000 annual AIDS deaths [1,2]. In response to the raging epidemic of HIV/AIDS, the government of Nigeria in partnership with international collaborators established the national antiretroviral therapy (ART) program in 2002 which led to increased access to HIV care and treatment [3]. The total number of PLHIV on ART steadily increased from 50,581 at the early stages of ART in Nigeria in 2005 to 302,973 in 2009 [2]. So far, the efforts are still sub-optimal as only one-third of individuals requiring treatment in Nigeria have access to ART [2].

The hallmark of HIV infection is immunosuppression which predisposes to opportunistic infections (OIs) and malignancies. Opportunistic infections constitute a major cause of morbidity and mortality in PLHIV [4,5]. This is even more critical in sub-Saharan Africa (SSA) where the standard of living is generally poor and access to ART is still inadequate. A striking feature of the reported clinical spectra of OIs in HIV/AIDS has been the contrasting findings from divergent socio-economic settings. In developed regions such as North America, Europe, and Australia, *Pneumocystis carinii* pneumonia (PCP), Kaposi's sarcoma (KS), oesophageal candidiasis, cytomegalovirus (CMV)-related disease and disseminated *Mycobacterium avium* complex (MAC) infection were the prevalent OIs in PLHIV in the pre-ART era [6,7]. In developing regions such as SSA and South East Asia, where an estimated 90% of PLHIV reside, the predominant HIV-associated OIs in the pre-ART era were tuberculosis (TB), candidiasis, infective diarrhea, meningitis, dermatitis and recurrent *Herpes simplex* infection [8,9].

Since the introduction of Highly Active Anti-retroviral Therapy (HAART), a significant decline in OIs and AIDS progression has been observed [10-12]. However, significant differences still exist in the burden of OIs between high income and resource-limited settings. Most of the evidence for decline in OIs has come from high-income settings with relatively less burden of OIs in the pre-HAART era, early and widespread access to ART and sophisticated diagnostic tools. There is insufficient knowledge about the burden and risk factors for OIs in

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HIV-infected populations receiving HAART in SSA. Unfortunately, the findings of studies in high-income settings may not be generalizable to resource-limited settings.

An evidence-based assessment of the prevalent OIs in PLHIV in the era of HAART is necessary in order to define local priorities in HIV care and inform targeted expenditure on prophylaxis and treatment of HIV-related co-morbidities. Since the current spectrum of OIs and their associated risk factors in HAART-experienced populations in Nigeria remain largely undetermined, it will be difficult to fully assess the impact of the ART program in the country. This study determined the prevalence of OIs in HIV-infected Nigerian adults on HAART and also investigated the socio-demographic and clinical risk factors associated with their occurrence.

Methodology

Study design and study population

This was a descriptive and analytical cross-sectional study carried out between April and September, 2012. The study population comprised of adult HIV-infected patients, 15 years or more, who were receiving HAART at the Federal Medical Centre in Owerri, Imo State, South East Nigeria. Owerri is the capital of Imo State and is made up of three Local Government areas including Owerri Municipal, Owerri West and Owerri North. According to the 2006 Census, Imo State has a population of 3.9 million [13]. According to the 2010 national HIV seroprevalence survey, Owerri has an HIV prevalence of 2.9% while that of the entire Imo State is 3.0% [2]. The HIV prevalence in Imo State as reported in national surveys has generally experienced a steady decline from 7.8% in 1999 to 3.0% in 2010 [2]. The burden of HIV infection in the State is higher in rural communities (5.6%) than in urban areas (2.2%) [2]. However, in a study involving 17, 964 individuals who underwent HIV counseling and testing between April 2007 and September 2009 at General Hospital Umuguma, Owerri West Local Government Area of Imo State, 8.1% were found to be HIV positive [14]. It was reported that about 60% of the HIV-infected individuals were females while 83.3% were 25 years or more [14].

The HIV clinic where this study was conducted provides ambulatory services for about 5,000 patients out of whom approximately 2,000 adults were on HAART at the time of the study. The hospital also has adequate facilities for in-patient management of HIV/AIDS patients. Ethical approval for the study was obtained from the Ethics committee of the hospital. Patients included in the study were those whose HIV seropositive status was confirmed by Western blot, and they consented to the study. In addition, they were required to have received HAART for a minimum of 12 weeks. This was to ascertain that they had received HAART long enough to achieve virological suppression and immune recovery [15,16]. HAART was defined as the use of at least three antiretroviral drugs from at least two different classes. HAART-naïve patients and those currently manifesting an OI whose onset ante-dated the commencement of HAART were excluded from the study.

Sample size and sampling technique

Bearing in mind a population of approximately 2,000 HIV-infected adults receiving HAART at the study site, a minimum sample size of 322 patients was calculated using a 95% confidence interval based on a prevalence of OIs of 47.6% in the mortality data of HIV-infected patients on HAART in a previous study in SSA [17]. However, considering that some patients may have incomplete data, additional 10% of the minimum sample size was enrolled which increased the sample size to 354. A simple random sampling technique was used to select the participants from among the HAART-experienced patients scheduled to visit the clinic during the period of data collection. After applying the exclusion criteria, a sampling frame was generated which comprised of 1,560 HAART-experienced HIV-infected patients. On each day of data collection, individuals in the sampling frame attending the clinic that day were identified. From the subset of HAART-experienced patients attending the clinic on specific days, a random starting point was first chosen and subsequently every third person was selected. This was continued until the required sample size of 354 was attained.

Data collection

A structured questionnaire was used to collect data about socio-demographic, clinical and laboratory parameters. For the clinical and laboratory information, available baseline data at the time of commencement of HAART were first captured including date of HIV diagnosis, WHO clinical stage, body mass index (BMI), CD4 cell count, and hemoglobin concentration. For each participant, detailed history and physical examination were carried out to identify features suggestive of on-going OIs. Irrespective of the presence of OI, every participant had blood sampling for current CD4 cell count and hemoglobin tests. Depending on the specific clinical diagnosis of OI made, appropriate investigations such as sputum acid fast bacilli (AFB), chest x-ray, stool microscopy, cerebrospinal fluid (CSF) analysis; blood, sputum and urine cultures as well as tissue histology were carried out to confirm the diagnosis where possible. The laboratory results were captured as soon as they were available. Individuals diagnosed to have any OI were referred for appropriate treatment.

Opportunistic infection diagnostic criteria

The diagnosis of OI was made according to standard guidelines where possible and facilities available. Where diagnosis was entirely based on clinical grounds, two independent physicians involved in HIV care and management were required to have the same assessment before such diagnosis was accepted.

Candidiasis was detected by clinical examination followed by isolation of the yeasts from oropharyngeal or vaginal swabs.

Tuberculosis Screening was offered to the patients based on a TB screening algorithm for HIV-infected patients [18]. Tuberculosis diagnostic algorithm was subsequently used to evaluate patients with a positive TB screening response (i.e. patients who reported having at least one of the 3 screening symptoms of cough of any duration, fever of any duration or night sweats of ≥ 3 weeks in the preceding 4 weeks).

Pulmonary TB was defined as presence of cough with or without fever, weight loss, night sweats or haemoptysis and demonstration of acid fast bacilli (AFB) in two or more sputum samples and/or chest X-ray features compatible with TB [4,19].

Extra-pulmonary TB was defined as clinical evidence suggestive of TB without features of pulmonary involvement followed by histology of lymph node biopsy [for *TB lymphadenitis*], or followed by findings of exudative pleural effusion accompanied by clinical response to anti-tuberculous drugs [for *pleural TB*], or followed by ultrasonography of the abdomen for evidence of lymph nodes accompanied by clinical response to anti-tuberculous drugs [for *abdominal TB*] [4,19].

Disseminated TB was defined as clinical features suggestive of TB with concurrent involvement of at least two non-contiguous organs, with positive sputum smear and/or histopathological and/or radiological evidence of TB [4].

For patients with negative sputum AFB despite strongly suggestive

clinical and/or radiological features and patients whose diagnosis of extra pulmonary TB was not based on definitive tests such as histology, further supportive laboratory evidence especially elevated erythrocyte sedimentation rate (ESR), followed by clinical response to anti-tuberculous drugs at least in the intensive phase of treatment was further required before diagnosis of TB was accepted. For any patient in this category whose anti-tuberculous drug response was not ascertained, the diagnosis of TB was not upheld.

Cryptococcal meningitis was diagnosed based on clinical evidence of meningitis with demonstration of cryptococcal yeast cells in the cerebrospinal fluid by Indian ink staining.

Chronic diarrhea was initially diagnosed based on history and the responsible etiologic agent was then isolated by appropriate stool analysis.

Sepsis was defined as the presence of ≥ 2 of the following: body temperature >38°C or <36°C; pulse rate >90 beats/min, respiratory rate >20 breaths/min, white cell count >12 × 10^9/l or <4 X 10^9/l or >10% immature (band) forms, in the presence of infection [20]. The responsible etiologic organism for the sepsis was subsequently identified by blood culture.

Bacterial pneumonia was diagnosed as clinical evidence of pneumonia with supportive chest X-ray infiltrates and positive sputum bacteriological test.

Kaposi's sarcoma was confirmed by histology of tissue biopsy obtained from the skin lesion following clinical evaluation.

Herpes zoster was diagnosed based on clinical evidence of prototypic painful skin eruptions with characteristic dermatomal distribution.

Genital herpes was diagnosed based on clinical evidence of painful genital ulcer preceded by vesicles with negative veneral disease research laboratory (VDRL) test for syphilis.

Genital wart was diagnosed based on the characteristic lesion on clinical examination.

Other case definitions

Socio-economic classification: The socio-economic class of the family was assessed using the father's occupation/income and the maternal educational attainment as recommended for Nigeria by Olusanya et al. [21]. This method stratifies socio-economic class into five classes I to V. Class I represents the upper cadre, classes II and III the middle cadre while classes IV and V are the lower cadre. The father's occupation had a cumulative score of 3 while the mothers' educational attainment had a cumulative score of 2. The total score from both parameters placed each participant in the respective classes. This classification system is judged relevant in developing countries like Nigeria where most mothers are uneducated considering that mother's education has been shown to be positively associated with health care knowledge and heath seeking behavior in the family irrespective of household income [22].

HAART adherence: HAART adherence was assessed using both tablet counting and self-reporting methods. In the tablet counting method, pharmacy medication records for patients were matched by the pharmacist against the not-yet-used medicines brought to the pharmacy by the patients as a routine for refill of prescriptions and the number of doses that ought to have been taken that were missed were recorded [23]. Patient's self-reporting method was carried out as previously described by Weiser et al. [24]. In this method, patients were interviewed about their adherence over the previous day, previous week and previous month successively in an attempt to minimize recall bias. In both methods, adherence was defined as taking 95% of prescribed doses over the previous month which corresponded to missing no more than one dose in a 10-day period [in a 2 times a day dosing regimen], one dose per week [in a 3 times a day regimen] or one dose per month [in a once daily regimen] [23]. Patients were therefore said to have HAART non-adherence if they missed more than 5% of their doses. Where there was discrepancy between the rates obtained by the two methods, adherence rate obtained by the counting method was used.

Data analysis

Data analysis was carried out using the Epi Info version 3.5.1 statistical software (CDC, Atlanta, Georgia and USA). Prevalence of HIV-related OIs was described as a simple proportion in percentage first as an aggregate variable and then for the individual infections. For univariate statistical analysis, the Chi-square test where appropriate was used to determine significance of association between OIs and various socio-demographic and clinical variables. The Student "t"-test or Kruskal–Wallis test was used to compare group means. For multivariate analysis, backward stepwise logistic regression was used to determine the independent socio-demographic and clinical risk factors for the occurrence of OIs (as an aggregate variable) using parameters that had a p-value of <0.25 on univariate analysis. However, parameters which *a priori* were known risk factors for HIV-related OIs which had p-value >0.25 were also included in the logistic model. All reported p-values <0.05 were considered statistically significant.

Results

Socio-demographic and clinical characteristics of the study participants

Out of the 354 patients enrolled in the study, only 339 had complete data and laboratory results. The socio-demographic and clinical characteristics of the study participants are shown in Table 1. The participants were between 18 and 68 years with a mean age of 41.1 ± 10.0 years. Female subjects were in the majority (65.8%). Men were significantly older with a mean age of 46.8 ± 9.2 years compared to 38.1 ± 9.2 years in women, p<0.0001. Most of the participants were married (59.3%). The majority (73.1%) of them had at least secondary level of education. The predominant occupations were trading (41%), civil service (19.8%) and farming (8.3%) while 10.0% were unemployed. They were largely of Igbo ethnicity (93.2%). Urban dwellers had a slight majority (56.3%). Ninety eight (28.9%) of them reported having more than two people living in one room. One hundred and eighty six (54.9%) patients had a household income below the national minimum wage of about ₦ 20,000 per month (i.e. <133 US dollars per month). Half (50.4%) belonged to the lower socio-economic class.

The duration of HIV diagnosis ranged from 6 months to 10 years with a median (IQR) of 3.4 (2.0-6.0) years. There was no difference between men and women in terms of duration of HIV diagnosis; 3.5 (2.0-6.0) and 3.3 (2.0-5.6) years respectively, p=0.77. The duration of HAART ranged from 4 months to 118 months (9.8 years) with a median of 35 (20-50) months. There was also no difference between men and women in the median duration of HAART, 36 (22-54) months and 34 (20-48) months respectively, p=0.11. The majority (77.6%) were adherent on HAART. Two hundred and ninety seven (87.6%) participants were receiving cotrimoxazole prophylaxis with an adherence rate of 75.1%.

At baseline (pre-HAART), 72.3% of the participants belonged to WHO clinical stage 1 or 2. The median baseline CD4 cell count of the patients was 200 (110-263) cells/µl. Their mean baseline hemoglobin was 11.2 ± 2.0 g/dl and 76 (22.4%) had hemoglobin concentration <10g/dl at baseline. Their median current CD4 cell count was 357 (211-496) cells/µl. Their mean current hemoglobin was 11.6 ± 1.8 g/dl and only 36 (10.6%) had current hemoglobin concentration <10g/dl. The mean current BMI of the participants was 24.5 ± 5.5 kg/m^2. Fifty two (15.3%) had hypertension, and 11 (3.2%) had diabetes mellitus. Positive history of alcohol consumption was recorded in 72 (21.2%) while 24 (7.1%) were current smokers.

Characteristic	N=339 n (%)
Gender	
Female	223 (65.8)
Male	116 (34.2)
Age (years)	
≤ 40	173 (51.0)
>40	166 (49.0)
Marital status	
Married	201 (59.3)
Single	46 (13.6)
Separated/divorced	22 (6.5)
Widowed	70 (20.6)
Educational status	
None/Primary	91 (26.9)
Secondary	158 (46.6)
Tertiary	90 (26.5)
Residence	
Urban	191 (56.3)
Rural	148 (43.7)
Household income (Naira)	
<20,000	186 (54.9)
20-50,000	73 (21.5)
51-100,000	50 (14.7)
>100,000	30 (8.8)
Household size/No of dependents	
≤4	114 (34.3)
5-8	158 (47.6)
>8	60 (18.1)
People per room	
≤2	241 (71.1)
>2	98 (28.9)
Socio-economic class	
Upper (class I)	27 (8.0)
Middle (class II & III)	141 (41.6)
Lower (class IV & V)	171 (50.4)
Duration of HIV diagnosis (years), median (IQR)	3.4 (2.0-6.0)
HAART duration (months), median (IQR)	35.0 (20.0-50.0)
HAART adherence, n (%)	263 (77.6)
Baseline WHO clinical stage	
1-2	245 (72.3)
3-4	94 (27.7)
Baseline CD4 cell count (cells/µL)	
<200	168 (49.6)
200-499	159 (46.9)
≥500	12 (3.5)
Current CD4 cell count (cells/µL)	
<200	75 (22.1)
200-499	180 (53.1)
≥500	84 (24.8)
Baseline hemoglobin (g/dl), mean ± SD	11.2 ± 2.0
Current hemoglobin (g/dl), mean ± SD	11.6 ± 1.8

HAART= Highly Active Antiretroviral Therapy; HIV=Human Immunodeficiency Virus;

IQR= Interquartile Range; SD= Standard Deviation; WHO= World Health Organization

Table 1: Socio-demographic and clinical characteristics of the study participants.

	Overall N=339 n (%)	Female N=223 n (%)	Male N=116 n (%)	p-value
Total no of diagnosed OIs	96	72	24	----
Number patients with single OIs	55 (16.2)	36 (16.1)	19 (16.4)	0.96
Number patients with dual OIs	20 (5.9)	15 (6.7)	5 (4.3)	0.37
Number of patients with triple OIs	1 (0.3)	1(0.4)	0 (0.0)	----
Overall prevalence of OIs	76 (22.4)	52 (23.3)	24 (20.7)	0.58
Bacterial pneumonia	3 (0.9)	3	0	----
Candidiasis†	29 (8.6)	24	5	0.04
Chronic diarrhea‡	5 (1.5)	5	0	---
Cryptococcal meningitis	2 (0.6)	0	2	---
Dermatitis	19 (5.6)	16 (7.2)	3 (2.6)	0.08
Genital herpes simplex	2 (0.6)	2	0	---
Genital warts	2 (0.6)	2	0	---
Herpes Zoster	2 (0.6)	2	0	---
Kaposi's sarcoma	1 (0.3)	0	1	---
Sepsis	5 (1.5)	5	0	---
Tuberculosis#	26 (7.7)	13 (5.8)	13 (11.2)	0.08

†Out of the 29 cases, 12 were oral, 10 genital (all women) and 7 oral + genital candidiasis (all women); excluding the women with genital candidiasis, there was no significant gender difference in oral candidiasis (p=0.45).

‡ Isolates were *Cryptosporidium parvum* [3] and *Giardia intestinalis* [2].

This comprised of pulmonary TB [11], extra-pulmonary TB [6] and disseminated TB [9]

OIs= opportunistic infections

Table 2: Prevalence/frequency of opportunistic infections.

Prevalence of opportunistic infections

The prevalence/frequency of opportunistic infections is shown in Table 2. Out of 339 patients, 76 had diagnosed OIs giving an overall prevalence of 22.4%. There were a total of 96 opportunistic infections diagnosed in the 76 patients. Fifty five (16.2%) patients had single OI, 20 (5.9%) had dual OIs while 1 (0.3%) had triple OIs. The most frequent conditions were candidiasis, 29 (8.6%); TB, 26 (7.7%); dermatitis 19 (5.6%); chronic diarrhea, 5 (1.5%); and sepsis 5 (1.5%). Bacterial pneumonia was diagnosed in 3 (0.9%) patients, cryptococcal meningitis, herpes zoster, genital herpes, and genital warts were each diagnosed in 2 (0.6%) patients while only 1 (0.3%) patient had Kaposi's sarcoma. In relative terms, candidiasis, TB and dermatitis, constituted 38.2%, 34.2%, and 25% of the OIs respectively. As shown in Table 2, there was no significant difference in frequency of most OIs when the participants were stratified according to gender.

Risk factors for opportunistic infections

As shown in Table 3, the socio-demographic variables that had significant positive association with the presence of OIs on univariate analysis included the following: age ≤ 40 years (Odds ratio [OR]=1.89, 95% CI=1.12-3.20, p=0.02), household income ₦ 20,000 (OR=2.86, 95% CI=1.57-5.25, p=0.0002), and having >2 people per room (OR= 2.34, 95% CI=1.36-3.98, p=0.002). Although the risk of having OIs was higher in individuals with lower socio-economic status, the difference did not attain statistical significance (OR=1.69, 95% CI= 0.98-2.94, p= 0.05). The risk of OIs did not significantly differ according to gender (OR=1.17, 95% CI=0.68-2.01, p=0.58), place of residence (OR=1.39, 95% CI= 0.83-2.32, p=0.21) or marital status (OR=1.33, 95% CI=0.79-2.22, p=0.28).

The univariate analysis of clinical risk factors for OIs is shown in Table 4. Occurrence of OIs had a significant positive association with duration of HIV diagnosis <3 years (OR= 2.88, 95% CI= 1.65-5.04,

Variable	OI present (N=76)	OI absent (N= 263)	Odds ratio (95% CI)	p-value
Age (years)				
≤ 40 (N=173)	48 (27.7%, 63.2%)	125 (72.3%, 47.5%)	1.89 (1.12-3.20)	0.02
> 40 (N=166)	28 (16.9%, 36.8%)	138 (83.1%, 52.5)	1.0	
Gender				
Female (N= 223)	52 (23.3%, 68.4%)	171 (76.7%, 65.0%)	1.17 (0.68-2.01)	0.58
Male (N= 116)	24 (20.7%, 31.6%)	92 (79.3%, 35.0%)	1.0	
Socio-economic class				
Lower (N=171)	46 (26.9%, 60.5%)	125 (73.1%, 47.5%)	1.69 (0.98-2.94)	0.05
Upper/Middle (N=168)	30 (17.9%, 39.5%)	138 (82.1%, 52.5%)	1.0	
Residence				
Rural (N=148)	38 (25.7%, 50.0%)	110 (74.3%, 41.8%)	1.39 (0.83-2.32)	0.21
Urban (N= 191)	38 (19.9%, 50.0%)	153 (80.1%, 58.2%)	1.0	
Marital status				
Single† (N=138)	35 (25.4%, 46.1%)	103 (74.6%, 39.2%)	1.33 (0.79-2.22)	0.28
Married (N=201)	41 (20.4%, 53.9%)	160 (79.6%, 60.8%)	1.0	
Household income				
<20,000 (N=186)	56 (30.1%, 73.7%)	130 (69.9%, 49.4%)	2.86 (1.57-5.25)	0.0002
≥20,000 (N= 153)	20 (13.1%, 26.3%)	133 (86.9%, 50.6%)	1.0	
People per room				
> 2 (N= 98)	33 (33.7%, 43.4%)	65 (66.3%, 24.7%)	2.34 (1.36-3.98)	0.002
≤ 2 (N= 241)	43 (17.8%, 56.6%)	198 (82.2%, 75.3%)	1.0	

OI= opportunistic infection; Percentages in bracket are for rows and columns respectively.

†Single in this context refers to those whose marital status is single, separated, divorced or widowed

Table 3: Socio-demographic risk factors for opportunistic infections in patients on HAART (univariate analysis)

p<0.0001), duration of HAART <36 months (OR= 2.19, 95% CI= 1.29-3.89, p<0.003), and HAART non-adherence (OR= 7.63, 95% CI= 4.30-13.55, p<0.0001). The following baseline parameters were positively associated with increased risk of OIs: WHO clinical stage 3-4 (OR= 9.48, 95% CI= 5.37-17.05, p<0.0001), CD4 cell count < 200 cells/μl (OR= 3.76, 95% CI= 2.14-6.65, p<0.0001), and hemoglobin <10 g/dl (OR= 4.62, 95% CI= 2.64-8.10, p<0.0001). In addition, the risk of OIs was significantly higher in participants with the following current parameters: CD4 cell count <200 cells/μl (OR= 6.11, 95% CI= 3.46-10.78, p<0.0001), and hemoglobin <10 g/dl (OR= 4.22, 95% CI= 2.07-8.62, p<0.0001). The risk of OIs was higher in patients with BMI <25 kg/m^2 but the difference was not statistically significant (OR= 1.74, 95% CI=0.97-3.11, p=0.05). There was no significant relationship between OIs and cotrimoxazole prophylaxis, diabetes, hypertension, alcohol consumption or smoking.

In order to determine the independent risk factors for OIs, age, household income, residence, number of people per room, socio-economic status, duration of HIV diagnosis, HAART duration, HAART adherence, baseline WHO clinical stage, CD4 cell count (baseline and current), hemoglobin (baseline and current), and BMI were included in multivariate analysis (logistic regression) as they all had p<0.25 on univariate analysis. Although gender had a p-value of 0.58 on univariate analysis, it was also included in the logistic model as it was one of the variables considered *a priori* to be associated with OI risk [5,25]. Finally, the independent risk factors for development of OIs were household income ₦ 20,000 (Adjusted odds ratio [AOR] = 2.70, 95% CI=1.18-6.18, p=0.02), baseline WHO clinical stage 3-4 (AOR= 9.49, 95% CI= 4.20-21.42, p<0.0001), HAART non-adherence (AOR= 5.28, 95% CI= 2.52-11.08, p<0.0001), baseline hemoglobin <10 g/dl (AOR= 3.50, 95% CI= 1.47-8.36, p=0.005), and current CD4 cell count <200 cells/μl (AOR=3.43, 95% CI=1.49-7.92, p=0.003) (Table 5).

Discussion

This study determined the prevalence and risk factors for opportunistic infections (OIs) in patients receiving HAART in a resource-limited setting in Nigeria. The overall prevalence of OIs was 22.4%. This is in agreement with the prevalence of 20% documented by Corey et al. [26] in a 5-year observational cohort study of 564 patients receiving HAART in Peru, South America. It is also comparable with the report of 30% by De Beaudrap et al. [27] in Senegalese cohorts receiving HAART. Variable prevalence rates of OIs in patients receiving HAART have been reported in other settings, 8% in Thailand by Manosuthi et al. [25]; 8.3% in India by Srirangaraj et al. [28]; 47.6% both in Taiwan [29] and South Africa [17]. The high rate of 47.6% found in Taiwan sharply contrasts with the much lower rate of 8% in two other HAART-experienced Asian populations [25,28]. Although the pre-HAART burden of OIs was not stated in most of the reports, the high rate of 47.6% reported by Sun et al. [29] in Taiwan may be attributable to the high OI prevalence of 77.7% in their patients before commencement of HAART. Mzileni et al. [17] studied a large cohort of 2,605 between 2004 and 2006 in South Africa. Beyond differences in sample size and study design, as well as possible differences in pre-HAART OI burden between their cohorts in South Africa and our patients, Mzileni et al. [17] primarily set out to investigate causes of mortality in their cohorts on HAART unlike our study that focused on OI prevalence and associated risk factors. Furthermore, the variable duration of HAART in the various studies may partly explain the differences in the prevalence of OIs.

The frequency of individual OIs was low. However, in relative terms, candidiasis, TB, and dermatitis were the commonest accounting for 38.2%, 34.2%, and 25% of cases respectively. The most frequent OIs seen in our patients are similar to those documented in patients receiving HAART in other low-income settings with TB and candidiasis as the leading conditions [12,17,27,29]. The spectrum of OIs in this study is similar to what was reported in HAART-naïve patients in Nigeria [30,31]. Lack of change in the spectrum of OIs post-HAART compared to the pre-HAART era has been observed by several authors [11,27,29,32]. It is worth mentioning that unlike most of these studies, TB was not the commonest OI among our patients despite the well-known high burden of TB in Nigeria. While the use of fairly strict criteria for TB diagnosis in this study was adopted to avoid over diagnosis, it is not certain if TB was under-diagnosed in our patients considering the difficulty associated with TB diagnosis in PLHIV especially in the absence of sputum mycobacterial cultures. Globally,

Variable	OI present (N= 76)	OI absent (N = 263)	Odds ratio (95% CI)	p-value
HIV duration (years) <3 (N= 117) ≥3 (N= 222)	 41 (35.0%, 53.9%) 35 (15.8%, 46.1%)	 76 (65.0%, 28.9%) 187 (84.2%, 71.1%)	2.88 (1.65-5.04) 1.0	<0.0001
HAART duration <36 months (N= 173) ≥36 months (N= 166)	 50 (28.9%, 65.8%) 26 (15.7%, 34.2%)	 123 (71.1%, 46.8%) 140 (84.3%, 53.2%)	2.19 (1.29-3.89) 1.0	0.003
HAART non-adherence Yes (N= 76) No (N= 263)	 41 (53.9%, 53.9%) 35 (13.3%, 46.1%)	 35 (46.1%, 13.3%) 228 (86.7%, 86.7%)	7.63 (4.30-13.55) 1.0	<0.0001
Cotrim. prophylaxis No (N= 42) Yes (N= 297)	 10 (23.8%, 13.2%) 66 (22.2%, 86.8%)	 32 (76.2%, 12.2%) 231 (77.8%, 87.8%)	1.09 (0.48-2.47) 1.0	0.82
Baseline WHO stage 3-4 (N= 99) 1-2 (N= 245)	 50 (53.2%, 65.8%) 26 (10.6%, 34.2%)	 44 (46.8%, 16.7%) 219 (89.4%, 83.3%)	9.57 (5.19-17.74) 1.0	<0.0001
Baseline CD4 (cells/µl) <200 (N= 168) ≥200 (N= 171)	 56 (33.3%, 73.7%) 20 (11.7%, 26.3%)	 112 (66.7%, 42.6%) 151 (88.3%, 57.4%)	3.76 (2.14-6.65) 1.0	<0.0001
Current CD4 (cells/µl) <200 (N= 75) ≥200 (N= 264)	 38 (50.7%, 50.0%) 38 (14.4%, 50.05)	 37 (49.3%, 14.1%) 226 (85.6%, 85.9%)	6.11 (3.46-10.78) 1.0	<0.0001
Baseline Hb (g/dl) <10 (N= 76) ≥10 (N= 263)	 35 (46.1%, 46.1%) 41 (15.6%, 53.9%)	 41 (53.9%, 15.6%) 222 (84.4%, 84.4%)	4.62 (2.64-8.10) 1.0	<0.0001
Current Hb (g/dl) <10 (N= 36) ≥10 (N= 303)	 18 (50.0%, 23.7%) 58 (19.1%, 76.3%)	 18 (50.0%, 6.8%) 245 (80.9%, 93.2%)	4.22 (2.07-8.62) 1.0	<0.0001
BMI (current) [Kg/m^2] <25 (N= 203) ≥25 (N= 136)	 53 (26.1%, 69.7%) 23 (16.9%, 30.3%)	 150 (73.9%, 57.0%) 113 (83.1%, 43.0%)	1.74 (0.97-3.11) 1.0	0.05
Diabetes Yes (N= 11) No (N= 328)	 1 (9.1%, 1.3%) 75 (22.9%, 98.7%)	 10 (90.9%, 3.8%) 253 (77.1%, 96.2%)	0.34 (0.02-2.62) 1.0	0.47
Hypertension Yes (N= 52) No (N=287)	 9 (17.3%, 11.8%) 67 (23.3%, 88.2%)	 43 (82.7%, 16.3) 220 (76.7%, 83.6%)	0.69 (0.30-1.56) 1.0	0.34
Alcohol consumption Yes (N= 72) No (N= 267)	 15 (20.8%, 19.7%) 61 (22.8%, 80.3%)	 57 (79.2%, 21.7%) 206 (77.2%, 78.3%)	0.89 (0.45-1.75) 1.0	0.72
Smoking Yes (N= 24) No (N= 315)	 6 (25.0%, 7.9%) 70 (22.2%, 92.1%)	 18 (75.0%, 6.8%) 245 (77.8%, 93.2%)	1.17 (0.40-3.27) 1.0	0.75

BMI= body mass index; HAART= highly active antiretroviral therapy; Hb= hemoglobin

OI= opportunistic infection; WHO= world health organization

Percentages in bracket are for rows and columns respectively.

Table 4: Clinical risk factors for opportunistic infections in patients on HAART (univariate analysis).

	Adjusted Odds ratio	95% CI	P-value
Age ≤ 40 years	1.67	0.69 - 4.05	0.25
Baseline CD4 cell count <200 cells/µL	0.85	0.36 - 2.01	0.72
Baseline hemoglobin <10 g/dl	3.50	1.47 - 8.36	0.005
Baseline WHO clinical stage 3-4	9.49	4.20 - 21.42	<0.0001
Current BMI <25 Kg/m^2	1.06	0.51 - 2.20	0.86
Current CD4 cell count <200 cells/µL	3.43	1.49 - 7.92	0.003
Current hemoglobin <10 g/dl	0.55	0.16 - 1.91	0.34
Duration of HIV diagnosis <3 years	2.30	0.79 - 6.67	0.12
Female gender	1.03	0.41 - 2.55	0.95
HAART non-adherence	5.28	2.52 - 11.08	<0.0001
HAART duration <36 months	0.99	0.35 - 2.85	0.99
Household income < 20,000	2.70	1.18 - 6.18	0.02
People per room >2	1.11	0.49 - 2.53	0.80
Rural residence	0.98	0.46 - 2.07	0.95
Lower socio-economic class	0.70	0.31 - 1.62	0.41

BMI= body mass index; HAART= highly active antiretroviral therapy; WHO= world health organization

Table 5: Risk factors for opportunistic infections in patients on HAART (multivariate analysis)..

TB diagnosis remains a challenge in PLHIV due to absence of classical features, high rate of smear negative disease, and relatively high burden of extra-pulmonary disease all of which were seen in the majority of our patients. This is not the case for candidiasis which is a lot easier to diagnose whether on clinical or laboratory grounds.

Compared to OI prevalence of 57-69% previously reported in HAART-naïve HIV-infected patients in Nigeria [30,31,33], the rate of 22.4% documented in our patients who had received HAART for a median duration of three years suggests more than 60% decline in the burden of HIV-related OIs. However, since the pre-HAART burden of OIs among the patients in this study was not assessed, this assumption cannot be stretched too far. In Senegal, De Beaudrap et al. [27] reported an impressive decline of 79% in OIs among their cohorts during the fourth year of HAART. Unfortunately, this was not sustained beyond this time as the incidence began to rise by 5% per month after the fourth year. In Taiwan [29], the rate of decline in OIs was only 39% after 12 months of HAART. Despite the longer duration of HAART use in Western countries, the rate of decline of OIs in the era of HAART has remained consistent and more impressive with over 80% decline [11,34,35]. While it is not in doubt that that the relatively lower burden of OIs in the pre-HAART era, and widespread access to ART in high-income settings have reasonably contributed to this difference, efforts to identify possible contributions of clinical and socio-demographic characteristics of PLHIV in developing countries are worthwhile.

A number of independent clinical risk factors for the occurrence of OIs were identified in this study including advanced WHO clinical stage at baseline, anemia at baseline, current CD4 cell count below 200 cells/µl and HAART non-adherence. Similarly, the clinical risk factors for OIs in HAART–experienced patients in other studies include low level of current CD4 cell count, advanced baseline WHO clinical stage, and baseline anemia [5,11,27,28,35,36]. Additional clinical parameters which were also identified as determinants of OIs in patients receiving HAART in those studies include low baseline CD4 cell count, shorter duration of HAART, high HIV viral load at baseline or in the course of treatment, and low BMI. Apart from viral load which was not quantified in this study due to economic constraints, nearly all the other additional factors had positive significant associations with the presence of OIs on univariate analysis in this study but their effect was not significant on multivariate analysis. It is possible that this study did not have enough power to investigate the relationship between some of these additional clinical parameters and OIs.

The positive association between HAART non-adherence and occurrence of OIs documented in this study should be taken seriously. This observation was made despite the relatively good adherence rate of 78% among our patients. There is a tendency to focus on patient-related factors when HAART non-adherence is discussed in HIV treatment centers. Nevertheless, we cannot afford to lose sight of the fact that non-adherence may partly result from system failure in ART programs. In 2004, the national ART program of Nigeria suffered a major setback when it was hit by shortage of drugs [37]. As a result, many patients were off drugs or staggered their dosages for up to three months which led to a structurally-induced adherence problem. Although the program subsequently resumed when drug supplies were recommenced, till date, we probably do not know the exact contribution of that tragedy to antiretroviral treatment failure in Nigeria. In appreciation of the challenge non-adherence poses to the current benefits of HAART, Yazdanpanah et al. [38] noted that many HV-infected patients would remain at a major risk of OIs due to adherence issues, drug resistance and treatment failure.

In developed nations, emphasis on the risk factors for OIs has largely been on clinical parameters which have led to baseline CD4 cell count and post-treatment CD4 cell count being acknowledged as the strongest predictors of HIV-related OIs [11,39]. Sub-Saharan Africa with its long list of socio-economic determinants of health cannot afford to endlessly tow this line. In this study, poor household income was found to be an independent predictor of OIs. It may also be noteworthy that overcrowding (having more than 2 people per room) which is an index of poverty was associated with increased risk of OIs on univariate analysis. Overcrowding and poor hygiene have been suggested as contributory factors to high burden of HIV-related OIs in developing countries [28]. Bearing in mind the finding of this study, household income on its own may be more intimately associated with health challenges than other factors such as educational status and occupation which in addition to income contribute to the socio-economic designation of the individual. If the positive association between poverty and OIs in low-income countries is supported by more studies, PLHIV in Nigeria will be in great danger considering that 55% of the participants of this study had a household income below the national minimum wage.

In this study, neither age nor gender had a significant relationship with occurrence of OIs after controlling for other factors. While Lawn et al. [36] demonstrated increased risk of TB in younger patients (<33 years), Ghate et al. [19] in a predominantly HAART-naïve population in India reported that older age was a strong determinant of OIs. Pallela et al. [34] found no signification association between age and OIs in a cohort of US patients. In line with the observations of Pallela et al. [34] and Lawn et al. [36], we did not find gender to be a risk factor for OIs. Contrarily, male gender was found to be strongly associated with the occurrence of OIs in other reports [5,25]. Large prospective cohort studies are needed to further investigate the relationship between socio-demographic variables and HIV-related OIs in developing countries.

This study had some limitations. HIV viral load of the patients was not tested. This is due to the fact that most HIV treatment programs in Nigeria are currently running on very tight budgets such that HIV viral load assay which is very expensive is no longer frequently tested except in some centers. The diagnosis of herpes zoster and genital warts were entirely based on clinical grounds. In addition, some relatively less common HIV-related OIs for which diagnostic facilities are not readily available such as PCP, MAC and CMV disease were not diagnosed. Although a high index of suspicion was maintained for PCP, none of the participants met the clinical criteria for its presumptive diagnosis. Due to cost constraints, it was not possible to carry out sputum mycobacterial culture for the diagnosis of pulmonary TB which would have significantly increased the sensitivity of pulmonary TB diagnosis. However, the TB screening and diagnostic algorithm in HIV-infected patients was combined with sputum AFB test, radiological investigations and treatment response (in some cases) to improve the sensitivity of TB diagnosis. The impact of antiretroviral drug resistance was not determined as the sophisticated facilities for antiretroviral resistance testing are not available in most parts of Nigeria. In the few places this could be done, the cost is usually prohibitive. We also acknowledge the fact that conditions such as sepsis and bacterial pneumonia are not necessarily opportunistic infections. However, considering that HIV/AIDS patients have increased predisposition to these conditions [40,41], the authors have loosely classified them as opportunistic infections.

In conclusion, the findings of this study suggest that OIs remain a challenge in patients receiving HAART in Nigeria. Beyond the well recognized clinical predictors of HIV-related OIs, poverty may emerge

a strong risk factor in developing countries. A high index of suspicion should be maintained for OIs in PLHIV despite the use of HAART. Early presentation and access to HAART should further be intensified in SSA. Anemia should be properly investigated for during baseline evaluation in PLHIV and when present should be appropriately corrected. Individuals who continue to have low CD4 cell count while on HAART should be aggressively evaluated for OIs and practical efforts to optimize their immunological recovery should be made. Prophylaxis for TB and fungal infections especially candidiasis should be widely implemented in the routine management PLHIV in SSA after exclusion of active disease, irrespective of HAART use. Low-income groups should become a target for a more aggressive evaluation for HIV-related OIs. HAART adherence counseling should be intensified in patients receiving HAART. The need for improved commitments of indigenous governments in SSA towards sustained availability and accessibility of ART cannot be overemphasized.

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