Types and prevalence of HIV-related opportunistic infections/conditions among HIV-positive patients attending Kenyatta National Hospital in Nairobi, Kenya

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Abstract

Background: Although antiretroviral therapy (ART) has resulted in significant decrease in opportunistic infections (OIs), OIs continue to cause significant morbidity and mortality among HIV patients.

Objective: To determine the prevalence and types of HIV/AIDS-related OIs among patients attending Kenyatta National Hospital (KNH) in Nairobi, Kenya.

Methods: A cross-sectional study was conducted from May to August 2010 among patients ≥19 years. An interviewer-administered questionnaire was used to collect data on socio-demographic factors, HIV and OIs. CD4 data were extracted from clinical records.

Results: Most patients (72%) had lived with HIV for ≤ 5 years and 78.8% had an OI. The 3 most common OIs were TB (35%), Herpes Zoster (HZ; 15.4%) and oral thrush (OT; 8%). Years of HIV infection significantly predicted TB (p=0.01). Patients with CD4 ≤ 349 were almost twice as likely to have TB, than those with CD4 ≥500. Type of occupation predicted OT (p=0.04) with skilled workers less likely to have OT. Patients with primary/vocational/technical education were >3 times more likely to have HZ than those with tertiary education.

Conclusion: Due to the complex management of HIV and its associated OIs, appropriate implementation of the recommended guidelines for care and prevention among patients at KNH is important.

Keywords: HIV-related opportunistic infections, Kenyatta National Hospital, Kenya.

Introduction

Human Immunodeficiency Virus (HIV) and Tuberculosis (TB) co-infection is a major public health problem among people living with HIV, especially in developing countries in Africa. The prevalence of TB is a threat for the general public especially for those with immuno-suppressive illnesses other than HIV. The World Health Organization (WHO) estimates that around one-third of people living with HIV in the world are co-infected with TB and that approximately 750,000 people living with HIV develop TB yearly, mostly in sub-Saharan Africa[1]. Kenya has the fourth largest HIV epidemic in the world with an overall prevalence rate of 4.8 %[2]. Although there has been a decline in HIV prevalence

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in Kenya from 10.5% at its peak in 1996, 1.5 million Kenyans were living with HIV in 2017 and 53,000 were newly infected that year[2]. Forty-two percent of HIV-positive Kenyan adults were on antiretroviral therapy (ART) in 2013[3]. Despite the availability and use of ART, opportunistic infections (OIs) continue to cause significant morbidity and mortality among HIV/AIDS patients in low and middle-income countries (LMIC)[4]. This is because approximately 25% of HIV-infected individuals globally are unaware of their infection status and others who know their status are not on ART, or take ART inconsistently[5]. Further, with the 2013 WHO treatment guidelines that recommend ART initiation in HIV-positive individuals with a CD4 count of ≥350 cells/mm3, and the 2016 "Treat All" guidelines, access to ART is much lower due to a higher number of people who are eligible for treatment[6,7].

Among the common HIV OIs in Kenya, TB is the most prevalent (approximately 268 cases per 100,000 populations)[8]. TB is also the single leading cause of death among people living with HIV/AIDS (PLWHA) in Kenya[9]; up to 38% of people with TB are co-infected with HIV[2]. One study showed a TB/HIV co-infection rate of 42% in Western Kenya[10]. A case-control study conducted in Nairobi Province in 2007 found that 61.5% of TB cases were co-infected with HIV compared to 38.5 % of non-TB cases[11]. The emergence of drug resistant TB in countries with high HIV prevalence is an additional public health threat to those living with HIV, as well as to the general population. Because of the complex nature of the management of HIV and associated OIs, appropriate implementation of the recommended guidelines for care including prevention and treatment of OIs, use of ART and laboratory and clinical follow-up of patients is of paramount importance. Kenyatta National Hospital (KNH), which is located in the capital city of Nairobi, is the largest referral and teaching hospital in Kenya with an 1,800 bed capacity. KNH serves as the primary hospital for the 4 million residents in Nairobi. KNH has national guidelines for the management of OIs and use of ART to manage HIV-positive persons[12]. This study was conducted to determine the prevalence and types of HIV/AIDS-related OIs among patients attending KNH and to provide information that can be used in interventions for early diagnosis, treatment, and prevention of OIs among HIV patients. This information is essential for review of methods in use for treatment and control of OIs and implementation of clinical strategies and programs to mitigate the significant burden and cost of these infections.

Methods
Study design, participant recruitment and data collection.
A cross-sectional study was conducted from May to August 2010 among HIV-positive adults ≥19 years old who attended outpatient clinics at KNH. All patients were verified to be on cotrimoxazole or alternate prophylaxis for Pneumocystis jirovecii pneumonia (PCP) and on ART. Selection of the study population was done with the assistance of the clinic staff who reviewed the patient files, identified patients who met the eligibility criteria, informed them of the study and asked if they would be willing to participate. Patients who expressed willingness to participate were then introduced to the research staff by the clinic staff. The research staff informed potential participants about the purpose of the study and asked them to read the informed consent form and to ask questions. After all questions were answered to the satisfaction of the participants, they were asked to sign the informed consent form signifying their willingness to participate in the study. An interviewer-administered questionnaire was then used to collect information on socio-demographic characteristics (age, marital status, level of education, employment, occupation) and years of living with HIV from the participants. Clinical information, such as the most recent CD4+ T-cell count and diagnosis and treatment of OIs, was extracted from the participants' clinical files that are used by the clinicians during the patients' clinic visits. Diagnosis of OIs was done through clinical diagnosis and verified through laboratory testing where possible. A unique identification number was assigned to each participant's questionnaire (which also contained the clinical data) instead of the patient's name and the highest level of confidentiality of participant information was maintained.

Ethical approval
This study was reviewed and approved by the Institutional Review Board of the University of Alabama at Birmingham, and University of Nairobi-Kenyatta National Hospital Ethics and Research Committee.

Sample size calculation
The prevalence of OIs at KNH was previously estimated to be 14%[13]. Using this prevalence, we estimated that a total sample of 500 persons was required to capture a representative sample of this population with a 95% confidence and a 5% margin of error (Statcalc, Epi Info Version 6)

Statistical analysis

Statistical analyses of sociodemographic factors, years of living with HIV and CD4 count were conducted on the sample of 500 patients. Categorical variables were reported as counts and percentages, and the Chi-squared or Fisher's exact tests were used to compare categorical variables. Multivariable logistic regression models were fit on the whole dataset to determine factors associated with the three most commonly occurring OIs. The factors included in the models were: age, sex, level of education, employment status, occupation, years living with HIV and CD4 count. Odds ratios (OR), 95% confidence intervals (CIs), and the p-values for testing the significance of the variables in the model were obtained. All tests with a p-value ≤5% were deemed statistically significant. All analyses were done using the Statistical Analytical System (SAS) software version 9.4 (SAS Institute, Cary, North Carolina).

Results

Table 1 shows the socio-demographic characteristics and CD4 counts of the 500 participants in the study. Most of the participants (56.2%) were <40 years old and the highest proportion was in the 33-39 age-group. The majority of participants were married or cohabiting (54%), while 15.8% were divorced or separated, and 14.0% reported being single (never married). Most participants had received secondary education (46%), while 29% had received primary education and 17% had received tertiary or university education. Overall, 63% of the patients were unemployed; 71% reported that they were skilled and 29% reported being unskilled. A majority of the patients (72%) had lived with HIV for ≤ 5 years while 28% had lived with HIV for ≥ 6 years. Most participants had a CD4 count of 200-349 (31%), while 19.3% had a CD4 count of 0-199, 23.2% had a CD4 count of 350-499, and 26.1% had a CD4 count of ≥500.

Table 1. Socio-demographic characteristics and CD4 counts of participants

Variable	Total (n = 500) n (%)
Age	
19-25	17 (3.4)
26-32	103 (20.6)
33-39	161 (32.2)
40-46	105 (21.0)
47-53	114 (22.8)
Marital Status	
Married or Cohabiting	270 (54.0)
Widowed	79 (15.8)
Divorced/Separated	79 (15.8)
Single (never married)	72 (14.4)
Level of education	
None	14 (2.8)
Primary	146 (29.2)
Secondary	230 (46.0)
Vocational/Technical	25 ((5.0)
Tertiary/College/University	85 (17.0)
Employed	
Yes	185 (37.0)
No	315 (63.0)
Occupation	
Skilled	353 (70.6)
Unskilled	147 (29.4)
Years with HIV	
0-5	360 (72.0)
6-25	140 (28.0)

Table 2 shows the types and percentages of common HIV-related OIs or conditions among the study participants by years of living with HIV. TB, herpes zoster (HZ) and oral thrush (OT) were the three most commonly occurring OIs among participants (see Figure 1). OT (candida infection in the mouth, throat, and esoph-

agus) was differentiated from other forms of candidiasis such as vaginal candidiasis and invasive candidiasis. Of all the conditions studied, only TB was significantly associated with years of HIV infection (p = 0.02). Overall, 35% of the participants had TB. Of those living with HIV for ≤5 years, 31.7% had TB compared to 43.6% of participants living with HIV for ≥ 6 years.

Table 2. Types and prevalence of HIV-related opportunistic infections/conditions by years of HIV infection

| Variable	Total n (%)	Years with HIV n (%)		P-value
	n = 500	0-5	6-25	
Overall Prevalence of OIs	394 (78.8)			
TB				0.02
Yes	175 (35.0)	114 (31.7)	61 (43.6)	
No	325 (65.0)	246 (68.3)	79 (56.4)	
Herpes Zoster				0.1
Yes	77 (15.4)	49 (13.6)	28 (20.0)	
No	423 (84.6)	311 (86.4)	112 (80.0)	
Oral Thrush				0.1
Yes	40 (8.0)	24 (6.7)	16 (11.4)	
No	460 (92.0)	336 (93.3)	124 (88.6)	
URI				0.13
Yes	29 (5.8)	17 (4.7)	12 (8.6)	
No	471 (94.2)	343 (95.3)	128 (91.4)	
Candidiasis				0.18
Yes	26 (5.2)	22 (6.1)	4 (2.9)	
No	474 (94.8)	338 (93.9)	136 (97.1)	
Cryptococcal Meningitis				0.64
Yes	23 (4.6)	18 (5.0	5 (3.6)	
No	477 (95.4)	342 (95.0)	135 (96.4)	
Diarrhea				0.42
Yes	17 (3.4)	14 (3.9)	3 (2.1)	
No	483 (96.6)	346 (96.1)	137 (97.9)	
Kaposi's Sarcoma				0.68
Yes	7 (1.4)	6 (1.7)	1 (0.7)	
No	493 (98.6)	354 (98.3)	139 (99.3)	

P<0.05 statistically significant
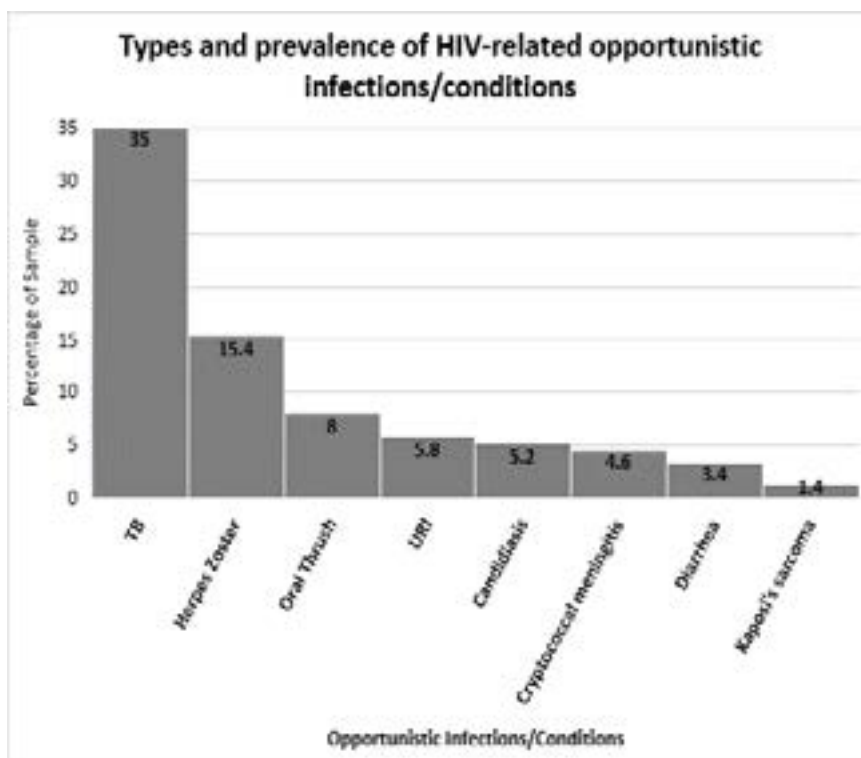
Figure 1: Types and prevalence of HIV-related opportunistic infections/conditions

Table 3 shows the odds ratio and 95% CIs of sociodemographic factors, years of living with HIV, and CD4 count associated with TB, HZ, and OT. Only years of living with HIV significantly predicted participants having TB (p=0.01). Patients who lived with HIV for ≤5 years had lower odds of developing TB compare with those who lived with HIV for ≥6 years (AOR = 0.53, 95% CI = 0.34, 0.83). Participants with lower CD4 counts of 0-199 and 200-349 had two times greater odds of having TB than those with CD4 count of ≥ 500 (AOR = 1.94, 95% CI = 1.04, 3.64 and AOR = 1.84, 95% CI = 1.05, 3.22, respectively).

None of the factors predicted HZ. However, it is interesting to note that patients with primary and vocational/technical education had 3 times and almost 5 times greater odds of having HZ than participants with tertiary or college education (AOR = 3.05, 95% CI = 1.01, 9.23 and AOR = 4.98, 95% CI = 1.24, 20.07, respectively). Type of occupation was a predictor of OT (p=0.04); skilled workers had lower odds of having OT than unskilled workers (AOR = 0.37, 95% CI = 0.41, 0.97).

Table 3: Adjusted odds ratios (AOR) and 95% Confidence Intervals (CIs) for factors associated with tuberculosis, herpes zoster, and oral thrush

Variable	AOR(95%CI)		
	Tuberculosis	**Herpes Zoster**	**Oral Thrush**
Age (years)	(P-value = 0.15)	(P-value = 0.81)	(P-value = 0.63)
19-25	0.86(0.21, 3.57)	1.16(0.21, 6.3)	0.73(0.08, 6.90)
26-32	1.8(0.94, 3.43)	0.91(0.42, 1.98)	0.40(0.12, 1.39)
33-39	**1.91(1.07, 3.42)**	0.70(0.34, 1.43)	0.91(0.35, 2.33)
40-46	**1.89(1.00, 3.55)**	1.06(0.51, 2.20)	1.06(0.39, 2.88)
47-53	Referent	Referent	Referent
Sex	(P-value = 0.2)	(P-value = 0.87)	(P-value = 0.66)
Male	1.35(0.85, 2.14)	1.05(0.58, 1.90)	0.83(0.37, 1.89)
Female	Referent	Referent	Referent
Level of Education	(P-value = 0.79)	(P-value = 0.2)	(P-value = 0.66)
None	1.06(0.23, 4.81)	1.93(0.30, 12.63)	0.38(0.03, 4.12)
Primary	1.3(0.63, 2.66)	**3.05(1.01, 9.23)**	0.58(0.18, 1.91)
Secondary	1.47(0.78, 2.75)	2.74(0.99, 7.63)	0.54(0.19, 1.50)
Vocational/Technical	1.47(0.49, 4.37)	**4.98(1.24, 20.07)**	0.24(0.03, 2.22)
Tertiary/College/University	Referent	Referent	Referent
Employed	(P-value = 0.47)	(P-value = 0.34)	(P-value = 0.21)
Yes	0.83(0.50, 1.37)	1.38(0.71, 2.67)	1.79(0.72, 4.46)
No	Referent	Referent	Referent
Occupation	(P-value = 0.2)	(P-value = 0.08)	**(P-value = 0.04***)
Skilled	1.43(0.83, 2.46)	0.54(0.28, 1.07)	**0.37(0.41, 0.97)**
Unskilled	Referent	Referent	Referent
Years with HIV	**(P-value = 0.01***)	(P-value = 0.09)	(P-value = 0.15)
0-5	**0.53(0.34, 0.83)**	0.63(0.36, 1.08)	0.58(0.28, 1.21)
6+	Referent	Referent	Referent
CD4 count (cells/mm3 blood)	(P-value = 0.12)	(P-value = 0.67)	(P-value = 0.93)
0-199	**1.94(1.04, 3.64)**	1.00(0.44, 2.27)	1.41(0.49, 4.04)
200-349	**1.84(1.05, 3.22)**	1.46(0.72, 2.95)	1.10(0.42, 2.88)
350-499	1.42(0.78, 2.61)	1.25(0.59, 2.65)	1.10(0.40, 3.08)
≥ 500	Referent	Referent	Referent

* Significant association with the OI, P<0.05 statistically significant.

Discussion

In this study participants presented with common HIV-related OIs or conditions such as TB, herpes zoster (HZ), oral thrush (OT), diarrhea and Kaposi's sarcoma. The World Health Organization (WHO) and the Joint United Nations Programme on HIV/AIDS (UNAIDS) recommended the use of co-trimoxazole prophylaxis for HIV-infected adults in Africa with symptomatic HIV disease (stage II, III or IV of the WHO classification of HIV infection and disease) and for asymptomatic individuals with CD4 T-lymphocyte count of ≤500×106/l or total lymphocyte count (TLC) equivalent in late 2000[14]. Thus all of the patients were on cotrimoxazole prophylaxis and none presented with Pneumocystis Jerovencii pneumonia (PCP) indicating that cotrimoxazole prophylaxis implementation was effective. However, this study was conducted in 2010 shortly after the WHO 2010 ART guidelines were implemented. Although KNH began implementing the guidelines, the patients might not have been on ART

long enough for their immune systems to recover enough to prevent the HIV-related OIs/conditions that were observed. Further, since the study was cross-sectional, we were recruiting patients at different stages of HIV infection and who were on ART for different periods of time.

In this study years of living with HIV was found to be a predictor of TB infection. Participants who were living with HIV for ≤5 years were 47% less likely to have TB compared to those living with HIV for ≥ 6 years. This is understandable since HIV weakens the immune system over time and increases the risk for TB infection[15]. An earlier study done in Kenya showed that as the HIV epidemic peaked in the mid-1990s (1994-1996) the annual risk of TB infection was higher than during the earlier years of 1986-1990[16]. Other studies conducted in Zambia and the US also showed significant associations between HIV infection and prevalent TB[17,18]. The study by Ayles et al. showed that 36% of prevalent TB could be attributed to HIV infection, while the study by DeRiemer et al. found that TB cases were nearly eight times higher among HIV-infected than non-HIV-infected persons[17,18]. A recent case-control study on factors associated with TB infection among people living with HIV/AIDS in China found that 15.7% of subjects were diagnosed with active TB. Similar to our study, this study showed that long duration of HIV infection was an independent risk factor for TB 19. Our study also showed a significant relationship between CD4 count and TB infection. Patients with CD4 counts of 0-199 or 200-349 had approximately 2 times higher odds of having TB infection. This has also been seen in other studies and is known to occur as a result of loss of CD4 cells and impairment of the immune system in HIV[19-21].

At the time of our study in 2010, the Kenyan standard ART regimen was in-line with the WHO's recommendation of November 2009 which called for ART initiation when the CD4 count dropped to 350 cells/μL or below[22]. With timely initiation of appropriate ART, and adherence to ART, less cases of TB and other OIs should be observed. Many studies have shown that the use of ART has substantially reduced morbidity and mortality from OIs among HIV-positive individuals since its introduction[19,23]. However, in Kenya and other developing countries, many HIV cases are diagnosed late in infection when the CD4 count has already dropped low and patients present to clinics with OIs. The ART guidelines were revised in 2013 calling for initiation of ART in all HIV-positive individuals with a CD4 count of >350 cells/mm³ and ≤ 500 cells/mm³ regardless of WHO clinical stage, and initiation of ART in all HIV-positive individuals with active TB disease[6]. The WHO again revised the ART guidelines in 2015 to recommend that ART should be initiated in everyone living with HIV at any CD4 cell count[7]. TB may go undiagnosed in HIV patients with mild clinical signs and atypical imaging as occurs in people with impaired immune systems[17]. Undiagnosed TB is a major challenge to TB control; therefore, vigilant clinical evaluations for HIV patients with atypical TB presentation need to be worked into the management of HIV patients, especially those who have been infected with HIV for a longer duration of time or those with lower CD4 counts.

In this study, 15.4% of patients had HZ, similar to the rate of HZ infection in HIV patients found in another study24. Other studies have shown that HIV-infected patients have a higher incidence of HZ than the general population even after the institution of ART[25-27]. We found that patients with lower levels of education (primary and vocational/technical) were 3 and 5 times more likely to have HZ infection, respectively, than those with tertiary or college education. Although none of the studies that we reviewed looked at educational level of HIV patients with HZ, they showed a higher incidence of HZ among white patients at an urban Veterans Affairs Medical Center or that HZ infection occurred predominantly among urban African-American patients who may be of lower economic status and educational level[24-26]. Our finding that patients with lower educational levels were more likely to have HZ may indicate that it took a longer time for these patients to be diagnosed with HIV or to receive ART. Before ART, the incidence of HZ in HIV patients was 10-30 times higher than in HIV-negative individuals[28,29]. Studies have shown that although HZ seems to increase shortly after initiation of ART due to Immune Reconstitution Inflammatory Syndrome (IRIS), there has been a significant decrease in HZ incidence since the introduction of ART[24,25,30,31].

The prevalence of OT in our study was 8% which is in agreement with the lower level reported from a recent meta-analysis of oral candida among HIV-infected individuals in African populations; prevalence rates ranging from 7.6% to 75.3% were reported[32]. The variations in prevalence may be due to differences in diagnostic techniques, geographic and/or ethnic differences, and oral hygiene among the participants. We found an association between type of occupation and OT among our

HIV patients; patients with skilled occupations were 63% less likely to have OT than those with unskilled occupations. Unskilled workers may have had poorer oral hygienic practices, less health care, and poorer access to early HIV care than skilled workers. There is need to strengthen the capacity for oral hygiene and fungal diagnosis and effective treatment in Kenya and other African populations.

Conclusion

The findings of this study highlight the need for improvement of the rates of screening, early detection of TB and HIV infections and management of HIV and OIs in Kenya. Coordination and integration of diagnostic services and preventive care for TB and HIV is essential for their control. Active case finding programs should be initiated so that ART can be initiated early among those infected with HIV to decrease the burden of OIs. Patients found with latent TB should be given preventive therapy to avoid active TB disease. Additionally, annual TB screening of HIV-positive individuals, with increased clinical evaluation of those infected with HIV for a longer duration of time (or with a low CD4 count), regardless of clinical symptoms, should help to reduce the occurrence of TB and other OIs. Physicians should look carefully for indicators of TB such as IRIS during treatment of HIV patients especially as TB may present atypically in HIV patients[33]. Enhancement of TB infection control measures to prevent transmission of disease within health care facilities, and appropriate management of both HIV and TB infections should be instituted in order to decrease morbidity and mortality among infected persons. Since TB is both curable and preventable, urgent action is required to prevent, diagnose, and treat the infection in people living with HIV, their families and community members.

Study Limitations

This study has certain limitations that should be considered in interpreting the results. The main limitation is the cross-sectional study design which does not allow determination of causality. Some OIs and other HIV/AIDS related conditions may have gone undetected due to subclinical presentation and incomplete screening resulting in potential underestimation of the different conditions. Since our study sample was drawn from patients attending outpatient clinics at KNH, the sample may not be fully representative of the population of Nairobi. However, KNH draws people from all over Nairobi and other areas of Kenya.

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