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The Burden of Opportunistic-Infections and Associated Exposure Factors among HIV-Patients Admitted at a Botswana Hospital

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Abstract

Background

Botswana is among countries most affected by the human immunodeficiency virus (HIV) pandemic. Since 2001, aggressive interventions have been launched by the government including free access to combination antiretroviral treatment (cART). cART is known to reduce HIV transmission, related morbidities and hospital admissions among people living with HIV (PLWH). However, hospital admissions among PLWH in Botswana still remain high. Factors associated with such admissions have not yet been highlighted. Even though opportunistic infections (OIs) have been incriminated as the major cause of admissions among PLWH, the OIs have not yet been meticulously studied in Botswana.

Aim

The aims of this study were to highlight OIs causing admissions among PLWH at Princess Marina Hospital (PMH), estimate the proportions of such admissions and elucidate associated exposure factors.

Methods

Hospital records of 179 HIV positive patients admitted at PMH from April to June 2014 were reviewed. Their biomedical and socio-demographic data were collected. All potential correlates of OIs admissions were investigated through bivariate analysis and a logistic regression model. Adjusted odds ratios (AOR) and their 95% confidence intervals (CIs) were estimated for factors that were retained in the final model.

Results

OIs were the leading cause of admissions at PMH among PLWH. Patients' CD4-cell count, not being on cART, being on co-tri-

moxazole as well as being male were the most important correlates of these admissions.

Conclusion

Programs aiming at addressing the burden of OIs among PLWH should primarily target to put more people on cART and raise their CD4-cell count.

Keywords: Antiretroviral Therapy; Biomedical; Economic and Socio-Demographic Characteristics; HIV; Hospital Admission; Opportunistic Infections; Botswana

Introduction

People living with the human immunodeficiency virus (HIV) (PLWH) are constantly challenged by an array of diseases caused by different types of agents, essentially by those that do not cause diseases in people with intact immunity, e. g., *Cryptococcus neoformans* and *bacterial pneumonia,* reason why such infections are generally referred to as opportunistic infections (OIs) [1].

OIs account for most hospital admissions among PLWH throughout the world [2]. However, since the advent of combination antiretroviral treatment (cART), the severity of OIs on PLWH has remarkably changed in Western countries [3]. Tremendous changes have also been documented in a number of resource-poor countries since the Global Fund to fight AIDS, Tuberculosis and Malaria (GFATM) stepped in to provide free access to cART [4]. These drugs are known to increase the number of CD4 T lymphocytes while improving their function and re-establishing the host defense mechanisms and thus reducing HIV viral replication rates as well as OI-related admissions [5, 6]. OI-related admissions are thus a critical indicator for measuring the burden of these infections among PLWH in today's free cART era.

In partnership with GFATM [4] and other stakeholders like US Centers for Disease Control (CDC) and the World Health Organization (WHO), programs aiming at reducing the burden of OIs among PLWH are being implemented in different parts of the world including Southern Africa where the prevalence of HIV is one of the highest [7, 8]. But, data on admissions due to OIs and biomedical and socio demographic factors associated with such admissions in these countries are scarce, yet such data are critical for planning and designing effective prevention and control programs of OIs among PLWH.

In Southern Africa, Botswana stands as one of the countries most affected by HIV [7]. An estimated 300,000 adults and children or a sixth of the country's two million population were found to be HIV positive in 2009 [7]. In 2007 alone, an estimated 11,000 children and adults died of HIV-related illnesses [8]. Whether these deaths were due to OIs alone or to other HIV-related conditions like diabetes [9] and suicide [10], to date is still unclear. Reports from the Ministry of Health of Botswana lack this information [11]. However, given the ultimate goal of cART implementation programs of increasing populations' number of CD4 T lymphocytes and decreasing OI-related morbidities [5, 6], it is hard to believe that HIV admissions and mortalities reported back in 2007 [8] were due to OIs. This is because of the relative inability of OIs to cause disease in the presence of CD4-cell count < 350μ/L [12] and that by then the free cART intervention program in Botswana was already on for 7 almost years.

That is to say that after more than a decade and half of free cART intervention, at this particular point in time, proportions of OI-related morbidities and mortalities among PLWH in Botswana should be significantly lower than those reported in 2007 [8]. Unfortunately, proportion of such admissions is still not well documented thus hindering efforts needed for prevention and control. Biomedical and demographic factors commonly associated with OI-related morbidities among PLWH, e.g., CD4 cells level [13], co-trimoxazole use [14], gender [15] also need to be well investigated to highlight their relative contributions to the outcome based on Batswana own particularities to help tailor suitable control and prevention measures. This discussion on OIs and HIV raises crucial questions such as those pertaining to: (i) common causes for admission of PLWH in hospitals, (ii) proportions of admissions yet attributable to OIs among HIV patients in this new era of free cART and, (iii) correlates of such admissions. To date these questions are still unanswered in Botswana yet they are critical for addressing the burden of OIs among PLWH. We aim through this work to: (i) characterize common causes for admission among HIV patients at PMH medical wards, (ii) estimate the proportion of admissions attributable to OIs among HIV patients and, (iii) identify important correlates of such admissions.

Methods

Operational case definition

HIV/AIDS patient: any patient recorded by the physician as having HIV/AIDS based on International Code of Diseases (ICD) 10 (B20-B24)

HIV-related mortality: any case of death recorded by the physician as caused by HIV/AIDS or clinical immunosuppression consistent with ICD 10(B.20-24), excluding any death from suicide, drug overdose or accident of an HIV patient

HIV-related admission: any case of admission recorded by the physician as linked to HIV/AIDS or clinical immunosuppression consistent with ICD 10(B.20-24) , excluding admissions for delivery, elective surgeries and any other unrelated condition

Patient with opportunistic infection (OI): any patient with a

physician's record of having any of the following infection/ affections based on International Code of Diseases (ICD) 10 (B20-B24) was considered as having that specific OI in this study: Mycobacterium tuberculosis, Pulmonary TB, Extra-pulmonary TB, Disseminated TB, Cryptococcus neoformans (meningitis), Cryptosporidium Parvum infection (Chronic diarrhea), Bacterial Pneumonia, Pneumocystis carinii pneumonia(PCP), Candidiasis and Herpes zoster

Rural areas, Urban Villages and Urban centers- Areas were placed under each category in accordance with the Botswana AIDS Impact Survey 2008.

Low socioeconomic status (LSES): monthly income of US $300 or below (Excluded from paying taxes)

Middle socioeconomic status (MSES): monthly income of US $310 and above but less than US $ 1500

High socioeconomic status (HSES): monthly income of US $≥ 1,500

cART Adherence partner: Self-selected relative or friend to support HIV patients on cART psycho-socially in accordance with the Botswana National HIV and treatment guidelines of 2012 [16].

Anemia: Using WHO Hemoglobin concentrations for the diagnosis of anemia and assessment of severity 2011, normal hemoglobin levels were defined as below;

Men (15years and above)130 g/l or higher

Non pregnant women (15 years and above)120 g/l or higher

Neutrop[hil count: Normal neutrophil levels for adults range between 40-80% in accordance with the Botswana National Reference Laboratory

Study design

This was a cross-sectional study using a quantitative analytical approach to investigate hospital admissions due to OIs among HIV positive patients and associations with biomedical, socio-demographic and economic characteristics of patients.

Study site

The study was conducted at PMH, the main referral hospital in Botswana. The hospital receives both referred and non-referral patients from the rest of the country making it the busiest hospital in the country. It has a bed capacity of 567.

Data collection

The sample size was estimated to be 185 participants following an approach used by Arya and colleagues [17] for sample size estimation in prevalence studies. Participants were identified from hospital admission lists between April and June 2014. The lists were used as the sampling frame from which participants were selected using computer-generated random numbers. Selected numbers falling to HIV-negative patients or to those with unknown HIV status were replaced by new numbers so as to enrol only HIV infected patients in the study. Prospective participants were approached in the hospital wards and written consent to participate in the study was obtained. Respondents' medical records were reviewed and biomedical and socio-demographic data collected. A subsequent face-to-face interview was conducted with the patients to collect further socio-demographic and economic data missing from their records. Patients aged less than 18 years of age were excluded from the study in compliance with the University of Botswana Institutional Review Board requirement and published literature [N = 18]. Also excluded from the study were pregnant women admitted for control of any pregnancy-related OI [N = 1] and patients admitted in the high dependency cubicles as they were severely ill and had no relative beside them to answer our questions [N=18].

Data analysis

Data were entered into a computer using MS Excel (Redmond, WA). The data were then imported into IBM SPSS version 21 (IBM Corp., Armonk, NY) for analysis. Frequency distributions (%) of patients' by age group, gender and reason for admission were estimated. Common causes of admissions to PMH were characterized, and proportions of admissions attributable to OIs were computed by dividing the admissions attributable to OIs by the total HIV admissions times 1000 and comparisons were made among sub-groups.

Crude associations of admissions due to OIs with biomedical, socio-demographic and economic characteristic of patients were investigated through bivariate analyses. All potential correlates of OIs admissions were further investigated in a logistic regression model. Adjusted odds ratios (AOR) and their 95% CIs were estimated for every factor retained in our final models. Variance inflation factor diagnostic was performed for redundancy and multicollinearity of covariates. How well the model fits the data was estimated using the Hosmer-Lemeshow test of goodness-of-fit. The level of significance in the final model was set at $p < 0.05$.

Results

In total, 179 HIV positive patients were recruited in the study; of these participants 82 (45.8%) were males and 97 (54.2%) were female. The mean age (± SE) was 38.23 (±0.92) years. The youngest patient was 18 years old while the oldest was 67 years old.

A total of 59 medical conditions led to hospital admissions among PLWH at PMH. Results presented in Table 1 show the

top 11 specific reasons for admission at PMH between April and June 2014. Ninety three participants or 520 per 1000 admissions were attributable to OIs while 86 inpatients or 480 per 1000 admissions were due to non-OI conditions.

Table 1. Distribution pattern (per 1000) of HIV patients by cause of admission between April and June 2014 at Princess Marina Hospital in Gaborone, Botswana.

Rank	Cause of admission	Number	OI	Proportion per 1000
1	Tuberculosis	42	Yes	234.6
2	Cryptococcus meningitis	29	Yes	162.0
3	Para-suicide	12	No	67.0
4	Cryptosporidium	10	Yes	55.9
5	Bacterial pneumonia	6	Yes	33.5
6	Seizures	3	No	17.0
7	Sepsis	3	No	17.0
8	Pneumocystis carinii pneumonia	3	Yes	16.8
9	Herpes	2	Yes	11.2
10	Diabetes	2	No	11.2
11	Candidiasis	1	Yes	5.6
12	Other	69	No	385.5
	All Causes	179	-	1000

OI opportunistic infection.

Results presented in Table 2 are baseline characteristics of participants. Only 19 or 10.6% of participants had no formal education, the rest had different educational levels as presented in the Table 2. We described 151 or 84.4% participants as having low socio-economic status (SES) and 28 or 15.6% has having middle income SES. There was no patient with a high SES or with income of more than US $1,500/month. Forty four or 24.6% of the patients were not yet on cART, 99 or 55% were anemic, 91 had abnormal absolute neutrophil count and 94 or 52.5% had CD4-cell count less than 350/μL while 135 or 75.4% were on cART and 44 or 24.6 did not start cART yet.

Table 2. Baseline characteristics of HIV patients admitted at Princess Marina Hospital in Gaborone between April and June 2014.

Characteristic	N	Percentage (%)
Gender		
-Male	82	45.8
Education Level		
-No formal education	19	10.6
-Primary School education	29	16.2
-High school education	102	57.0
-Tertiary education	29	16.2
Religion affiliation		
-Christians or Muslim	113	63.1
-None or traditional belief	66	36.9
Residential Area		
-Urban area	86	48
Marital status		
-Never married	133	74.3
-Currently married/lived with a partner	30	16.8
-Divorcees/ widows	16	8.9
Living arrangement (with)		
-Family	131	73.2
-Relatives	16	8.9
-Friends	12	6.7
-Alone	20	11.2
Live with adherence partner		
-Yes	114	63.7
Consumed alcohol in the last 12 months		
-Yes	29	16.2
Currently smoking		
-Yes	18	10.1
Socio-economic (SES)		
-High SES (income > US $1,500/ month)	0	0
-Middle SES (income ≥ US $310/ month)	28	15.6
-Low SES (income ≤ US $300/month)	151	84.4
Participant on cART		
-Yes	135	75.0
cART Regimen		
-First line	132	73.7
Missed cART in the past 30 days		
-Never missed	97	71.3
-Missed once	7	5.2
-Missed several times	31	23.5
Participants on co-trimoxazole		
-Yes	96	53.6
Underlying medical conditions		
-Anemia present	80	45.5
-High blood pressure present	56	31.3
Participants with abnormal absolute neutrophil count		
-Yes	88	49.2
Participants' CD4-cell count		

->350/µL	85	47.5
Participants on cART		
Yes	135	75.4
Alternative treatment Taken		
-No alternative treatment	84	46.9
-Traditional Medicines	78	43.6
-Pastor prayers for holy healing	13	7.3
-Traditional medicine and prayers	4	2.2

Results from bivariate analyses using OI-related admissions at PMH as a dependent variable and patients' baseline characteristics as independent variables are presented in Table 3. Negative associations (p <0.05) are observed between female (UOR 0.42 95% CI 0.23 – 0.77), age < 36 years old (UOR 0.52, 95% CI 0.29 – 0.95), not being on co-trimoxazole prophylaxis (UOR 0.20, 95% CI 0.10 – 0.37) and OI-related admissions. Positive relationships are identified between CD4-cell count < 350µ/L (UOR 4.56 95% CI 2.46 – 8.56), not being on cART (UOR 3.23 95% CI 1.46 – 6.51) and OI-related admissions.

Table 3. Socio demographic, economic and biomedical factors associations with OIs admissions at Princess Marina Hospital, Gaborone, Botswana between April and June 2014 (Results from Bivariate Analysis).

Variable	OI (%)	Unadjusted OR	95% CI
Female	41 (44.1)	0.42**	0.23 – 0.77
Male	52 (55.9)	1†	-
Age < 36 years old	37 (39.8)	0.52**	0.29 – 0.95
Age > 36 years old	56 (60.2)	1†	-
No religion or traditional belief	37 (39.8)	1.30*	0.71 – 2.39
Christians or Muslim	56 (60.2)	1†	-
Rural area residence	44 (47.3)	1.47*	0.82 – 2.66
Urban area residence	49 (52.7)	1†	-
Live alone	8 (8.6)	1.62*	0.62 – 4.22
Live with family	68 (73.1)	1.93*	0.51 – 7.31
Live with relative	9 (9.7)	3.00*	0.67 – 13.40
Live with friends	8 (8.6)	1†	-
Not living with adherence partner	64 (68.8)	0.14*	0.63 – 1.16
Live with adherence partner	29 (31.2)	1†	-
Did not consumed alcohol	80 (86.0)	1.41*	0.63 – 3.13
Consumed alcohol	13 (14.0)	1†	-
Low SES	76 (81.7)	0.66*	0.29 – 1.49
Middle SES	17 (18.3)	1†	-
Not on cART	32 (34.4)	3.23**	1.46 – 6.51
On cART	61 (65.6)	1†	-
Missed cART once	4 (6.6)	1.82*	0.39 – 8.58
Missed cART many times	16 (26.2)	1.46*	0.65 – 3.28
Never missed cART	41 (67.2)	1†	-
Not on Cotrimoxazole	26 (28.0)	0.20**	0.10 – 0.37
On Cotrimoxazole	67 (72.0)	1†	-
CD4 < 350	65 (69.9)	4.56**	2.46 – 8.56
CD4 ≥ 350	28 (30.1)	1†	-

Legend: **P < 0.05; *P ≤ 0.5 = not significant but considered for further analysis in multivariate models; 1† = reference category; SES = Socioeconomic status. Note that factors in Table 2 that do not appear here had a P > 0.5.

Results in Table 4 show that participants who were not on cART had 2.13 times the risk of being admitted for OIs than those who were not on cART (AOR 2.13, 95% CI: 0.92-4.90). Participants who were not on co-trimoxazole were 29% less likely to be admitted for OIs than those who were on co-trimoxazole prophylaxis (AOR 0.29, 95% CI: 0.15-0.59). Patients with CD4-cell count < 350/µL had 3.21 times the risk of being admitted for OIs compared to those with CD4-cell count > 350/µL (AOR 3.21, 95% CI 1.61-6.42). Females were 42% less likely to be admitted than males (AOR 0.42, 95% CI 0.24-0.95).

Table 4. Biomedical, socio-demographic and economic characteristics of HIV patients independently associated with OI-related admissions at Princess Marina Hospital in Botswana between April and June 2014.

Dependent variable: aggregated OIs-admissions (N = 179).

	Proportion%	Unadjusted		Adjusted	
Independent variables		**OR**	**95%CI**	**OR**	**95%CI**
Not on cART	25.0	3.23*	1.46 – 6.51	2.13©	0.92 – 4.90
On cART	75.0	1	-	1	-
Not on co-trimoxazole	46.4	0.20*	0.10 – 0.37	0.29**	0.15 – 0.59
On co-trimoxazole	53.6	1	-	1	-
CD4 < 350/µL	52.5	4.56*	2.46 – 8.56	3.21**	1.61 – 6.42
CD4 ≥ 350/µL	47.5	1	-	1	-
Female	54.2	0.42*	0.23 – 0.77	0.48**	0.24 – 0.95
Male	45.8	1	-	1	-

*P < 0.5; **P < 0.05, ©P = 0.07; Hosmer-Lemeshow test of goodness-of-fit ΨP = 0.48.

Discussion

This study examined the major reasons why PLWH were admitted at PMH between April and June 2014 and investigated PLWH baseline characteristics that correlated with OIs' related admissions. Fifty nine different conditions were found to be responsible for hospital admissions among PLWH. Of those, 7 were due to OIs and accounted for 520 per 1000 admissions namely tuberculosis, cryptococcal meningitis, cryptosporidium, bacterial pneumonia, pneumocyst carinii pneumonia (PCP), herpes and candidiasis. Non-OIs accounted for only 480 per 1000 admissions. Patients with CD4-cell count <350/μL and those not on cART had a greater risk of OI-related admission than patients with CD4-cell count >350/μL and those on cART. Results also indicated that female HIV patients were generally less likely to be admitted for OIs than their male counterparts.

These results have provided evidence that the burden of OIs among PLWH is the most important reason for their admission to PMH and therefore suggesting that programs aiming at controlling and preventing morbidities among PLWH in Botswana should primarily focus on OIs control, CD4-cell count and cART. Our finding that show that CD4-cell count <350/μL and not being on cART were important correlates of OIs-related admissions among PLWH are strongly supported by the literature [18 - 20] and thus, set up a base for policy and decision making. The fact that when the participants were not on co-trimoxazole, they were found to be less likely to be admitted for OIs compared to those who were on co-trimoxazole could be explained here by the fact that participants who were not on co-trimoxazole in this study were mostly patients with CD4-cell count >350/μL compared to those who were on co-trimoxazole. This observation corroborates results from Ruskin and LaRivière [14]. Nonetheless, there are studies with different results too [15, 21, 22]. While both scenarios find support in the literature [22 -23], they are both amenable to speculations that the prophylactic action of co-trimoxazole depends somewhat on CD4-cell modulation. Indeed, co-trimoxazole is recommended for persons whose CD4-cell count is ≤ 200/μL and is discontinued when the CD4-cell count increase.

On why females were at less risk for OI-related admissions than men, differences between women and men with respect to the types of OIs may be the key. For instance, cryptococcal meningitis was found to be more predominant in men than in women [15]. On the other hand, women were found to be more likely to develop herpes infections than men [22]. In this study where cryptococcal meningitis was the predominant OI, this may explain why women were less likely to be admitted for OIs than men.

The fact that our data were from one single hospital setting, PMH, may be a limitation of this study as such data might vary from one setting to the other. However, PMH being the main referral hospital and center for HIV care and management in the country, receiving referred and non-referral patients from every part of Botswana, is with no doubt the busiest setting in the country for HIV care and management. Studies that have collected and used data from such one single setting and results successfully used for implementing public health policies and decisions are found in the literature [18]. The fact that our participants came from more than 44 different communities adds support to the sample representativeness. While the exclusion of very sick patients and those with unknown HIV status may have underestimated the study outcome, that is well justified by the fact that the study addressed only issues related with PLWH. Based on this, it is doubtful that factors other than those discussed herein might explain the results.

Conclusion

Outstanding findings in this study are that OIs were major causes of admission to hospital among PLWH in Botswana. Inpatients' CD4-cell count, whether or not on cART, whether on or not on co-trimoxazole and gender were important correlates of admission for OIs at PMH among PLWH.

Recommendations

These results clearly suggest that programs aiming at addressing the burden of OIs among PLWH in Botswana should primarily target OIs and their correlates namely CD4-cell count < 350/μL and patients not on cART. We hope that this work will stimulate more research along the same line so as to provide more evidence critical for formulating and implementing new policies to improve the quality of life of PLWH.

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Disclaimer

The content and conclusions of this paper are those of the authors and should not be construed as the official position or policy of, nor should any endorsements be inferred by HRSA, HHS or the U.S. Government.

Competing Interests

The authors declare no conflict of interest.

Ethical Issues

Ethical clearance was obtained from the Office of Research and Development of the University of Botswana and the Ministry of Health of Botswana. Permission to access and review patients' records was sought from PMH Institutional Review Board. Before the interviews and access to patients' records, written signed consent was obtained from the patients. To ensure confidentiality, an identification number was assigned to every participant in lieu of patient names or any direct identifier.

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