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Original Research Article

Likelihood of Pneumocystis Pneumonia, Cryptococcus Meningitis and Tuberculosis after Experiencing Symptoms of Shortness of Breath, Fever and Cough among Patients on Antiretroviral Therapy in Tanzania

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ABSTRACT

Background: Opportunistic infections (OI) still remain a major cause of morbidity and mortality among HIV-infected persons presenting with advanced infection. We examine the proportion of deceased patients who were on antiretroviral therapy (ART) with symptoms of shortness of breath, fever and cough and its effect in determining the likelihood for Pneumocystis Pneumonia (PCP), Cryptococcal Meningitis (CM) and Tuberculosis (TB).

Methods: A retrospective analysis of routinely collected program data was done for assessing factors related to mortality of 987 deceased adult patients who received ART at 6 health facilities between 1st January 2007 and 31st December 2012. Bivariate and multiple regression analyses were conducted using STATA 12.0 to identify the risk of common opportunistic infections.

Results: About fifty two percent of all the deceased patients had experienced at least one symptom. Those who experienced shortness of breath 6 months before death were 10 times (95% CI: 5.9 – 17.6) more likely to have PCP and 4 times (95% CI: 2.8 – 5.6) more likely to have TB compared to those who did not have shortness of breath. ART patients who had experienced fever and cough 6 months before death were more likely to have PCP (OR= 5.8: 95% CI 2.9 – 11.6), likelihood for TB was 4.2 (95% CI: 3.0 – 5.8) and CM (OR = 2.1: 95% CI 1.2 - 3.6; p<0.008) compared to those who did not experience fever ad cough symptoms.

Conclusion: Despite increased access to ART, People living with HIV in resource limited settings continue to die due to opportunistic infections. These deaths could be averted if more aggressive screening and detection of OI is carried out. Appropriate diagnoses of OI in such settings are essential to the reduction of early mortality and overall success of HIV care and treatment. Retraining of health care workers and introduction of a simple prognostic tool could be useful in improving risk assessment of PCP, CM and TB.

Key Words: ART patients, Opportunistic Infection, Tuberculosis, Cryptococcal Meningitis, Pneumocystis Pneumonia

INTRODUCTION

As HIV/AIDS programs continue to scale up, an understanding of the pattern and burden of major opportunistic infections (OI) is imperative. Early reports of OI prophylaxis and ART efficacy in low-income countries have suggested that the per-person survival gains in these settings may be comparable to those in high-income countries, even in the absence of customized and highly monitored care. [1] However, despite improvements in access to antiretroviral therapy (ART), 8 - 26% of people living with HIV (PLHIV) on ART in sub-Saharan Africa die within a few months of treatment initiation, largely because many PLHIV only access ART when they have advanced disease and manifestation of undiagnosed OI. [2] A 2009 study suggested that early ART was always beneficial even when the difference in the time to initiation of ART among patients following an OI was only about one month. [3] The 2010 update to the Clinical Practice Guidelines for the Management of Cryptococcal Disease issued by the Infectious Diseases Society of America submits that if diagnosed early, cryptococcosis can be managed successfully in the majority of patients. [4] This indicates that ART seems to have an early effect on the clinical course of HIV/AIDS following an OI. For HIV care and treatment programs to be effective, interventions to prevent mortality associated with OI need to be targeted at patients showing early symptoms of major OI and improve early initiation on ART.

Tuberculosis (TB), cryptococcal meningitis (CM), Pneumocystis Pneumonia (PCP) and acute sepsis are among the main causes of death. [2] Pulmonary TB is the leading cause of death among patients with AIDS, killing 1 of 3 patients, [5] and remains the most common OI in low-income countries.[6] In sub-Saharan Africa, approximately 80% of HIV related mortality cases are associated with TB. [6] Interestingly, studies in other regions show the same trend. On the Indian subcontinent, TB is the most reported OI among HIV patients. [7] In high burden settings, most of the prevalent TB disease remains undetected among PLHIV. Post-mortem studies conducted in hospitals across sub-Saharan Africa over the past 20 years have repeatedly shown that between 30% and 50% of HIV-infected adult inpatients who died had evidence of TB, which was neither clinically suspected nor diagnosed before death. [8-11]

PCP formerly known as pneumocystis carinii pneumonia is another major opportunistic infection in PLHIV. Recent estimates indicate that the prevalence of PCP among HIV-infected patients with pneumonia may be as high as 27% in some African countries. [12,13] In the developed countries, its incidence has decreased dramatically among HIV-infected patients owing to the twin interventions of antimicrobial prophylaxis of high-risk patients and ART. However, in sub-Saharan Africa, access to these interventions remains limited for millions of PLHIV. [14] CM related mortality remains high [15-17] accounting for up to 20%AIDS related deaths [18] among PLHIV with advanced immunosuppression in India, Democratic Republic of Congo, Thailand and Brazil. [7,19] Among patients with CM in Tanzania and Uganda, 80–90% had a CD4+ T cell count ≤100 cells/μL. [20]

The use of treatment guidelines in sub-Saharan Africa has increased over the years [21] but under or misdiagnosis of OI, is common leading to rapid HIV/AIDS disease progression, which could account for high mortality rates observed in several studies conducted in Zimbabwe, Uganda, Botswana and South Africa. [22-24] A syndromic approach for diagnosis and treatment of OI is critical in assessing HIV-infected patients

especially in settings in which laboratory diagnostics are inadequate. [25] Most of the OI occurring in HIV-infected individuals are signaled by symptoms or signs that should prompt suspicion for specific conditions. There is evidence addressing the question of the benefits of when to initiate ART, however, there are few studies examining the presence of major symptoms of the three leading OI among HIV/AIDS related cases of mortality. In this study we examine the proportion of deceased patients received ART with symptoms of shortness of breath, fever and cough and the effect in determining the likelihood for PCP, CM and TB.

MATERIALS AND METHODS

Study Setting

Currently many African countries are receiving HIV care and treatment support through the President's Emergency Plan for AIDS Relief in Africa (PEPFAR), the Global Fund, and other private donors. These funds have made ART available to thousands of people who are now receiving life-sustaining medications. The government of Tanzania implemented a regionalization program leading stakeholders to direct attention to specific areas in an attempt to bring comprehensive or cohesive therapy and management to an entire geographical region. This was directed first to reference-level hospitals followed by Regional then District Hospitals and later extending to health centers and dispensaries. In this study we specifically examine the characteristics of all mortality patients experiencing symptoms of fever, cough and/or shortness of breath in six hospitals: one Referral, two Regional, 2 District and one Faith-Based.

Data Collection

As part of routine quality improvement initiative, a retrospective medical records abstraction of 991 deceased patients who were on ART between January 1, 2007 and December 31, 2012 was conducted. Medical record abstraction is one of quality performance measurement technique, which can be used to evaluate health outcomes. [26,27] Independently, chart audit merely measures improvement in performance not competence although studies have shown that systematic medical records abstraction influence meaningful healthcare behavior changes, patient care and health databases. [28,29]

Data were abstracted on demographic, clinical and laboratory variables including age, sex, date of enrollment into HIV care, ART start date, TB, WHO staging, CD4 and other laboratory tests, opportunistic infections at last visit, and cause of death were also ascertained through the medical chart review. Data were entered into an excel sheet by Quality Improvement teams from the six hospitals who were trained in data ethics and data abstraction procedures. Data were cleaned and recorded by senior level program staff to identify any anomalies during the entry into the excel sheet.

Statistical analysis

All statistical analysis was conducted using STATA 12 (StataCorp LP, College Station, TX, USA for Windows). Descriptive statistics (mean, standard deviations, and median) were computed to examine the distribution of demographic characteristics of the study population for categorical variables and means (SD) for continuous variables. At the bivariate level, we performed Chi-square (χ^2) test of independence for categorical variables. Unadjusted logistic regression analysis was performed to identify factors significantly associated with symptoms (fever and cough, and shortness of breath). Variables found to be statistically significant ($p < 0.05$) on unadjusted analysis were included in multivariate analysis. Odd ratios as well as

confidence intervals were used to identify independent predictors. Further, we computed the 95% confidence interval for the respective adjusted odds ratios along with the p-value. An alpha (α) level of 0.05 was used as the threshold for statistical significance.

Ethical considerations

This study is based on data gathered from a routine programmatic quality improvement exercise for patient care. Permission and access to the data for this analysis was obtained from the Hospital Management Teams before embarking on this quality improvement exercise. This exercise was highly participatory, with the hospital administration and quality improvement teams taking the lead to ensure that all-personal identification information for the patients were removed. There were no patient identifiers and data was kept confidential. Initial results of this exercise were jointly summarized and communicated with the respective hospitals in the region and adapted by the quality improvement (QI) teams at each facility for programmatic enhancement and improve patient care.

RESULTS

Out of the 991 patient records reviewed, a total of 987 (98.9%) cases were included in this study. Records with missing data on the variables of interest were excluded from the analysis. Of all cases reviewed there were almost an equal proportion of both males and females (Table 1).

Fever and Cough

In relation to deceased patients who experienced fever and cough 6 months before death, the mean age was 39.9 (SD = 11.0), compared to 41.1 (SD= 11.7)among those who had not experienced fever and cough. Among patients with fever and cough 50.1% (n = 243) were men compared to 49.9 % (n = 242) women, the difference was not statistically significant (figure 2).

About 35.9% of the deceased patients who experienced fever and cough 6 months before death were from the referral hospital (p-value <0.001). Approximately 179 (18.4%) of the deceased patients had shortness of breath. For patients who had experienced fever and cough 6 months before death 31.9% (p-value <0.001) had experienced shortness of breath. Among deceased patients who had experienced fever and cough 38.1%, 8.5%, and 10.9% were diagnosed with TB, CM, and PCP respectively. In regard to laboratory testing 485 (49.6%) patients had received both biochemistry testing and hematology testing (Table 1)

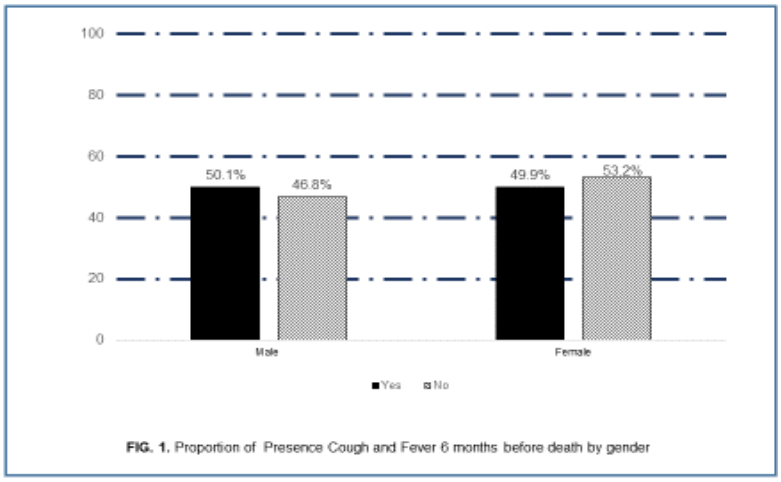

FIG. 1. Proportion of Presence Cough and Fever 6 months before death by gender

Table 1: Demographic, clinical and laboratory characteristics of deceased ART patients with presence of fever and cough 6 months before death.

Characteristics	Presence of Fever and Cough		
	No	Yes	p-value
Age n=977 (Mean, SD)	41.1 (11.7)	39.9 (11.0)	0.054
Gender (n=977)			0.294
Male	230 (46.8%)	243 (50.1%)	
Female	262 (53.2%)	242 (49.9%)	
Fever and Cough per each site (n=977)			<0.001
Referral Hospital	102 (20.7%)	174 (35.9%)	
Regional Hospital 1	51 (10.4%)	141 (29.1%)	
District Hospital	29 (5.9%)	51 (10.5%)	
Regional Hospital 2	125 (22.4%)	63 (13.0%)	
District Hospital 2	126 (25.6%)	54 (11.1%)	
Faith Based District Hospital	59 (12.0%)	2 (3.3%)	
Baseline WHO staging (n=966)			0.366
Stage 1	24(4.9%)	23 (4.8%)	
Stage 2	91 (18.8%)	91 (18.9%)	
Stage 3	205 (42.3%)	227 (47.2%)	
Stage 4	165 (34.0%)	140 (29.1%)	
Last Recorded WHO staging (n=958)			0.020
Stage 1	6 (1.3%)	6 (1.3%)	
Stage 2	36 (7.5%)	38 (7.9%)	
Stage 3	171 (35.8%)	217 (45.2%)	
Stage 4	265 (55.4%)	219 (45.6%)	
Baseline CD4 (n=859) Mean (SD)	157 (154.8)	147 (146.7)	0.812
0 – 200 /mm3	289 (69.1%)	317 (73.6%)	
201 – 350 /mm3	90 (21.6%)	72 (16.7%)	
>350 /mm3	39 (9.3%)	42 (9.7%)	
Symptoms			
Shortness of breath (n=974)	25 (5.1%)	154 (31.9%)	<0.001
OI 6 months prior to death			
Tuberculosis (n=977)	63 (12.8%)	184 (38.1%)	<0.001
Cryptococcal Meningitis (n=975)	21 (4.3%)	41 (8.5%)	0.007
Pneumocystic Pneumonia (n=971)	11 (2.1%)	52 (10.9%)	<0.001
Laboratory testing during illness			
Biochemistry (n=977)	185 (38.2%)	300 (61.8)	<0.001
Haematology (n=977)	146 (30.1%)	339 (69.0)	<0.001

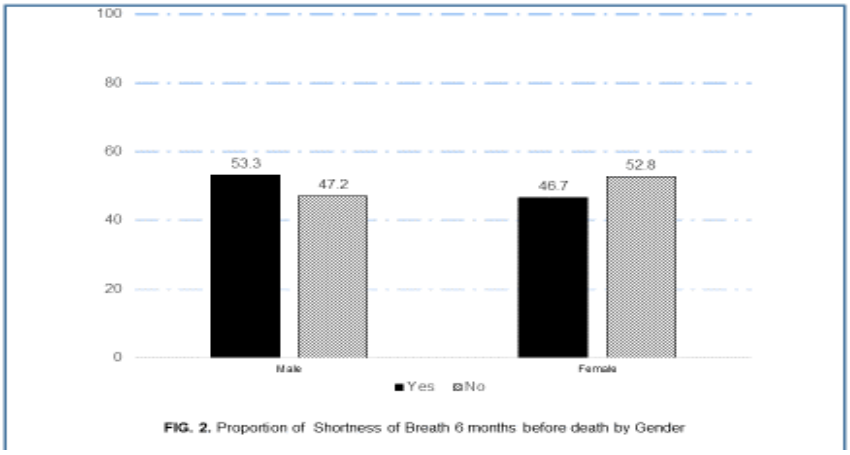

FIG. 2. Proportion of Shortness of Breath 6 months before death by Gender

Shortness of breath

Demographic, clinical and laboratory characteristics of deceased patients who were on ART with presence of shortness of breath 6 months before death are summarized in table 2. In relation to deceased patients who experienced shortness of breath 6 months before death, the mean

age was 40.2 (SD = 11.4) among those who had shortness of breath as compared to 41.4 (SD = 10.9) for those who had not experienced this symptom (Table 2). Among patients with shortness of breath 53.3% (n = 96) were men compared to 46.6% women, the difference was not statistically significant (Fig.2).

About 46.7% of the deceased patients who had experienced shortness of breath 6 months before death were from the referral hospital (p <0.001). For deceased patients who had experienced shortness of breath 6 months prior to death, 86 % also had experienced fever and cough in the same period. Among deceased patients who had experienced shortness of breath 90 (50%), 26 (14.5%) and 40 (22.5%) had TB, CM, and PCP respectively. Out of the 987 patients, 180 (18.2%) patients had received a biochemistry and hematology comprehensive test (Table 2)

Table 2: Demographic, clinical and laboratory characteristics of deceased patients who were on ART with presence of shortness of breath 6 months before death.

Characteristics	Presence of Shortness of Breath 6 months before death		
	No	Yes	p-value
Age n=977 (Mean, SD)	40.2 (11.4)	41.4 (10.9)	0.908
Gender (n=987)			0.137
Male	381 (47.2%)	96 (53.3%)	
Female	426(52.8%)	84 (46.7%)	
Symptoms per each site (n=987)			<0.001
Referral Hospital	191 (23.7%)	84 (46.7%)	
Regional Hospital 1	141(17.5%)	53 (29.4%)	
District Hospital	53 (6.6%)	27 (15.0%)	
Regional Hospital 2	175 (21.7%)	12 (6.7%)	
District Hospital 2	176 (21.8%)	4 (2.2%)	
Faith Based District Hospital	71(8.8%)	0 (0%)	
Baseline WHO staging (n=976)			0.051
Stage 1	43(5.4%)	4 (2.3%)	
Stage 2	153(19.2%)	30 (16.9%)	
Stage 3	366 (45.9%)	75 (42.1%)	
Stage 4	236(77.4%)	69(38.8%)	
Last Recorded WHO staging (n=968)			0.020
Stage 1	11(91.7%)	1 (0.6%)	
Stage 2	66 (8.4%)	9 (5.0%)	
Stage 3	321 (40.7%)	73 (40.8%)	
Stage 4	391(49.6%)	96 (53.6%)	
Baseline CD4 (n=855) Mean (95% CI)	155 (151.3)	137.6 (145.7)	0.08
0 – 200 /mm3	492(80.6%)	119 (19.5%)	
201 – 350 /mm3	140 (20.1%)	23 (14.6%)	
>350 /mm3	65 (9.3%)	16 (19.9%)	
Symptoms			
Fever and Cough (n=974)	331(41.5%)	154 (86.0%)	<0.001
OI 6 months prior to death			
Tuberculosis (n=977)	157(19.2%)	90 (50.0%)	<0.001
Cryptococcal Meningitis (n=975)	36(4.5%)	26 (14.5%)	<0.001
PneumocysticPneumonia (n=971)	23 (2.9%)	40 (22.5%)	<0.001
Laboratory testing during illness			
Biochemistry (n=987)	58 (32.3%)	122 (67.7)	<0.001
Haematology (n=987)	53(29.5%)	127 (70.6)	<0.001

Multivariate Analysis

Those who experienced fever and cough 6 months before death were 10 times (OR = 10.2; 95% CI: 5.9 – 17.6; p < 0.001) more likely to have PCP and 4 times (OR = 4.0: 95% CI: 2.8 – 5.6) more likely to have TB compared to those who did not (Table 3). Patients who had experienced fever and cough 6 months before their death were more likely to have CM (OR: 3:5: 95% CI: 2.1 – 6.0; p < 0.001) compared to those who did not.

Table 3: Predictability of common opportunistic infections (TB /PCP/CM) and shortness of breath among ART deceased Patients exhibiting fever and cough

Characteristic (before 6 months to death)	Crude OR	P Value	Adjusted OR	P value
Shortness of Breath	8.75 (5.6-13.6)	<0.001	7.0	<0.001
Pneumocystic Pneumonia	10.2 (5.9-17.6)	<0.001	2.0	0.033
Tuberculosis	4 (2.8-5.6)	<0.001	2.3	<0.001
CryptococcalMenengitis	3.5 (2.1-6.0)	<0.001	1.9	0.048

Those who experienced shortness of breath 6 months prior to death were almost 9 times more likely (OR = 8.75; 95% CI: 5.6 – 13.6; p<0.001) to also fever and cough before death (Table 4). Patients who had shortness of breath before death were 5.8 times likely to have PCP (OR = 5.8; 95% CI: 2.9 – 11-6; p < 0.001) than those who had not experienced shortness of breath. Those who had the symptom of shortness of breath before death were more likely to have TB (OR = 4.2; 95% CI: 3.0 - 5.8) compared to those who did not. ART patients who had experienced shortness of breath 6 months before their death were more likely to have CM (OR= 2.1; 95% CI 1.2 – 3.6; p-value: 0.008 as compared to those who did not.

Table 4: Predictability of common opportunistic infections (TB /PCP/CM) and Fever/cough among deceased Patients on ART exhibiting Shortness of breath

Characteristic (before 6 months to death)	Crude OR	P Value	Adjusted OR	P value
Fever and Cough	8.75 (5.6-13.6)	<0.001	6.7	<0.001
Pneumocystic Pneumonia	5.8 (2.90-11.6)	<0.001	2.5	<0.001
Tuberculosis	4.2 (3.0-5.8)	<0.001	3.2	<0.001
CryptococcalMenengitis	2.1 (1.2-3.6)	0.008	1.1	0.814

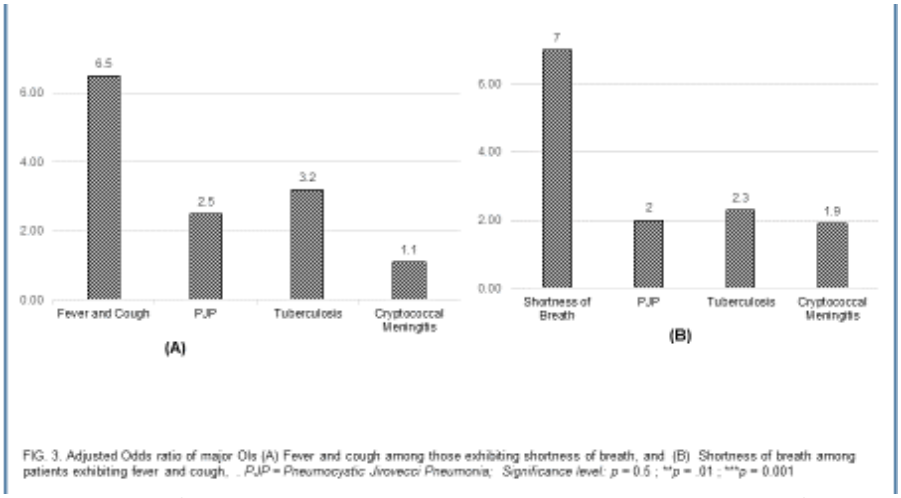

FIG. 3. Adjusted Odds ratio of major OIs (A) Fever and cough among those exhibiting shortness of breath, and (B) Shortness of breath among patients exhibiting fever and cough. . PJP = Pneumocystic Jirovecci Pneumonia; Significance level: p = 0.5 ; **p = .01 ; ***p = 0.001

Fig.3 shows the adjusted Odds Ratio of Major OI (A) Fever and cough among those exhibiting shortness of breath and, (B) Shortness of breath among patients exhibiting fever and cough.

DISCUSSION

Our findings suggest that PLHIV typically accessed ART when they had advanced symptomatic disease and undiagnosed OI. This is confirmed by the fact that up to 70.5% of the sample had a baseline CD4 count of less than 200/mm^3, which is much less than the average for a normal person (500-1500/mm^3).This suggests late presentation for ART, and is consistent with other findings in Sub-Saharan Africa [2]. The low CD4 counts had a significant bearing on the occurrence of OI and early mortality. A similar study in the North of Ethiopia equally demonstrated that CD4 counts < 200 cells/µL and WHO

clinical stage III and IV were strongly associated with prevalence of OI. [30]

A major setback for individuals who present for clinical care with advanced disease or late stage of AIDS without prior ART is that they are often seen as being at high risk for non-adherence and poor medical follow up. [31] A study conducted in Haiti demonstrated that starting ART at a CD4 count of 200-350 cells/µL compared to waiting until the CD4 count is <200 cells/µL reduced the risk of active TB by 50%. [32] Findings from the same study indicate that initiation of ART at a CD4 count ≥350 cells/µL instead of waiting until the CD4 count dropped to <250 cells/µL is associated with approximately 47% reduction in the risk of active TB.

Fever, Cough and Shortness of breath were more observable and manifested more in men than women, though by a small margin not statistically significant. These results are consistent with those from the India by Ghatea et al. in 2009. [7] Among the three OI highlighted in our findings, TB was predominant among the deceased patients at 25.3% (n = 247) compared to PCP at 6.5% (n = 63) and CM at 6.4% (n = 62). These results are lower than findings by WHO in 2012 where 79% of HIV cases in sub-Saharan Africa had pulmonary TB. [5] However, postmortem studies conducted in hospitals across sub-Saharan Africa as early as 1993 by Lucas et aland as recently as 2010 by Cohen showed a closer pattern to our findings with 30-50% of patients having died of pulmonary TB.

A multi-centre study by Zolopa et al, which excluded TB patients, reported that the most common entry OI included PCP (63%) and CM (12%), [3] which is higher than what noted from our findings. In a study by Ghate et al 2009 in India, CM was associated with early mortality in ART patients and could be attributed to late presentation for therapy because the CD4 cell counts were significantly low. [7] Another study identified pulmonary TB as the most common AIDS-defining illness and concluded that TB and CM are leading causes of mortality in patients initiating ART in Africa. [22-35] The fact that many HIV patients are accessing ART late presents a major clinical challenge due to the complexities involved in the concurrent management of OI. [36] The evidence suggests that patients suspected of PCP should therefore be carefully assessed and treated to reduce or avert premature death. [37] Additionally, given the high rates of mortality in these regions of the world where HIV/AIDS burden is also high, identification of cases of TB, and CM and PCP early on in the course of the disease and initiation of ART could reduce mortality. [13,38-40]

CONCLUSION

In low-income settings, knowledge regarding prevalence of the major OI might aid decision-making regarding empirical treatment and would help to prioritize limited resources for training, diagnostics, and therapy. Enhancing OI diagnoses and optimizing OI disease management will lead to a strengthening, scalable and sustainable path for ART care and treatment services and reduction in mortality. Our findings demonstrate the striking scientific and clinical benefits achieved in the fight against HIV/AIDS disease by using a deliberate simple, pragmatic clinical and public health approach that can help describe the spectrum of OI and may help define a clinical training package that will enhance the capacity of health care workers and laboratory technicians to appropriately diagnose and timely treat OI even in resource-constrained settings.

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Conflict of Interests

All authors declare that they have no conflict of interests associated with the publication of this paper.

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