Causes and outcome of hospitalization among HIV-infected adults receiving antiretroviral therapy in Mulago hospital, Uganda

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Abstract

Background: Cohorts describing cause specific mortality in HIV-infected patients initiating antiretroviral therapy (ART) operate on an outpatient basis. Hospitalized patients represent the spectrum and burden of severe morbidity and mortality in patients on ART.

Objective: To determine the causes and outcomes of hospitalization among adults receiving ART.

Methods: A prospective cohort study. We enrolled 201 participants (50% female) with median (IQR) age and CD4 count of 34 (28-40) years and 91(29-211) cells/uL respectively.

Results: The most frequent causes of hospitalization were tuberculosis (TB) (37, 18%), cryptococcal meningitis (22, 11%), zidovudine (AZT) - associated anemia (19, 10%), sepsis (10, 5%) and Kaposi's sarcoma (10, 5%).

Forty two patients (21%) died: 10 (24%) had TB, 8 (19%) had cryptococcal meningitis and 5 (12%) had sepsis, 9 (21%) had undiagnosed neurological syndromes while 10 (24%) had other illnesses. Predictors of death included low Karnofsky performance score of < 40 (OR, 21.1; CI 1.43- 31.6) and age >34 years (OR, 7.65; CI 1.09- 53.8).

Conclusions: Opportunistic infections, malignancy and AZT-associated anemia contributed to most hospitalizations and mortality. It is important to intensify prevention, screening, and treatment for these opportunistic diseases and early ART initiation in HIV-infected patients. Tenofovir-based regimens, unless contraindicated should be scaled up to replace AZT-based regimens as first line ART drugs.

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Introduction

Infection with the human immune deficiency virus (HIV) has been a global pandemic and major cause of morbidity and mortality for over three decades. Sub-Saharan Africa bears the greatest burden of disease with 68% of the global burden[1]. Significant effort has been put into scaling up antiretroviral therapy (ART) coverage worldwide; increasing coverage from 7% in 2003 to 37% in 2008 in sub-Saharan Africa. In Uganda ART coverage increased from 39% in 2006 to 53% in 2009[2, 3]. Effective ART greatly reduces HIV-related morbidity and mortality with marked improvement in survival of HIV-infected individuals.

An increasing number of studies have reported excellent short and long term virological, immunological and clinical outcomes of patients receiving ART with similar responses demonstrated in patients living in low and high income countries[4-6]. A reduction in incidence of opportunistic infections and mortality has been observed in patients receiving ART[7, 8]. In spite of these gains, 8-26% of African patients die in the first year of initiating ART, with most deaths occurring in the first three months[9-11]. Mortality is attributed to late initiation of ART when patients have advanced disease with increased risk of opportunistic infections and immune reconstitution inflammatory syndrome [12-14].

Previous studies conducted among cohorts of HIV-infected individuals seen in out-patient clinics have reported cryptococcal disease, tuberculosis (TB), septicaemia, malignancy and HIV wasting syndrome to be the leading causes of death[9]. Data on morbidity and mortality of hospitalized HIV-infected patients receiving ART are sparse. A recent autopsy study on cause- specific mortality among hospitalized patients on ART in South Africa showed infections with *Mycobacteria tuberculosis*, gram negative bacteria, fungi and neoplasms to cause mortality and more importantly, revealed the existence and contribution of comorbidities to morbidity and mortality of hospitalized patients[15]. Because hospitalized patients represent the burden and spectrum of severe morbidity and mortality, more studies on such patients in the ART era are needed.

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We evaluated the causes and outcomes of hospitalization among HIV-infected adults receiving ART at Mulago National Referral and Teaching Hospital, Uganda.

Methods

Study site

This study was conducted between January and March 2011 at Mulago National Referral and Teaching Hospital, a 1500 bed-capacity tertiary facility situated in Uganda's capital city, Kampala. Mulago Hospital provides specialized inpatient care to patients referred from district and regional hospitals around the country and from various outpatient HIV care centers. HIV prevalence in the general adult population in Uganda is 7.3%, and approximately 64% of patients hospitalized in Mulago hospital are infected with HIV [16,17]. In addition, Uganda is among the high TB burden countries with a TB incidence rate of 193 cases of all forms of TB per100, 000 population annually. 53% of TB patients are co-infected with HIV [18]. On average 15000 emergency medical visits are made to Mulago hospital annually and between 900- 1200 patients are admitted to the medical wards per month [19]. Participants were recruited from the medical emergency ward as well as the three medical wards of the hospital.

Ethical considerations

The study was approved by the Makerere University School of Medicine Research and Ethics Committee and was conducted according to Good Clinical Practice standards. All participants provided written informed consent prior to enrollment.

Study design and population

We conducted a prospective cohort study of hospitalized HIV-infected adult patients receiving ART. Study participants were enrolled at the time of presentation to hospital if they were 18 years and above and had initiated ART at least 2 weeks prior to hospitalization. A patient on ART was defined as one who had received ART for at least two weeks prior to hospitalization and was taking ART at the time of hospitalization. We excluded patients who had interrupted ART for more than a month before hospitalization. Participants were evaluated to determine the causes of hospitalization using detailed medical history, physical examination and appropriate laboratory investigations. They received treatment according to the national treatment guidelines and were followed-up till discharge, death or for a maximum of thirty days if hospitalization exceeded thirty days to determine outcomes.

Study procedures

Study participants were identified by reviewing charts of hospitalized patients on the emergency and medical wards. Participants who fulfilled study criteria were enrolled consecutively after providing written informed consent. The informed consent process as well as questionnaire interviews were conducted in the local language (Luganda) for the majority of patients and in English for a few patients who understood English but not the local language. The study doctor obtained demographic and clinical data by administering a questionnaire interview to each participant or their next of kin if the participant was too ill to provide information. Detailed medical history was obtained following which thorough physical examination was performed. Medical history included an in-depth assessment of presenting complaints, systematically solicited symptoms to review all body systems, past and concomitant illnesses and medications. Anthropometric measurements were performed to assess the body mass index. The Karnofsky performace status score was used to assess the general wellbeing of the patient at admission. This score has been previously validated as a measure of quality of life in cancer patients and a predictor of mortality among Ugandan adults hospitalized with severe sepsis [20,21].

Blood samples were collected by venipuncture for full blood count (Beckman Coulter ACT 5 diff), renal and liver function evaluation (Cobas Integra 400) and CD4 count measurement by FACS Calibur (Becton Dickinson). The study doctor made a presumptive diagnosis. Additional tests to aid in determining the cause of hospitalization were performed at the discretion of the attending clinicians (consisting of intern, resident and specialist doctors). These included sputum analysis, chest radiography, abdominal ultrasound scan, computed tomography scan, cerebrospinal fluid analysis, blood smears for parasites, biopsy and histology for suspicious lesions. Final causes of hospitalization and mortality were determined after additional tests had been done. Causes of hospitalization were definite, probable or syndromic. A definite cause was determined when a specific etiology of illness was ascertained, such as a definite diagnosis of cryptococcal meningitis if yeast cells were identified in cerebral spinal fluid on India ink staining. A probable cause was determined if patients presented

with symptoms and signs suggestive of a particular disease, did not have test results revealing the specific cause of illness, but responded to specific treatment for that disease. For instance, a diagnosis of probable TB was made if there was clinical response to empirical TB treatment as defined by reported improvement in cough, fever or anorexia during hospitalization among patients with negative sputum smears for acid fast bacilli on Ziehl Nielsen or flourochrome (Auramine-O) staining and suggestive lymph node and pleural histological findings. Patients without a definite or probable diagnosis had a syndromic diagnosis made according to the predominant organ system manifesting disease, such as neurological syndromes. Participants were followed up till discharge, death or for a maximum of thirty days if hospitalization exceeded thirty days to determine the outcome. The diagnosis at the time of death was considered the cause of death.

Statistical analysis

Data were entered into Epi-data version 3.1 and analyzed using SPSS version 16. Demographic and baseline clinical and laboratory characteristics were summarized into frequencies, medians and inter-quartile ranges (IQR). Causes and outcomes of hospitalization were summarized into frequencies and proportions. The Chi-square test was used to test for association between baseline categorical clinical and laboratory variables and death. All p values were 2 sided. Factors associated with death, with a p value less than 0.2 at bivariate analysis were considered potential covariates in multi-variate analysis. Binary logistic regression was performed for multivariate analysis. A p value less than 0.05 was considered statistically significant.

Results

Patients' characteristics at the time of hospitalization

We screened 227 participants of whom 201 (89%) were enrolled. Twenty six (11%) patients were excluded for various reasons as shown in Figure 1. Of the 201 participants enrolled 101 (50%) were female. Table 1 shows study participants' demographic and clinical characteristics. The median (IQR) age, hemoglobin, Karnofsky performance score and CD4 count were 34 (28-40) years, 8.4 (5.5- 11.3) g/dl, 50 (50- 60) and 91 (29-211) cells/ uL respectively. Sixty four (32%) patients had a BMI < 18, 46 (23%) patients were too weak to stand on a weighing scale so their BMI was not established. Majority (171, 85%) participants were classified as stage 3 or 4 using the World Health Organization (WHO) classification system, while 30 (15%) had stage 1 or 2 disease. Patients with stage 1 or 2 disease had a median (IQR) CD4 count of 221(89- 366).

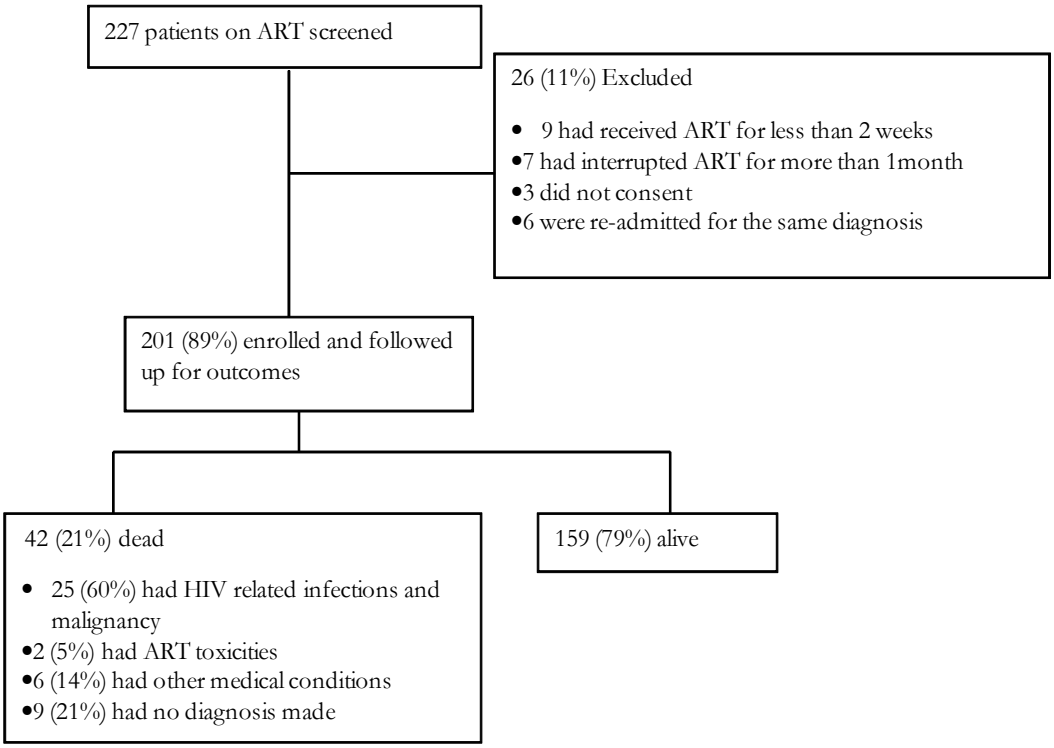

Figure 1: Flow diagram for study enrollment and outcomes

Most participants (114, 57%) were receiving zidovudine based first-line ART regimens. Majority (150, 75%) were assessed to have more than 90% adherence using self reports. Median (IQR) duration on ART was 20 (8- 104) weeks with 79 (39%) patients having received ART for not longer than 12 weeks. Sixty one (30%) participants were receiving treatment for co-morbidities diagnosed before hospitalization, of whom 35 (17%) were receiving anti-TB treatment, 8 (4%) antihypertension treatment, 5 (2%) chemotherapy for Kaposi's sarcoma, 7 (3%) fluconazole as secondary prophylaxis for cryptococcal meningitis and 6 (3%) were on various other drugs (table 1). Notably all patients reported to be receiving cotrimoxazole or dapsone preventive therapy.

Causes of hospitalization

Table 2 shows the causes of hospitalisation; 72 (35%) were definite, 102 (50%) were probable and 31 (15%) were syndromic. Four patients had dual diagnoses; 2 with TB and deep venous thrombosis (DVT), one with DVT and liver cirrhosis and one with fungating Kaposi's sarcoma and sepsis. Major causes accounting for 79 (39%) were TB, cryptococcal meningitis, sepsis and Kaposi's sarcoma. Two (1%) patients on fluconazole preventive therapy were admitted with features of cryptococcal immune reconstitution inflammatory syndrome (IRIS) and all 4 (2%) patients who had defaulted on fluconazole preventive therapy were admitted with a relapse of cryptococcal meningitis.

Nineteen (10%) patients had anemia probably associated with AZT intake and requiring transfusion. Other ART toxicities included 6 (3%) patients with nevirapine associated dermatitis, one (1%) with nevirapine associated hepatotoxicity, two (1%) with profuse diarrhea and one (1%) with severe headache.

Table 1: Demographic and clinical characteristics of study participants

Variable	Frequencies (%) n = 201
Age (yrs) *	34 (28-40)
Sex: Female	101(50)
Time on ART at time of hospitalization (weeks) *	20 (8- 104)
ART regimens used	
AZT/ 3TC/ NVP or EFV	114 (57)
TDF/ 3TC/ NVP or EFV	66 (33)
TDF/ 3TC/ ABC or AZT	2 (1)
d4T/ 3TC/ NVP	2 (1)
ABC/ 3TC/ NVP or EFV	2 (1)1
TDF or AZT/ 3TC/ Alluvia	4(7)
Alluvia monotherapy	1
CD4 count at time of admission (cell/ μL)	
< 50	66 (33)
50- 100	36 (18)
101- 200	44 (22)
201- 500	49 (24)
> 500	6 (3)
Co-morbid conditions at time of admission	
Tuberculosis	35 (17)
Hypertension	8 (4)
Kaposi's sarcoma	5 (2)
Cryptococcal meningitis	5 (2)
Others: Depression, psychoses	6 (3)
Cotrimoxazole/ Dapsone preventive therapy	201 (100)
Fluconazole preventive therapy	
Patients with a prior diagnosis of cryptococcal meningitis	11 (5)
Patients on Fluconazole preventive therapy	7 (3)
Length of stay (days) *	8 (5.5-13)

* Median (interquartile range)

Four patients were receiving Dapsone preventive therapy

Table 2: Causes of Hospitalization and Mortality among study participants

Diagnosis	Frequency n (%)	Duration on ART (weeks) Median(IQR)	CD4 count Median (IQR)	Deaths n (%)
Tuberculosis				
Definite TB	9			1
Probable TB	28 (18)	13 (4-70)	40(20-100)	9 (24)
Cryptococcal meningitis	22 (11)	14 (6-48)	37 (14-71)	8 (19)
AZT associated anemia	19 (10)	16 (12-35)	196 (89-411)	
Other ART toxicities	10 (5)	3 (2-5)	150 (93-273)	2 (4)
Kaposi's sarcoma	10 (5)	8 (4-16)	68 (27-234)	1 (2)
Sepsis	10 (5)	14 (8-208)	153 (12- 224)	5 (12)
Pneumonia	9 (5)	108 (38-338)	301 (143-456)	
Chronic diarrhoea (syndromic diagnosis)	7 (4)	224 (15-260)	76 (16-177)	1 (2)
Deep venous thrombosis (DVT)	7 (4)	32 (10-64)	36 (12-101)	
Renal failure	6 (3)	50 (14-260)	156 (67-330)	2 (4)
Ischemic brain infarcts	5 (2)	128 (104-156)	135 (41-176)	
Hypertensive heart disease	5 (2)	16 (12-156)	243 (201-317)	
Liver cirrhosis	3 (1)	20 (20-52)	118 (15-169)	1(2)
Malaria	3 (1)	260 (2-416)	332 (160-360)	
Lymphoma	3 (1)	60 (24-166)	216 (28-354)	1 (2)
Other HIV related illnesses	8 (4)	20 (6-28)	50 (16-65)	
Other medical illnesses	17 (8)	38 (12-208)	157 (52- 247)	2 (4)
Neurological syndrome	19 (10)	52 (16- 260)	263 (73-385)	9 (21)
Pancytopenia syndrome	5 (2)	16 (12-16)	71 (58- 195)	
Total	205 (101)*			

* Four patients had dual diagnoses as described above

Outcomes of hospitalization

Forty two patients died, giving mortality of 21%, of whom 10 (24%) had TB, 8 (19%) had cryptococcal meningitis 5 (12%) had sepsis, 9 (21%) had undiagnosed neurological syndromes, 1(2%) had confirmed bacterial meningitis and 1(2%), probable myocardial infarction (see table 2). More than half (22, 52%) of the deaths occurred within the first 12 weeks of ART initiation. None of the patients with cryptococcal IRIS died, while one of the patients with a relapse of cryptococcal meningitis died. Patients with WHO stage 1 or 2 disease were admitted with non-AIDS defining illnesses. Significant predictors of death included Karnorfsky score of < 40% (OR, 21.1, CI 1.43 - 31.6) and age> 34years (OR 7.65, CI 1.09 - 53.8) (table 3).

Table 3: Predictors of death among study participants

	Bivariate analysis OR(CI)	P value	Multivariate analysisOR (CI)	P value
Age > 34 years	0.15 (0.82-3.44)	0.152	7.65 (1.09- 53.8)	0.041
Unemployment	0.51 (0.23- 1.15)	0.099	6.96 (0.87-55.59)	0.067
Receiving ART <12 weeks	1.92 (0.94- 3.92)	0.07	0.23 (0.38- 1.44)	0.232
BMI< 18	1.96 (0.69- 5.58)	0.199	0.20 (.042-0.97)	0.046
WHO Stage 3-4	1.67 (0.55- 5.12)	0.362	1.61 (0.15- 17.62)	0.696
Karnofsky Performance Score < 40%	11.76 (4.8- 28.31)	0.000	21.1 (1.43- 31.6)	0.026
Heamoglobin < 8g/dl	1.33 (0.65- 2.72)	0.436	1.28 (0.27-5.98)	0.756
CD4 < 50cells/ul	1.56 (0.75- 3.22)	0.230	1.76 (0.33- 9.53)	0.512
Creatinine > 1.4mg/dl	1.87 (0.89- 3.95)	0.096	0.23 (0.05- 1.12)	0.068

The chi- square test was employed at bivariate analysis and binary logistic regression at multivariate analysis to test for association

Discussion

We investigated the causes and outcomes of hospitalization among HIV-infected patients receiving ART in Mulago Hospital. Most frequent causes of hospitalization included TB, cryptococcal meningitis, sepsis and Kaposi's sarcoma. We observed high mortality, with majority of admissions and deaths occurring within 12 weeks of initiating ART. These findings are similar to those reported by out-patient cohorts of HIV-infected patients in Africa [9]. Most patients in this study were severely immunocompromised which explains the majority causes of hospitalization. It is likely that majority of these infections were existent before ART initiation and worsened following immune reconstitution after ART initiation. These infections can be prevented if patients start ART at CD4 counts above 500cell/ul, a departure from the 2010 WHO HIV treatment guidelines which recommend ART initiation at CD4 counts below 350cells/uL[22]. Patients with the CD4 counts below 350 cell/μL are still at risk of acquiring TB and there is increasing evidence of reduction in morbidity and mortality when patients start ART at higher baseline CD4 counts[23]. Early ART initiation is also hindered by late presentation for care by majority of HIV-infected patients[9-11, 24]. In a study performed at Mulago Hospital to determine HIV prevalence and eligibility for ART among patients presenting to the medical emergency unit, only 40 of 223 (18 %) patients knew their HIV serostatus, 68% of patients had advanced HIV but had not received an HIV test before, while 76% of HIV positive patients had not received any form of HIV/ AIDS care [25]. Late presentation is mainly hinged on poor uptake of HIV counseling and testing services, linkage to care and stigma [3, 26, 27]. Strategies such as mobile HIV counseling and testing, community based door to door HIV counseling and testing with linkage to care will serve the dual purpose of early diagnosis of HIV and early ART initiation thus improving outcomes[28, 29].

It is likely that some of the causes of hospitalization were due to IRIS following ART initiation; however we were unable to determine this using our study design. Screening and treatment for opportunistic diseases pre-ART initiation reduces the morbidity related to IRIS [30-33]. All HIV-infected patients should be screened for TB prior to ART initiation because TB affects HIV infected patients across all CD4 count strata. Intensified case finding could be implemented for all new patients enrolling into HIV care programs followed by a simple, rapid, low-cost, point-of-care testing assay for TB such as the urine Lipoarabinomannan (LAM) in patients with low CD4 count below 150cell/ uL and those who report symptoms suggestive of TB [30, 34]. The World Health Organization in 2009 recommended Isoniazid preventive therapy to prevent incident TB in HIV infected patients with latent TB [35]. Studies on its feasibility, acceptability and efficacy in this setting are needed.

Patients with advanced immune suppression should be screened for cryptococcosis prior to ART initiation. The lateral flow assay for cryptococcal antigenemia has been validated as a good diagnostic screening test for cryptococcosis and could be integrated into primary health care, to detect the disease in patients with CD4 counts below 100 cell/ uL pre-ART [36].

There is also need for intensified community mobilization and sensitization on diseases such as TB, cryptococcal meningitis and Kaposi's sarcoma to raise the index of suspicion among communities to enable early treatment seeking. The incidence of Kaposi's sarcoma IRIS as well as mortality associated with it is higher in African patients because patients initiate ART with advanced Kaposi's sarcoma [37]. Educating patients on symptoms of Kaposi's sarcoma as well as involving expert patients in symptom surveillance within self-formed community peer groups is a strategy that can be employed to enhance early detection and treatment of Kaposi's sarcoma. Expert patients have been successfully integrated into care of people living with HIV/ AIDS as peer supporters, improving ART delivery, adherence and congestion in health facilities [38, 39].

We did not investigate the treatment options for sepsis, however, a previous study performed in Mulago hospital showed a high prevalence of sepsis in patients with HIV. In this study, sepsis was attributed to infection with mycobacteria, non typhoidal *Salmonella*, *Staphylococcus aureus*, *Streptococcus pneumonia*, *Proteus species*, *Escherichia coli*, *Proteus species* and *Cryptococcus neoformans*. Death was mainly attributable to inappropriate fluid resuscitation and antimicrobial therapy [21]. This information suggests that improving fluid resuscitation to recommended standards and prescribing appropriate antimicrobials could reduce mortality in patients with sepsis. However, as discussed above for TB and cryptococcal meningitis, prevention by early ART initiation offers the best alternative.

The rate of AZT- associated anemia necessitating blood transfusion in this study is in keeping with that reported in other studies (7-16%) [40, 41]. Although the Uganda national ART guidelines recommend monthly monitoring of hemoglobin in the first 3 months for patients on AZT- based regimens, this is not feasible in most ART clinic settings, owing to high patient loads, unavailability of laboratory equipment and reagents, amongst other limitations. Our study findings suggest that safer ART regimens should be rolled out in the large scale public health setting.

Predictors of mortality included age of 34 years or more and Karnorfsky performance score of 40 or less. HIV and aging are thought to cause additive depletion of naïve T-cells as well as replicating senescence of T-lymphocytes, which effects cause poor treatment outcomes in patients with advanced age when compared to younger patients [42]. Initiating ART at higher CD4+ counts in older patients could improve outcomes. The Karnorfsky score is a measure of morbidity and a low baseline score reflects severe debility at presentation. Our data indicates that majority of patients admitted to the medical wards of Mulago National Referral Hospital present very late with severe morbidity and high risk for death. The hospital being a tertiary referral facility, coupled with the practice by some patients of using traditional medicine [43] before seeking professional help, may be the reason for severe debility at presentation. In addition, late diagnosis of HIV, poor referral systems and HIV-related stigma may contribute to late presentation. However complex HIV related stigma is, research and interventions to reduce it are needed in order to optimize outcomes of ART [44]. The protective association of BMI with death in this study (see table 3) is considered spurious owing to the fact that BMI was not determined in 46 (23%) patients. Our inability to determine definite causes of hospitalization for some participants plus lack of autopsy were major limitations of our study. Diagnostic challenges are a common problem in many heath systems in Africa which portend poor treatment outcomes [45].We recommend strengthening of diagnostic services and scaling up of point of care testing in resource limited settings to enable prompt diagnosis and institution of appropriate treatment.

Conclusion

Major causes of hospitalization were TB, cryptococcal meningitis, AZT- associated anemia, sepsis and Kaposi's sarcoma. Mortality was high, mostly among patients with tuberculosis, cryptococcal meningitis and sepsis. Predictors of death included Karnofsky performance score less than 40 and age older than 34 years. These data highlight the significance of intensified prevention, screening, and treatment for these opportunistic diseases and early ART initiation in HIV-infected patients. Tenofovir-based regimens, unless contraindicated should be scaled up to replace AZT-based regimens as first line ART drugs to avoid morbidity caused by AZT-associated anemia.

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